Edoardo Spina
Gianluca Trifirò *Editors*

Pharmacovigilance in Psychiatry

Adis

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Preface and Acknowledgements

Primum non nocere (first, do no harm) is a guiding principle for all physicians including psychiatrists that, whatever the intervention or procedure, the patient's well-being is the primary consideration.

Rational use of psychotropic drugs may improve the quality of life and the functional status of patients with neuropsychiatric diseases while minimizing adverse effects potentially associated to the pharmacological treatment. However, currently, psychotropic medications are often misused and overused, especially in elderly patients; thus, exposing this frail population to unmotivated and potentially life-threatening risks.

In general terms, it is well known that premarketing randomized clinical trials are designed to investigate, primarily, the efficacy of the drugs and may only partly explore the drug safety profile. Therefore, the risks associated with newly marketed drugs can be properly quantified and characterized only after their use in clinical practice (i.e. post-marketing phase). For this reason, post-marketing pharmacovigilance monitoring has been long recognized as the last phase of drug development.

Pharmacovigilance is a discipline that entails both cultural and scientific aspects. On one hand, traditional pharmacovigilance activities based on spontaneous reporting of adverse drug reactions from patients and healthcare professionals are essential to increase the awareness of prescribers and users about the potential risks associated to exposure to medicines. On the other, in the last few years, pharmacovigilance as a science is rapidly evolving towards a more proactive approach in terms of emerging safety issues detection, strengthening and validation, thanks to innovative methodologies that have been developed in the context of outstanding initiatives, such as US FDA-endorsed Sentinel and European FP-7-funded EU-ADR and IMI-funded PROTECT.

It is nowadays well acknowledged that continuously growing availability of databases with longitudinal electronic health records of millions of persons worldwide offers the opportunity to get better insight, rapidly and cheaply, into real-life psychotropic drug use and the benefit-risk profile of those medications in the general population, as well as in specific frail categories of patients such as older people, children and pregnant women.

A number of large-size observational studies have been conducted in several continents in the last decades, exploring and confirming the associations of potentially serious safety outcomes and use of drugs commonly prescribed in psychiatry, ranging from risk of hemorrhagic stroke and use of antidepressants, especially selective serotonin reuptake inhibitors, to risk of all-cause mortality and use of both atypical and conventional antipsychotics in older people with dementia, to risk of falls and benzodiazepine use and so on. Those data sources can complement the traditional spontaneous adverse drug reaction reporting system in drug safety signal management, also regarding psychotropic drugs.

Knowledge in pharmacovigilance is dynamic and requires rapid (re)assessment of risk associated with currently marketed drugs, including psychotropic drugs.

This book presents a timely overview of updated evidence about the safety profile of drugs that are commonly used in psychiatry, as well as of established and advanced methodologies that have been used up to now for the conduct of post-marketing pharmacovigilance studies.

We gratefully acknowledge the continuous advice from Prof. Bruno Stricker (Erasmus University Medical Center of Rotterdam, the Netherlands) and Prof. Achille P. Caputi (University of Messina, Italy), who inspired relevant parts of this book through their innovative research in the field of pharmacovigilance.

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Part I
General Aspects of Pharmacovigilance in Psychiatry

Chapter 1
Pharmacovigilance in Psychiatry: An Introduction

Edoardo Spina, Gianluca Trifirò, and Achille Patrizio Caputi

Abstract The discipline of pharmacovigilance is of particular importance in the field of psychiatry. Pharmacotherapy is the principal modality of management in several psychiatric disorders and psychotropic drugs are associated with a variety of adverse drug reactions. Over the past decades, pharmacovigilance activity has led to the identification of several adverse drug reactions caused by psychotropic drugs, resulting in their withdrawal from the market or restrictions in use. Psychotropic medications are often administered for longer periods and are commonly prescribed in combination with other drugs and, therefore, may be involved in clinically relevant drug interactions. Psychotropic agents may be prescribed to populations at higher risk of developing adverse effects. In particular, they are increasingly used to treat psychiatric disorders in children and adolescents, as well as in the elderly, and may be used by pregnant or lactating women. The main source of knowledge on tolerability and safety of psychotropic drugs comes from clinical trials, but this is associated with several limitations. Pharmacovigilance programs are designed to gather information on what effects drugs have in the real world rather than in groups of carefully selected clinical trial populations. For the abovementioned reasons, it is important that psychiatrists become familiar with the concepts and methods of pharmacovigilance as they have a key role in identifying and reporting new or serious adverse drug effects.

Keywords Pharmacovigilance • Psychiatry • Psychotropic drugs • Adverse drug reactions

The World Health Organization (WHO) defines pharmacovigilance as "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" (WHO 2000). As a result, a wide range of healthcare professionals, including doctors, nurses, and pharmacists can

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contribute to pharmacovigilance activities. Such activities are a critical aspect of medical practice and have the potential to reduce and possibly prevent drug-related harm and associated costs.

Pharmacovigilance is of particular importance in the field of psychiatry (Rajkumar and Melvin 2014). Most psychiatric disorders are primarily treated with drugs, all of which are associated with their own adverse drug reactions (ADRs). Soon after the advent of modern psychopharmacology in the early 1950s, it became clear that the use of first available psychotropic drugs was sometimes associated with life-threatening or disabling adverse effects. This is the case with neuroleptic malignant syndrome and tardive dyskinesia associated with traditional antipsychotics or the potentially fatal hypertensive crises occurring when irreversible monoamine oxidase inhibitors, the first clinically effective antidepressants, are given in combination with tyramine-rich food.

The birth of pharmacovigilance is closely related to psychiatry. In the late 1950s, thalidomide was widely used in several countries as an antiemetic and a "safe sedative," particularly effective when given to pregnant women. It was soon noticed by physicians that babies exposed to the drug in utero developed congenital malformations (McBride 1961). Widespread use of thalidomide in Europe, Australia, and Japan resulted in approximately 10,000 children born with phocomelia, leading to the ban of thalidomide in most countries. The thalidomide tragedy is generally regarded as the beginning of legislated pharmacovigilance (Moore 2013). This disaster marked a turning point in toxicity testing, as it prompted international regulatory agencies to develop systematic toxicity testing protocols. From such a tragedy, national pharmacovigilance centers emerged, as well as the development of spontaneous reporting to identify ADRs that could justify or mandate regulatory action.

Over the years that followed, pharmacovigilance activity has led to the identification of several adverse drug reactions caused by psychotropic drugs, resulting in their withdrawal from the market or restrictions in use. In 1973, a number of fatal cases of agranulocytosis cases occurred with clozapine treatment which led to the withdrawal of this efficacious antipsychotic drug in some countries and to restriction of use in many others (McKenna and Bailey 1993). Zimelidine was the first selective serotonin reuptake inhibitor (SSRI) antidepressant to be marketed in the early 1980s. Within a year and a half of its introduction, rare case reports of Guillain-Barré syndrome emerged that appeared to be caused by the drug, prompting its manufacturer to remove it from the market (Fagius et al. 1985). The antidepressant nomifensine, a noradrenaline and dopamine reuptake inhibitor, was withdrawn worldwide by the manufacturer in January 1986 following a rising incidence of reports of acute immune hemolytic anemia with serious clinical sequelae, including a number of fatalities (Stonier 1992). The clinical use of the atypical antipsychotic remoxipride was severely restricted in 1993, soon after its marketing, due to reports of aplastic anemia (Nadal 2001). In 1994, alpidem, an anxiolytic drug from the imidazopyridine family, was withdrawn from the market following reports of severe liver damage (Berson et al. 2001). The atypical tricyclic antidepressant (TCA) amineptine, a selective inhibitor of the reuptake of dopamine and, to a lesser extent,

noradrenaline, was marketed in some European countries as an antidepressant and soon gained a reputation for abuse potential due to its short-lived, but pleasant, stimulant effect experienced by some patients. The emergence of severe cases of hepatotoxicity, along with the potential for abuse, led to the suspension of marketing authorization in 1999 (Lazaros et al 1996, No authors listed 1999). More recently, there were concerns on the propensity of some antipsychotics to prolong corrected QT (QTc) interval and to cause severe cardiac arrhythmias including *torsades de pointes* and sudden death. This led to the withdrawal of some antipsychotics from the market (e.g., thioridazine), temporary suspension (e.g., sertindole), or restriction of use (e.g., pimozide) (Glassman 2005).

A study investigating FDA ADR reports from 1998 to 2005 found that several of the drugs in question were psychotropic agents such as antipsychotics (clozapine, olanzapine, and risperidone), antidepressants (duloxetine, sertraline, paroxetine, bupropion), mood stabilizers (carbamazepine, valproate, and lamotrigine), and also anti-ADHD medication such as atomoxetine (Moore et al. 2007). Another study reviewing nine major ADRs reported in Europe from 1995 to 2008 found that psychotropic drugs were implicated in two ADRs, seizures caused by bupropion, and suicidality in children prescribed SSRIs (Harmark and van Groothest 2008). Interestingly, the latter was identified on reanalyzing data provided from pharmaceutical companies, while the former was identified from analysis of physician reports. A more recent investigation concluded that of the 19 drugs withdrawn from the European market between 2002 and 2011, 4 were psychotropic agents (nefazodone, thioridazine, veralipride, and acepromethazine+acepromazine) (McNaughton et al. 2014).

There are several reasons why pharmacovigilance is important to psychiatry (Rajkumar and Melvin 2014). As psychiatric disorders are often chronic, prolonged pharmacological treatment may be required, thus increasing the possibility of long-term ADRs. Psychotropic medications are commonly prescribed in combination with other drugs used to treat comorbid psychiatric or somatic disorders and, therefore, may be involved in clinically relevant drug interactions. Psychotropic agents are increasingly used to treat psychiatric disorders in children and adolescents, as well as in the elderly, and may be used by pregnant or lactating women. Side effects of psychotropic medications can mimic psychiatric symptoms (anxiety, insomnia, somnolence, suicidality) and distinguishing between ADRs and symptoms of the underlying illness can be difficult. Moreover, chronic use of many psychiatric medications may lead to physical dependence, and abrupt discontinuation may result in withdrawal symptoms.

The main source of knowledge on tolerability and safety of psychotropic drugs comes from clinical trials, but this is associated with several limitations (Stricker and Psaty 2004). Clinical trials are inherently limited in their ability to produce data regarding adverse effects, especially when these are rare and unexpected. In brief, clinical trials recruit patients who are not representative of the persons who will use the drug/s under study in clinical practice and expose these trial participants to the study drug/s in a similarly ideal manner. Recruited adult patients are likely to be healthier, younger, and not on multidrug regimens. On the other hand, elderly

persons, children, and pregnant or lactating women and ethnic minorities are likely to be underrepresented. Drug use in a clinical trial is necessarily controlled, with the result that there is likely to be high drug adherence and drug use at optimal doses. A consequence of all of this is that the safety profile of a drug in the clinical setting where patients are much more heterogeneous and drug use may involve low adherence, incorrect dose and/or administration and drug interactions is not known. Furthermore, clinical trials are typically of short duration, whereas psychiatric drugs are often used for long periods of time. Based on these considerations, at the time of marketing of a drug, the knowledge of its tolerability is inevitably incomplete. The more complete safety profile of a newly marketed drug must therefore be discovered over time as it is used in clinical practice and is dependent on pharmacovigilance activities that identify, report, and describe ADRs as they occur.

For all these reasons, it is important that psychiatrists become familiar with the concepts and methods of pharmacovigilance as they have a key role in identifying and reporting new or serious adverse drug effects. The first step in this process is the identification of potential ADRs. ADR detection can take place through various methods, all of which start with signal detection or generation. The gold standard of signal generation is spontaneous reporting, with reports being submitted to a central authority; however, signals can also be generated from pharmaceutical company data or from hospital or academic center data. Spontaneous reporting has several advantages, for example, it is cost-effective and quick. On the other hand, it is known that this approach is associated with significant underreporting. Signals derived from spontaneous reports are not necessarily authentic and signal strengthening is required to confirm the causal link between drug and adverse effect. Causality is a central issue in identifying authentic signals in spontaneous reports. The assigning of causality by clinicians is guided by general considerations such as whether the putative cause (i.e., the drug) precedes the effect, whether a greater exposure results in a more severe reaction, whether the ADR disappears on discontinuing the drug and reappears on rechallenge, whether there is a known similar effect caused by a similar drug, and whether there is a biologically plausible mechanism for the ADRs. Such considerations undoubtedly have their limitations, particularly in the case of previously unknown ADRs and/or newly marketed drugs. Once a causal link between a drug and an ADR is confirmed and the use of a drug is diffuse, different methodological approaches, such as population-based studies, can be used to evaluate the frequency as well as the risk of an ADR within a population. Such studies provide information on different aspects of causality, such as the strength of an association between a drug and an ADR as well as whether the occurrence of an ADR after drug exposure is consistent across different populations. Population-based studies also have a role in the drug regulatory sector and are often the way in which pharmaceutical companies satisfy legislation such as EU guidance EMA/813938/2011 Revision 1, in which the European Medicines Agency (EMA) made the request for post-authorization safety studies (PASS) legally binding. In this way, carrying out pharmacovigilance activities is given a regulatory-legal framework and can be enforced. PASS studies are an example of an increasing awareness and commitment of regulatory agencies towards understanding the risks associated with drug use as fully as possible.

The constant developments in pharmacovigilance and psychiatry led to the development of this book, which aims to describe the most important themes in pharmacovigilance within the field of psychiatry. The first section gives a broad overview of the topic, including important definitions and ADR pathogenesis and methods and data sources used for pharmacovigilance activities. The second section focuses on specific psychotropic drug class, namely, antidepressants, antipsychotics, anxiolytics and sedatives, mood stabilizers, and medications for attention deficit hyperactivity disorder. The final section focuses further on psychotropic drug use in special populations such as children and adolescents, the elderly, and pregnant or breast-feeding women.

References

Berson A, Descatoire V, Sutton A, Fau D, Maulny B, Vadrot N, Feldmann G, Berthon B, Tordjmann T, Pessayre D (2001) Toxicity of alpidem, a peripheral benzodiazepine receptor ligand, but not zolpidem, in rat hepatocytes: role of mitochondrial permeability transition and metabolic activation. J Pharmacol Exp Ther 299:793–800

Fagius J, Osterman PO, Sidén A, Wiholm BE (1985) Guillain-Barré syndrome following zimeldine treatment. J Neurol Neurosurg Psychiatry 48:65–69

Glassman AH (2005) Schizophrenia, antipsychotic drugs, and cardiovascular disease. J Clin Psychiatry 66(Suppl 6):5–10

Harmark L, van Groothest AC (2008) Pharmacovigilance: methods recent developments and future perspectives. Eur J Pharmacol 64:743–752

Lazaros GA, Stavrinos C, Papatheodoridis GV, Delladetsima JK, Toliopoulos A, Tassopoulos NC (1996) Amineptine induced liver injury. Report of two cases and brief review of the literature. Hepatogastroenterology 43:1015–1019

McBride WG (1961) Thalidomide and congenital abnormalities. Lancet 2:1358

McKenna PJ, Bailey PE (1993) The strange story of clozapine. Br J Psychiatry 162:32–37

McNaughton R, Huet G, Shakir S (2014) An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support the decision-making. BMJ Open 4:e004221

Moore N (2013) The past, present and perhaps future of pharmacovigilance: homage to Folke Sjoqvist. Eur J Clin Pharmacol 69(Suppl 1):S33–S41

Moore TJ, Cohen MR, Furberg CD (2007) Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. Arch Intern Med 167:1752–1759

Nadal R (2001) Pharmacology of the atypical antipsychotic remoxipride, a dopamine D2 receptor antagonist. CNS Drug Rev 7:265–282

No authors listed (1999) Welcome withdrawal of amineptine in France. Prescrire Int 8:51

Rajkumar RP, Melvin G (2014) Pharmacovigilance for psychiatrists: an introduction. Ind J Psychiatry 56:176–181

Stonier PD (1992) Nomifensine and hemolytic anemia – experience of a post-marketing alert. Pharmacoepidemiol Drug Saf 1:177–185

Stricker BH, Psaty BM (2004) Detection, verification, and quantification of adverse drug reactions. BMJ 329:44–47

World Health Organization (WHO) (2000) Safety monitoring of medicinal products: guidelines for setting up and running of a pharmacovigilance centre. World Health Organization, Geneva; 2000. Available from: http://apps.who.int/medicinedocs/en/d/Jh2934e. Accessed on 11 Dec 2011

Chapter 2
Adverse Drug Reactions: Definitions, Classifications and Regulatory Aspects

Paola Maria Cutroneo and Giovanni Polimeni

Abstract Adverse drug reactions (ADRs) are a common and important cause of morbidity and mortality that represent a major health problem worldwide, with high social costs for communities. Several studies have shown that ADR-related hospital admissions comprise up to 10 % of the total number of hospitalizations.

Owing to the well-known limitations of pre-marketing research, it is now generally accepted that part of the process of evaluating drug safety needs to take place in the post-marketing (approval) phase. Thus, once approval is granted, it becomes essential to detect and to evaluate unrecognized ADRs related to medicines for protecting the public health. This activity, known as post-marketing surveillance or "pharmacovigilance," can lead to the identification of important safety problems, which may even result in the withdrawal of drugs from the market. The main goal of pharmacovigilance is the early detection of new, rare, or serious ADRs and the communication of these risks to the public.

ADRs occur by a number of mechanisms, some of which remain unclear. Besides the intrinsic danger associated with the drug, patients might have a particular, unpredictable hypersensitivity to certain drugs, which requires careful monitoring. Furthermore, several risk factors are important in determining susceptibility to ADRs. Knowledge and use of ADR classification systems can give the health professional greater clarity about an ADR and in some cases suggest ways of managing or avoiding a future event.

Keywords Adverse drug reactions • Pharmacovigilance • Adverse events • Safety withdrawals

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2.1 Adverse Drug Reactions: Terminologies and Definitions

An *adverse drug reaction* (ADR) is described by the World Health Organization (WHO) as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." The term "response" in this context means that a clear pharmacological link between the drug and the event is not present, but a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Importantly, this definition underlines the fact that the phenomenon is noxious (differentiating between adverse drug reaction and side effects which can also be beneficial) and that it includes doses prescribed clinically, excluding accidental or deliberate overdose.

According to the new European pharmacovigilance legislation, which came into effect in July 2012, an adverse drug reaction is "a response to a medicinal product which is noxious and unintended" (Directive 2010/84/EU). Compared to the definition from the WHO, this definition also covers ADRs resulting from doses other than those normally used in therapy, including off-label use, overdose, misuse, abuse, medication errors, and those caused by occupational exposure. Furthermore, the term "medicinal products" implicitly encompasses also reactions caused by products not classically included in the definition of "drugs," such as herbal substances or homeopathic products.

An alternative definition of ADR, proposed by Edwards and Aronson (2000), is the following: "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product."

Adverse drug reactions are further classified for regulatory purposes according to their seriousness and expectedness. The seriousness of an ADR is the extent to which the reaction causes harm to the patient. A *serious suspected adverse reaction* is defined as "an adverse reaction which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect."

However, besides these specific situations, with regard to the seriousness of an ADR, the medical individual opinion is also taken into account; in fact, as specified in current international guidelines, "medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above." (European Medicines Agency and Heads of Medicines Agencies 2014 GVP-Annex I). Examples of such events are allergic bronchospasm intensively treated at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. In contrast to seriousness, which is based on the patient and

event outcome, the "severity" of an adverse reaction is often used to describe the intensity of a medical event, as in the grading "mild," "moderate," and "severe." Thus, a severe reaction can be of relatively minor medical significance, such as a severe headache.

With regard to the preventability of ADRs, an *unexpected suspected adverse reaction* has been defined by the WHO as "an adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug" (WHO 2002) or according to EMA, "an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics" (European Medicines Agency and Heads of Medicines Agencies 2014 GVP-Annex I). Reports that add significant information on specificity or severity of a known, already documented serious ADRs constitute unexpected events (e.g., an event more specific or more severe than described in the reference document would be considered as "unexpected").

A *side effect* is "any unintended effect of a pharmaceutical product occurring at doses normally used by a patient, which is related to the pharmacological properties of the drug." This definition was formulated to include side effects that, although are not the main aim of the therapy, may be beneficial rather than harmful. For example, a tricyclic antidepressant may incidentally also relieve symptoms of irritable bowel syndrome in a depressed patient.

2.2 Social and Economic Impact of Adverse Drug Reactions

In spite of the apparent rarity of serious reactions to individual drugs, ADRs are effectively a global epidemic, with large economic effects on healthcare. Several epidemiological studies have been conducted in order to determine the frequency of ADRs and the related healthcare costs in both in- and outpatient settings, mainly focusing on drug-related hospital admission, prolongation of hospital stay, and emergency department visits due to ADRs (Sultana et al. 2013).

Based on 37 studies mostly conducted in the USA, Taché et al. reviewed the prevalence of adverse drug events in ambulatory care and reported that 5.1 % of hospital admissions were due to ADRs (Taché et al. 2011).

Budnitz et al. reported the USA estimates of emergency department (ED) visits for adverse drug events, derived from data of 58 hospitals participating in the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) System (Budnitz et al. 2006). Over a 2-year study period, 21,298 adverse drug event cases were reported. The estimated annual population rate of adverse drug events treated in EDs was 2.4 per 1000 individuals (95 % CI, 1.7–3.0). Furthermore, adverse drug events led to hospitalization of 3487 individuals (annual estimate, 117,318 [16.7 %]; 95 % CI, 13.1–20.3 %).

Several studies focused on more vulnerable populations such as geriatric patients. People aged 65 years or older are in fact more likely than younger individuals to develop adverse drug events. In another study, Budnitz et al. estimated that 99,628

emergency hospitalizations (95 % CI 55,531–143,724) occurred annually for adverse drug events in elderly patients. Nearly half of these hospitalizations involved adults 80 years of age or older. Most hospitalizations were attributed to four medications or medication classes alone or in combination: warfarin (33.3 %), insulins (13.9 %), oral antiplatelet agents (13.3 %), and oral hypoglycemic agents (10.7 %). The majority of these cases resulted from unintentional overdoses (Budnitz et al. 2011).

The frequency of hospital admissions caused by ADRs in general adult population has been estimated at about 6.5 % of all admissions to UK general medical wards, with a mortality rate of 2 % (Pirmohamed et al. 2004). Interestingly, although media attention often focuses on the safety of new drugs, the major causes of these admissions to hospital were older-established drugs with relatively well-described safety profiles, the most common being caused by NSAIDs, aspirin, warfarin, or diuretics (Pirmohamed et al. 2004). In the same study, the projected economic costs of ADR-related admissions to UK hospitals were estimated to be £466 million.

A recent systematic review reported the percentage of hospitalizations resulting from medicine-related problems and identified a median of prevalence rates of hospitalization due to ADRs corresponding to 7 % (interquartile range, 2.4–14.9 %) (Al Hamid et al. 2014). Another review showed that ADRs account for 4.2–30 % of hospital admissions in the USA and Canada, 5.7–18.8 % of admissions in Australia, and 2.5–10.6 % of admissions in Europe (Howard et al. 2007). More than 6 % of inpatients may also experience an adverse drug event (Krähenbühl-Melcher et al. 2007).

Preventable adverse drug reactions are a significant burden to healthcare. A meta-analysis in 2012, including studies on outpatients with emergency visits or hospital admissions and inpatients, showed that 2.0 % of outpatients (95 % CI, 1.2–3.2 %) had preventable ADR and 52 % (95 % CI, 42–62 %) of detected ADR were preventable. Among inpatients, 1.6 % (95 % CI, 0.1–51 %) had preventable ADR and 45 % (95 % CI, 33–58 %) of ADR was preventable (Hakkarainen et al. 2012).

Apart from the medical impact, pharmacoeconomic studies on the costs of ADRs suggest that governments pay considerable amounts from health budgets toward covering costs associated with them. In most countries, the extent of this expenditure has not been measured. It has been suggested that patients who developed adverse effects during hospitalization were hospitalized in an average of 1.2–3.8 days longer than patients who did not, with a substantial increase of the healthcare costs (Rodriguez-Monguio et al. 2003). Furthermore, up to 57 % of the community-acquired ADRs are not being recognized by the attending physician upon hospital admission, leading to inappropriate management of the adverse event, exposure of the patient to additional hazards of the drug, and prolonged hospitalization (Dormann et al. 2003).

In the European Union (EU), on the basis of a report published by the European Commission in 2008, 197,000 deaths per year are caused by ADRs, which also accounted for the fifth most common cause of hospital death. Furthermore, it has been estimated that ADRs are responsible for approximately 5 % of all hospital admissions, and almost 5 % of hospitalized patients will experience an ADR during their hospital stay in the EU. Overall, the total cost to society of ADRs is estimated

to be €79 billion per year (European Commission 2008). Similarly, ADRs are listed as one of the top ten causes of death in the USA, with more than 100,000 deaths annually attributed to various ADRs (Riedl and Casillas 2003).

2.3 Pharmacovigilance for Evaluating Adverse Drug Reactions

A medicinal product is authorized by competent authorities if the benefit–risk balance is judged to be positive for the target population at the time of authorization. Before medicinal products are marketed, they are extensively tested in animals and in clinical trials in humans, and sufficient evidence is required to show the new drug to be of good quality, effective, and safe. Pre-approval studies include double-blind randomized controlled trials (RCT) that are considered to be the most rigorous approach to establish whether a cause–effect relationship exists between a treatment and an outcome.

However, the design of pre-marketing clinical trials is not optimal to monitor the safety of a drug. There are several issues that limit the generalizability of RCT results to clinical practice. The relatively short duration of clinical trials and narrow study population size makes it difficult to detect rare ADRs, or those with a long latency. Furthermore, the selective recruitment of patients (with resulting exclusion of special subgroups of patients or those receiving certain concurrent medicines) and the consideration of few predefined ADRs will considerably limit the generalizability of results from the pre-approval phase. Consequently, once a product is marketed, new information will be generated from clinical practice, which can have an impact on the benefits or risks of the product.

These issues lead to uncertainties about the safety of a new drug once it is marketed and used in a wider population, over longer periods of time, in patients with comorbidities and concomitant medications and for off-label indications not previously evaluated. Therefore, the true picture of a product safety actually evolves over the months and even years during the product's lifetime in the marketplace.

In the course of medical history, there have been many examples of the potential danger associated with medication use. During the last century, the most striking was the thalidomide disaster emerged in 1961, with the sudden upsurge in the number of severe deformities (phocomelia or micromelia) occurred in thousands of newborns whose mother had taken the drug during pregnancy. As a result of this catastrophic epidemic, it has become evident that continuing, post-marketing drug safety monitoring, often referred to as "pharmacovigilance," is essential for protecting the public health by assuring the security of human medicines and helping the public and healthcare providers get the accurate science-based information that they need to use medicines properly (Kavitha 2010).

Once approval is granted, drug regulatory authorities, such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the USA, are responsible for post-marketing safety evaluation. This risk assessment activity encompasses the entire period the drug is on the market and is mainly focused

on collecting and analyzing case reports of ADRs, distinguishing signals from background "noise," making regulatory decisions based on strengthened signals, and alerting prescribers, manufacturers, and the public to new risks of adverse reactions.

2.3.1 Pharmacovigilance: Definitions and Objectives

The World Health Organization has defined *pharmacovigilance* as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (World Health Organization 2002).

The main goal of pharmacovigilance is the early detection of new, rare, and serious ADRs. Other objectives encompass the identification of the increases of the frequency of known adverse effects, the recognition of mechanisms or risk factors relevant for the occurrence of ADRs, and the communication of information about adverse effects to healthcare professionals and consumers (World Health Organization 2002).

An important cornerstone in further clarifying the risk profile of a medical product is the detection of "safety signals" in the post-marketing phase. There are several different definitions of "signal" in pharmacovigilance. According to WHO, a *signal* is defined as a "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" (World Health Organization 2002). Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. On the basis of the Council for International Organizations of Medical Sciences (CIOMS) definition (2010), a *signal* is "an information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action." For the purpose of monitoring data in pharmacovigilance, only signals related to an adverse reaction are generally considered.

Specific sources for pharmacovigilance data include spontaneous ADR reporting systems, active surveillance systems, post-authorization non-interventional studies, clinical trials, and other sources of information.

A spontaneous reporting system (SRS) relies primarily on unsolicited reports by healthcare professionals or consumers to established national or regional pharmacovigilance centers or alternatively to marketing authorization holders (MAHs) that describe one or more suspected adverse reactions in a patient who was given one or more medicinal products (European Medicines Agency and Heads of Medicines Agencies, GVP – Module VI 2014).

Safety signals may be detected from monitoring of SRS databases collecting spontaneous ADR reports or from review of information provided by MAHs in the context of regulatory procedures.

However, the presence of a safety signal does not actually mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by other medicines taken by the patient. Thus, a deep evaluation of safety signals is required to establish the likelihood of a causal relation between the suspected medicine and the reported adverse event, and a systematic process of verification and quantification should follow the detection of signals of a potential adverse event. Any signal should be validated taking into account all other relevant sources of information, such as aggregated data from active surveillance systems or pharmacoepidemiological studies and medical literature.

Despite the vast underreporting of adverse effects, spontaneous reporting remains the most frequent source of safety signals in pharmacovigilance (Ishiguro et al. 2012; Pacurariu et al. 2014). Nevertheless, such systems cannot reliably quantify incidence rates, confirm causality, understand risk factors, or elucidate patterns of use. For hypothesis testing and quantification of risks, observational studies have proved useful.

2.3.2 Examples of Safety Regulatory Actions and Drug Withdrawals for Safety Reasons

As discussed above, the prescribing of medications in the "real world" often yields safety concerns related to new drugs or to medicines on the market for many years, probably due to a change in the patterns of their use or to a better implementation of safety monitoring (Pacurariu et al. 2014).

Once an adverse reaction is detected, appropriate measures will be taken, and regulatory authorities have responsibility to safeguard public health in such a situation.

Safety concerns referred back to the regulatory authorities may lead to revision of drug labeling (i.e., restriction of an indication, new contraindication, change in the recommended dose, major warnings, or precautions for use), addition of a black box warning (available only in the USA), a direct communication to healthcare professionals, or the suspension/withdrawal from the market.

The regulatory authorities may withdraw the approval of an application with respect to any drug for reasons of safety or efficacy, taking account of the seriousness of the condition and the range of optional treatments available. Safety issues are largely responsible for decisions to remove pharmaceutical products from the market. Nineteen drugs were discontinued, throughout the EU, for safety reasons from 2002 to 2011. The main therapeutic categories represented among banned pharmaceutical products were "nervous system," "musculoskeletal system," and nonsteroidal anti-inflammatory drugs. Cardiovascular adverse reactions were the main reason for withdrawal, followed by hepatic disorders and neuropsychiatric conditions (McNaughton et al. 2014).

In the USA from 1980 to 2009, safety reasons accounted for 26 drug discontinuations (3.5 % of the drugs approved in the study period). Severe cardiovascular

effects and hepatic toxicity were the major problems that caused the withdrawal of these products (Qureshi et al. 2011).

A total of 22 pharmaceuticals were removed from the market in France between 2005 and 2011. The number of drug discontinuations increased during this period (Paludetto et al. 2012).

Several nervous system drugs were withdrawn for safety reasons (Table 2.1) (Aronson 2012; Jones and Kingery 2014; McNaughton et al. 2014). For instance, pemoline, a CNS stimulant approved in 1975 for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), was removed from the US market because of fatal hepatotoxicity in 2005.

Rimonabant is a selective CB1 endocannabinoid receptor antagonist indicated for the treatment of obesity. Although available in Europe since 2006 for use as an adjunct to diet and exercise for obese or overweight patients with associated risk factors, rimonabant failed to secure FDA approval in the USA. Concerns had been growing that patients taking rimonabant were at increased risk of psychiatric adverse events, including suicidality. In October 2008, following a review of post-marketing data, the EMEA recommended suspension of the drug's marketing authorization on safety grounds. Data had shown a doubling of the risk of psychiatric disorders in patients taking rimonabant in comparison with placebo.

Another drug that has been banned in the USA is pergolide, an ergot-derived dopamine receptor agonist used for the treatment of Parkinson's disease. In 2007, it was discontinued due to increased rates of cardiac valve regurgitation, along with pleuropulmonary or retroperitoneal fibrosis related to its use.

The suspension of the marketing authorizations of tetrazepam-containing medicines across the European Union in 2013 is derived from the evidence of a low but

Table 2.1 Examples of psychotropic drugs removed from the market for safety reasons, 1980–2013 (Aronson 2012; Jones and Kingery 2014; McNaughton et al. 2014)

Year withdrawn	Drug (generic name)	Reason withdrawn
1982	Clomacron	Hepatotoxicity (UK)
1983	Zimeldine	Hypersensitivity, Guillain-Barre syndrome (worldwide)
1986	Nomifensine	Hemolytic anemia (worldwide)
1991	Triazolam	Depression, amnesia (UK, France, and other countries)
1994	Remoxipride	Aplastic anemia (worldwide)
1995	Alpidem	Hepatotoxicity (worldwide)
1999	Amineptine	Hepatotoxicity, abuse (France and other countries)
2005	Thioridazine	Cardiotoxicity (UK and other countries)
2005	Pemoline	Hepatotoxicity (USA)
2011	Acepromethazine/acepromazine/clorazepate	Cumulative adverse effects, misuse, fatal side effects (EU)
2013	Tetrazepam	Serious cutaneous reactions (EU)

increased risk of serious skin reactions of tetrazepam compared with other benzodiazepines (European Medicines Agency 2013).

In addition, psychotropic medications represent a group of drugs for which several boxed warnings or other product labeling changes were performed by all the regulatory agencies (Table 2.2). For instance, the US FDA issued a series of advisories culminating in a black box warning for all antidepressants for patients under age 18 (Food and Drug Administration 2004), following a consistent finding of an

Table 2.2 Examples of safety warnings issued by the drug regulatory agencies concerning psychotropic drugs (Clavenna and Bonati 2009; Foy et al. 2014)

Medicine	Adverse events	Actions taken
ADHD drugs	Cardiovascular adverse events, neuropsychiatric symptoms	Black box warning, medication guides, contraindications in at-risk patients
Agomelatine	Hepatotoxicity	Monitoring of liver function, warning in patients aged 75 years or over, medication guide for patients
Antidepressants	Increased risk of suicidality in children, adolescents, and young adults	Boxed warnings or other product labeling changes
Antiepileptics	Adverse effects on the bone	Vitamin D supplementation for at-risk patients
Antipsychotics	Venous tromboembolic events	SpC updated
Atomoxetine	Increased risk of suicidal thinking in children and adolescents	Boxed warning, SpC updated
Buproprion	Seizures	Improved warnings and revised dosing instructions
Citalopram/ escitalopram	QT interval prolongation	Daily dose restrictions, contraindications
Codeine	Risk of severe ADRs for infants with ultra-rapid metabolizer breastfeeding mothers	SpC updated, warnings
	Respiratory depression	Restrictions on the use in children contraindicated in at-risk patients, boxed warning
Lamotrigine	Increased risk of potentially fatal rash, particularly in children	Warnings, SpC updated
Topiramate	Oligohydrosis, hyperthermia	SpC updated
Varenicline	Depression, increased risk of suicidal thinking and behavior	Boxed warnings, SpC updated
Ziprasidone	Drug reaction with eosinophilia and systemic symptoms (DRESS)	SpC updated
Zoplicone	Risk of next-day impairment	Dosage recommendations, SpC updated
Zonisamide	Oligohydrosis and hyperthermia in pediatric patients	SpC updated, monitoring for evidence of decreased sweating and increased body temperature

SpC summary of product characteristics

increased risk of suicidality in children and adolescents. Moreover, epidemiologic findings led to an update to the 2004 boxed warnings to include information about an increased risk of suicidality in young adults ages 18–24 during initial treatment with all antidepressants in 2007 (Food and Drug Administration 2007). The EMA issued analogous warnings for SSRIs and, additionally, contraindicated prescriptions of SSRIs in youths (European Medicines Agency 2005).

Similarly, in 2005 FDA and Health Canada warned of increased suicidality in children and adolescents being treated with atomoxetine for ADHD. Furthermore, all ADHD medications were involved in warnings about their cardiac risks (Clavenna and Bonati 2009).

Post-marketing safety regulatory actions frequently concern liver injury related to drug treatment. Hepatotoxic reactions, even severe forms with fatal outcomes, have been reported for many antidepressants, like nefazodone, which was suspended from the US market in 2003 (Choi 2003), or amineptine, which was withdrawn from the market in France in 1999 due to its potential of abuse (Prescrire Editorial Staff 1999).

More recently, liver problems have been reported in patients taking agomelatine, a novel antidepressant, first approved in 2009 by the EMA for major depression in adults. The attention to its hepatic side effect profile has gradually increased, leading the EMA to recommend in 2014 further measures aimed to minimize the risk of liver toxicity, such as monitoring of liver function during treatment and contraindication in patients aged 75 years or above, since they might be at an increased risk of severe hepatic effects (European Medicines Agency 2014).

Safety issues have also appeared recently for psychotropic drugs that have been on the market for more than 50 years (e.g., thiopental, codeine). An example is the signal concerning codeine and life-threatening toxicity (in particular, respiratory depression) in specific subgroups of patients at special risk of such side effects, such as cytochrome P450 2D6 ultra-rapid metabolizers or children below 12 years (European Medicines Agency 2013). This safety issue, due to a more striking conversion of codeine into morphine in the body of at-risk patients, resulted in several restrictions or contraindications being introduced in order to minimize the risk of serious side effects.

Among recent safety communications related to nervous system drugs, an example is the advisory issued in 2014 by Health Canada to healthcare professionals to inform about the risks of next-day impairment after exposure to the hypnotic zopiclone and ways to minimize it, including new dosing recommendations (Health Canada 2014). A recent warning issued by FDA in 2014 concerns the association between the use of ziprasidone and the onset of drug rash with eosinophilia and systemic symptom (DRESS) syndrome (Food and Drug Administration 2014).

Finally, several alerts released by regulatory agencies in 2011 on the potential cardiac toxicity (dose-dependent QTc prolongation) of citalopram and escitalopram resulted in daily dose restrictions (including in elderly patients) and contraindications of use of these drugs (Food and Drug Administration 2011; Italian Medicines Agency 2011).

2.4 Classification of ADRs

Adverse drug reactions can be difficult and sometimes impossible to distinguish from the patient's disease as they act through the same physiological and pathological pathways. Moreover, some distinctive and specific physical signs can be considered with a high probability drug-related (e.g., extrapyramidal disorders or Stevens-Johnson syndrome). Because adverse drug reactions can mimic or precipitate different pathological conditions, if the physician does not consider medications as a potential cause of the patient's symptoms, additional drug therapy may be prescribed to treat the adverse effect of the original drug, causing what is called a "prescribing cascade." The use of metoclopramide may induce parkinsonism, which will be treated with levodopa. Drug-induced cognitive impairment is among the most common causes of reversible dementia (e.g., narcotics, antihistamines). Falls can be precipitated by a wide variety of drugs (e.g., psychotropics, antihypertensives), and the anticholinergic effect of many drugs (e.g., amitriptyline, oxybutynin) can result in dry mouth, constipation, urinary retention, blurred vision, and confusion.

Knowledge and use of ADR classification systems can give the health professional greater clarity about an ADR and suggest ways of managing or avoiding a future event.

Adverse drug reactions can be classified in various ways: immunologic or non-immunologic, predictable or unpredictable, and common or rare.

The most common classification, proposed by Rawlings and Thompson (1977), divides ADRs into type A and type B reactions on the basis of the mechanism of action.

2.4.1 Type A Adverse Event

Type A reactions are due to an exaggerated, but otherwise normal, pharmacological action of a drug (*A* indicates *augmented*) given in the usual therapeutic doses. They are therefore largely predictable on the basis of the drug's known pharmacologic action (Riedl and Casillas 2003) and usually reversible on either adjusting the dose or withdrawing the drug. Examples of a type A reaction include antipsychotic-induced parkinsonism (a known and predictable side effect caused by the block of dopamine receptors), or daytime somnolence after a sedative-hypnotic taken for sleep. Furthermore, these reactions are expected to possibly occur in a certain percentage of individuals based on current scientific evidence. More than 80 % of all occurring ADRs are type A reactions, which include toxic effects (such as digoxin toxicity and serotonin syndrome caused by selective serotonin reuptake inhibitors), side effects, secondary effects (e.g., antibiotic-associated diarrhea), and drug interactions (e.g., lithium toxicity due to NSAID-induced inhibition of its excretion).

The effect of type A ADRs is generally less severe than type B events and is dose related; for example, some degree of anticholinergic symptoms can be observed in nearly everyone taking tricyclic antidepressants, provided the dose is large enough. However, they are not necessarily caused by overdosage but can be also seen after a normal dose is administered in a susceptible subject (e.g., constipation due to morphine or gastrointestinal irritation with nonsteroidal anti-inflammatory drugs).

Generally, type A reactions can be reproduced and studied experimentally and are often already identified during the clinical trials done before marketing.

2.4.2 Type B Adverse Event

Unlike type A reactions, type B ADRs cannot be explained based on the pharmacologic actions of the offending agent, are not dose related in most patients, and may develop quite unpredictably in susceptible individuals (the *B* indicates *bizarre*) (Riedl and Casillas 2003; Pillans 2008). They are generally serious and notoriously difficult to study. The majority of type B reactions can occur in predisposed patients as a result of an immune-mediated mechanism (*allergic* or *hypersensitivity* reactions, *pseudoallergy* or *anaphylactoid* reaction), where the drug acts as an antigen or allergen. Less frequently, type B ADRs may occur with a mechanism not yet understood (*idiosyncratic reactions*), generally due to a genetic or acquired enzyme abnormality with the formation of toxic metabolites. Neuroleptic malignant syndrome, hyperthermia of anesthesia, and tardive dyskinesia caused by neuroleptic drugs fall into this category.

ADRs classified as type B reactions are usually quite rare, representing about 10–15 % of all ADRs but are the more troublesome than type A. Differently from type A reactions, in patients with a type B ADR, it is usually necessary to withdraw therapy. They are not identified in pre-marketing trials and are only exhibited when the drug has been on the market for some time and used in a wide variety of patient populations. These side effects came to light after further studies were conducted or various case reports were supplied via post-marketing surveillance documenting the adverse events.

Type B drug allergies can be further subdivided in several ways and can induce severe responses that are deadly to susceptible individuals.

- Type I allergic reactions are classified as immunoglobulin E (IgE) mediated. An example of this type of allergy is anaphylaxis induced by beta-lactam antibiotics (penicillin allergy).
- Type II reactions are cytotoxic. An example of this is a specific type of thrombocytopenia induced by heparin, which can be quite severe.
- Type III reactions are categorized as immune complexes and occur when antigens and antibodies (immunoglobulin G [IgG] or immunoglobulin M [IgM]) accumulate in the body in equal amounts, causing extensive cross-linking. An example of this reaction is hydralazine-induced systemic lupus erythematosus (SLE).

- Type IV reactions are described as delayed or hypersensitivity reactions. These generally take 2–3 days to develop and are not described as antibody mediated but instead are induced by a cell-mediated response. Contact dermatitis caused by an offending skin product is an excellent example of this type of reaction.

There are other groups in this system of classification, but these may also be considered as subclasses or hybrids of type A and B ADRs. These are type C ADRs (chronic reactions, dose and time related), type D (delayed reactions, time related), type E (end of use reactions), and type F (failure of therapy) (Edwards and Aronson 2000; Meyboom et al. 2000; Rehan et al. 2009).

The characteristics, some examples, and the management of these ADRs are listed in Table 2.3. Another ADR classification scheme is based on frequency of the occurrence of a particular drug-induced reaction. Based on pre-approval studies and post-marketing reports, the frequency of a particular ADR can also be hypothesized. ADR frequency categories for adverse events are generally defined as very common (≥1/10), common (≥1/100 but <1/10), uncommon (≥1/1000 but <1/100), rare

Table 2.3 Classification of adverse drug reactions

Type of reaction	Mnemonic	Features	Examples relevant to psychiatry
A: Dose related	Augmented	Common Related to pharmacological action of the drug Predictable Low mortality	Serotonin syndrome with SSRIs Anticholinergic effects of tricyclic antidepressants Phenytoin toxicity
B: Nondose related	Bizarre	Uncommon Not related to pharmacological action of the drug Unpredictable High mortality	Anticonvulsant syndrome Clozapine-induced agranulocytosis
C: Dose related and time related	Chronic	Uncommon Related to the cumulative dose	Propofol infusion syndrome Malignant hyperthermia with halothane
D: Time related	Delayed	Uncommon Usually dose related Occurs or becomes apparent some time after the use of the drug	Tardive dyskinesia with chlorpromazine
E: Withdrawal	End of use	Uncommon Occurs soon after the withdrawal of the drug	Opiate withdrawal syndrome
F: Unexpected failure of therapy	Failure	Common Dose related Often caused by drug interactions	Unwanted pregnancies following interaction between oral contraceptives and St. John's wort (hypericum)

Adapted from Edwards and Aronson (2000)
SSRIs serotonin selective reuptake inhibitors

(≥1/10,000 but <1/1000), and very rare (<1/10,000). These basic definitions are utilized to describe and classify adverse drug events. These data attempt to quantify adverse drug reactions to some degree and may simply refer to the general population. However, a particular ADR may be common in specific groups of patients. Stratifying those patients in whom ADRs may be more prevalent is important, as some ADRs are restricted to a small segment of the population at greatest risk. ADRs are usually more prevalent in the elderly, because of potential interactions with other agents, as medication use is much more prevalent in the elderly than in the general population. Geriatric patients might also be at greater risk for developing a Type A ADR because of the potential for reduced hepatic or renal metabolism due to age, which results in higher drug concentrations. In some cases, age-related changes may involve not only pharmacokinetics but also pharmacodynamics, with significant clinical consequences. An excellent example of pharmacodynamic changes in the older adult has been demonstrated with benzodiazepines. Older adults have more sedation and lower performance than younger persons at the same plasma concentration (Reidenberg et al. 1978).

A more recent classification (Table 2.4) accounts for the dose relatedness, time course, and susceptibility of the patient (DoTS) to a reaction, and this classification is increasingly used (Aronson and Ferner 2003). Malignant hyperpyrexia, for example, occurs at any dose in susceptible individuals (Do) and occurs on first dose (T),

Table 2.4 DoTS (dose relatedness, time course, and susceptibility) classification of adverse drug reactions

Classification	Subclassification	Explanation/further classification
Dose	Toxic Collateral Hypersusceptibility	Reactions occurring at supratherapeutic doses Reactions occurring at therapeutic doses Reactions occurring at subtherapeutic doses in susceptible individuals
Time course	Time independent Time dependent	Occur at any time during therapy Occur: Due to *rapid administration* After the *first dose* of a medication but not always after subsequent doses *Early reactions* that resolve (i.e., due to tolerance) *Intermediate reactions* after some time (i.e., nonallergic hypersensitivity reactions) *Late reactions* (incidence increases with longer duration of therapy) *Delayed reactions* much later after administration, even after cessation of the drug (i.e., carcinogenesis)
Susceptibility	Genetic Age Gender Physiological variation Exogenous factors Diseases	Single or multiple factors associated with risk of an adverse drug reaction

Adapted from Aronson and Ferner (2003)

and individual susceptibility factors are an inherited mutation for the ryanodine receptor (S). The advantage of this system consists in the fact that an ADR can be profiled in such a way that implications for its management may be more obvious. For example, the dystonic reactions to metoclopramide can be characterized as a collateral time-dependent reaction, with both sex and age acting as susceptibilities. Future management would therefore focus on avoiding the use of the drug in susceptible groups such as children and young women.

It is important to realize, however, that it is not always possible to classify an adverse drug reaction into one of these categories; furthermore, in any one individual, more than one mechanism may be responsible for any particular adverse effect.

References

Al Hamid A, Ghaleb M, Aljadhey H et al (2014) A systematic review of hospitalization resulting from medicine-related problems in adult patients. Br J Clin Pharmacol 78:202–217

Aronson JK (2012) Adverse drug reactions: history, terminology, classification, causality, frequency, preventability. In: Talbot J, Aronson JK (eds) Stephens' detection and evaluation of adverse drug reactions, 6th edn. Wiley-Blackwell, Chichester (UK), pp 1–119

Aronson JK, Ferner RE (2003) Joining the DoTS: new approach to classifying adverse drug reactions. BMJ 327:1222–1225

Budnitz DS, Pollock DA, Weidenbach KN et al (2006) National surveillance of emergency department visits for outpatient adverse drug events. JAMA 296:1858–1866

Budnitz DS, Lovegrove MC, Shehab N et al (2011) Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 365:2002–2012

Choi S (2003) Nefazodone (Serzone) withdrawn because of hepatotoxicity. CMAJ 169(11):1187

Clavenna A, Bonati M (2009) Adverse drug reactions in childhood: a review of prospective studies and safety alerts. Arch Dis Child 94:724–728

Council for International Organizations of Medical Sciences (CIOMS) (2010) Practical aspects of signal detection in pharmacovigilance: report of CIOMS Working Group VIII. CIOMS, Geneva

Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal of the Eur Union, 31 Dec 2010

Dormann H, Criegee-Rieck M, Neubert A et al (2003) Lack of awareness of community-acquired adverse drug reactions upon hospital admission. Drug Saf 26:353–362

Edwards IR, Aronson JK (2000) Adverse drug reactions: definitions, diagnosis, and management. Lancet 356:1255–1259

European Commission (2008) Proposal for a regulation amending, as regards pharmacovigilance of medicinal products for human use. Regulation (EC) No 726/2004. Impact assessment. Available at: http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/pharmacovigilance-ia-vol1_en.pdf

European Medicines Agency (2005) European medicines agency finalises review of antidepressants in children and adolescents. EMEA/CHMP/128918/2005, Press release April 25, 2005. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/

European Medicines Agency (2013) Recommendation to suspend tetrazepam-containing medicines endorsed by CMDh, EMA/256383/2013, Press release, April 29 2013. Available at: http://www.ema.europa.eu

European Medicines Agency (2013) Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation. EMA/385716/2013, Press release, June 28 2013. Available at: http://www.ema.europa.eu

European Medicines Agency (2014) EMA confirms positive benefit-risk for antidepressant Valdoxan/Thymanax (agomelatine). EMA/577812/2014, Press release September 26, 2014. Available at: http://www.ema.europa.eu

European Medicines Agency and Heads of Medicines Agencies (2014) Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 3) EMA/876333/2011 Rev 3. Available at: www.ema.europa.eu

European Medicines Agency and Heads of Medicines Agencies (2014) Guideline on good pharmacovigilance practices (GVP) – Module VI. EMA/873138/2011. Available at: www.ema.europa.eu

FDA (2004) FDA launches a multi-pronged strategy to strengthen safeguards for children treated with antidepressant medications. FDA News Release October 15, 2004. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/

FDA (2007) FDA proposes new warnings about suicidal thinking, behavior in young adults who take antidepressant medications. News Release May 2, 2007. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/

FDA (2011) FDA drug safety communication: abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). Safety Announcement August 24, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety

FDA (2014) FDA drug safety communication: FDA reporting mental health drug ziprasidone (Geodon) associated with rare but potentially fatal skin reactions. Safety Announcement, November 12, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety

Foy M, Barrow P, Raine JM (2014) Spontaneous reporting: United Kingdom. In: Andrews EB, Moore N (eds) Mann's pharmacovigilance, 3rd edn. Wiley-Blackwell, Chichester (UK), pp 185–201

Hakkarainen KM, Hedna K, Petzold M et al (2012) Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions – a meta-analysis. PLoS One 7(3):e33236

Health Canada (2014) IMOVANE (zopiclone) – new dosage recommendations to minimize the risk of next-day impairment – for health professionals. RA-42253, Recalls and alerts, November 19, 2014. Available at: http://healthycanadians.gc.ca

Howard RL, Avery AJ, Slavenburg S et al (2007) Which drugs cause preventable admissions to hospital? A systematic review. Br J Clin Pharmacol 63:136–147

Ishiguro C, Hall M, Neyarapally GA et al (2012) Post-market drug safety evidence sources: an analysis of FDA drug safety communications. Pharmacoepidemiol Drug Saf 21:1134–1136

Italian Medicines Agency (2011) Associazione tra Seropram®/Elopram® (Citalopram) e prolungamento dose dipendente dell'intervallo QT. Nota Informativa Importante October 2011. Available at: http://www.agenziafarmaco.gov.it

Jones JK, Kingery E (2014) History of pharmacovigilance. In: Andrews EB, Moore N (eds) Mann's pharmacovigilance, 3rd edn. Wiley-Blackwell, Chichester (UK), pp 11–24

Kavitha D (2010) Adverse drug reaction (ADR) monitoring and pharmacovigilance. J Pharm Res Health Care 2:127–134

Krähenbühl-Melcher A, Schlienger R, Lampert M et al (2007) Drug-related problems in hospitals: a review of the recent literature. Drug Saf 30:379–407

McNaughton R, Huet G, Shakir S (2014) An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support the decision-making. BMJ Open 4:e004221

Meyboom RH, Lindquist M, Egberts AC (2000) An ABC of drug-related problems. Drug Saf 22:415–423

Pacurariu AC, Coloma PM, van Haren A et al (2014) A description of signals during the first 18 months of the EMA pharmacovigilance risk assessment committee. Drug Saf 37:1059–1066

Paludetto MN, Olivier-Abbal P, Montastruc JL (2012) Is spontaneous reporting always the most important information supporting drug withdrawals for pharmacovigilance reasons in France? Pharmacoepidemiol Drug Saf 21:1289–1294

Pillans PI (2008) Clinical perspectives in drug safety and adverse drug reactions. Expert Rev Clin Pharm 1:695–705

Pirmohamed M, James S, Meakin S et al (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 329:15–19

Prescrire Editorial Staff (1999) Welcome withdrawal of amineptine in France. Prescrire Int 8(40):51

Qureshi ZP, Seoane-Vazquez E, Rodriguez-Monguio R et al (2011) Market withdrawal of new molecular entities approved in the United States from 1980 to 2009. Pharmacoepidemiol Drug Saf 20:772–777

Rawlings TJP (1977) Pathogenesis of adverse drug reactions. In: Davies DM (ed) Textbook of adverse drug reactions. Oxford University Press, Oxford, p 44

Rehan HS, Chopra D, Kakkar AK (2009) Physician's guide to pharmacovigilance: terminology and causality assessment. Eur J Intern Med 20:3–8

Reidenberg MM, Levy M, Warner H et al (1978) Relationship between diazepam dose, plasma level, age, and central nervous system depression. Clin Pharmacol Ther 23:371–374

Riedl MA, Casillas AM (2003) Adverse drug reactions: types and treatment options. Am Fam Physician 68:1781–1790

Rodriguez-Monguio R, Otero MJ, Rovira J (2003) Assessing the economic impact of adverse drug effects. Pharmacoeconomics 21:623–650

Sultana J, Cutroneo P, Trifirò G (2013) Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother 4(suppl 1):s73–s77

Taché SV, Sönnichsen A, Ashcroft DM (2011) Prevalence of adverse drug events in ambulatory care: a systematic review. Ann Pharmacother 45(7–8):977–989

World Health Organization (2002) The importance of pharmacovigilance: safety monitoring of medicinal products. World Health Organization, Genève, pp 40–43, Available at: http://www.who.int/

Chapter 3
Methods for the Post-Marketing Monitoring of Psychotropics Safety: Interests and Pitfalls

Francesco Salvo, Annie Fourrier-Réglat, Nicholas Moore, Bernard Bégaud, and Antoine Pariente

Abstract Psychotropics are among the most widely used drugs, which makes their safety monitoring absolutely crucial. This monitoring is also especially important given the frequency and potential seriousness of adverse effects related to psychotropic drug use. The impact of benzodiazepine use, for instance, has been estimated to more than 20,000 serious falls per year in French elderly, around 2000 of these being fatal. None of the antidepressants existing is considered completely safe. If serotonin reuptake inhibitors have extremely low cardiac toxicity compared to tricyclic antidepressants, they can still be incriminated for QT prolongation and have been shown to significantly increase the risk of bleeding. Finally antipsychotics are associated with numerous serious side effects that only appear acceptable with regard to the seriousness of their indication. However, drug monitoring is not an end in itself; it has to be associated to a specific goal. Apart from safety signal detection and risk confirmation, the usual objectives of pharmacovigilance and pharmacoepidemiology, it needs to help clinicians to choose which therapeutic they should consider within those presenting a benefit in a given indication. The tools that can be used for the post-marketing monitoring of psychotropics safety include (i) pharmacovigilance and individual case analysis, (ii) pharmacoepidemiology and population data analysis and (iii) meta-analysis and clinical trial data analysis. In the

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following sections, we will present the interests, pitfalls and complementarity of these three approaches for this monitoring activity.

Keywords Psychotropic drugs • Safety • Monitoring • Limitations • Pharmacovigilance

3.1 Introduction

Psychotropics are among the most widely used drugs, which makes their safety monitoring absolutely crucial. This monitoring is also especially important given the frequency and potential seriousness of adverse effects related to psychotropic drug use. The impact of benzodiazepine use, for instance, has been estimated to more than 20,000 serious falls per year in French elderly, around 2000 of these being fatal. None of the antidepressants existing is considered completely safe. If serotonin reuptake inhibitors have extremely low cardiac toxicity compared to tricyclic antidepressants, they can still be incriminated for QT prolongation and have been shown to significantly increase the risk of bleeding. Finally antipsychotics are associated with numerous serious side effects that only appear acceptable with regard to the seriousness of their indication. However, drug monitoring is not an end in itself; it has to be associated to a specific goal. Apart from safety signal detection and risk confirmation, the usual objectives of pharmacovigilance and pharmacoepidemiology, it needs to help clinicians to choose which therapeutic they should consider within those presenting a benefit in a given indication. The tools that can be used for the post-marketing monitoring of psychotropics safety include (i) pharmacovigilance and individual case analysis, (ii) pharmacoepidemiology and population data analysis and (iii) meta-analysis and clinical trial data analysis. In the following sections, we will present the interests, pitfalls and complementarity of these three approaches for this monitoring activity.

3.2 Strengths and Limitations of Pharmacovigilance for Psychotropic Safety Monitoring

Post-marketing pharmacovigilance is mostly based on spontaneous reporting, through which physicians, health professionals and patients can notify adverse experiences related to medical drugs to their healthcare system.

Pharmacovigilance relies on the analysis of the information contained in these reports. The analysis of this information can consist on an individual case analysis aiming to determine the likelihood of the drug causality in the occurrence of a given adverse event. It can also consist in comparative statistical analyses of the frequencies of adverse event reporting observed for the different drugs, the so-called *disproportionality analyses*.

3.2.1 Strengths and Limitations of Individual Case Reports

The analysis of individual case reports is historically how clinicians specialised in drug safety initially identified unknown drug adverse effects. This exercise is what led to the identification of the link between thalidomide and a/phocomelia and is also related to the classical etiological activities that clinicians routinely engage when trying to identify the cause of a disease. In drug safety monitoring, individual case report analysis is mostly useful for the detection of unknown adverse events, mostly in the early stages of drug marketing, even though it also allows the identification of drug adverse events long after their marketing date. The most notable psychotropic-related adverse effects identified through individual case report analysis include amnesia automatism with benzodiazepines (Hugues et al. 1987), serious cutaneous reactions with tetrazepam (Breuer et al. 2009; Sanchez-Morillas et al. 2008), bleeding with antidepressants (Aarts et al. 2014) and/or metabolic syndrome with atypical antipsychotics (Falissard et al. 2011; Tournier et al. 2012).

However, this approach has some limitations. Reporting varies with time and it is almost impossible, among all reports, to identify those that clearly constitute a signal. Individual case analysis, which needs robust and extensive data to be performed, can be carried out by comparative statistical analyses of reporting frequencies, which does not require high data quality. The latter can indeed be performed only if drug use and reaction type are well documented, in addition to basic information on patient age and sex.

3.2.2 Strengths and Limitations of Disproportionality Analyses

The principles of disproportionality analyses are simple: using data from a spontaneous reporting database (i.e. a collection of data compiled from individual reports), the reporting rate of one event for one drug is compared to the reporting rate of the same event for other drugs. The potential safety signals identified by applying statistical methods to spontaneous reporting data are called Signals of Disproportionate Reporting (SDRs). SDR detection is currently routinely performed by numerous drug agencies (EMA, WHO, FDA etc.) as part of their drug safety signal detection activities. The main limitations of SDR monitoring concern event-competition bias and drug-competition bias.

3.2.2.1 Event-Competition Bias

The reporting rate of an event for a given drug corresponds to the proportion of reports for that drug (among all reports present for that drug in a spontaneous reporting database) that mentions the event of interest. The more an event is reported for a drug, the higher its reporting rate will be and the lower the reporting rates of other

events. If the event of interest is reported significantly more with one drug than with another, its reporting rate has a differential impact on the reporting rates of other events for that drug of interest as well as for all other drugs. When the reporting rate is high for a drug, it will lower its reporting rates for other events significantly, while it will not decrease reporting rates of other events for other drugs with a lower reporting rate. Thus, the difference in reporting for one event between drugs can actually artificially induce numerous other differences for the drugs and lead to biased associations when performing disproportionality analyses. This bias has been called event-competition bias, or masking effect (Salvo et al. 2013; Pariente et al. 2010, 2012a). It can affect disproportionality analysis and safety signal detection for psychotropics in many ways but was mostly demonstrated for antipsychotics considering the potential competition induced by reporting of extrapyramidal syndrome which hinders signal detection that could otherwise be reliably performed though disproportionality analyses.

In the study that demonstrated the impact of event-competition bias due to antipsychotic-related safety signalling (Pariente et al. 2012a), data was used from the French Pharmacovigilance Database, which includes all adverse drug reactions reported to the 31 French regional pharmacovigilance centres by health professionals but not those reported to manufacturers. The regional centre reviews and assesses each report before entering them into the database and ensures that the diagnosis and associated coding for all ADRs are accurate. The potential event-competition bias induced by antipsychotic-related reports of extrapyramidal syndrome was explored by performing two data-mining analyses to identify SDRs related to antipsychotics. In the first analysis, SDR detection was performed in the whole database. In the second, it was performed on a restricted database obtained after removing all the reports mentioning extrapyramidal syndromes, irrespective of the drugs mentioned in the omitted reports. In doing so, the differences in extrapyramidal syndrome reporting between drugs could no longer differentially affect the reporting rates of other events related to other drugs. The results of the two procedures were then compared to see if new SDRs appeared for antipsychotics once the influence of reporting of extrapyramidal syndrome for any drugs had been removed from the database. The data-mining algorithm chosen for the SDR detection was the Reporting Odds Ratio (ROR) of the case/non-case method (Moore et al. 2005). To focus only on potential signals that would have been considered relevant for the examination in routine pharmacovigilance practice, only SDRs with three or more exposed cases were selected.

In the French Pharmacovigilance Database, extrapyramidal syndrome represented 3.1 % of all reports entered for the 15-year period of reporting considered and 16.3 % of all reports mentioning antipsychotics. Removing all reports of extrapyramidal syndrome from the database (i.e. the related 3.1 % of all the database reports, including those representing 16.3 % of reports mentioning antipsychotics) allowed the identification of six SDRs previously undetected using the standard procedure as currently applied in pharmacovigilance systems performing SDR detection. The safety issues already widely identified for three SDRs were gynecomastia or galactorrhoea, metabolic disorders, and hepatic disorders, while

one potential spurious SDR (perception disturbance) was likely related more to the indication of antipsychotics than to their adverse effects. The two potential new safety signals identified were cleft palate abnormalities and congenital gastrointestinal abnormalities. Few data are currently available from the literature for the latter two, which need to be further investigated.

This study illustrates one of the pitfalls associated with the use of spontaneous reporting data for the post-marketing assessment of antipsychotics. Dealing with this pitfall is however easy and should be systematically performed, at least as a sensitivity analysis, when performing pharmacovigilance studies aiming to identify or explore SDRs concerning antipsychotics.

3.2.2.2 Drug-Competition Bias

Drug-competition bias is a bias similar to that previously described for events, by which reports for a given drug for one event will hamper the detection of SDRs associating this event to other drugs. This bias has been demonstrated, for instance, for rhabdomyolysis, for which very few SDRs can be detected other than for statins and fibrates, except when excluding all reports related to these drugs from spontaneous reporting datasets, whatever the event reported. To which extent this bias could affect SDR detection for psychotropics is still being investigated.

Among other biases affecting SDR detection, most concern differences in underreporting between drugs and events, which can lead to statistically significant signals of disproportion that do not reflect differences in true incidence of adverse events in any way. Among the many possible reasons for differential underreporting, notoriety bias and differences associated to time of marketing are of specific importance as they vary with time and can even combine to create challenges regarding SDR detection activity. This was especially illustrated for psychotropic drugs regarding differences in SDR detected for the risk of suicide with antidepressants, with the bias in SDR detection being designated as “dilution bias” (Pariente et al. 2009). On May 2003, a TV show was aired on the British Broadcasting Corporation channel (BBC) focussing on the risk of suicide associated with antidepressants, which was considered a prominent issue at that time. The show was highly publicised and drew much attention to these drugs from the general population as well as from health professionals. Consequently, a significant rise in the reporting of suicide with antidepressants occurred. Interestingly, this was responsible for the detection of SDR for suicide not for all antidepressants but only for escitalopram, the most recently introduced drug of this class at that time. The mechanism leading to this difference in SDR detection was very simple: escitalopram had been involved in very few reports at the time the programme was aired. Thus, the stimulated high number of reports associating suicides with antidepressants (and escitalopram) following the broadcasting of the show constituted a very important proportion of all reports for escitalopram. Conversely, despite being similar to other antidepressants, it was hidden among all cases of adverse events that had been notified since their launching. Results of SDR detection were no longer different

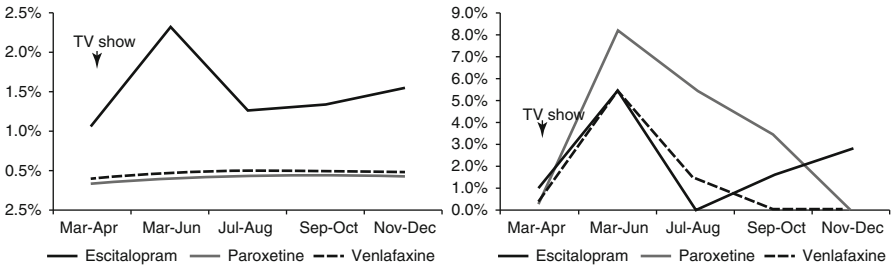

Fig. 3.1 Dilution bias: cumulative (*left*) and instantaneous (*right*) reporting rates for death by suicide among all reports for three antidepressants in the UK. After a TV show discussed this possible issue, a signal of disproportionate reporting (cumulative) was found for the newest antidepressant, escitalopram, but not the older drugs (Adapted from Pariente et al. 2009)

among antidepressants when considering all only the reports corresponding to a comparable time period. In the case of our study, the chosen period was that between escitalopram marketing and the 6 months following the BBC programme airing. Figure 3.1 illustrates this phenomenon of dilution of cases within an important preexisting amount of reports for three of the studied drugs with different marketing time: escitalopram (year of marketing, 2002), paroxetine (year of marketing, 1991) and venlafaxine (year of marketing, 1997). When looking at cumulative amount of reports, no increase in the spontaneous reporting of suicides can be observed for paroxetine or venlafaxine after the show. This is completely unmasked when looking at instantaneous reporting rate (that of the 2-month period and not that of all reports from marketing to the end of the period). This observation excluded the potential role of escitalopram in inducing a higher risk of suicides than any other antidepressants in the UK and prevented the drug from being erroneously withdrawn.

3.2.2.3 Strategies to Improve Drug Monitoring Using Spontaneous Reporting Data

Used in a more sophisticated way, disproportionality analyses can be used, in addition to other methods, to rank drugs from the same therapeutic/pharmacologic class for the risk of reporting of one event. This innovative method has been developed recently in the context of the ARITMO project aiming to study the ventricular arrhythmogenic potential of drugs (i.e. all events of this type from simple QT prolongation to torsade de pointes or sudden cardiac death). Using this approach, antipsychotics were ranked for the risk of such conduction disorders. As this ranking also considered the global number of reports (number of cases), the global number of cases for which no other at-risk drug was mentioned in the report and the seriousness of the reported event, this approach integrated all aspects of reporting information for the assessed drugs (Salvo et al. 2014).

3.3 Strengths and Limitations of Pharmacoepidemiology for Psychotropic Drug Safety Monitoring

Pharmacoepidemiology studies consist in the analysis of information from a population, either performed from data collected prospectively specifically for the study or performed from data of an existing database. These existing databases can consist in a specific cohort database or in electronic healthcare record database, of which there are different types, such as claim databases, hospital databases etc. Pharmacoepidemiology research mostly consists of drug utilisation studies and of drug safety studies aiming to identify and quantify health risks associated with the use of marketed drugs. The aim of drug utilisation studies is to facilitate the rational use of drugs in populations. To achieve this goal, it is necessary to have information on how drugs are being prescribed and used, in order to identify potential misuse, to improve drug use and to design interventions such as educational programmes and drug safety communications, thus optimising the use of marketed drugs. Drug safety studies follow two main types of designs: the cohort design that allows the investigation of an initial exposure on multiples outcomes, provided that the outcomes are sufficiently frequent to be observed in the studied population, and case-control design that allows the investigation of potential effects of various exposures on a given outcome, provided that these exposures are sufficiently frequent in the studied population. In the following sections, we will describe the use and limitations of (i) drug utilisation studies and (ii) drug safety studies performed using databases for the post-marketing monitoring of psychotropics. Examples will be taken from studies performed in paediatric and adult psychiatric populations, as well as from populations of elderly dementia patients.

3.3.1 Strengths and Limitations of Drug Utilisation Studies

The main role of drug utilisation studies in the context of psychotropic drugs is to describe the use of these drugs, including misuse, abuse or otherwise inappropriate use through which the prescribed drugs can be harmful or ineffective. Studying psychotropic drug use is also an indirect way to investigate the psychiatric health of a region/state/country and how this changes over time, for instance, in relation to changes in society, employment rate within a population, financial difficulties etc. Drug utilisation studies targeting psychotropic drugs are thus powerful tools to study and monitor population health indirectly.

Considering benzodiazepines, the use of which is a concern in most European countries (especially France and Northern Europe), and drug utilisation studies performed from cohort databases demonstrated that almost one third of persons aged 65 and over were frequent users and that approximately 60 % of persons aged 70 and over were frequent benzodiazepines users (i.e. several days per week) for at least 2 years. There are several studies on this topic, all of which illustrate that the

most important problem related to benzodiazepine use in the elderly is the difficulty of discontinuing these drugs. This in turn leads to prolonged risks associated with the use of these drugs, which have only short-term efficacy in sleep disorders or anxiety. A particular limitation of these studies is that nowadays most are performed using electronic healthcare databases that lack detailed medical information. Due to the biases inherent to each pharmacoepidemiology safety study (see following section), the lack of medical information on psychotropic drug users constitutes an important limitation. If proxies of this medical information can be found from data entered in these electronic databases, they imply drawing hypotheses instead of making direct observations and significantly limit the potential of pharmacoepidemiology studies to establish causal associations. An example is given below concerning the patterns of use of cholinesterase inhibitors in dementia patients. In a study published in 2009, persistence to cholinesterase inhibitors was found to be higher in patients younger than 80, exposed to antidepressants at the time cholinesterase inhibitors were initiated and also exposed to antipsychotics. The assumptions were thus made that there was a greater interest in pursuing treatment among younger dementia patients as well as in those suffering behavioural disorders (explaining the use of antipsychotics and antidepressant). However, the alternative hypothesis would be that these younger patients just receive more intensive care than older ones, independently of the seriousness of symptoms. Not being able to conclude which hypothesis really reflects the truth hampers the provision of recommendations concerning the use of psychotropic drugs in this case as in many others. If the first hypothesis was true, recommendations would focus on improving drug persistence (in this case, to cholinesterase inhibitors) whatever the age and mostly in early stage dementia. If the second hypothesis was true, recommendations would have completely differed, focusing instead on the more judicious use of psychotropics irrespective of age, reserving them only for patients with mood or behaviour disorders, as their use in dementia is associated with serious adverse events.

3.3.2 Strengths and Limitations of Pharmacoepidemiological Drug Safety Studies

Pharmacoepidemiological drug safety studies are performed to provide information which complements that provided by RCTs with respect to the risks associated to drug use in routine care because RCTs are too short and their populations too small and homogeneous to allow the investigation of harmful drug effects. However, drug safety studies cannot provide information on causal associations. Among their many limitations, the ones inherent to these studies that have to be addressed are the following: (i) protopathic bias, (ii) indication bias and (iii) confounding. Protopathic bias can link drug to disease occurrence when the drug is actually used to treat the very early symptoms of an unrecognised disease. Indication bias can link drug to disease occurrence when the indication in which the drug is used is itself a risk factor for the disease being studied as a potential drug side effect. Finally confounders can link drug to disease when the risk of a drug being used is increased in people

presenting with confounding conditions increasing the risk of developing the disease being studied. In these three situations, the drug is not at all involved in the development of the disease but can however be statistically associated with it in the sense that drug users can be found to present with higher risk of developing the disease than drug non-users.

3.3.2.1 Protopathic Bias

Antidepressants are mainly prescribed to treat depressive episodes, but their prescription should preferentially concern major depressive episodes as their efficacy has been shown to be very limited in the management of mild to moderate depressive disorders. Anxiety and depressive symptomatology can constitute early symptoms of dementia. For this reason, it is very difficult to assess properly the causal association between antidepressants or anxiolytic drug and the subsequent occurrence of dementia. This situation is made even more complex by the very long prodromal phase of dementia, in which pathological lesion and prodromal symptoms can be observed more than 20 years and more than 10 years before diagnosis, respectively. Two different studies were published in the BMJ specifically regarding the potential increase in the risk of dementia associated with the use of benzodiazepines. To deal with the potential protopathic bias, the authors used different methods. The first study (Billioti de Gage et al. 2012) excluded people with dementia at benzodiazepine initiation and carried out systematic screening of included subjects for dementia allowing the identification of numerous dementia cases in subjects without a dementia diagnosis. This also allowed the authors to take into account the existence and seriousness of cognitive decline, depressive symptomatology and anxiety at the time benzodiazepine was initiated, which cannot be done presently from electronic healthcare databases. This study demonstrated a potential 50 % increase in the risk of dementia for incident benzodiazepine users aged 70 and over, over a follow-up of 15 years, most of which was observed more than 10 years after starting benzodiazepine. A similar increase was demonstrated by the second study (Billioti de Gage et al. 2014), which used data from the Quebec reimbursement database, that provides more power due to the larger number of patients included. To eliminate prescriptions potentially related to prodromal symptoms of dementia, the information on benzodiazepine use was censored for the 5–6 year period preceding the diagnosis of cases and the selection date of controls. In doing so, exposure to benzodiazepines during the 5–10 year period preceding the first prescription of benzodiazepines was found to be associated with a 50 % increase in the risk of developing dementia, with the risk being higher for drugs with long half-life compared to short-acting ones.

3.3.2.2 Indication Bias

Indication bias leads to spurious associations when the indication of a drug corresponds to a situation increasing or decreasing the risk of an event. The drug indicated can thus be associated to an increase or a decrease in the risk of an event not

because of its effect but only because of its indication. Regarding psychotropics, depression is a risk factor of cognitive decline, dementia or suicide in the patient and cognitive development disorder in children having parents. Anxiety is a risk factor for cardiovascular disorders, mostly for ischemic heart disease but also for depression.

Cholinesterase inhibitors are indicated in patients with mild to moderate dementia, who are of course at lower risk of institutionalisation than patients with advanced dementia. The use of cholinesterase inhibitors should therefore be found to be associated with a decrease in the risk of institutionalisation, not because of its pharmacological effect but because of its indication in demented in a condition being at low risk of this event compared to others. When trying to evaluate the risk of institutionalisation associated with nonpersistence to cholinesterase inhibitors, Pariente et al. had to take indication bias into account, even though the data available from the electronic healthcare database used lacked information on the stage of dementia (Pariente et al. 2012b). To do so, they considered for their analysis all information potentially indicating a more advanced disease (as the use of antipsychotics or antidepressants, for instance). Another example can be given in which despite the advanced study design, controlling for indication bias was incomplete (Pariente et al. 2012c). For numerous reasons that have been cited before, patients taking antipsychotics have increased risk of presenting with an MI, independently of the potential role of antipsychotics. To limit this potential bias in a study performed among dementia patients, we used different methods including traditional adjustment, propensity score adjustment and the use of a self-controlled case series design. This was done to take into account confounding related to any time-independent risk factor but not time-dependent ones. In the case of incident antipsychotic treatment, we had to acknowledge that residual confounding by indication could not be excluded. Indeed, if a dementia patient was prescribed an antipsychotic, it is possible that the main factors contributing to the acute risk of MI are symptoms of delusion and agitation which increase stress and anxiety, thus potentially accounting for a temporary indication bias.

3.3.2.3 Confounding and Confounding Factors

Grimes and Schultz give a very clear definition of confounding in their paper on biases published in the Lancet series on epidemiology. They explain it as follows: “Confounding is a mixing or blurring of effects. A researcher attempts to relate an exposure to an outcome, but actually measures the effect of a third factor, termed a confounding variable. A confounding variable is associated with the exposure and it affects the outcome, but it is not an intermediate link in the chain of causation between exposure and outcome.” They finally state: “Confounding is often easier to understand from examples than from definitions.” We will therefore give some famous example of confounding that occurred, were suspected or are still present in the context of psychotropic post-marketing assessment.

One such example concerns the potential association between antipsychotic use and myocardial infarction (MI) in patients with psychosis. Clearly, these patients have an increased baseline risk of MI compared to nonpsychotic patients but whether antipsychotics add to this risk remains unclear. Psychotic patients tend to be heavy smokers and have several deleterious life habits regarding their cardiovascular health as compared to nonpsychotic patients. They also tend to have a generally much lower socioeconomic status and are thus less likely to have an ideal lifestyle in terms of diet and physical activity. All the above factors clearly expose them to an increased risk of MI. Adding antipsychotics to the risk factors for MI, the real risk of MI attributable to antipsychotics is unclear. Is the use of antipsychotics really responsible for the increased risk of MI observed in antipsychotic users? The proper way to deal with this confounding is to try to compare the risk of MI in antipsychotic users and non-users with similar status regarding smoking, diet, physical activity and so on. This was attempted but was nevertheless not completely convincing either to clearly incriminate antipsychotics or to clearly dismiss their potential harmful effects in that situation. The fact that their use has been found to increase the risk of thrombotic events in other contexts (e.g. stroke or MI in dementia patient) for which such confounders would not act supports the likelihood of a causal effect, but there is still insufficient evidence to reach a conclusion. Confounding occurs in every non-randomised study and is always treated with caution to avoid reaching conclusions on the basis of spurious associations. Large electronic healthcare databases, particularly those lacking detail on medical history, are powerful tools as they include numerous variables that allow a large number of confounders to be considered. This can be addressed using traditional adjustment in the study of psychotropics (Trifirò et al. 2007, 2010a, b) but also the earlier mentioned self-controlled design in which a case constitutes its own control, as is done in crossover trials (Douglas and Smeeth 2008; Whitaker et al. 2009; Maclure 2014).

As one can moreover consider that the information contained in such databases reflects many characteristics of subjects' lifestyle and propensity to use healthcare services, etc., it has been demonstrated that taking this information into account could control for confounding. This is mostly the principle underlying the use of propensity scores or disease risk scores that have been widely used in the pharmacoepidemiologic assessment of psychotropics (Rassen et al. 2013; Wang et al. 2005) and have allowed this research to provide more compelling evidence about the associations under investigation.

3.4 Strengths and Limitations of Meta-analyses for Psychotropic Drug Safety Monitoring

Meta-analysis is a research method in which studies, rather than people, are surveyed; it represents one way to summarise, integrate and interpret selected studies related to one or more outcomes of interest. In doing so, it circumvents the sample

power limitations of individual studies and increases the generalisability of the results. Of course, it is necessary that included studies share enough characteristics as to allow a meaningful comparison, especially in terms of outcome(s) of interest and in terms of study design. As an example, it is well known that antipsychotics can induce QT prolongation. Although this could be a causal factor for potentially fatal cardiac arrhythmias, both cardiac arrhythmias and sudden cardiac death can be due to other causes. Thus, pooling events such as QT prolongation and cardiac arrhythmias in a single meta-analysis are inappropriate.

From a general point of view, two main sources of data are available to carry out meta-analyses aiming to study the safety of drugs: clinical trials and observational studies. These two settings have important differences and different limitations that have to be taken into account. Even if the information they provide is interesting, it is generally inappropriate to pool the results from clinical trials and observational studies.

3.4.1 Strengths and Limitations of Meta-analysis of Clinical Trials

Randomised clinical trials (RCTs) are without doubt the best study design for the assessment of health intervention efficacy. However, existing clinical trials are not the best sources of information for the evaluation of the safety of drugs, especially for heterogeneous drug classes such as psychotropic drugs. Among these drugs, antipsychotics are probably the most heterogeneous. They have several definitions and classifications, the most common of which refers to them as first- and second-generation antipsychotics. This classification has several limitations, as, for example, it does not take into account the differences in the molecular structure of these drugs or in their pharmacological action. Aside from a potential difference in the safety profile of antipsychotics regarding antipsychotic-induced Parkinsonism, the concept of first- and second-generation antipsychotics also implies important differences regarding drug monitoring and assessment: development and marketing of these drugs relate to a very different era of drug safety evaluation and to significant differences in evidence-based standards. This is important to take into account when planning a meta-analysis: comparing clinical trials performed about 50 years ago with studies performed in the last 10 years can be inappropriate, whether evaluating efficacy or safety. Safety was not a concern for the first antipsychotics initially, as no pharmacological alternatives were available. Over time, safety aspects became more and more central and were used to develop and market the so-called second-generation antipsychotics, which were supposed to reduce the frequency and severity of induced Parkinsonism (Simpson and Varga 1974). After the marketing of clozapine and other second-generation antipsychotics, Parkinsonism gradually stopped being a drug safety issue. At the same time, other events were discovered that became the key to the benefit/risk ratio of antipsychotics, such as agranulocytosis, metabolic syndrome and diabetes and cardiovascular events (Newcomer 2005).

Haematological adverse events and cardiovascular events were neither searched for nor reported systematically in clinical trials performed on first-generation antipsychotics. Thus, searching for related information in the original RCTs will certainly be time-consuming and will also lead to the retrieval of biased information relating to a screening or diagnostic bias between first- and second-generation antipsychotics, relating in turn to differences in procedures for the detection and reporting of these events between RCTs evaluating first-generation antipsychotics and RCTs evaluating second-generation ones.

Randomisation remains the ideal tool to evaluate differences among two or more interventions. Nevertheless, a critical eye on randomisation of studies included in a safety meta-analysis needs to be maintained, in particular for small-size studies. When a large number of subjects are included in the study, we can assume that the distribution of risk factors for the event(s) of interest will have made the group comparable for any measured or unmeasured characteristics. When the study size is small, this is unlikely to be true. Thus, performing a meta-analysis to assess the risk of drug-related harm in small trials (e.g. first-generation antipsychotics) together with other drugs studied through large studies (e.g. second-generation antipsychotics) could lead to a wrong interpretation of data if this aspect is not correctly taken into account.

The technique of network meta-analysis (also referred to as multiple treatment comparison meta-analysis) has advantages over conventional pairwise meta-analysis, as the technique borrows strength from indirect evidence to gain certainty about all treatment comparisons. In other words, network meta-analysis allows indirect comparison for the estimation of comparative effects of drugs and yields more reliable and definitive results than would a pairwise meta-analysis (Mills et al. 2013). As for conventional meta-analysis, the sample size of the included studies is per se crucial, as the chance to find outcome(s) of interest has to be taken into account when a meta-analysis is planned. The more rare the event, the more difficult it will be to find in clinical trials. If the principle of meta-analysis is to aggregate data to increase the power of the analysis in order to find any differences, a meta-analysis will be useless without a sufficient number of cases. It will thus have to be postponed until the likelihood of identifying a minimal number of events from existing RCTs is judged acceptable. This can be assessed before starting the time-consuming exercise of systematic review that precedes each meta-analysis. If the aim of a meta-analysis is to evaluate the risk of sudden cardiac death associated with the use of antipsychotics using data from RCTs, for instance, this likelihood could currently be estimated as follows: consider a scenario where 212 RCTs are being considered for a meta-analysis where 43,049 patients are treated with 15 different antipsychotics or placebo for 6–14 weeks (Leucht et al. 2013). Under the conservative hypothesis that all patients were followed for 14 weeks, this would correspond at best to a total follow-up of 11,590 patient-years. The incidence of sudden cardiac death in the general population is 1.4 per 1000 person-years (95 % CI 1.3–1.5) (Ray et al. 2009). Assuming that antipsychotics as a class increase the risk of sudden cardiac death by 300 %, no more than 45–50 cases of sudden cardiac death would be expected in these RCTs for the 15 antipsychotics considered together. This is

clearly insufficient to allow the comparison of risk of sudden cardiac death between individual antipsychotics using RCT data.

One can assume that meta-analysis of RCTs is of limited interest when rare or very rare events are studied. Another limitation regarding meta-analysis of RCTs is that they highly depend on the quality of the RCTs involved. Reporting bias is an aspect of note when meta-analyses aim to evaluate safety of treatments from RCTs, as safety is mostly a secondary objective of the RCTs, which is often affected by under-reporting. At the international level, there is currently no clear rule for the reporting of adverse events in the manuscripts issued from a RCT. This does not allow the exclusion of reporting bias, as the quality and exhaustiveness of the listed adverse events detailed in the publications mainly depends on the authors' choices or the journal instructions. Sometimes this selectivity in reporting is transparent (e.g. adverse event with ≥2 % of frequency), and sometimes it is more complex to picture: the reader can find no mention of adverse events (serious or otherwise), these is a lack of a clear definition of the considered adverse events, it is not possible to clearly distinguish between number of events and number of patients with an event, groups of events are considered together, etc. For old RCTs, even if a request for additional data to authors or drug companies is successful, these data can frequently be impossible to interpret. The obligation to annex to the principal publication or public report a list of every adverse events which occurred in every included patient would easily solve this issue and allow a much more efficient meta-analysis process. Regarding psychotropics, this approach would allow a much more efficient response to patient expectations as well as helping clinicians to make informed therapeutic choices (Tiihonen et al. 2006).

3.4.2 Role and Limitations of Meta-analysis of Observational Studies

Meta-analyses of observational studies are considered to provide "weaker" evidence than those using clinical trial data. The absence of randomisation in the source studies has a key role in this relative downgrading of the evidence (Guyatt et al. 2011). A certain degree of residual confounding remains in all real-life studies, even if matching or adjustment techniques are used. As a consequence, performing a meta-analysis only using observational studies for frequent events, which could be easily retrieved from clinical trial data, is certainly inadequate. Thus, once again, the expected frequency of the event has to be taken into account when planning a systematic review and a meta-analysis. For a frequent event, a larger systematic review is preferable in order to include evidence from randomised studies. The principal results will come from the randomised studies, while the observational data will be an additional data source for a deeper interpretation of the results. Conflicting results will be due to residual confounding or different pattern of drug use, which are not taken into account in observational studies or not represented in clinical trials.

For rarer events, meta-analysis of observational studies is the only source of data and has to be considered as the best option to investigate them. As a direct consequence, the quality of the included studies is the most crucial aspect in the interpretation of the meta-analysis results. The use of the Newcastle-Ottawa scale (Wells et al. 2014) is recommended by the Cochrane Collaboration to evaluate the quality of non-randomised studies (Higgins 2011). This tool scores each study from zero to nine stars for the selection and the comparability of the groups and for the ascertainment of either the exposure for case control or outcome of interest for cohort studies. Unfortunately, this guidance is too unspecific to investigate the methodological issues of observational studies with respect to a specific event. Its use may produce highly arbitrary results (Stang 2010), and even studies that have received the maximum score with this scale have to be interpreted with caution, in particular where the appropriateness (and consistency) of timeframe between drug exposure and event is questionable and where for the article-by-article evaluation of residual confounders is involved.

Meta-analysis of observational studies can pool data coming from prospective or retrospective study design. Cohort or case-control approaches, the most frequently used observational study designs, have some intrinsic differences. In general, cohort studies are supposed to provide a higher level of scientific evidence than case-control studies (Tiihonen et al. 2006), and the latter tend to overestimate the strength of associations as compared to cohort studies. The influence of study design as a source of heterogeneity has thus to be carefully investigated.

Publication bias is a significant concern for meta-analyses of observational studies. It is particularly difficult to detect and to evaluate in this setting as registries for the recording of observational studies are not as used as are those of clinical trials. In contrast to clinical trials, observational studies that do not find an increase in the risk of an event have more difficulty in getting published than RCTs which do not find an increased risk. This publication bias can be explored using funnel plots when at least ten estimates for the same drug are available (Higgins 2011). More than using statistic tools, the existence of publication bias for meta-analyses using observational studies could be assessed by following points:

1. Number of studies privately funded on a specific drug: the more published studies are sponsored studies, the higher the risk of publication bias is
2. Number of studies which investigated a psychotropic drug class: the more published studies investigate a drug class as a whole without a priori hypotheses of differences between drugs, the more the results can be considered unbiased
3. Effect size of a meta-analysis: when a large effect size is found from a meta-analysis, the chance that new published evidence changes substantially the results is remote
4. Consistency of results and pharmacological profile of the drugs under investigation: it will be always be more convincing if preclinical data corroborate meta-analysis of observational studies (and vice versa)

Classically, heterogeneity is another important issue of meta-analyses: it relates to significant differences in risk estimates between the studies pooled in the meta-analysis. Heterogeneity in risk for a drug (intra-drug heterogeneity) could be

related to its different pattern of use or in terms of dose or indication of use or both. Thus, this heterogeneity could be considered as a source of a potential safety signal and has to be further analysed, by meta-regressions or by further and more specific studies (even randomised, if required). Furthermore, heterogeneity among different drugs of the same classes (inter-drug heterogeneity) could reveal a different risk profile and merit even more attention than results that are entirely homogeneous. If the pharmacological profile supports the hypothesis of a differential risk, heterogeneity could be more important than the pooled risk estimate; thus, it could be the principal result of a meta-analysis and drive regulatory decisions on drugs.

As reporting bias is an issue in clinical trial settings that could be easily solved by single patient data availability, the meta-analysis of observational studies would have increased value if raw data could be used. This would allow the harmonisation of the event definition, adjustment and matching and even allow the construction of a network of observational studies starting from the pseudo-randomised patient numbers to gain certainty about treatment safety in real life.

3.5 Conclusion

Post-marketing monitoring of psychotropics is an essential and difficult activity. Powerful tools exist for such ends, all having their advantages and disadvantages. Pharmacovigilance can provide clinically meaningful information on the risk associated with the use of a psychotropic drug, but it is plagued by under-reporting and so many biases that it has to be used with extreme caution, even in the modest exercise of signal detection. Pharmacoepidemiology safety studies became very powerful with the use of large electronic healthcare databases which allow the direct or indirect control of confounding. However, the lack of medical information especially regarding the seriousness of symptoms limits their ability to fully exclude protopathic or indication bias. The best remedy for this is to perform such safety studies using large cohorts. Finally, the data on drug safety available from RCTs should be kept in mind, even if mostly relating to pre-marketing information. While a single RCT is insufficient to draw robust conclusions on drug safety, the pooling and meta-analysis of such studies are informative as well as being free from confounding. Network meta-analyses are also a powerful tool in the investigation of drug safety, although little has been published in this field concerning psychotropics to date.

References

Aarts N, Akoudad S, Noordam R, Hofman A, Ikram MA, Stricker BH et al (2014) Inhibition of serotonin reuptake by antidepressants and cerebral microbleeds in the general population. Stroke J Cereb Circ 45(7):1951–1957

Billioti de Gage S, Begaud B, Bazin F, Verdoux H, Dartigues JF, Peres K et al (2012) Benzodiazepine use and risk of dementia: prospective population based study. BMJ 345:e6231

Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M et al (2014) Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ 349:g5205

Breuer K, Worm M, Skudlik C, Schroder C, John SM (2009) Occupational airborne contact allergy to tetrazepam in a geriatric nurse. J Dtsch Dermatol Ges J Ger Soc Dermatol JDDG 7(10):896–898

Douglas IJ, Smeeth L (2008) Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ 337:a1227

Falissard B, Mauri M, Shaw K, Wetterling T, Doble A, Giudicelli A et al (2011) The METEOR study: frequency of metabolic disorders in patients with schizophrenia. Focus on first and second generation and level of risk of antipsychotic drugs. Int Clin Psychopharmacol 26(6):291–302

Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A (2011) GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 64(4):380–382

Higgins JPT (2011) Cochrane handbook for systematic reviews of interventions: the cochrane collaboration. Available from: http://www.cochrane-handbook.org

Hugues FC, Jouglard J, Le Jeunne C, Moulin M, Begaud B (1987) Psychotic disorders linked to the inhibition of benzodiazepine catabolism. La Rev Med Interne/fondee Soc Natl Fr Med Interne 8(4):433–436

Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F et al (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382(9896):951–962

Maclure M (2014) Case-crossover designs for more patient-centred epidemiology. Paediatr Perinat Epidemiol 28(2):77–78

Mills EJ, Thorlund K, Ioannidis JP (2013) Demystifying trial networks and network meta-analysis. BMJ 346:f2914

Moore N, Thiessard F, Begaud B (2005) The history of disproportionality measures (reporting odds ratio, proportional reporting rates) in spontaneous reporting of adverse drug reactions. Pharmacoepidemiol Drug Saf 14(4):285–286

Newcomer JW (2005) Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 19(S 1):1–93

Pariente A, Daveluy A, Laribiere-Benard A, Miremont-Salame G, Begaud B, Moore N (2009) Effect of date of drug marketing on disproportionality measures in pharmacovigilance: the example of suicide with SSRIs using data from the UK MHRA. Drug Saf 32(5):441–447

Pariente A, Didailler M, Avillach P, Miremont-Salame G, Fourrier-Reglat A, Haramburu F et al (2010) A potential competition bias in the detection of safety signals from spontaneous reporting databases. Pharmacoepidemiol Drug Saf 19(11):1166–1171

Pariente A, Avillach P, Salvo F, Thiessard F, Miremont-Salame G, Fourrier-Reglat A et al (2012a) Effect of competition bias in safety signal generation: analysis of a research database of spontaneous reports in France. Drug Saf 35(10):855–864

Pariente A, Fourrier-Reglat A, Bazin F, Ducruet T, Dartigues JF, Dragomir A et al (2012b) Effect of treatment gaps in elderly patients with dementia treated with cholinesterase inhibitors. Neurology 78(13):957–963

Pariente A, Fourrier-Reglat A, Ducruet T, Farrington P, Beland SG, Dartigues JF et al (2012c) Antipsychotic use and myocardial infarction in older patients with treated dementia. Arch Intern Med 172(8):648–653; discussion 54–5

Rassen JA, Shelat AA, Franklin JM, Glynn RJ, Solomon DH, Schneeweiss S (2013) Matching by propensity score in cohort studies with three treatment groups. Epidemiology 24(3): 401–409

Ray WA, Chung CP, Murray KT, Hall K, Stein CM (2009) Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 360(3):225–235

Salvo F, Leborgne F, Thiessard F, Moore N, Begaud B, Pariente A (2013) A potential event-competition bias in safety signal detection: results from a spontaneous reporting research database in France. Drug Saf 36(7):565–572

Salvo F, Raschi E, Moretti U, Chiarolanza A, Fourrier-Reglat A, Moore N et al (2014) Pharmacological prioritisation of signals of disproportionate reporting: proposal of an algorithm and pilot evaluation. Eur J Clin Pharmacol 70(5):617–625

Sanchez-Morillas L, Laguna-Martinez JJ, Reano-Martos M, Rojo-Andres E, Ubeda PG (2008) Systemic dermatitis due to tetrazepam. J Investig Allergol Clin Immunol 18(5):404–406

Simpson GM, Varga E (1974) Clozapine – a new antipsychotic agent. Curr Ther Res Clin Exp 16(7):679–686

Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605

Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J (2006) Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry 63(12):1358–1367

Tournier M, Begaud B, Cougnard A, Auleley GR, Deligne J, Blum-Boisgard C et al (2012) Influence of the drug exposure definition on the assessment of the antipsychotic metabolic impact in patients initially treated with mood-stabilizers. Br J Clin Pharmacol 74(1):189–196

Trifirò G, Verhamme KM, Ziere G, Caputi AP, Ch Stricker BH, Sturkenboom MC (2007) All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. Pharmacoepidemiol Drug Saf 16(5):538–544

Trifirò G, Dieleman J, Sen EF, Gambassi G, Sturkenboom MC (2010a) Risk of ischemic stroke associated with antidepressant drug use in elderly persons. J Clin Psychopharmacol 30(3):252–258

Trifirò G, Gambassi G, Sen EF, Caputi AP, Bagnardi V, Brea J et al (2010b) Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. Ann Intern Med 152(7):418–425, W139-40

Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH et al (2005) Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 353(22):2335–2341

Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al (2014) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses2010. Available from: http://www.ohri.ca/Programs/clinical_epidemiology/oxford.asp

Whitaker HJ, Hocine MN, Farrington CP (2009) The methodology of self-controlled case series studies. Stat Methods Med Res 18(1):7–26

Chapter 4
Contribution of UK Prescription-Based Event Monitoring Methods in the Pharmacovigilance of Psychotropic Medications

Deborah Layton

Abstract Psychotropic drugs are widely used in clinical practice. The balance between drug safety and efficacy is affected by many factors including the prescriber, the patient, the disease as well as other environmental effects. Physician factors include failure to diagnosis conditions because of the complex nature and pattern of presenting symptoms. Thus patients may not receive the treatment they need, whether that is a particular medication or the appropriate medication at sub-therapeutic doses. Patient factors include failure to recognize existence of a condition accompanied by denial and reluctance to seek medical attention. In addition, many patients prescribed antipsychotic medications do not take their medicines in accordance with instructions. Such factors, accompanied by large inter- and intra- individual manifestation of mental health disease severity contribute to difficulties in appropriately managing such patients, especially long -term. In this chapter, examples of real-life studies about some of these challenging issues will be described, as reported from the post-marketing event-monitoring systems, now known as Modified Prescription-Event Monitoring (M-PEM) and Specialist Cohort Event Monitoring (SCEM).

Keywords Prescription-based event monitoring • Psychotropic drugs • Observational research • Drug utilization • Methodology

4.1 Introduction

In the past three decades, a host of new psychotropic medicines have been introduced for the treatment of mental health disorders. An examination of trends in prescriptions and costs of all classes of psychiatric medication in England between 1998 and 2010 reported that prescribing of psychotropics has increased by

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7 % per year on average (in line with other drugs of other therapeutic classes) from 8.3 % of all prescription items in 1998 to 8.6 % in 2010. However there were highly statistically significant upward trends in prescriptions of all classes of psychiatric medications, except for hypnotics and anxiolytics (Ilyas and Moncrieff 2012). In contrast the corresponding costs of psychiatric medications increased by 5 % per year on average (adjusted for inflation) during the same period, which was statistically significantly different to the costs of other prescription drugs (which rose by 3 %). Rising prescription numbers and drug costs do not imply a rising number of psychotropic medication users in the UK. However, according to the UK Adult Psychiatric Morbidity Survey (APMS) conducted in 2007, the prevalence of at least one common mental health disorder in people aged 16–64 is increasing (15.5 % 1993, 17.5 % in 2000, 17.6 % 2007) (National Health Service 2009).

Psychotropic medications have been shown to be effective in the treatment of manifestations of mental health conditions, yet a delicate balance exists between efficacy and safety. This balance is affected by many factors including the prescriber, the patient, the disease as well as other environmental effects. Physician factors include failure to diagnosis conditions because of the complex nature and pattern of presenting symptoms. Thus, patients may not receive the treatment required, whether that is a particular medication or the appropriate medication but given at subtherapeutic doses. Patient factors include failure to recognise existence of a condition accompanied by denial and reluctance to seek medical attention. In addition, many patients prescribed antipsychotic medications do not take their medicines in accordance with instructions. Such factors, accompanied by large inter- and intra-individual manifestation of mental health disease severity, contribute to difficulties in appropriately managing such patients, especially long term. In this chapter, examples of real-life studies about some of these challenging issues will be described, as reported from the post-marketing event-monitoring systems, now known as Modified Prescription-Event Monitoring (M-PEM) (Layton and Shakir 2014) and Specialist Cohort Event Monitoring (SCEM) (Layton and Shakir 2015).

4.2 Event Monitoring: Fulfilling a Need for Observational Research

The limitations of randomised controlled trials (RCTs) in terms of statistical power to detect rare but serious adverse events and exclusion of high-risk populations which can impact on generalisability of results to real-world clinical practice are well known (Singh and Loke 2012). Observational studies can help examine natural variation in disease and treatment effects. Issues that are fundamental in making prescribing decisions include understanding the risk of potential adverse events in different types of patients that are treated with psychoactive medications, particularly those where there is limited information available from premarketing development programmes. The reason for this relates partly to the process by which a medicinal product is approved and partly to design. The initial marketing authorisation (MA) for a product may be applied for by a pharmaceutical company on the basis of a

particular clinical indication, which may be in a narrowly defined population. Clinical trials may have been conducted in a relatively healthy patient population to obtain sufficient information on efficacy and safety in that population to satisfy a regulatory authority's requirements. The patient population selected may exclude those groups that are difficult to recruit for whom issues of ethics and consent arise, such as children, the elderly, patients with comprehension and learning difficulties or those who are acutely ill. In terms of study design, clinical trials are experiments where the circumstances of treatment (such as setting, treatment regimens, duration and intensiveness of monitoring) are often controlled by the study investigator.

For the last five decades, since the thalidomide disaster (Lenz et al. 1962), there has been recognition for the need for post-marketing observational research to identify safety issues associated with the use of a new drug in all populations likely to receive it in routine clinical practice (Finney 1965). This is because the populations likely to be studied are a more heterogeneous population than those observed in clinical trials. The importance of observational studies has increased dramatically since the revised EU Pharmacovigilance Legislation came into force, July 2012 (European Commission 2012). Accordingly every new medicinal product must have comprehensive Risk Management Plan (RMP) in place as part of its approval and to retain its approved status (European Medicines Agency 2014). M-PEM, previously known as PEM, is a national surveillance system whose origins stem from the recognition that spontaneous reporting systems may fail to identify all safety hazards post-marketing. M-PEM is an enhanced application of PEM that offers a targeted safety surveillance system that can be readily adapted to meet the specific needs of a RMP and systematically collect information on large cohorts about patient baseline characteristics in relation to prespecified risks and can quantify the incidence and prevalence of risks of adverse events after treatment initiation (Layton and Shakir 2014). SCEM is a recent adaptation of the technique, which focuses on surveillance in secondary care setting (Layton and Shakir 2015). This application was developed in the recognition that safety studies conducted exclusively in the primary care setting may be at risk of biased conclusions about the prevalence of the types of patients prescribed new medications and also the frequency of adverse events, because of the potential exclusion of patients who are managed predominantly within the secondary care setting. These patients, who may be initiated under the care of a specialist health care professional, may have different characteristics and health experiences to those treated by physicians in the primary care setting for similar indications. Since the adoption of a new medicine into clinical practice in the UK is often initially facilitated by hospital specialists, there is a need for data capture across both the primary and secondary care setting, to ensure all relevant exposed populations are characterised and monitored. SCEM enables cohorts of patients prescribed a new medicine in the secondary care setting to be monitored.

Both M-PEM and SCEM collect additional information that can inform on patient and physician behaviours and also highlight 'off-label' prescribing which refers to the use of a drug *in situations where a medicinal product is intentionally used for a medicinal purpose not in accordance with the authorised product information* (European Medicines Agency 2012). Both M-PEM and SCEM are recognised as tools to conduct real-world post-authorisation safety studies (PASS) to

gather additional safety monitoring information or assess patterns of drug utilisation (European Medicines Agency 2013). Each study is conducted in accordance with national and international guidelines (British Medical Association Board of Science and British Medical Association Science and Education 2006; Council for International Organizations of Medical Sciences and World Health Organisation 2002; General Medical Council 2009a, b).

The general methodology uses a retrospective non-interventional observational cohort design to provide active surveillance of targeted medicines on a national scale in England. Specific details of the study methodologies have been provided elsewhere (Layton and Shakir 2011). In brief, for M-PEM, primary care dispensed prescription data sources, and medical record-based data sources are used to provide data for eligible patients (Table 4.1). For all studies, exposure (index/exit) data are derived from dispensed prescriptions issued by general practitioners (GPs) immediately after market launch until sufficient numbers have been identified (per protocol often several thousands). In contrast, for SCEM, networks of specialists are established (facilitated by the UK National Institute of Health Research (NIHR) Clinical Research Network (CRN)) (Department of Health 2014) and patients are identified by these practitioners subsequently. For all approaches, outcome data (indication, events and reasons for stopping) that have been recorded in the patient's medical records may be derived from questionnaires sent to each physician at some predefined period after the date of each patient's first prescription, but at a minimum of 3 months to allow information to be shared between patient and prescriber. This duration of follow-up is often driven by the expected pattern of risk for events identified within the study primary objectives. However, for general surveillance in M-PEM, the desire is to capture at least 6 months observation. There are no specific exclusion criteria. Specific to M-PEM and SCEM, more detailed information on posology, identified and potential risks, selected risk factors-prior medical history/concomitant medicines and selected prescriber or patient behaviours may be collected.

For each approach, events of interest (e.g. identified risks, such as suicide events) may be followed up for purposes of further evaluation. For each patient, trained coding staff prepared a computerised, longitudinal, chronological record of demographic, exposure and outcome data (including additional follow-up). Quantitative and qualitative data analyses are conducted. Quantitative analyses include descriptive statistics to summarise patient and prescriber (where provided) characteristics such that drug utilisation and compliance with recommended prescribing regimens may be described. Calculations of event risk and rates (incidence densities for a fixed period (t) – ID_t- usually expressed in units of first event reports per 1000 patient-months) can give estimates of real-world frequency. Calculation ID differences between periods of observation are effective methods by which disproportionality in risk or ID may be observed, suggestive of signals of treatment effects. Inter-cohort IDs and ID difference estimates may be calculated, as well as intra-cohort estimates for special populations of interest. Other complementary analyses include describing frequency of events given as reasons for stopping and also application of survival methods to provide further detail on pattern and time to onset of an event after starting treatment with a study drug. Qualitative analyses are undertaken for exploration

Table 4.1 Characteristics of standard Prescription-Event Monitoring (PEM), Modified PEM (M-PEM) and Specialist Cohort Event Monitoring (SCEM) studies

Study Characteristics	PEM	M-PEM	SCEM
Setting	Primary care		Secondary care
Prescribers	General Practitioner		Specialist
Design	Non-interventional observational cohort		
Data Source	Secondary use of data from existing medical records		
Ethics	Waiver under Section 251 of NHS Act 2006		Yes
Sample size	10,000+	Bespoke to targeted events	
Period of Observation	6–12 months	3–12+ months	≤3 months
Questionnaire	Standard (single A5) across all studies	Bespoke design (multiple A4), by study	
Drug Utilization	All populations	Targeted sub-populations considered at risk	
Surveillance	General surveillance	General and targeted events (identified, potential and missing risks)[a]	
Risk factors	Event (case) specific on follow-up	For targeted identified and potential risks for all patients	
Analysis	Crude and age/sex adjusted measures of occurrence and association	Multiple covariate adjusted measures of occurrence and association; survival methods for signal generation; intra- and inter- cohort comparisons possible	
PASS RMP	No	Yes	
ENCEPP registration	No	Yes	
Prescriber remuneration	No	Yes	

Grey highlights indicate common aspects of the method
ENCEPP European Network of Centres of Excellence in Pharmacoepidemiology and Pharmacovigilance, *NHS* National Health Service, *PASS* Post-authorisation safety study, *RMP* Risk Management Plan. A4: page dimension 210 by 297 mm; A5: page dimension 148 by 210 mm
[a]Identified risks (known from clinical trials), potential risks (effects not observed in trials but expected e.g. class effects) and missing risks (identified and potential effects that may occur in populations not studied)

of signals or events of interest. Through medical evaluation, individual or clusters of event reports are examined and important attributes identified. Examples of these approaches will be presented in the remainder of this chapter.

4.3 Completed Studies

A wide range of drugs used to manage mental health conditions have been studied using standard and modified approaches. These include agents to manage depressive disorders, anxiety disorders, attention deficit hyperactivity disorder (ADHD), schizophrenia and dementia (Table 4.2). Treatments used to manage conditions

Table 4.2 List of completed studies (standard (PEM)/modified (M-PEM)) of psychotropic medicines, by ATC code (World Health Organisation 2015)

Therapeutic class and ATC code	Name: generic [UK proprietary]	Design/cohort size	Collection period
Antiobesity preparations (excl. diet products)			
A08AA10	Sibutramine [REDUCTIL™]	Standard ($N=12,336$)	Oct 2001–Jun 2002
A08AX01	Rimonabant [ACOMPLIA™]	Modified ($N=10,008$)	Jun 2006–Oct 2008
Opioids			
N02AB03	Fentanyl buccal [EFFENTORA™]	Modified ($N=556$)	Mar 2009–Jun 2011
N02AB03	Fentanyl nasal [PECFENT™]	Modified ($N=63$)	Dec 2010–Sep 2012
Antipsychotics			
N05AE05	Sertindole [SERDOLECT™]	Standard ($N=436$)	Dec 1996–Dec 1997
N05AH03	Olanzapine [ZYPREXA™]	Standard ($N=8858$)	Dec 1996–May 1998
N05AH04	Quetiapine [SEROQUEL™]	Standard ($N=1728$)	Jun 1998–Jan 2000
N05AH04	Quetiapine [SEROQUEL XL™]	Modified ($N=13,276$)	Sep 2008–Feb 2013
N05AX08	Risperidone [RISPERDAL™]	Standard ($N=7684$)	Jul 1993–Dec 1996
Anxiolytics			
N05BE01	Buspirone [BUSPAR™]	Standard ($N=11,113$)	Mar 1988–Feb 1989
Hypnotics and sedatives			
N05CF01	Zopiclone [ZIMOVANE™]	Standard ($N=11,543$)	Mar 1991–Jul 1991
N05CF02	Zolpidem [STILNOCT™]	Standard ($N=13,460$)	Jul 1994–Jan 1996
Antidepressants			
N06AB03	Fluoxetine [PROZAC™]	Standard ($N=12,692$)	Mar 1989–Mar1990
N06AB05	Paroxetine [SEROXAT™]	Standard ($N=13,741$)	Mar 1991–Mar1992
N06AB06	Sertraline [LUSTRAL™]	Standard ($N=12,734$)	Jan 1991–Sep1992
N06AB08	Fluvoxamine [FAVERIN™]	Standard ($N=10,983$)	Feb 1987–Feb 1988
N06AG02	Moclobemide [MANERIX™]	Standard ($N=10,835$)	Jun 1993–Aug 1995
N06AX06	Nefazodone [DUONIN™]	Standard ($N=11,834$)	Jan 1996–Feb 1997

N06AX11	Mirtazapine [ZISPIN™]	Standard (N = 13,554)	Sep 1997–Feb 1999
N06AX12	Bupropion [ZYBAN™]	Standard (N = 11,735)	Jul 2000–Aug 2000
N06AX16	Venlafaxine [EFEXOR™]	Standard (N = 12,642)	May 1995–Jun 1996
N06AX21	Duloxetine [CYMBALTA/YENTREVE™]	Standard (N = 19,485)	Sep 2004–Apr 2005
Psychostimulants (agents used for ADHD and nootropics)			
N06BA07	Modafinil [PROVIGIL™]	Modified (N = 2092)	Jul 2004–Aug 2005
N06BA09	Atomoxetine [STRATTERA™]	Modified (N = 5079)	May 2004–Oct 2004
Antidementia drugs			
N06DA02	Donepezil [ARICEPT™]	Standard (N = 1762)	Apr 1997–Feb 1999
Drugs used in addictive disorders			
N07BA03	Varenicline [CHAMPIX™]	Modified (N = 12,135)	Dec 2006–March 2007

associated with addictive behaviours such as smoking habit, obesity and chronic non-cancer pain are also presented for purposes of demonstrating particular methodological considerations. All these medicines were all intended for wide-spread, long-term use in primary care. Other medications have also been studied (Layton and Shakir 2011), but these are not the focus of this chapter and so will not be described further.

The sample sizes of standard, M-PEM and SCEM studies of psychotropics are remarkably different. The median cohort size of the 19 standard PEM studies of psychotropic medicines presented is 11735 (IQR 9847, 12713), whilst that of the 7 M-PEM studies is 5079 (IQR 1324,11072). One SCEM study has been completed to date ($N = 869$). The explanation is related to the difference in principle study objective: standard PEM studies were intended for general surveillance with a target sample size of at least 10,000 patients to allow for the detection of rare events occurring with a frequency of at least 1 in 2000 patients (assuming the background rate is zero) with 85 % power (Machin et al. 1997a, b). The lower sample size for M-PEM and SCEM reflects a bespoke study specific need, which generally requires fewer numbers than the general surveillance studies.

4.4 Exploring Drug Utilisation Factors Within Pharmacovigilance

Drug utilisation research is an essential part of pharmacoepidemiology, as it describes the extent, nature and determinants of drug exposure at the patient level. Collectively standard, M-PEM and SCEM approaches permit the examination of the characteristics of prescriber and new drug user populations and contribute to the accumulation of safety data, particularly with regard to vulnerable populations for whom off-label prescribing has occurred.

There are several ways in which this may occur: by prescribing a dose in excess of that specified by the MA, prescribing for an unlicenced indication, prescribing for a special group outside of the MA specification and altering the dosage form. Off-label prescribing is permitted in circumstances where a physician concludes that for medical reasons, treatment with the product is necessary to meet the specific needs of the patient (General Medical Council 2015).

Situations leading to a warning or precaution use include conditions to be fulfilled before or during use, special populations at increased risk, risks associated with starting or stopping the product and possible medication errors. These situations represent vulnerable populations that require more careful management in order to avoid harm. They also represent areas of potential risk for pharmacovigilance because the populations being exposed have not been studied, or there is limited information.

4.4.1 *Off-Label Use*

As an example, the summary demographic information on the study populations identified for the four antipsychotic studies conducted using standard methods is presented in Table 4.3 (Mackay et al. 1999). It is notable that all drugs listed first gained MA for the treatment of schizophrenia. This is consistent with the narrowly defined patient population studied premarketing. Also notable in Table 4.3 is the frequency of apparent 'off-label' prescribing. In terms of indication, quetiapine IR was the antipsychotic for which the proportion of use was highest (47.4 %) followed by risperidone (44.9 %) for indications other than within the MA at launch. The observation that quetiapine IR appeared to have the highest frequency is not unexpected, given it was the last of the four drugs listed to be marketed. Nevertheless, off-label prescribing in terms of indication was very common. This observation is supported by similar findings elsewhere (Hodgson and Belgamwar 2006).

None of these products studied were indicated for the use in children <15 years. However, the frequency of prescribing appeared to be consistently of the order of 1 %. The literature suggests that in the UK, antipsychotics are prescribed generally for aggressive behaviour in this population (Doerry and Kent 2003). Indeed the study for risperidone reported that of the 98 children aged <15 years, 49 (50 %) had been prescribed risperidone for hyperactivity. For all the antipsychotics studied, the use in the elderly was considered a special warning for use, and the proportions of each cohort aged >65 years was consistently between 10 % and 20 %. Whilst this in itself does not constitute off-label prescribing, the frequency of use in elderly patients for the treatment of behavioural and psychological manifestations of dementia is. In the majority of these studies, such prescribing was common (>1 % of population studied) although the frequency was the highest for quetiapine (4 %). Further discussion on the contribution of use and safety antipsychotics in patients with dementia is given later in this chapter.

One of the limitations of standard PEM methodology was that information on baseline characteristics, such as prior medical history, concurrent morbidities, as well as treatment patterns was limited. M-PEM retains all the strengths of the original method, with the same underlying process, but also tried to overcome these limitations through bespoke targeted surveillance, enhanced data collection and application of new analytical methods. This permits more detailed exploration of the heterogeneity of the new user population, as well as appropriate or inappropriate use.

There are a number of examples in the published literature where off-label prescribing has been reported within M-PEM studies conducted on psychotropic medicines. Davies et al. reported on the prescribing of modafinil (Provigil™),which was marketed in the UK in 1998 to promote wakefulness in the treatment of narcolepsy (Davies et al. 2013). Its licence was extended in 2004 to include chronic pathological conditions. Following a review of the safety of modafinil (European Medicines

Table 4.3 Completed standard PEM studies of antipsychotics (Mackay et al. 1999)

Drug (n)		Study population				
	MA	Sex		Age		
Indication [year]	Min age years	Male *n* (%[a])	Female *n* (%[a])	Mean (SD) years [Range]	MA Indication *n* (%[a])	Comments on use in elderly and children
Risperidone (*n* = 7684)						
Acute and chronic schizophrenic psychoses, other psychoses and affective symptoms [1993]	15	4124/7624 (54.1)	3500/7624 (45.9)	44.1 (19.4) [4–99] *N* = 6678	3376/6129 (55.1)	98/6678 (1.5 %) <15 years; 1271/6678 (19.0 %) ≥65 years Indication: 1120/6129 (18.3 %) had psychosis; 87/6129 (1.4 %) dementia[b]
Sertindole (*n* = 462)						
Schizophrenia [1996]	18	230/459 (50.1)	229/459 (49.9)	40.8 16.4) [16–95] *N* = 402	210/311 (67.5)	2/402 (0.5 %) <18 years; 48/402 (11.9 %) ≥65 years Indication: 54/311 (17.4 %) had psychosis; 3/311 (1.0 %) dementia[b]
Olanzapine (*n* = 8858)						
Schizophrenia [1996]	18	4972/8810 (56.4)	3838/8810 (43.6)	42.2 (17.1) [14–97] *N* = 7455	3470/5902 (58.8)	81/7455 (1.1 %) <18 years; 995/7455 (13.3 %) ≥65 years Indication: 1104/5902 (18.7 %) had psychosis; 47/5902 (0.8 %) dementia[b]
Quetiapine immediate release (*n* = 1728)						
Schizophrenia [1997]	18	807/1725 (46.8)	918/1725 (53.2)	44.6 (19.3) [15–98] *N* = 1425	596/1133 (52.6)	20/1425 (1.4 %) <18 years; 266/1425 (18.6 %) ≥65 years Indication: 215/1133 (18.9 %) had psychosis; 45/1133 (4.0 %) dementia[b]

MA Marketing authorisation, *SD* standard deviation

[a]% where specified

[b]Reported terms: Alzheimers, dementia, dementia senile, dementia presenile, Lewy body dementia, multifarct dementia, Pick's disease, vascular dementia, arteriosclerotic dementia, alcoholic dementia

Agency 2011), risk minimisation measures were introduced. These included updates to the SPC to reflect nature of adverse reactions, additions to types of patients with conditions contraindicated for use and restriction of indication to patients with shift work sleep disorder, narcolepsy and obstructive sleep apnoea/hypopnoea syndrome. The M-PEM study looked specifically at use post the 2004 extension in 1096 patients prescribed modafinil in primary care. Study results reported that the prevalence of use in multiple sclerosis was very common ($n=372$, 33.9 %) and use in children aged 16 years or under was uncommon ($n=9$, 0.8 %) – both regarded as off-label (Davies et al. 2013).

4.4.2 Contraindications and Special Warnings and Precautions for Use

M-PEM studies were recently conducted to support a regulatory requirement to examine the use in general medical practice in England of two novel formulations of an opioid analgesic. Fentanyl citrate buccal tablets (Effentora™; Cephalon), were approved in the EU on April 2008 for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Effentora™ was launched in the UK in January 2009 (Cephalon 2010). Fentanyl pectin nasal spray (PecFent™; Archimedes Development Ltd.), licenced for the same indication, gained marketing approval in the EU in August 2010 and was launched in the UK in October 2010 (Archimedes Pharma UK Ltd. 2012). An objective of both studies study was to examine the frequency of inappropriate use, i.e. use without long-term opioid therapy and off-label use. Prescribing indicators were developed based on the SPC Sects. 4.3 and 4.4. The results from both studies regarding the number of reports of contraindications are summarised in Table 4.4. The majority of patients within either Effentora™ or PecFent™ cohorts had no contraindications for use ($n=482$, 87.5 % vs $n=56$, 88.9 %). However, the remainder were contraindicated because they were reported to be opioid naïve or not receiving maintenance opioids and had pre-existing COPD or respiratory depression. The prevalence was similar for both products ($n=69$, 12.5 % vs $n=7$, 11.1 %) albeit the study cohort size was small for PecFent™.

These two studies also demonstrate that vulnerable sub-groups within the primary care setting can also be identified; the number of reports of patients requiring special warnings for use are also summarised in Table 4.4. These include elderly, those with particular conditions and or those receiving treatments that place them at risk for important identified adverse events. In the studies of the two fentanyl products, nearly half of the Effentora™ or PecFent™ cohorts could be considered vulnerable ($n=285$, 51.7 % vs $n=34$, 54.0 %).

Table 4.4 Characteristics of Effentora™ or PecFent™ M-PEM cohorts

Characteristic *n* (% cohort)	Effentora™ (*N* = 551)	PecFent™(*N* = 63)
Age at start of treatment (years): median (IQR)	62 (50–72)	62 (49–73)
Sex:		
Male	248 (45.1)	22 (34.9)
Female	302 (54.6)	41 (65.1)
Not specified	*1*	–
Indication:		
Break through pain	341 (61.9)	41 (65.1)
Break through pain and other	2 (0.4)	2 (3.2)
Other indications	133 (24.1)	16 (25.4)
Not specified	*75* (*13.6*)	*4* (*6.3*)
Contraindications:		
Opioid naïve/non-tolerant	31 (5.6)	3 (4.8)
Age <18 years	1 (0.2)	0 (0)
COPD	35 (6.4)	3 (4.8)
Respiratory depression	7 (1.3)	1 (1.6)
Respiratory failure	3 (0.5)	0 (0)
Obliterative bronchiolitis	1 (0.2)	0 (0)
Breastfeeding	0 (0)	0 (0)
MAOI use <15 days of starting (or concomitant)	1 (0.2)	0 (0)
Indicators of special warning/precautions for use:		
65+ years	235 (42.6)	28 (44.4)
CKD stage >=3	43 (7.8)	7 (11.1)
Liver disease (moderate/severe)	33 (6.0)	2 (3.2)
Hypovolaemia	3 (0.5)	0 (0)
Hypotension	4 (0.7)	2 (3.2)
Bradyarrhythmia	0 (0)	0 (0)
Increased ICP	4 (0.7)	0 (0)
Pregnancy	0 (0)	0 (0)
Concomitant CYP3A4 moderate/strong inhibitors	13 (2.4)	1 (1.6)

CKD Chronic kidney disease, *CYP* Cytochrome P450, *COPD* Chronic obstructive pulmonary disease, *ICP* Intracranial pressure, *IQR* Interquartile range, *MAOI* Monoamine oxidase inhibitor

4.4.3 Prescriber Characteristics

Alternatively, SCEM studies permit the characterisation not only of vulnerable patients within secondary care setting but the prescribing physicians. The Observational Assessment of Safety in Seroquel (OASIS) study was also conducted to support part of the PV requirements to extend the post-authorisation safety knowledge of quetiapine extended release (Seroquel XL™), with particular emphasis on short-term (within 12 weeks of starting) safety during titration and at higher doses (European Network of Centres of Excellence for Pharmacoepidemiology and Pharmacovigilance 2014a). An internal comparator cohort of patients prescribed

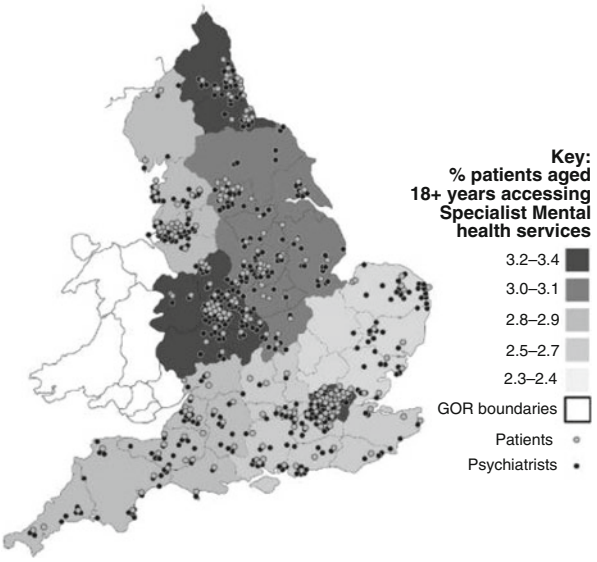

Fig. 4.1 Site of OASIS psychiatrist and patient recruitment within UK Government Office regions (*GOR*) which define percentage of adults accessing specialist mental health services (Figure adapted from Patterns of Specialist Mental Health Service usage in England, 2010 (Office for National Statistics 2010))

quetiapine immediate release (IR) was collected concurrently. Seroquel XL™ was launched in the UK in 2008 (AstraZeneca UK Limited 2014).

From over 50 trusts throughout England over 3 years from December 2009 to December 2012, a total of 407 psychiatrists identified 948 patients who consented. Of these 948, 869 (91.6 %) with a clinical diagnosis of schizophrenia or bipolar mania, newly initiated on quetiapine XL or IR were eligible for inclusion and had evaluable data for analysis. The distribution of participating psychiatrists' trusts and consented patients is provided in Fig. 4.1. The pattern and spread reflected density of mental health care service utilisation in England, with the densest areas around London, Birmingham and North West of England. The majority of psychiatrists were male [68.9 % (275/399)] and had been qualified for 10 years or more [94.6 % (336/355)]. The most frequent area of psychiatrist specialisation, where reported, was general psychiatry [65.4 % (193/295)]. The most frequently reported prescribing setting was in the community ($n=83$, 20.4 %) or within community mental health teams ($n=80$, 19.7 %). Investigators were asked to provide the supporting reasons for prescribing quetiapine for the primary diagnosis indicated. Reasons (other than indication) for prescribing were also collected. Although multiple reasons for prescribing could be reported, the most frequently provided reason for prescribing in all indications and for the whole cohort was 'prescriber clinical decision' [90.2 % (767/850)].

Such information is important to understand the drivers of adoption of a new medicine within the UK NHS. The process by which patients are referred, treated and monitored affects the availability and accessibility of relevant information to support safety surveillance for PV purposes. Within the UK, mental health service provision crosses many boundaries in terms of clinical settings and the type of healthcare professionals providing services. Only the most severely ill patients (prevalence estimated to be (<10 %)) (Health and Social Care Information Centre 2013)

will be admitted to hospital as an in-patient. Reports from psychiatrists participating in OASIS indicated that seeking informed consent from such acutely ill patients was not possible at the time of quetiapine initiation. Therefore, systematic surveillance of this high-risk population may not be possible, and the responsibility for routine PV activities remains with the responsible physician. In prescribing newly licenced drugs, hospital specialist prescribers can be classified as adopters of innovation. Generally, early adopters have been classified as opinion leaders who greatly influence the prescribing habits of others (Rogers 2004). However, they are also described as risk takers. As such, there have been assertions that early adopters may prescribe irrationally (Inman and Pearce 1993). This may be true for some, but further study is needed to investigate relationships between prescriber and patient characteristics.

4.4.4 Reasons for Treatment Discontinuation

Quantifying and exploring reasons for stopping treatment are regarded as one of the complementary and unique signal generation processes in standard, M-PEM and SCEM. Specific data are requested in all of these studies regarding clinical or non-clinical events that lead to treatment withdrawal. Clinical events inform on possible issues associated with short- or long-term tolerability, whilst non-clinical event may highlight patient adherence issues and external influences on persistence, such as media reports of adverse effects. Early treatment discontinuation of psychotropic medication will have a negative effect on a medications benefit risk profile, particularly if discontinued before the positive effects of the psychotropic treatment can be established. Two examples are described below.

Rimonabant (Acomplia™, Sanofi-Aventis) is a centrally acting medication first marketed in UK in June 2006. It was licenced as an adjunct to diet and exercise for the treatment of obese patients (BMI $\geq$30 kg/m^2) or overweight patients (BMI >27 kg/m^2) with associated risk factors such as type 2 diabetes mellitus or dyslipidaemia. In October 2008, the MA was suspended because of psychiatric safety concerns (European Medicines Agency 2008). One of the objectives of the M-PEM study was to explore utilisation and duration of treatment (Buggy et al. 2011). A supplementary analysis (Willemen et al. 2012) examined these data according to four categories: (1) discontinuation due to any clinical event (with a focus on psychiatric events); (2) discontinuation due to lack of effectiveness; (3) discontinuation due to target weight loss achieved (as a proxy for effectiveness); (4) other events reported as reasons for stopping; and (5) stopped but no reason specified. The study results reported that 7204 (72.0 %) of patients stopped treatment, of which 50 % stopped within 1 year (323 (IQR 279, 371)). Where specified (n=5763, 80.0 % patients who stopped), at least one clinical event was given as the reason for stopping for 1896 patients (32.9 %). Of these 1896 patients, the most frequent reason was depression (n=284 cases, 15.0 %). The most frequent non-medical reason for stopping was due to lack of effectiveness was reported for 2480 (3.0 % where reason specified) patients, whilst stopping due to achieving target weight loss was reported for only 215 (3.7 %) patients. Factors that were associated with stopping (all reasons) included female gender, prior

history of antiobesity drug use and prior history of psychiatric illness. Those with a prior history of psychiatric disease had a higher rate of stopping because of psychiatric events (hazard ratio 1.8 (95 % CI 1.5, 2.09)) than those with no history.

A second example looks at reasons for and time to antipsychotic treatment discontinuation. As for treatment of obesity, there are also specific determinants that affect choice and maintenance of antipsychotic agents. Accordingly, such issues can be explored using M-PEM data. In addition to the OASIS SCEM study with quetiapine described earlier, an M-PEM study was conducted to further understand safety of quetiapine extended release (Seroquel XL™) during titration and use at higher doses as prescribed in primary care (Gilchrist et al. 2011). Of 13,276 patients, 3753 (28.4 %) were reported to have stopped treatment within 12 months of starting. Ten percent of patients were no longer on treatment by day 56 and 25 % by day 220. In total 4844 events were given as reasons for stopping were specified for 3086 patients (82.2 % who stopped within 12 months of starting). Of 1750 clinical (medical) reasons for stopping, the most frequent was sedation (269, 15.4 %), whilst of the other 3094 non-medical reasons given for stopping, the most frequent was drug ineffective (581, 18.8 %).

In both the Acomplia™ and Seroquel XL™ M-PEM studies, high proportions of patients stopped treatment within 12 months of starting, and reasons for stopping were varied. Certain patient characteristics were also associated with a higher risk of stopping. M-PEM can provide provides information on frequency of medication discontinuation, reasons thereof and patients who may require more intense monitoring. Accordingly, these data can help support physicians decisions on prescribing and management to prevent premature treatment cessation.

4.5 Describing the Safety of Psychotropic Medicines

Psychotropicmedicines are a heterogeneous group of chemically unrelated compounds which share a broad range of pharmacological effects, principally as a result of broad receptor-blocking properties. These effects can involve every system of the body, although many are non-serious. Drugs which possess anticholinergic activity are associated adverse effects such as dry mouth, constipation, visual disturbances and urine hesitancy, whilst the use of drugs that affect noradrenaline activity can, for example, cause sexual dysfunction and postural hypotension. Interference with the dopaminergic activity can lead to endocrinological adverse effects such as hyperprolactinaemia, conditions associated with hyperglycaemia, weight gain and extrapyramidal symptoms. As described earlier, non-serious adverse effects play an important role in persistence with medication. Other more serious adverse effects include seizures, blood dyscrasias, neuroleptic malignant syndrome and enhanced propensity for suicidal acts. Such serious effects have played an important role in the restriction, suspension or ultimately withdrawal of some psychotropic medicines. Some examples of key findings from the PEM and M-PEM studies of psychotropic medicines are provided below.

In each of these examples, as described previously, the investigations are possible because the methodology (standard, M-PEM or SCEM) permits a more detailed

examination of particular risks. The underlying architecture of each study is that of survival data – therefore treatment effect over time can be explored. Furthermore, data are collected in an identical manner, and, for the majority of studies, cohorts of new user subjects are identified at the same stage of a drug's lifecycle in the immediate post-marketing period. By excluding prevalent users, bias introduced by (1) under-ascertainment of events early in therapy and (2) inability to control for disease risk factors before treatment started is minimised (Ray 2003). As such, inter-cohort comparisons of risk and rate can be undertaken. Where no suitable comparator may be found, intra-cohort comparisons are generally used. The limitations of PEM and M-PEM should however be acknowledged. These include: loss of statistical power where observed final sample size is different to that expected because of dependency on level of prescribing of a study drug by GPs in England, missing data arising from incomplete questionnaires or non-response and assumptions about data for signal detection purposes. These limitations are described in further detail elsewhere (Layton and Shakir 2014).

4.5.1 General Surveillance

National Institute of Clinical Excellence (NICE) guidelines for the prescribing of antidepressants in adults advocate that choice be determined, taking into account anticipated adverse events and concomitant medication for physical health problems (National Institute of Clinical Excellence 2009). Tricyclic antidepressants are one of the oldest classes of antidepressants and are still used extensively. However, these are now used second line in favour of newer antidepressants associated with a low propensity for anticholinergic effects.

As shown in Table 4.2, ten products used in the treatment of depression have been studied using either the standard or M-PEM approach. A study was conducted to compare the general tolerability and safety profile of six antidepressants (fluoxetine, sertraline, paroxetine, moclobemide, venlafaxine and nefazodone), as reported within the PEM study conducted for each (Mackay et al. 1999). A minimum of 6 months observation was collected. Analysis included calculation of incidence densities in (ID – per 1000 patient-months) all events, ID ratios for events of specific interest (adjusted by age, sex and indication) and odds ratios for deaths (adjusted by age, sex and indication). The most frequently reported event consistent across all drugs in the first month was nausea and vomiting [range 26.3 (fluoxetine) to 71.9 (venlafaxine)], followed by malaise [range 9.9 (moclobemide) to 25.0 (nefazodone)]. The results of the comparisons for selected events are presented in Fig. 4.2. Compared to fluoxetine (as reference group), the variability of event rates of agitation/anxiety, drowsiness/sedation and hypertension across the different drugs examined is evident. There were no significant differences in odds of death between drugs after adjustment. A limitation of this particular study was that the products were marketed sequentially between 1989 and 1996; therefore changes in clinical practice are possible. Nevertheless, this study demonstrates the contribution of the methodology as a whole to inform on event profiles between drugs.

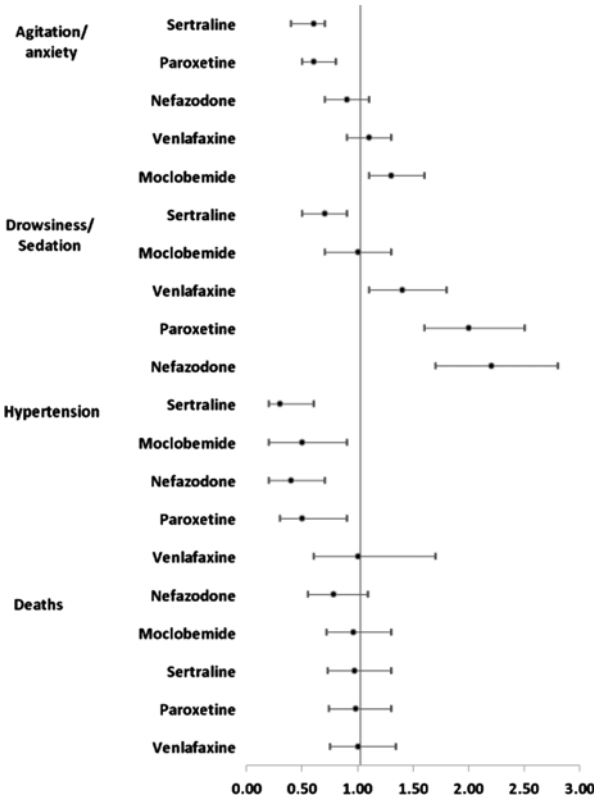

Fig. 4.2 Relative risks for selected events observed in users of non-tricyclic antidepressants (sertraline, paroxetine, nefazodone, venlafaxine and moclobemide) compared to fluoxetine as reference in first 6 months of treatment, adjusted for age, sex and indication. Adjusted incidence density ratios (+95 % CI) are presented for the events of agitation/anxiety, drowsiness/sedation and hypertension. Adjusted odds ratios (+95 % CI) are presented for the event of death (all-cause)

4.5.2 Antipsychotics and Stroke

Initial concerns about an increased risk of cerebrovascular (CVA) adverse effects such as stroke and transient ischemic attack initially focused on risperidone in 2002 and olanzapine in 2004 (Committee on Safety of Medicine 2004). In particular, the number of fatalities in RCTs of elderly patients prescribed these drugs for dementia and also in patients with no pre-existing cardiovascular problems was of concern (Dear Healthcare Professional 2004). Prescribing restrictions were added to the labels in the EU, US and Canada. In 2005 the European PV Working Party assessed additional evidence from three observational studies and concluded that the risk of CVA adverse events was possibly a class effect (European Medicines Agency 2005).

In support of this review in 2005, the DSRU conducted a retrospective analysis to examine and compare the incidence rates of CVA and/or transient ischaemic attack (TIA) as reported in the PEM studies conducted on risperidone, olanzapine

and quetiapine (Layton et al. 2005). Crude rate ratios (RR) and RR adjusted for age, gender and indication (dementia vs other) were calculated using Poisson regression modelling and time to event was modelled using survival methods. For comparative purposes, the reference cohort was olanzapine. Person-time was calculated between date of first dispensed prescription and date of first event or, for non-cases, censored at end of 180 days or date of loss to follow-up, which ever occurred sooner.

When risperidone was compared to olanzapine, the age and sex-adjusted RR was non-significant [RR1.2 (95 % CI 0.4, 3.0); $n=23$ (0.3 %) vs $n=10$ (0.11 %)]. Similarly, the RR was non-significant for the comparison between quetiapine and olanzapine [RR 2.1 (95 % CI 0.6, 7.7); $n=6$ (0.35 %) vs $n=10$ (0.11 %)]. Likewise, when risperidone was compared to quetiapine, the adjusted RR was not significantly different. When data were stratified by indication, there were no cases of CVA/TIA in the olanzapine cohort treated for indication, so this could not be examined. The age and sex-adjusted RR was non-significantly different [2.1 (95 % CI 0.5, 10.1)] between those prescribed risperidone for dementia and those prescribed quetiapine for dementia. Of the three drugs, the time to onset was shortest for risperidone and the subgroup with dementia. The intra-cohort analysis which compared indication groups identified a sixfold difference in rate of CVA/TIA in patients with dementia compared to those treated for other indications. This retrospective comparison did not reveal any difference in rates between the three antipsychotics but did support the observations that dementia is an important risk factor.

Irrespective of treatment, dementia is associated with a two- to fourfold increased risk of mortality compared to those without such diagnosis (Xie et al. 2008). Yet, despite additional regulatory activity since 2005, and the introduction of best practice guidelines for rational and safe use of antipsychotics in people with dementia, there remain concerns that antipsychotic medications are being overprescribed as first line choice of pharmacological management of BPSD. In the UK, estimates from the published literature range from 5 % to 15 %, despite limited clinical effectiveness (IMS Health 2009; Child et al. 2012). In the UK, NICE recommends that antipsychotics can be used in elderly patients, but under strict guidelines (Oxford Health NHS Foundation Trust 2013). Risperidone is recommended as the antipsychotic of first choice, plus a low dose, with slow dose titration is advocated.

4.5.3 Cardiovascular Safety

Sibutramine is a serotonin-noradrenaline re-uptake inhibitor, indicated for the treatment of obesity. It was licenced in the UK in May 2001. A safety signal regarding adverse cardiovascular effects was reported shortly after marketing and a review conducted by the European Medicines Agency in 1999 and 2002 in light of these concerns. At that time, CHMP concluded that the benefits of sibutramine for the management of obsess and overweight patients outweighed its risks (European Medicine Agency 2002). However the MAH was asked to start a study of use of sibutramine in patients with cardiovascular risk factors – the Sibutramine

Cardiovascular Outcome Trial (SCOUT) study. This study started in 2002; its aim was to determine the impact of weight loss with sibutramine on cardiovascular problems in a large group of overweight and obese patients at high risk for cardiovascular disease.

During that period, a PEM study of sibutramine was undertaken between October 2001 and June 2002 (Perrio et al. 2007). This study provided information on the 'real-world' use of sibutramine in general practice, irrespective of co-morbidities and concomitant use of other medicines. As the prescribing recommendations already had contraindications and precaution for use in patients with cardiovascular risk factors, prescribers were asked to provide additional information specifically regarding prior medical history of diabetes mellitus, hypertension or ischaemic heart disease, plus prior use of other antiobesity drugs. Patient characteristics, events and reasons for stopping were examined according to the prescribing guidelines. The full details of this analysis are published elsewhere. In summary, the PEM cohort comprised 12,336 patients. In terms of cardiovascular risk factors, the prevalence of pre-existing IHD was 1.9 % ($n=238$), this being a contraindication for use. Three cardiovascular events were considered signals associated with starting treatment (cardiovascular tests, faintness and palpitations). Within 3 months of starting treatment, 5157 patients (41.8 % of total cohort) had stopped taking sibutramine. Of 5280 reasons specified for 4554 patients (88.3 % who stopped within 3 months), the events of hypertension and raised blood pressure were commonly reported as reasons for stopping ($n=203$ (3.8 % of reasons) and $n=179$ (3.4 % of reasons), respectively), whilst palpitation, disorders of heart rate, chest pain and raised pulse were uncommon. Causality assessment of reports of arrhythmia, cerebrovascular events, angina and myocardial infarction identified 14 events assessed as possibly ($n=13$) or probably ($n=1$) related to sibutramine: 'arrhythmia' ($n=3$), 'fibrillation atrial' ($n=4$), angina ($n=4$) syncope ($n=2$) and myocardial infarction ($n=1$). Although there is limited information on other risk factors for cardiovascular safety, this study gave an indication of how particular safety aspects highlighted within prescribing recommendations, including the identification of vulnerable populations at risk can be investigated.

Notably in January 2010, the European Agency's Committee for Medicinal Products for Human (CHMP) recommended suspension of the marketing authorisation of medicinal products containing sibutramine, following a safety review of interim data from the SCOUT study which indicated that sibutramine is associated with more cardiovascular problems than placebo (European Medicines Agency 2010; Maggioni 2009).

4.5.4 Sudden Unexpected Deaths

PEM study data has also been used to investigate cardiovascular concerns including sudden unexpected deaths for an atypical antipsychotic sertindole (Serdolect™) (Wilton et al. 2001). This product was voluntarily suspended in the EU in 1998, following regulatory concerns over reports of serious cardiac dysrhythmias and sudden

unexpected deaths. The reported causes of death, their frequency, prolongation of the rate corrected QT interval (QTc) and cardiac dysrhythmias in patients within the sertindole PEM cohort were compared with PEM data obtained those for patients treated with two other atypical antipsychotics (olanzapine and risperidone) (Wilton et al. 2001). Age and gender Standardise Mortality Ratios (SMRs) (+95 % CI) were calculated using the indirect method (dos Santos Silva 1999). There was no statistically significant difference in all-cause mortality rates between sertindole and the comparator cohort according to the SMR (0.87 95 % CI; 0.35, 1.80) based on $n=7$ vs 397 deaths. Similarly, there was no statistically significant difference in CV mortality (SMR 0.73 (0.009, 2.63)) based on $n=2$ vs $n=133$ CV deaths, though confidence intervals were wide due to small numbers in the sertindole cohort. Six cases of prolongation of QTc interval were identified in 462 patients (1.3 %, 95 % CI; 0.5 %, 2.8 %) treated with sertindole and one with unspecified electrocardiogram changes in the comparator cohort of 16,542 patients. Although no statistically significant difference was shown in mortality rates between sertindole and comparator cohort, the sertindole cohort was too small to rule out an association between the use of this drug and cardiovascular deaths.

This example shows how calculations of SMRs area an alternative method for inter-cohort comparisons when an external comparator cannot be identified. In this example, because the mortality rate in schizophrenic patients was known to be different to that of the general population (Brown 1997), national mortality figures were not considered appropriate for comparison purposes. Therefore, data from the cohorts of two PEM studies of other atypical antipsychotic drugs were considered most appropriate to calculate the 'expected' mortality rates because the same methodology had been used for all three studies.

4.6 Methodological Developments in Design to Enhance Evaluation of Safety Concerns

4.6.1 Treating Dose Flexibly

When initiating pharmacological treatments for mental health conditions, prescribing guideline recommend individualisation of the dosing regimen. This in turn introduces added complexity in exploring associations between dose and an event because dose may be rapidly changing over time. Traditional approaches to modelling such associations need to extend beyond simple categorical measures based on arbitrary values at a fixed time point (such as start dose) and assumptions of homogeneity within each stratum (Greenland 1995). In studies of psychotropic medicines, particularly antipsychotics, nonlinear dose patterns should be anticipated with appropriate analytical methods to describe such patterns of change. As described earlier, targeted questions within M-PEM and SCEM design permit information on dose to be collected at multiple intervals during the observation period for each individual patient. In treatments where sub- or supra-optimal dose regimes

may significantly affect the benefit: risk ratio, knowledge of possible changes risk of clinical or adherence outcomes due to variation in dynamics of dose over time are extremely important.

Such methods to analyses repeated dose measurement over time in M-PEM and SCEM studies are being explored. One of the objectives of the OASIS SCEM study was to examine posology and titration patterns over the 12-week observation period (European Network of Centres of Excellence for Pharmacoepidemiology and Pharmacovigilance 2014a). The relationship of dose with time, *by formulation*, was explored by such methods; however the results have not yet been published. This type of analysis can be used to model general trend at group level and permits simple univariate explorations of associations between dose, predictors and outcomes in defined periods for signal detection purposes.

In addition to the challenge of modelling changes of dose over time, there is a need to be able to better account for multiple combinations of treatment or where multiple indications exist, particularly as seen in psychiatric medicine. In the UK, the Ready Reckoner is a tool used in clinical practice to monitor antipsychotic doses in high-risk patients with complex dosing regimens. It was developed by the UK Prescribing Observatory for Mental Health (POMH-UK), based within the Centre for Quality Improvement at the Royal College of Psychiatrists (Prescribing Observatory for Mental Health 2015). The principal is that at any stage of treatment, the total daily dose of each individual antipsychotic is converted to a percentage of the maximum dose for the indication being treated. Where the total sum of percent exceeds 100 %, then the patient is identified as a high-risk patient that requires more intensive monitoring (Royal College of Psychiatrists 2006). The potential advantages of modelling dose using this alternative metric include automatic adjustment by indication and loss of power due to creation of multiple strata of small sample size. The limitations include possible underestimating where dose data are missing, or concomitant medications are not reported. This Ready Reckoner is currently being applied to model antipsychotic treatment effects using M-PEM data.

4.6.2 Modelling Patterns of Events

In this chapter, examples have been provided of signals generated through quantitative means, such as calculation of crude incidence rates and risks. It is acknowledged in signal detection that the artificial segregation of time periods may not be appropriate for all events with respect to their most relevant time periods of excess (Guess 2006). More recently survival methods have been used to support signal detection and strengthening in M-PEM to more appropriately model the hazard function with the aim of detecting adverse drug reactions (Cornelius et al. 2012). Both non-parametric and parametric regression modelling of time to event data are considered to be useful adjuncts to signal detection methods and been used to explore safety signals with M-PEM and SCEM studies. A key difference between the two modelling approaches is that parametric methods allow more flexibility

when the associated hazard is not (expected to be) constant with respect to time. The construction of the M-PEM cohort is suitable for modelling time to event because the time origin is unambiguously defined (prescription start date), there is a metric for measuring time (person-time exposed), and failures are defined according to events. Since study data are collected over a finite period of time, such that not all 'time to event' may be observed for all patients, the study data are right censored. This means that the distribution of time to event cannot be described usual summary statistics because such sample parameters may no longer be unbiased estimators of the population parameter.

One example was the evaluation of the association between neuropsychiatric symptoms (including depression, suicidal thoughts and behaviour) and use of varenicline (Champix™) – indicated for the treatment of smoking cessation in adults (≥18 years of age) (Buggy et al. 2013). This study was conducted as part of the M-PEM study in response to the regulatory warnings issued in 2008 (Medicines and Healthcare products Regulatory Agency 2008). It was known that patients with a prior history of psychiatric disorders or users of psychotropic medicines were excluded from premarketing clinical trials. Therefore, the possibility existed that prior history of psychiatric disease could have had a profound effect on risk of neuropsychiatric events after starting treatment. For five events (depression, anxiety, aggression, suicidal ideation and nonfatal self-harm), analysis included using a the semi-parametric method to provide a smoothed estimate of the empirical hazard function and the parametric Weibull model to test for non-constant hazard using the shape parameter estimate in the first 3 months after starting treatment (Cornelius et al. 2012). Events reported on prescription start date were excluded, as they were considered pre-existing. The shapes of the smoothed hazards for depression and anxiety were suggestive of a non-constant hazard over time, but this was not observed for aggression, suicidal ideation and nonfatal self-harm. The corresponding predicted hazard function shape parameter estimated using the Weibull‡ model suggested that the hazard of anxiety increased over time ($p=0.009$), whilst there was no evidence of change for the other four events. In this particular example, the parametric model was crude, and the purpose was simply to detect whether hazards for prespecified events were non-constant or not, and not to model hazards accurately. Further exploration of the feasibility of integrating age and sex-adjusted parametric regression models as an additional tool for general surveillance purposes to support the identification of multiple safety signals within M-PEM studies is currently underway (Layton and Kimber 2014).

4.6.3 Assessing Suicidality

Assessing causal relationships between a drug and a suicidal event is complicated by the high background rate of such events in the treated populations and the high prevalence of known risk factors for Suicidal Behaviour (SB). Furthermore, a lack of well-defined terminology in clinical practice and failure to correctly identify suicidal behaviour and ideation has negative implications on appropriate management

of suicidality by health care professionals as well as decreasing reliability in comparisons of rates of such events across studies as a result of misclassification. Tools to support identification in PASS are vital to help quantify incidence in at-risk groups. The FDA has endorsed standard suicide terms and the application of the Columbia-Classification Algorithm for Suicide Assessment (C-CASA) approach to identify and categorise suicidal events in clinical trials (Posner et al. 2007), but its application in PASS has been limited. The C-CASA instrument includes nine codes within three categories (suicidal events, indeterminate or potentially suicidal events and non-suicidal events) that assist in classifying and distinguishing those events representing suicidal intent from to those without. These domains have been expanded and incorporated into a new instrument used to prospectively assess Suicidal Ideation (SI) and SB in clinical trials, the Columbia Suicide Severity Rating Scale (C-SSRS) with five subtypes (Posner et al. 2011). Although the C-CASA and C-SSRS criteria were both developed for the use in a different population in clinical trials, the instruments were considered relevant to the exploratory objective of four PASS studies for two antipsychotics [Seroquel XL™ and asenapine (Sycrest™) (European Network of Centres of Excellence for Pharmacoepidemiology and Pharmacovigilance 2013, 2014b)] since reports of suicidal events were anticipated. Since there is uncertainty in predicting which patients are at risk, data are being collected on risk factors possibly associated with an increased risk of suicidality. Potential suicide events are being classified according to C-CASA expanded C-SSRS domains by DSRU clinicians. As of January 2015, the studies for asenapine are ongoing, whilst the Seroquel XL™ studies are complete, but data are not yet published.

Such systematic assessment of suicidal events using C-CASA/C-SSRS domains can help support post-marketing benefit: risk evaluation of treatment choices in categories of patients according to risk of suicide when starting treatment with psychotropic medicines.

4.6.4 Indicators of Drug-Seeking Aberrant Behaviour

Problematic prescription drug use includes misuse ('non-medical use') and addiction as well as unsanctioned diversion to third parties and is reflected by or associated with drug-seeking aberrant behaviours. However, important research gaps include missing information on the incidence of such events and the patients likely to be at high risk of dependency. Such data are needed in order to support the effectiveness of risk minimisation strategies for psychoactive medications aimed at mitigating problematic use, particularly in patients for whom long-term treatment may be necessary. The feasibility of estimating the prevalence of risk factors for dependence and aberrant behaviours inpatients prescribed psychotropic products with misuse potential was first explored in the M-PEM post-study for Effentora™ in response to a regulatory requirement (Osborne et al. 2014). A number of criteria and instruments used in clinical practice in various setting were examined. Surrogate markers of indicators of aberrant behaviour suggestive of addiction were proposed

Table 4.5 Indicators of aberrant behaviours during treatment

Overwhelming focus on opioid-related issues
Escalating drug use (early refills/larger amounts for longer periods) unexplained by change in clinical condition
Reports lost, spilled stolen medication
Unclear aetiology and/or exaggeration of pain
Requests for treatment from multiple prescribers
Accidental/unsanctioned diversion to third parties

based on the Chabal criteria (Chabal et al. 1997) that reflected behavioural rather than clinical manifestations (Table 4.5).

In addition, information on known risk factors strongly associated with substance dependence was collected on prior history of: psychiatric disorders, substance misuse, alcohol misuse and smoking. Information was also requested on clinical diagnosis of opioid withdrawal syndrome within 14 days of starting treatment since its manifestation would suggest pre-existing dependence. Simple (non-weighted) risk scores were constructed on aggregate counts of the indicators of dependence and aberrant behaviours (score >3 suggested a patient to be at high risk). In the Effentora™ M-PEM study, the prevalence of at least one pre-existing risk factor for dependence was 26 % ($n=145$), whilst the frequency of aberrant behaviours observed during treatment was 8 % ($n=46$). Patients with aberrant behaviours appeared to have different characteristics to those who did not.

Such reports do not confirm misuse but are potential signals of such. Since the systematic collection of physician reports of aberrant behaviours has shown to be feasible, these criteria have also been applied to the study of other psychotropic medicines using M-PEM and SCEM.

4.7 Final Remarks

This chapter describes the usefulness of standard, M-PEM and SCEM methodology in revealing insight into important characteristics of users of psychotropic medicines, including vulnerable populations, and prescribing patterns as well as providing further information on important safety issues. Through examples, a demonstration has been presented on how the methodology of the prescription-based event-monitoring surveillance system and pharmacovigilance as a whole has evolved and still is evolving.

References

Archimedes Pharma UK Ltd (2012) Summary of product characteristics: PecFent. eMC Available from: http://www.medicines.org.uk/emc/medicine/23962

AstraZeneca UK Limited (2014) Seroquel XL 50 mg, 150mg, 200 mg, 300 mg, 400 mg prolonged-release tablets: summary of product characteristics. Ref type: Pamphlet

British Medical Association Board of Science, British Medical Association Science & Education (2006) Reporting adverse drug reactions. A guide for healthcare professionals. Available at :http://bmaopac.hosted.exlibrisgroup.com/exlibris/aleph/a21_1/apache_media/GYVFNJ1RT2PFNDUJ8IUKPUNTFVRF8G.pdf. London

Brown S (1997) Excess mortality of schizophrenia. A meta-analysis. Br J Psychiatry 171: 502–508

Buggy Y, Cornelius V, Wilton L, Shakir SA (2011) Risk of depressive episodes with rimonabant: a before and after modified prescription event monitoring study conducted in England. Drug Saf 34(6):501–509

Buggy Y, Cornelius V, Fogg C, Kasliwal R, Layton D, Shakir SA (2013) Neuropsychiatric events with varenicline: a modified prescription-event monitoring study in general practice in England. Drug Saf 36(7):521–531

Cephalon (2010) Summary of product characteristics: Effentora 100, 200, 400, 600 and 800 micrograms buccal tablets. eMC Available from: http://www.medicines.org.uk/EMC/medicine/21401/SPC/Effentora+100%2c+200%2c+400%2c+600+and+800+micrograms+buccal+tablets/

Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E (1997) Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. Clin J Pain 13(2):150–155

Child A, Clarke A, Fox C, Maidment I (2012) A pharmacy led program to review anti-psychotic prescribing for people with dementia. BMC Psychiatry 12:155

Committee on Safety of Medicine LD (2004) Atypical antipsychotic drugs and stroke. Web address:http://www.mhra.gov.uk/news/antipsystroke_9304.htm. Ref type: Internet Communication

Cornelius VR, Sauzet O, Evans SJ (2012) A signal detection method to detect adverse drug reactions using a parametric time-to-event model in simulated cohort data. Drug Saf 35(7):599–610

Council for International Organizations of Medical Sciences(CIOMS), World Health Organisation (WHO) (2002) International ethical guidelines for biomedical research involving human subjects. [online] Available at: http://www.cioms.ch/publications/layout_guide2002.pdf. Geneva

Davies M, Wilton L, Shakir S (2013) Safety profile of modafinil across a range of prescribing indications, including off-label use, in a primary care setting in England: results of a modified prescription-event monitoring study. Drug Saf 36(4):237–246

Dear Healthcare Professional (2004) The risk of cerebrovascular adverse events (CVAE) in elderly patients with dementia:- important changes to the summary of product characteristics relating to use of risperidone. Janssen-Cilag Ltd., High Wycombe

Department of Health (2014) NIHR Clinical Research Network Support. Available at: http://www.nihr.ac.uk/about/clinical-research-network.htm. Date Accessed: 17/11/2014

Doerry UA, Kent L (2003) Prescribing practices of community child and adolescent psychiatrists. Br J Psychiatry Bull 27:407–410

European Commission(2012) Question and answers on transitional arrangements concerning the entering into force of the new pharmacovigilance rules provided by directive 2010/84/EU amending directive 2001/83/EC and regulation (EU) no 1235/2010 amending regulation (EC) no 726/2004. Available from: http://ec.europa.eu/health/files/pharmacovigilance/2012-07_qa_transitional_en.pdf

European Medicines Agency (2002) Opinion of the committee for proprietary medicinal products opinion following an Article 31 referral sibutramine. Doc Ref: EMEA/CPMP/4514/02/Final Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sibutramine_31/WC500013923.pdf)

European Medicines Agency (2005) European pharmacovigilance working party, 2005. Antipsychotics and cerebrovascular accident. Available at: www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024914&RevisionSelectionMethod

European Medicines Agency (2008) The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia. Doc Ref: EMEA/CHMP/537777/208. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014774.pdf. Date accessed: 30/01/2015

European Medicines Agency (2010) Questions and answers on the suspension of medicines containing sibutramine Doc Ref: EMA/808179/2009rev Available at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sibutramine_107/WC500094238.pdf

European Medicines Agency (2011) Press release. European Medicines Agency recommends restricting the use of modafinil. Doc Ref: EMEA/459173/2010 Web address: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/07/WC500094976.pdf. Date accessed: 31/01/2015. The European Medicines Agency (EMEA)

European Medicines Agency (2012) Guideline on good pharmacovigilance practices (GVP) annex I – definitions EMA/876333/2011 (Rev 1)

European Medicines Agency (2013) Guideline on good pharmacovigilance practices (GVP) module VIII – post-authorisation safety studies (Rev 1). EMA/813938/2011

European Medicines Agency (2014) Guideline on good pharmacovigilance practices (GVP): module V – risk management systems (Rev 1)

European Network of Centres of Excellence for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) (2013) E-register of studies. An observational post-authorization modified prescription-event monitoring safety study to monitor the safety and utilization of asenapine (Sycrest) in the primary care setting in England. Ref type: Online Source

European Network of Centres of Excellence for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) (2014a) E-register of Studies. A Cohort study to monitor the safety and use of prolonged-release quetiapine. Ref type: Online Source

European Network of Centres of Excellence for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) (2014b) E-register of studies. An observational post-authorisation safety specialist cohort monitoring study (SCEM) to monitor the safety and utilisation of asenapine (Sycrest) in the mental health trust setting in England. Ref type: Online Source

Finney DJ (1965) The design and logic of a monitor of drug use. J Chronic Dis 18:77–98

General Medical Council (2009a) Confidentiality. Web address: http://www.gmc-uk.org/static/documents/content/Confidentiality_0910.pdf Date accessed: 08/07/2011

General Medical Council (2009b) Confidentiality: disclosing information for education and training purposes. http://www.gmc-uk.org/Confidentiality_disclosing_info_education_2009.pdf_27493403.pdf

General Medical Council (2015) Good practice in prescribing and managing medicines and devices. Web address: http://www.gmc-uk.org/Prescribing_guidance.pdf_59055247.pdf

Gilchrist A, Davies M, Layton D, Shakir SAW (2011) Abstract no: 773. Drug utilisation data for Seroquel XL – results of a first interim modified PEM study report abstract no: 773 27th international conference on pharmacoepidemiology & therapeutic risk management. 14th–17th Aug 2011 -Chicago

Greenland S (1995) Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 6(4):356–365

Guess HA (2006) Exposure-time-varying hazard function ratios in case-control studies of drug effects. Pharmacoepidemiol Drug Saf 15(2):81–92

Hodgson R, Belgamwar R (2006) Off-label prescribing by psychiatrists. Psychiatr Bull 30:55–57

Ilyas S, Moncrieff J (2012) Trends in prescriptions and costs of drugs for mental disorders in England, 1998–2010. Br J Psychiatry 200(5):393–398

IMS Health (2009) The use of medicines in dementia care. IMS, London

Inman W, Pearce G (1993) Prescriber profile and post-marketing surveillance. Lancet 342(8872):658–661

Layton D, Kimber A (2014) Abstract no: 802. Feasibility of adjusted parametric methods to model survival data as a tool for signal strengthening: an example in Modified Prescription-Event Monitoring (M-PEM). 2014 30th international conference on pharmacoepidemiology & therapeutic risk management (ISPE). 24th–27th Oct 2014 – Teipei. Pharmacoepidmiology Drug Safety (S1), pp 1–497

Layton D, Shakir SAW (2011) Prescription-event monitoring. In: Strom BL, Kimmel SE, Hennessy S (eds) Pharmacoepidemiology, 5th edn. Wiley, Chichester, pp 301–330

Layton D, Shakir SAW (2014) Prescription-event monitoring (PEM): the evolution to the new modified PEM and its support of risk management. In: Mann RD, Andrews EB (eds) Pharmacovigilance, 3rd edn. Wiley Blackwell, Chichester, pp 359–384

Layton D, Shakir SA (2015) Specialist cohort event monitoring studies: a new study method for risk management in pharmacovigilance. Drug Saf 38(2):153–163

Layton D, Harris S, Wilton LV, Shakir SA (2005) Comparison of incidence rates of cerebrovascular accidents and transient ischaemic attacks in observational cohort studies of patients prescribed risperidone, quetiapine or olanzapine in general practice in England including patients with dementia. J Psychopharmacol 19(5):473–482

Lenz W, Pfeiffer R, Kosenow W, Hayman D (1962) Thalidomide and congenital abnormalities. Lancet 279(7219):45–46

Machin D, Campbell M, Fayers P et al (1997a) Sample size tables for clinical studies. Table 7.1. Blackwell Science Ltd, Oxford

Machin D, Campbell M, Fayers P et al (1997b) Sample size tables for clinical studies. Table 7.2. Blackwell Science Ltd, Oxford

Mackay FR, Dunn NR, Martin RM, Pearce GL, Freemantle SN, Mann RD (1999) Newer antidepressants: a comparison of tolerability in general practice. Br J Gen Pract 49(448):892–896

Maggioni AP (2009) SCOUT trial reports on the safety profile of sibutramine in patients with cardiovascular diseases. Phys Sportsmed 37(3):95–97

Measures of occurrence of disease and other health-related events (1999) In: dos Santos Silva I (ed) Cancer epidemiology: principles and methods. Lyon: International Agency for Research on Cancer Press, pp 57–82

Medicines and Healthcare products Regulatory Agency (2008) Varenicline: suicidal thoughts and behaviour. Drug Safety Update 1(12):2–3

National Health Service, The Information Centre (2009) Adult psychiatric morbidity in England, 2007. Results of a householde survey Available at: http://www.hscic.gov.uk/catalogue/PUB02931/adul-psyc-morb-res-hou-sur-eng-2007-rep.pdf. Date accessed: 31/01/2015

National Institute of Clinical Excellence (2009) Clinical guideline 90: depression in adults: the treatment and management of depression in adults. Department of Health, London

Office for National Statistics (2010) Patterns of specialist mental health service usage in England. Available at: http://www.neighbourhood.statistics.gov.uk/HTMLDocs/images/Mental-Health-Service-usage-small-analysis1_tcm97-97434.pdf. Date accessed 31/01/2015

Osborne V, Layton D, Fogg C, Al-Shukri M, Shakir SA (2014) Utilization of fentanyl buccal tablets in England: exploring off-label use reported in a cohort study. Eur J Pain 18(4):506–512

Oxford Health NHS Foundation Trust (2013) Prescribing antipsychotic medications for the treatment of behavioural symptoms in people with dementia, Milton Keynes 2012. NICE, London

Perrio MJ, Wilton LV, Shakir SA (2007) The safety profiles of orlistat and sibutramine: results of prescription-event monitoring studies in England. Obesity (Silver Spring) 15(11):2712–2722

Posner K, Oquendo MA, Gould M, Stanley B, Davies M (2007) Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 164(7):1035–1043

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA et al (2011) The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 168(12):1266–1277

Prescribing Observatory For Mental Health (POMH – UK) (2015) The antipsychotic dosage 'Ready Reckoner'. Royal College of Psychiatrists. Ref type: Online Source

Ray WA (2003) Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 158(9):915–920

Rogers EM (2004) A prospective and retrospective look at the diffusion model. J Health Commun 9(S 1):13–19

Royal College of Psychiatrists (2006) Council Report CR138. Concensus statement on high-dose antipsychotic medictaion. London, Royal College of Psychiatrists. Ref type: Pamphlet

Singh S, Loke YK (2012) Drug safety assessment in clinical trials: methodological challenges and opportunities. Trials 13:138

Health and Social Care Information Centre (2013) Mental health bulletin: annual report from MHMDS returns – England 2011–12, initial national figures

Willemen MJ, Mantel-Teeuwisse AK, Buggy Y, Layton D, Straus SM, Leufkens HG et al (2012) Reasons for and time to discontinuation of rimonabant therapy: a modified prescription-event monitoring study. Drug Saf 35(12):1147–1158

Wilton LV, Heeley EL, Pickering RM, Shakir SA (2001) Comparative study of mortality rates and cardiac dysrhythmias in post-marketing surveillance studies of sertindole and two other atypical antipsychotic drugs, risperidone and olanzapine. J Psychopharmacol 15(2):120–126

World Health Organisation (WHO) (2015) Collaborating centre for drug statistics methodology. ATC/DDD Index 2015. Ref type: Online Source

Xie J, Brayne C, Matthews FE (2008) Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up. BMJ 336(7638):258–262

Chapter 5
The Role of Healthcare Databases in Pharmacovigilance of Psychotropic Drugs

Gianluca Trifirò and Janet Sultana

Abstract Recent years have seen a rapidly growing number of healthcare databases that have been used worldwide for post-marketing assessment of use and safety of medicines including psychotropic drugs, as the result of the conversion of healthcare data storage systems from paper-based to electronic formats. Currently used databases include general practitioners' electronic medical records as well as administrative/claims healthcare databases which are, respectively, used for registering clinically relevant information of patients during routine care and for documentation of healthcare services provided to citizens for reimbursement reasons. In both cases data are collected irrespective of any research purpose. Nevertheless, secondary use of these data sources allowed the evaluation of prescribing pattern of and safety outcomes associated with a number of medicines widely used in psychiatry routine care such as antidepressants, antipsychotics (especially when used in older people with dementia), benzodiazepines, cholinesterase inhibitors, and others. In these databases, the collection of many clinical details for large populations and long follow-up period offers the opportunity to investigate even rare adverse events potentially associated to psychotropic drugs. On the other hand, observational database studies have inherent limitations including confounding by indication, protopathic bias, outcome, and exposure misclassification which need to be taken into account and addressed in the study design and analysis. In this chapter, examples of observational studies investigating the use and safety of drugs commonly used in psychiatry and limitations and solutions adopted in these studies are provided and discussed.

Keywords Healthcare databases • Observational studies • Drug utilization research • Drug safety studies • Healthcare interventions • Pharmacovigilance • Psychotropic drugs

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5.1 Introduction

Recent years have seen a rapidly growing number of observational studies that explored emerging safety issues associated with psychotropic drugs through the use of electronic healthcare databases. The increase in the utilization of healthcare databases worldwide is due to the conversion of healthcare data storage systems from paper-based to electronic formats as well to improved skills in automatic patient-level data extraction and elaboration. Administrative healthcare data such as data registered for health insurance purposes that may have been underused in the past is now often collected with great attention and subjected to scrutiny in the form of audits.

The type of information recorded in a healthcare database depends on the reason for which the database was set up. For example, data recorded in general practice databases during daily routine care is more likely to contain details of medical history, including information that is not associated with the use of healthcare resources, such as lifestyle information (e.g., cigarette smoking, alcohol use, medical diagnoses that do not require pharmacotherapy, medical procedures or hospitalization, etc.). In contrast, this type of data is unlikely to be registered in health insurance/claims databases, which are instead more likely to have accurately registered codes related to healthcare resource utilization (e.g., emergency department visit, hospital discharge diagnoses, outpatient diagnostic tests), as this is required for billing purposes. Using a (generally anonymized) unique patient identifier, several claims databases can be linked together and even general practice databases can be linked to claims databases as well as disease registries and surveys capturing information of the same catchment area while not violating any country-specific data privacy issues, thus enormously enlarging the potential of these sources for pharmacoepidemiology research.

5.2 Healthcare Databases

5.2.1 General Practice Databases

General practice (GP) databases have been extensively used in pharmacoepidemiological research. Examples of GP and other databases commonly used for pharmacoepidemiology studies are found in Table 5.1. GP databases are composed of electronic patient data (i.e., electronic medical records) registered during routine care; the purpose of such records is primarily related to healthcare (e.g., recording of patient medical and drug history for healthcare practitioner's perusal). In general, GP databases contain an extensive amount of information such as medical diagnosis, drug prescription data, and laboratory data. Data on smoking and socioeconomic status and obesity are not systematically recorded, even though in several countries educational interventions have been promoted to increase GP awareness

Table 5.1 Examples of commonly used general practice and family pediatrician databases used for safety studies of psychotropic drugs

	CPRD	THIN	IPCI	BIFAP	HSD	Arianna	Pedianet
Country/region	UK	UK	The Netherlands	Spain	Italy	Italy	Italy
Population	General population, including adults and children					Pediatric and adult population	Pediatric population
Disease codes used	ICD-10 CM and READ codes	READ codes	ICPC codes	ICD-10 codes	ICD-9 CM codes	ICD-9 CM codes	ICD-9 CM codes
Drug codes used	BNF/Multilex codes	BNF/Multilex codes	ATC codes	ATC codes	ATC codes	ATC codes	ATC codes

Abbreviations: ATC anatomic and therapeutic classification, *BIFAP Base de datos Informatizada para estudios Farmacoepidemiologicós en Atención Primaria* database, *BNF* British National Formulary, *CPRD* Clinical Practice Research Datalink database, *HSD* Health Search Database, *ICD-10 CM* 10th International Classification of Disease codes, clinical modification, *ICD-9 CM* 9th International Classification of Disease codes, Clinical Modification, *ICPC* International Classification for Primary Care, *IPCI* Integrated Primary Care Information database, *THIN* The Health Improvement Network database, *UK* United Kingdom

about benefits related to the registration of information on lifestyle of patients affected by specific chronic diseases (e.g., body mass index and cigarette smoking in patients with chronic obstructive pulmonary disease or history of myocardial infarction). GP databases used in pharmacoepidemiology research are often nationwide and representative of the geographical area where they are based and, although they are expensive to be initially set up, they are often cost-effective when used for research purposes. This is especially true for retrospective studies where the expenses related to data collection are significantly curtailed.

Electronic medical records from general practitioners are a relatively recent development, mainly due to the increasing computerization of health records in general practice, which is gradually replacing paper medical charts. These databases have several advantages, the most apparent of which is their large size: populations sampled from those databases can be in the order of millions, as with CPRD and THIN. This advantage is of particular importance in drug safety studies where the incidence of adverse drug effects or drug use (or both) can be very low. Patient data (e.g., on diagnosis, drug prescription, etc.) are generally recorded through structured and coded information. Nevertheless, the additional availability of unstructured free-text clinical notes, as in the Dutch GP database "IPCI," holds potential for manually validating and better characterizing clinical outcomes.

5.2.2 Administrative/Claims Databases

Data in claims/administrative databases are recorded when a patient uses healthcare resources that are provided free of charge to citizens as they are reimbursed by National Health Service (NHS) or when a commercial (e.g., Kaiser Permanente in various North American states) or national social insurance provider (e.g., Medicare in the USA) must be billed for the resources provided. The use and availability of these databases depend on the healthcare system used in each country. The availability of commercial insurance databases is more prominent in countries where healthcare is not provided publicly free of charge and persons must be insured/registered with a health plan to access healthcare resources. Administrative databases generally include pharmacy dispensing and hospital discharge diagnoses which can be linked through patient unique identifier to several other administrative databases (e.g., emergency department visits, outpatient diagnostic test, etc.). Pharmacy claims contain data collected when a patient is dispensed a drug from a pharmacy and its cost is covered by insurance/NHS. The advantage of this data source as opposed to prescription data from a GP database is that, while the latter records only the prescription of a drug, the former can at least ensure that prescribed drug has been dispensed. Neither of the database types can however ensure that a drug is ultimately taken, thus potentially leading to exposure misclassification in case of drug therapies with low adherence. Likewise pharmacy databases, hospital discharge diagnosis databases are built for claims/administrative purposes: healthcare resources related to the management of hospitalized medical event and eventually medical procedures undergone during hospital admission are recorded in order

to allow reimbursement by the insurance provider or National Healthcare Service. However, because the billing depends on the type of information that is registered as primary and secondary causes of hospital admission as well as hospital procedures, it is possible that diagnoses in administrative and claims data are recorded less accurately/rigorously than for medical record databases not used for billing purposes. An example of a hospital claims/administrative database is the Pediatric Health Information System (PHIS), which contains administrative data for over six million patients from 44 children's hospitals in the USA.

5.3 Observational Studies Concerning Psychotropic Drugs Using Healthcare Databases

Observational drug-related studies in psychiatry conducted using healthcare databases can be divided into two major types: drug utilization (e.g., exploring changes in prevalence and incidence of drug use over time and across different settings, adherence or persistence to drug use and drug switching patterns, etc.) and drug safety studies (risk of adverse outcomes associated with the use of a specific drug). Drug utilization studies are descriptive studies that can be conducted by analyzing an exposure of interest in the underlying general population or selected cohort of patients identified from a database. In the context of pharmacovigilance activities using healthcare databases, it is possible to evaluate the implementation and impact of public health interventions such as drug safety warnings issued by drug agencies and other risk minimization measures (RMMs) rapidly and cost-effectively. This kind of investigation is aimed at exploring any change, if at all, in the drug prescribing pattern occurred as a result of a drug-related public health intervention (i.e., implementation of RMMs) and measuring if the risk of an adverse outcome associated to specific drug treatment was actually minimized after the implementation of the RMM in routine care (Fig. 5.1). This assessment is essential to ensure that the RMMs led to the achievement of expected results in terms of drug-related risk prevention/dilution.

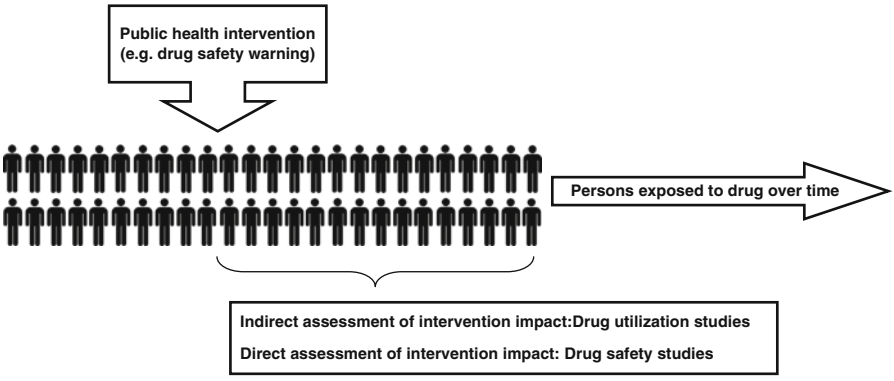

Fig. 5.1 The role of healthcare databases in the assessment of public health interventions

Drug safety studies can be conducted using analytical methods that can estimate the risk of an outcome following exposure to a drug. Nowadays, the assessment of specific associations of drugs and adverse events is mostly carried out using well-established study designs such as propensity score-matched new user cohorts or case-control designs, nested in a cohort of new users of the drugs under study. More recently, advance statistical techniques have been applied to data from healthcare databases also for post-marketing assessment and comparison of benefits of psychotropic drugs in the context of comparative effectiveness research.

5.3.1 Drug Utilization Studies

Healthcare databases have been widely used to analyze the prescribing pattern of psychotropic drugs in clinical practice, mainly antidepressants, antipsychotics, and benzodiazepines. Drug utilization studies have been carried out in the general population as well as in "special" subsets of population such as elderly or pediatric patients and pregnant women. Data on the prevalence/incidence of drug treatment, adherence, and persistence to drug therapy provides an indication of quality of care.

An example of how the drug prevalence proves useful can be seen in antidepressant utilization studies, which are commonly carried out at regional (Poluzzi et al. 2013; Parabiaghi et al. 2011), national (Sultana et al. 2014b; Chollet et al. 2013; Lam et al. 2013), or multinational (Abbing-Karahagopian et al. 2014) level. Such studies can give an indication of appropriate drug prescribing by confirming whether first-line agents are indeed most commonly used and if the drugs are used in agreement with international treatment guidelines and Summary of Products Characteristics. If the electronic data source also has the indication of use included in the prescription data, researchers can further investigate whether drug prescribing is prescribed appropriately or off-label. Another example of the usefulness of prevalence and incidence data concerns the assessment of the distribution of prescription of generic or branded drugs for drugs that are off- patent. Several clinical guidelines suggest that generic antidepressants, selective serotonin reuptake inhibitors in particular, should be prescribed as first-line agents to reduce the use of healthcare resources and promote sustainability of national healthcare systems. An example of a basic evaluation of prescribing appropriateness would be to compare the prevalence of generic and brand antidepressant drug use using pharmacy data (Ubeda et al. 2007). Such investigations have been put to use by national drug observatories to find out the extent of generic antidepressant penetration. A more complex investigation of generic antidepressant drug use might involve a comparison of selected outcomes that reflect drug safety such as mortality and other health resource consumption (hospitalizations, specialist examinations, other drugs) between generic and brand antidepressant users (Colombo et al. 2013).

Information on adherence/persistence complements prevalence data. A detailed analysis of antidepressant use consistently shows that adherence levels are usually low (Hansen et al. 2004). In fact, most of the drug utilization database studies on antidepressants found that these drugs are frequently withdrawn as early as 3 months

after the therapy starts in a large proportion of depressed patients even though guidelines suggest at least 1 year treatment (Poluzzi et al. 2013; Parabiaghi et al. 2011; Sultana et al. 2014b; Chollet et al. 2013). Analysis of persistence to drug treatment can be useful as it may indirectly imply tolerability or lack of efficacy: in the absence of economic reasons, a drug which is switched more often than others may be less effective and/or less tolerable than other drugs. For example, a US-based study using claims data found that patients prescribed with escitalopram were more likely to persist with their antidepressant treatment and less likely to switch to other antidepressants, compared to other SSRI users (Esposito et al. 2009).

Another class of drugs that has been the subject of many drug utilization studies is that of antipsychotics. This is particularly important given the diverse pharmacological and safety profile of antipsychotic drugs as well as their several indications of use apart from schizophrenia and mania, which currently include motor tics, nausea, and vomiting in palliative care and intractable hiccups for haloperidol and persistent aggression in pediatric conduct disorders and persistent aggression in Alzheimer's disease for risperidone. Drug utilization studies highlighted the increasing use of second-generation or atypical antipsychotics in the general population, particularly in elderly persons (Trifirò et al. 2005, 2010a). Studies investigating antipsychotic adherence were also pivotal, suggesting that nonadherence is a significant problem in schizophrenia and is associated with negative outcomes such as hospitalization (Tiihonen et al. 2006; Ascher-Svanum et al. 2006; Gilmer et al. 2004). Some examples of psychotropic drug utilization database studies are reported in Table 5.2.

5.3.2 Evaluation the Impact of Drug-Related Risk Minimization Measures in Psychiatry

Understanding prescriber behavior is important particularly from a public health perspective. Knowledge of drug safety is constantly expanding and clinical guidelines are continuously evolving in response to this. Sometimes rapid changes in prescriber behavior are critical, as when prescribers are expected to respond promptly to drug safety warnings. For example, studies of prescriber behavior are necessary to see whether citalopram-related drug safety warnings on the risk of cardiac arrhythmia resulted in a change of citalopram prescribing among persons at higher risk of such adverse effects. Similarly, healthcare databases have also been used to investigate changes in prescribing pattern after the antipsychotic-related safety warnings in older people with dementia. In short, Health Canada, the European Medicines Agency, the Food and Drug Administration, and other national drug agencies issued several warnings from 2002 onward on the risk of adverse events such as all-cause mortality and stroke when antipsychotics are used mostly off-label in elderly persons with dementia, highlighting their unfavorable risk-benefit ratio. A summary of studies investigating changes in antipsychotic prescribing pattern among elderly dementia patients is shown in Table 5.3. Such investigations can be said to be indirect evaluations of drug-related public health interventions, because the primary aim of such interventions is not the reduction of drug

Table 5.2 Examples of psychotropic drug utilization studies carried out using healthcare databases

Author (year)	Setting	Population	Exposure	Outcomes
Marston et al. (2014)	THIN database	General population	APs	APs prescribing rate in primary care
Petersen et al. (2014)	THIN database	Pregnant women	APs	Discontinuation of APs in pregnancy
Wijlaars et al. (2012)	THIN database	Children and adolescents	ADs	Trends in depression and antidepressant prescribing in children and adolescents
Man et al. (2012)	THIN database	Pregnant women	AED	Prevalence of AED use in pregnancy
Hayes et al. (2011)	THIN database	General population	Psychotropic drugs used in bipolar disorder	Prescribing trends of drugs used in bipolar disorder
Prah et al. (2011)	THIN database	General population	APs	Prescribing trends of APs for schizophrenia
Petersen et al. (2011)	THIN database	Pregnant women	ADs	AD discontinuation
Aguglia et al. (2012)	HSD	General population	SSRI and SNRI	SSRI/SNRI prescribing pattern
Parabiaghi et al. (2011)	HSD	Elderly population	ADs	AD utilization among elderly in Lombardy
Trifirò et al. (2010a)	HSD	Elderly persons with dementia	APs	AP prescribing pattern
Savica et al. (2007)	HSD	General population	AEDs	AED prescribing pattern
Trifirò et al. (2005)	HSD	General population	AP	AP prescribing pattern
Koopman et al. (2010)	IPCI	General population	Drugs used to treat neuropathic pain	Pharmacological treatment of neuropathic facial pain
Kraut et al. (2013)	GePaRD	Pediatric population	Methylphenidate	Comorbidities in ADHD children treated with methylphenidate
Lindemann et al. (2012)	GePaRD	Children and adolescents	ADHD drugs	Age-specific prevalence, incidence of new diagnoses, and drug treatment of attention-deficit/hyperactivity disorder
Jacobsen et al. (2014)	Aarhus University Prescription Database	Pediatric population	AEDs	Prenatal exposure to antiepileptic drugs

Table 5.2 (continued)

Author (year)	Setting	Population	Exposure	Outcomes
Laugesen et al. (2013)	Aarhus University Prescription Database	Female general population	SSRIs	Use of SSRIs and lifestyle among women of childbearing age
Hsia et al. (2010)	PEDIANET, IPCI, and IMS disease analyzer	Pediatric population	AEDs	AED prescribing among children

AD antidepressant, *ADHD* attention-deficit/hyperactivity disorder, *AED* antiepileptic drug, *AP* antipsychotic, *GeParD* German Pharmacoepidemiological Research Database, *HSD* Health Search Database, *IPCI* Integrated Primary Care Information database, *SNRI* serotonin-norepinephrine reuptake inhibitors, *SSRI* selective serotonin reuptake inhibitor, *THIN* The Health Improvement Network

prescribing per se but a reduction in the drug-related risk as a consequence of a more cautious use of the drug (Fig. 5.1). Healthcare databases can also be used to carry out a direct evaluation of a safety warning impact by measuring the occurrence of a known adverse drug reaction before and after a warning.

More recently, healthcare databases have been increasingly used to carry out postauthorization safety studies (PASS) also concerning psychotropic drugs. A PASS is a scientific investigation of the safety profile of a drug that has already been marketed with the aim of identifying and describing the safety profile of that drug, as indicated in the risk management plan (RMP) supporting the premarketing documentation. In this case, healthcare databases can be used to estimate the frequency of known ADRs within a given exposed population or to identify predictors of drug-related risks, thus identifying categories of patients at high risk of developing ADRs; on the other hand, it is unlikely for healthcare databases to have a major role in de novo signal detection (hypothesis generation) in the immediate future, despite the several international initiatives that have been carried out to better explore this issue in the last years (Trifirò et al. 2014a). A PASS can also be carried out with the aim of measuring whether any risk minimization measures implemented as part of a RMP were effective or otherwise. Among other things, RMPs also cover planning for how drug-related risks can be prevented or minimized as well as plans for studies aimed at increasing awareness on drug safety; healthcare databases have a pivotal role in both these aspects.

5.3.3 Drug Safety Studies

The safety profile of therapeutic drugs including psychotropic drugs is initially investigated in randomized clinical trials (RCTs) in the premarketing phase. However, drug safety data from RCTs is fraught with limitations such as small and

Table 5.3 Overview of database studies evaluating the impact of antipsychotic drug safety warnings on the pattern of use of these drugs in routine care

Author (year)	Setting	Population	Exposure	Outcomes
Gallini et al. (2014)	EGB database (France)	Elderly patients with and without dementia	All APs, APs by class and olanzapine and risperidone individually	Monthly prevalence of AP use
Schulze et al. (2013)	GEK database (Germany)	Elderly dementia patients	All APs and APs by class	Yearly prevalence of AP use, number of AP packages, and DDD per person per year
Guthrie et al. (2013)	PCCIU database (Scotland)	Elderly dementia patients	All APs and risperidone, olanzapine, quetiapine individually	Quarterly prevalence of oral AP prescribing, initiation, and discontinuation; prescription of hypnotics, anxiolytics, or antidepressants
Franchi et al. (2012)	Lombardy Region Drug Administrative Database (Italy)	Elderly dementia patients treated with AChEIs	All APs, APs by class and olanzapine, quetiapine, haloperidol, clotiapine, and risperidone individually	Number of AP prescriptions per person and gap between AP prescriptions; yearly prevalence of AP use, probability of continuing antipsychotic treatment
Dorsey et al. (2010)	IMS Health's National Disease and Therapeutic Index (USA)	Elderly dementia patients	All APs and APs by class	Monthly prevalence of AP use, monthly change in AP drug use, and annual growth rate of AP use
Sanfélix-Gimeno et al. (2009)	Valencia Health Agency pharmacy claims database (Spain)	Elderly patients and younger adults	Risperidone and olanzapine use (stratified by strength)	Monthly prevalence of AP use
Valiyeva et al. (2008)	Ontario Drug Benefit database (Canada)	Elderly dementia patients	All APs, APs by class and olanzapine, quetiapine, and risperidone individually	Monthly prevalence of AP use; change in the number of patients prescribed an AP and ratio of change of prescription rate after the safety warnings

AChEI acetylcholinesterase inhibitor, *AIFA Agenzia Italiana del Farmaco* (Italian Drug Agency), *AP* antipsychotic, *EGB Échantillon Généraliste de Bénéficiaires*, *EMA* European Medicines Agency, *DDD* defined daily dose, *FDA* Food and Drug Administration, *GEK Gmünder Ersatzkasse*, a German nationwide health insurance company database, *HSD-CSD LPD* Health Search Database – Cegedim Strategic Data, Longitudinal Patient Database, *MHRA* Medicines and Healthcare Products Regulatory Agency, *PCCIU* Primary Care Clinical Informatics Unit

highly selective study populations as well as limited duration of the observation period which preclude the possibility of identifying potentially severe adverse drug reactions with long-term onset or which are more likely to occur when used in patients affected by several comorbidities or receiving concomitant medications at interaction risk (Sultana et al. 2013). In fact RCT populations may be healthier than patients in real clinical practice and less likely to be prescribed a multidrug regimen as RCTs in the drug development phase tend to exclude the frailest patient categories such as very old patients who are generally affected by multiple comorbidities. Since the number of patients enrolled in a RCT is small compared to the number of patients that will be exposed to a drug in clinical practice, RCTs are unlikely to detect even life-threatening ADRs which occur rarely. These limitations can be addressed by observational studies, including those making use of databases, since such studies typically include data from long follow-up of large populations that are representative of real clinical settings, i.e., patients of all ages (pediatric and/or geriatric populations) and those at higher risk of an adverse drug reaction (the oldest old, patients with several comorbidities, and those with on a multidrug regimen).

The use of healthcare databases to monitor drug safety can be illustrated using the association of antipsychotic drug use in dementia patients and the risk of all-cause mortality as an example (Table 5.4). The employed study designs for studying this association were either cohort or (nested) case-control and were conducted with various types of healthcare databases, including government administrative, general practice, and health insurance databases. The setting of each study might limit its generalizability and should be considered in the interpretation of study findings. For example, veterans' affairs database populations are mostly white males and may not be generalizable to the general population and government claims databases covering Medicaid beneficiaries, who as persons having a lower socioeconomic status compared to non-Medicaid beneficiaries, might not be generalizable to the general US population.

Safety studies can be used to investigate various outcomes other than mortality. In keeping with the previous example of antipsychotic use in dementia, risk of adverse reactions such as cerebrovascular events, pneumonia, and venous thromboembolism has been investigated with AP use in elderly persons with/without dementia using healthcare databases (Trifirò et al. 2014b). Such studies were particularly useful from a clinical perspective as they explored the differential risk associated with individual antipsychotics, building on previous findings suggesting class-specific findings, such as that conventional antipsychotics are more likely to be associated specific outcomes (e.g., bacterial infections, myocardial infarction, and hip fractures) but less likely to be associated with cerebrovascular events compared with atypical antipsychotics when used in elderly dementia patients (Huybrechts et al. 2012a). For example, emerging evidence suggests that quetiapine appears to have a lower risk of all-cause mortality compared to risperidone, while haloperidol has much higher risk all-cause mortality than risperidone (Huybrechts et al. 2012b).

Table 5.4 Examples of safety studies on antipsychotic drugs carried out using healthcare databases

Author (year)	Study design	Setting	Population	Outcome	Exposure
Wang et al. (2005)	Retrospective cohort study	Pennsylvania Medicare	Patients ≥65 (N=22,890)	All-cause mortality	CAPs vs. AAPs
Trifirò et al. (2007)	Nested case-control study	Dutch general practice database (IPCI)	Dementia patients ≥65 (N=2,385)	All-cause mortality	Current use of AAP or CAP (nonuse of respective class as comparator unless otherwise specified)
Gill et al. (2007)	Retrospective cohort study	Four administrative databases in Ontario: Ontario Drug Benefit program Canadian Institute for Health Information Discharge Abstract Database Ontario Health Insurance Plan Registered Persons Database	Dementia patients ≥66 (N=27,259)	All-cause mortality at 30, 60, 120, and 180 days after the initial dispensing of antipsychotic medication	Incident use of AAPs (nonuse as comparator) and CAPs (AAP as comparator) stratified in CD LTC cohorts
Schneeweiss et al. (2007)	Retrospective cohort study	Linked administrative data from the British Columbia Ministry of Health, PharmaNet database British Columbia	Patients ≥65 year old with an AP prescription (N=37,241)	180-day all-cause mortality	Incident use of AAPs and CAPs (risperidone as comparator)
Kales et al. (2007)	Retrospective cohort study	US Department of Veteran Affairs registries	Dementia patients ≥65 year old with an AP prescription (N=10,615)	1-year all-cause mortality from National Death Index	Incident use of AAPs, CAPs, and combination of both types (CAP as comparator)

Hollis et al. (2007a)	Retrospective cohort study	Australian Department of Veteran Affairs claims-based pharmaceutical database	Veterans and war widows ≥65 (N=16,634)	All-cause mortality	Incident use of antipsychotics, carbamazepine and valproate (incident use of olanzapine as comparator)
Hollis et al. (2007b)	Cohort study	Department of Veterans' Affairs database and Medicare Australia	Incident users of APs	All-cause mortality	CAPs (chlorpromazine, haloperidol, pericyazine, trifluoperazine) AAPs (quetiapine, olanzapine, risperidone) (olanzapine as comparator)
Aparasu et al. (2012)	Retrospective cohort design matched on propensity score	Medicare and Medicaid data from Texas, Florida, New York, and California	Nursing home residents ≥65 years (N=7,218)	All-cause mortality	AAPs vs. CAPs (AAP as comparator)
Kales et al. (2012)	Retrospective cohort study	US Department of Veteran Affairs database	Dementia patients ≥65 years old (N=1,932)	180-day mortality	Risperidone, haloperidol, olanzapine, quetiapine (risperidone as comparator)
Huybrechts et al. (2012a)	Cohort study	Linked data from Medicaid, Medicare, the Minimum Data Set, the National Death Index, and a national assessment of nursing home quality	Nursing home patients ≥65 (N=75,445)	All-cause mortality (excluding cancer mortality) and cause-specific mortality	Incident use of haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone (risperidone as comparator)

(continued)

Table 5.4 (continued)

Author (year)	Study design	Setting	Population	Outcome	Exposure
Rafaniello et al. (2014)	Prospective cohort study	Dementia Evaluation Unit of Campania	Dementia patients with BPSD C65 years who were incident antipsychotic users (N=1,618)	All-cause mortality	Rate per 100 PY:
					Quetiapine: 5.8 (4.4–7.7)
					Risperidone: 7.3 (4.8–11.1)
					Olanzapine: 4.6 (2.5–8.3)
					Clozapine: 7.7 (1.9–30.9)
					Aripiprazole: 17.6 (2.5–125.0)
Sultana et al. (2014a)	Retrospective cohort study	South London and Maudsley NHS Foundation Trust (SLaM), Biomedical Research Centre database, Clinical Record Interactive Search (CRIS)	Vascular dementia patients (N=1,531)	All-cause mortality	AAPs (nonuse as comparator)

AAPs atypical antipsychotics, *Adj* adjusted, *AP* antipsychotic, *BSPD* behavioral and psychological symptoms of dementia, *CAPs* conventional antipsychotics, *CD* community dwelling, *HR* hazard ratio, *LTC* long-term care, *NHS* National Health Service, *OR* odds ratio, *RR* relative risk, *PY* person-years

5.3.4 Limitations of Healthcare Databases for the Conduct of Observational Studies Concerning Psychotropic Drugs

Studying the relationship between psychotropic drug use and new onset of adverse effects in electronic health record databases is extremely challenging due to a variety of potential biases and confounders (Brookhart et al. 2010). In all observational studies, various types of bias, e.g., selection bias, protopathic bias, information bias due to outcome and exposure misclassification and confounding by indication, may influence the study findings. The potential for selection bias in database safety studies is minimal as all data are obtained from prospectively collected medical records/claims that are maintained for patient care purposes or administrative/reimbursement reasons on a population-based level and independent of the patients' health status. All the other biases represent a real concern for this type of studies as discussed more into detail below.

5.3.4.1 Outcome Misclassification

Outcome misclassification may present more of a problem in claims healthcare data compared to general practice data registered for non-claims purposes, since the former may be less likely to register diagnosis codes accurately if this is not relevant to claims, compared to the latter. On the other hand, GP databases are less likely to register clinical outcomes which lead directly to emergency department visit/hospital admission or death.

All healthcare databases may be prone to the misclassification of disease for which symptoms may be missed. An example of this is the registration of transient ischemic attack (TIA) when assessing the risk of cerebrovascular accidents (CVAs) in association to the use of antipsychotics in older people with dementia. TIA may be the trigger of stroke but potentially misdiagnosed by clinicians (thus not properly registered in any type of healthcare databases), especially in patients suffering already cerebrovascular disorders such as dementia patients.

In general, in drug safety database studies, it is necessary to identify outcomes by using coding algorithms that have been previously validated in the same or a similar database or to manually validate outcome through revision of medical charts (in claims databases) or electronic medical records (in GP database) including unstructured free-text information. It may be helpful also to conduct sensitivity analyses while using different outcome definitions having different level of accuracy with the aim of exploring the possible effect and magnitude of bias due to outcome misclassification. This approach has been frequently used in most of observational database studies which explore the risk of CVAs, myocardial infarction, pneumonia, and others in association to several psychotropic drugs such as antidepressant and antipsychotics (Pariente et al. 2012; Trifirò et al. 2010b, c).

5.3.4.2 Exposure Misclassification

Prescription data in healthcare databases is free of recall bias as information on exposure is systematically registered for all drugs reimbursed by NHS, as it is the case for most of psychotropic drugs (except for benzodiazepines in several countries such as Italy where these drugs are directly charged to the citizens and thus not traceable with healthcare databases). General practice databases may have greater risk of exposure misclassification since, even if the prescribed drugs are registered correctly within the database, they may not necessarily be filled by patients. For this reason, pharmacy dispensing data is perhaps less likely to be associated with such exposure misclassification, even though exposure assessment is based on the assumption that patients take their medication as prescribed, once dispensed. A patient might prolong the duration of a prescription by tablet splitting but based on the prescription would be classified as exposed. Misclassification may also occur if patients discontinue a drug before their drug supply is finished. Drugs taken intermittently on an as-needed basis are at risk of being misclassified, as may be the case for antipsychotics or drugs for insomnia or benzodiazepines as drops formulation. Another issue concerns over-the-counter or privately purchased medicines which would not be captured by healthcare databases; however, this is not a significant issue for psychotropic drugs which are prescription drugs. Claims healthcare data may lead to exposure misclassification as far as prescriptions for drugs that are not covered by an insurance are not available, for example, if a patient pays for a medication himself without requesting reimbursement (Schneeweiss and Avorn 2005).

As for outcome misclassification, in database safety studies on psychotropic drugs, sensitivity analyses changing the criteria for exposure status measurement should be carried out to investigate the possible role and magnitude of the effect of bias on the risk estimates.

5.3.4.3 Confounding by Indication

In routine care the decision to prescribe a specific drug for the treatment of a certain indication in individual patients is based on several factors such as demographic characteristics of the patients, presence of concomitant medications and comorbidities, overall patients' health status, severity of the disease/symptom that is intended to be treated, as well as patients' and physicians' preference and, in some situations, affordability of the drug therapy by the patient if the purchase of the medicine is charged directly to the patient, and so on. As a result, it is possible that patients prescribed a given drug for a certain indication of use differ substantially from the patients treated with other drugs or not treated at all in terms of baseline risk of the studied safety outcome, which may lead to the so-called confounding by indication.

Confounding by indication is a commonly used term that refers to an extraneous determinant of the outcome parameter that is present if a perceived high risk or poor prognosis is an indication for intervention. The indication is a confounder of the

drug-adverse event association because it correlates with the intervention and is a risk indicator for the illness (Salas et al. 1999). Confounding by indication is likely in safety studies concerning the association of commonly investigated safety outcomes and psychotropic drugs, since the choice of psychotropic drug is often associated with the prognosis or condition of a patient, which in itself can be a risk factor for studies outcomes (e.g., stroke, pneumonia, all-cause mortality, etc.). As an example, older people with dementia requiring antipsychotic prescriptions for the treatment of behavioral and psychotic disturbances of dementia (BPSD) have an increased risk of dying as compared to those who do not require such a treatment as the occurrence of BPSD in dementia patients is per se a strong risk factor of death (Tschanz et al. 2004). It is essential to keep this in mind when selecting the comparator in the assessment of association of any outcome and specific drug use in observational database studies.

In observational studies using healthcare databases, this confounding may bias the drug-adverse event risk estimate and particular attention should be paid in the design (i.e., selection of proper comparator, nesting a case-control study in a new user cohort) as well as the analytical phase, i.e., carrying out sensitivity analyses changing comparator to explore possible effect and magnitude of the bias effect on the risk estimate due to confounding by indication.

5.3.4.4 Protopathic Bias

Protopathic bias occurs when a drug is used to treat prodromic symptoms of the study outcome; as a result, it may mistakenly appear that the drug is causing the occurrence of the outcome under investigation (Horwitz and Feinstein 1980). For example, SSRIs are frequently prescribed for the treatment of late life depression, which may represent a manifestation of subtle cerebrovascular disorders leading to stroke in the elderly (Krishnan 2000). Similarly, severe pneumonia may induce delirium and trigger subsequent antipsychotic drug use in elderly patients (Marrie 2000). In both situations, wrong assessment of the date of onset of study outcome could result in protopathic bias, thus mistakenly attributing stroke and pneumonia onset to SSRIs and antipsychotics, respectively. To deal with this protopathic bias in database safety studies, sensitivity analyses can be carried out by excluding from the analysis those patients who started the therapy within a short period prior to the occurrence of the outcome.

5.3.4.5 Residual Confounding

The impact of confounding in healthcare database research can be reduced through the use of a suitable study design and/or a statistical strategy to adjust for known confounders, such as propensity score matching (Patorno et al. 2013b). Nevertheless, is it difficult to fully exclude the possibility of bias due to unknown and unmeasured confounders in all database safety studies, irrespective of the

drug under investigation. Such confounders may include lifestyle factors (diet, level of exercise, etc.), the use of over-the-counter medications, and disease severity, which is often not registered, particularly in claims databases (Patorno et al. 2013a). If data is available on a single unmeasured variable suspected to be a confounder, for example, data from a subsample or supplementary data from another data source, it may be possible to remove or adjust for residual confounding due to that variable. If, on the other hand, data on several unmeasured variables that may be confounders is available, the propensity score method can be used to adjust estimates.

5.4 Concluding Remarks and Future Directions

Healthcare databases such as GPs' electronic medical records as well as administrative/claims databases are important data sources to carry out observational studies aimed at quantifying and describing emerging safety issues associated with the use psychotropic drugs, as shown by the large amount of database safety studies that have been published worldwide in the last decades. As observational studies lack randomization in the assignment of the drug treatment under study, confounding and bias are issues that should be taken carefully into consideration. Nevertheless, it is to be considered that in any case a single observational study (not being experimental) cannot establish the causal pathway of a drug-(adverse) event association. Instead, confirmation of the results from a significant number of observational studies that have been carried out using different methodologies and data sources to explore the same safety issues, together with evidence coming from different sources (e.g., biological plausibility, existence of randomized clinical trials or case reports, etc.), can support causal association. It is important however to acknowledge limitations of observational studies and databases being used so to interpret the study results properly and, if necessary, cautiously, in addition to, whenever possible, the use of sensitivity analyses which may contribute to strengthen the robustness of the findings.

In the context of safety studies using electronic healthcare databases, new opportunities are open through the carrying out of multiple databases' safety studies which have been developed in different international initiatives which created distributed database networks. Multiple database safety studies are extremely challenging from a logistical point of view, especially in case of combination of data sources from different countries with different underlying healthcare systems and healthcare data privacy and management legislations, as well as time- and resource-consuming from a methodological perspective. However, this approach may be particularly useful for the investigation of association of rare adverse events and rare drug exposure (e.g., cardiac valve regurgitation and use of ergot-derived dopamine agonists for the treatment of Parkinson's disease) or in very specific patients categories (e.g., older people with specific type of dementia) which requires large base populations to gain enough statistical power to investigate such associations.

References

Abbing-Karahagopian V, Huerta C, Souverein PC, de Abajo F, Leufkens HG, Slattery J, Alvarez Y, Miret M, Gil M, Oliva B, Hesse U, Requena G, de Vries F, Rottenkolber M, Schmiedl S, Reynolds R, Schlienger RG, de Groot MC, Klungel OH, van Staa TP, van Dijk L, Egberts AC, Gardarsdottir H, De Bruin ML (2014) Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. Eur J Clin Pharmacol 70(7):849–857

Aguglia E, Ravasio R, Simonetti M, Pecchioli S, Mazzoleni F (2012) Use and treatment modalities for SSRI and SNRI antidepressants in Italy during the period 2003–2009. Curr Med Res Opin 28(9):1475–1484

Aparasu RR, Chatterjee S, Mehta S, Chen H (2012) Risk of death in dual-eligible nursing home residents using typical or atypical antipsychotic agents. Med Care 50(11):961–969

Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW (2006) Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry 67(3):453–460

Brookhart MA, Stürmer T, Glynn RJ, Rassen J, Schneeweiss S (2010) Confounding control in healthcare database research: challenges and potential approaches. Med Care 48(6 Suppl):S114–S120

Chollet J, Saragoussi D, Clay E, François C (2013) A clinical research practice datalink analysis of antidepressant treatment patterns and health care costs in generalized anxiety disorder. Value Health 16(8):1133–1139

Colombo GL, Agabiti-Rosei E, Margonato A, Mencacci C, Montecucco CM, Trevisan R (2013) Off-patent generic medicines vs. off-patent brand medicines for six reference drugs: a retrospective claims data study from five local healthcare units in the Lombardy Region of Italy. PLoS One 8(12), e82990

Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander GC (2010) Impact of FDA black box advisory on antipsychotic medication use. Arch Intern Med 170(1):96–103

Esposito D, Wahl P, Daniel G, Stoto MA, Erder MH, Croghan TW (2009) Results of a retrospective claims database analysis of differences in antidepressant treatment persistence associated with escitalopram and other selective serotonin reuptake inhibitors in the United States. Clin Ther 31(3):644–656

Franchi C, Tettamanti M, Marengoni A, Bonometti F, Pasina L, Cortesi L, Fortino I, Bortolotti A, Merlino L, Lucca U, Riva E, Nobili A (2012) Changes in trend of antipsychotics prescription in patients treated with cholinesterase inhibitors after warnings from Italian Medicines Agency. Results from the EPIFARM-Elderly Project. Eur Neuropsychopharmacol 22(8):569–577

Gallini A, Andrieu S, Donohue JM, Oumouhou N, Lapeyre-Mestre M, Gardette V (2014) Trends in use of antipsychotics in elderly patients with dementia: impact of national safety warnings. Eur Neuropsychopharmacol 24(1):95–104

Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, Bell CM, Lee PE, Fischer HD, Herrmann N, Gurwitz JH, Rochon PA (2007) Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 146(11):775–786

Gilmer TP, Dolder CR, Lacro JP, Folsom DP, Lindamer L, Garcia P, Jeste DV (2004) Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. Am J Psychiatry 161:692–699

Guthrie B, Clark SA, Reynish EL, McCowan C, Morales DR (2013) Differential impact of two risk communications on antipsychotic prescribing to people with dementia in Scotland: segmented regression time series analysis 2001–2011. PLoS One 8(7), e68976

Hansen DG, Vach W, Rosholm JU, Søndergaard J, Gram LF, Kragstrup J (2004) Early discontinuation of antidepressants in general practice: association with patient and prescriber characteristics. Fam Pract 21(6):623–629

Hayes J, Prah P, Nazareth I, King M, Walters K, Petersen I, Osborn D (2011) In bipolar disorder: cohort study in the United Kingdom THIN primary care database 1995–2009. PLoS One 6(12):e28725

Hollis J, Grayson D, Forrester L, Brodaty H, Touyz S, Cumming R (2007a) Antipsychotic medication dispensing and risk of death in veterans and war widows 65 years and older. Am J Geriatr Psychiatry 15(11):932–941

Hollis J, Forrester L, Brodaty H, Touyz S, Cumming R, Grayson D (2007b) Risk of death associated with antipsychotic drug dispensing in residential aged care facilities. Aust N Z J Psychiatry 41(9):751–758

Horwitz RI, Feinstein AR (1980) The problem of "protopathic bias" in case-control studies. Am J Med 68(2):255–258

Hsia Y, Neubert A, Sturkenboom MC, Murray ML, Verhamme KM, Sen F, Giaquinto C, Ceci A, Wong IC, TEDDY Network of Excellence (2010) Comparison of antiepileptic drug prescribing in children in three European countries. Epilepsia 51(5):789–796

Huybrechts KF, Schneeweiss S, Gerhard T, Olfson M, Avorn J, Levin R, Lucas JA, Crystal S (2012a) Comparative safety of antipsychotic medications in nursing home residents. J Am Geriatr Soc 60(3):420–429

Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, Lucas JA, Schneeweiss S (2012b) Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ 344:e977

Jacobsen PE, Henriksen TB, Haubek D, Østergaard JR (2014) Prenatal exposure to antiepileptic drugs and dental agenesis. PLoS One 9(1):e84420

Kales HC, Valenstein M, Kim HM, McCarthy JF, Ganoczy D, Cunningham F, Blow FC (2007) Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. Am J Psychiatry 164(10):1568–1576

Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, Cunningham F, Schneider LS, Blow FC (2012) Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatr 169(1):71–79

Koopman JS, Huygen FJ, Dieleman JP, de Mos M, Sturkenboom MC (2010) Pharmacological treatment of neuropathic facial pain in the dutch general population. J Pain 11(3):264–272

Kraut AA, Langner I, Lindemann C, Banaschewski T, Petermann U, Petermann F, Mikolajczyk RT, Garbe E (2013) Comorbidities in ADHD children treated with methylphenidate: a database study. BMC Psychiatry 13:11

Krishnan KR (2000) Depression as a contributing factor in cerebrovascular disease. Am Heart 140(4 Suppl):70–76

Lam D, Gorman DA, Patten S, Pringsheim T (2013) The pharmacoepidemiology of selective serotonin reuptake inhibitors for children and adolescents in Canada from 2005 to 2009: a database analysis. Pediatr Drugs 15(4):319–327

Laugesen K, Telén Andersen AB, Nørgaard M, Nielsen RB, Thomsen RW, Larsen FB, Sørensen HT (2013) Use of selective serotonin reuptake inhibitors and lifestyle among women of childbearing age: a Danish cross-sectional survey. BMJ Open. Jul 31;3(7). pii: e003024.

Lindemann C, Langner I, Kraut AA, Banaschewski T, Schad-Hansjosten T, Petermann U, Petermann F, Schreyer-Mehlhop I, Garbe E, Mikolajczyk RT (2012) Age-specific prevalence, incidence of new diagnoses, and drug treatment of attention-deficit/hyperactivity disorder in Germany. J Child Adolesc Psychopharmacol 22(4):307–314

Man SL, Petersen I, Thompson M, Nazareth I (2012) Antiepileptic drugs during pregnancy in primary care: a UK population based study. PLoS One 7(12):e52339

Marrie TJ (2000) Community-acquired pneumonia in the elderly. Clin Infect Dis 31(4):1066–1078

Marston L, Nazareth I, Petersen I, Walters K, Osborn DP2 (2014) Prescribing of antipsychotics in UK primary care: a cohort study. BMJ Open 4(12):e006135

Parabiaghi A, Franchi, Tettamanti M, Barbato A, D'Avanzo B, Fortino I, Bortolotti A, Merlino L, Nobili A (2011) Antidepressants utilization among elderly in Lombardy from 2000 to 2007: dispensing trends and appropriateness. Eur J Clin Pharmacol 67(10):1077–1083

Pariente A, Fourrier-Réglat A, Ducruet T, Farrington P, Béland SG, Dartigues JF, Moore N, Moride Y (2012) Antipsychotic use and myocardial infarction in older patients with treated dementia. Arch Intern Med 172(8):648–653

Patorno E, Glynn RJ, Hernandez-Diaz S, Avorn J, Wahl PM, Bohn RL, Mines D, Liu J, Schneeweiss S (2013a) Risk of ischemic cerebrovascular and coronary events in adult users of anticonvulsant medications in routine care settings. J Am Heart Assoc 2(4), e000208

Patorno E, Grotta A, Bellocco R, Schneeweiss S (2013b) Propensity score methodology for confounding control in health care utilization databases. Epidemiol Biostat Public Health 10(3), e8940:1–16

Petersen I, Gilbert RE, Evans SJ, Man SL, Nazareth I (2011) Pregnancy as a major determinant for discontinuation of antidepressants: an analysis of data from The Health Improvement Network. J Clin Psychiatry 72(7):979–985

Petersen I, McCrea RL, Osborn DJP, Evans S, Pinfold V, Cowen PJ, Gilbert R, Nazareth I (2014) Discontinuation of antipsychotic medication in pregnancy: a cohort study. Schizophr Res 159(1):218–225

Poluzzi E, Piccinni C, Sangiorgi E, Clo M, Tarricone I, Menchetti M, De Ponti F (2013) Trend in SSRI-SNRI antidepressants prescription over a 6-year period and predictors of poor adherence. Eur J Clin Pharmacol 69(12):2095–2101

Prah P, Petersen I, Nazareth I, Walters K, Osborn D (2011) National changes in oral antipsychotic treatment for people with schizophrenia in primary care between 1998 and 2007 in the United Kingdom. Pharmacoepidemiol Drug Saf 21(2):161–169

Rafaniello C, Lombardo F, Ferrajolo C, Sportiello L, Parretta E, Formica R, Potenza S, Rinaldi B, Irpino A, Raschetti R, Vanacore N, Rossi F, Capuano A (2014) Predictors of mortality in atypical antipsychotic-treated community-dwelling elderly patients with behavioural and psychological symptoms of dementia: a prospective population-based cohort study from Italy. Eur J Clin Pharmacol 70(2):187–195

Salas M, Hofman A, Stricker BH (1999) Confounding by indication: an example of variation in the use of epidemiologic terminology. Am J Epidemiol 149:981–983, 72

Sanfélix-Gimeno G, Cervera-Casino P, Peiró S, López-Valcarcel BG, Blázquez A, Barbera T (2009) Effectiveness of safety warnings in atypical antipsychotic drugs: an interrupted time-series analysis in Spain. Drug Saf 32(11):1075–1087

Savica R, Beghi E, Mazzaglia G, Innocenti F, Brignoli O, Cricelli C, Caputi AP, Musolino R, Spina E, Trifiro G (2007) Prescribing patterns of antiepileptic drugs in Italy: a nationwide population-based study in the years 2000–2005. Eur J Neurol 14(12):1317–1321

Schneeweiss S, Avorn J (2005) A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 58(4):323–337

Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS (2007) Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 176(5):627–632

Schulze J, van den Bussche H, Glaeske G, Kaduszkiewicz H, Wiese B, Hoffmann F (2013) Impact of safety warnings on antipsychotic prescriptions in dementia: nothing has changed but the years and the substances. Eur Neuropsychopharmacol 23(9):1034–1042

Sultana J, Cutroneo P, Trifirò G (2013) Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother 4(Suppl 1):S73–S77

Sultana J, Chang CK, Hayes RD, Broadbent M, Stewart R, Corbett A, Ballard C (2014a) Associations between risk of mortality and atypical antipsychotic use in vascular dementia: a clinical cohort study. Int J Geriatr Psychiatry 29(12):1249–1254

Sultana J, Italiano D, Spina E, Cricelli C, Lapi F, Pecchioli S, Gambassi G, Trifirò G (2014b) Changes in the prescribing pattern of antidepressant drugs in elderly patients: an Italian, nationwide, population-based study. Eur J Clin Pharmacol 70(4):469–478

Tiihonen J, Wahlbeck K, Lönnqvist J, Klaukka T, Ioannidis JP, Volavka J, Haukka J (2006) Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ 333(7561):224

Trifirò G, Spina E, Brignoli O, Sessa E, Caputi AP, Mazzaglia G (2005) Antipsychotic prescribing pattern among Italian general practitioners: a population-based study during the years 1999–2002. Eur J Clin Pharmacol 61(1):47–53

Trifirò G, Verhamme KM, Ziere G, Caputi AP, Ch Stricker BH, Sturkenboom MC (2007) All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. Pharmacoepidemiol Drug Saf 16(5):538–544

Trifirò G, Sini G, Sturkenboom MC, Vanacore N, Mazzaglia G, Caputi AP, Cricelli C, Brignoli O, Aguglia E, Biggio G, Samani F (2010a) Prescribing pattern of antipsychotic drugs in the Italian general population 2000–2005: a focus on elderly with dementia. Int Clin Psychopharmacol 25(1):22–28

Trifirò G, Dieleman J, Sen EF, Gambassi G, Sturkenboom MC (2010b) Risk of ischemic stroke associated with antidepressant drug use in elderly persons. J Clin Psychopharmacol 30(3):252–258

Trifirò G, Gambassi G, Sen EF, Caputi AP, Bagnardi V, Brea J, Sturkenboom MC (2010c) Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. Ann Intern Med 152(7):418–2

Trifirò G, Coloma PM, Rijnbeek PR, Romio S, Mosseveld B, Weibel D, Bonhoeffer J, Schuemie M, van der Lei J, Sturkenboom M (2014a) Combining multiple healthcare databases for post-marketing drug and vaccine safety surveillance: why and how? Intern Med J 275(6):551–561

Trifiró G, Sultana J, Spina E (2014b) Are the safety profiles of antipsychotic drugs used in dementia the same? An updated review of observational studies. Drug Saf 37(7):501–520

Tschanz JT, Corcoran C, Skoog I, Khachaturian AS, Herrick J, Hayden KM, Welsh-Bohmer KA, Calvert T, Norton MC, Zandi P, Breitner JC, Cache County Study Group (2004) Dementia: the leading predictor of death in a defined elderly population: the Cache County Study. Neurology 62(7):1156–1162

Ubeda A, Cardo E, Sellés N, Broseta R, Trillo JL, Fernández-Llimós F (2007) Antidepressant utilization in primary care in a Spanish region: impact of generic and reference-based pricing policy (2000–2004). Soc Psychiatry Psychiatr Epidemiol 42(3):181–188

Valiyeva E, Herrmann N, Rochon PA, Gill SS, Anderson GM (2008) Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. CMAJ 179(5):438–446

Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, Brookhart MA (2005) Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 353(22):2335–2341

Wijlaars LPMM, Nazareth I, Petersen I (2012) Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN). PLoS One 7(3):e33181

Chapter 6
Monitoring of Plasma Concentrations of Psychotropic Drugs in Pharmacovigilance

Christoph Hiemke and Ekkehard Haen

Abstract The primary aims of pharmacovigilance are supervision and prevention of medication-related problems under everyday conditions. Pharmacovigilance is an indication for monitoring plasma concentrations, i.e. conducting therapeutic drug monitoring (TDM). Using TDM, it can be clarified if observed unwanted drug effects may be attributed to abnormally high or low drug concentrations. Utmost benefits from TDM are obtained for pharmacovigilance when the method is adequately integrated into the clinical treatment process. How to do this is described in consensus guidelines for TDM in psychiatry. During the last 20 years, TDM was very successful for detection of multiple pharmacokinetic drug-drug interactions. Many of them were discovered in individual cases. This gave rise to systematic prospective studies to verify or falsify such observations. Confirmatory studies, however, are critical when drug combinations are potentially harmful. Then TDM databases should be used for retrospective analysis. They enable to study retrospectively the safety and tolerability of psychotropic drugs and drug combinations taken in a broad spectrum of patients, including risk patients like children or adolescent patients, old-aged patients or patients with comorbid diseases. For such studies, however, TDM databases must contain not only laboratory but also clinical data. This is actually quite rare. Work in this regard is necessary. When functioning TDM software is available and TDM is widely used in psychiatry, data can be pooled to

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emerge large databases for data mining. TDM has thus the potential to be and become a valuable part of pharmacovigilance.

Keywords Therapeutic drug monitoring • Side effect • Plasma concentration • Reference range • Laboratory alert level • Data mining • Computerized physician order entry • Clinical decision systems • Drug-drug patients • Risk patients

6.1 Introduction

Drug therapies are commonly controlled by the dose. With the "right" dose, optimal clinical improvement is to be achieved without adverse effects. Therefore, a crucial factor is the concentration of the drug that reaches the site of action, in case of psychotropic drugs, the brain. In particular, because of interindividual differences in the equipment of the liver with drug-degrading enzymes or drug transporters, drug concentrations under the same dose can vary considerably from patient to patient. This is shown exemplary in Fig. 6.1 for 169 schizophrenic patients who were treated with amisulpride. Each point in this figure shows the concentration of the antipsychotic drug that was attained under the prescribed dose.

Similar patterns of dose-related drug concentrations are known for any psychotropic drug, e.g. antidepressants (Ostad Haji et al. 2012) or antipsychotic drugs (Hiemke et al. 2004; Hefner et al. 2013). Since the drug concentration in the blood usually correlates well with concentrations at the site of action, it has been proven

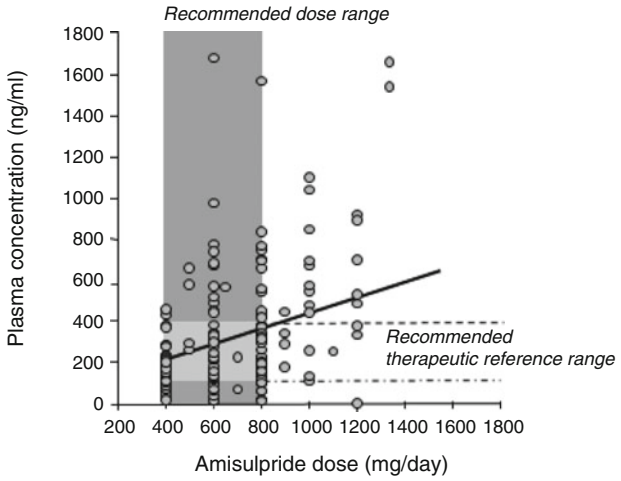

Fig. 6.1 Dose-dependent plasma concentrations of amisulpride in 179 schizophrenic patients treated and observed under everyday conditions. Drug concentrations are highly variable. Under recommended doses of 400–800 mg/day, many patients exhibit drug concentrations above or below the recommended therapeutic reference range of 100–320 ng/mL (Hiemke et al. 2011)

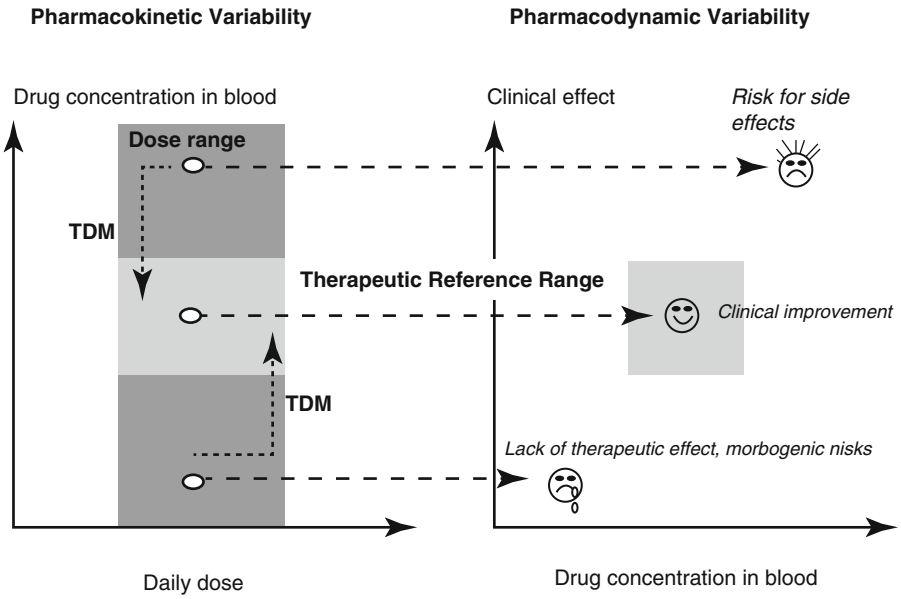

Fig. 6.2 The concept of therapeutic drug monitoring (TDM) for guidance of pharmacotherapy. Under recommended doses and steady concentration, drug in the blood should be within the therapeutic reference range to attain highest probability of drug response and good tolerability. In psychiatry, too low or too high drug concentrations are associated with risks. Too low doses/concentrations bear morbogenic risks due to treatment failure or relapse like psychotic exacerbation or self-harming. Too high drug concentrations can lead to reduced tolerance and poor compliance or adverse drug reactions

for many drugs to use blood level measurements to guide pharmacotherapy, i.e. to use therapeutic drug monitoring (TDM). Using TDM, the dose should be corrected individually as shown in Fig. 6.2 when the drug concentrations in the blood are not within the therapeutic reference range and the patient did not improve or suffers from side effects. At concentrations within the therapeutic range, the highest probability of response and good tolerability is expected. In psychiatry, both too low and too high drug doses or concentrations are associated with risks. Too low doses or drug concentrations can be associated with treatment failure or relapse which bear morbogenic risks such as psychotic exacerbation or self-harming. Too high doses or drug concentrations can lead to adverse drug reactions or intoxications.

TDM consists not only of determination and reporting of drug concentrations in blood. It is a process that begins with the indication for TDM and ends with the treatment decision for the patient. TDM was originally established for drugs with a narrow therapeutic index, such as digoxin or cyclosporin A, and in psychiatry, for lithium (Fry and Marks 1971), tricyclic antidepressants (Åsberg et al. 1971; Preskorn and Fast 1991) or the antipsychotic clozapine (Simpson and Cooper 1978). Primary aims of TDM in psychiatry were originally related to safety, drug defaulting and side effects (Preskorn and Fast 1992; Sjöqvist et al. 1980; Touw et al. 2005).

Since the first application of TDM between 1970 and 1980, enormous progress was made in psychopharmacotherapy not only by the development of new drugs but also by many new findings on the pharmacokinetics and pharmacodynamics of available drugs. Cytochromes P450 (CYP) enzymes have been recognized as a major source of variability in drug pharmacokinetics and response (Zanger et al. 2014). Of 57 putatively functional human CYP enzymes, seven were found to be relevant for about 90 % of phase I metabolism of psychoactive drugs, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The expression of each CYP is influenced by multiple mechanisms and factors including genetic polymorphisms, induction by xenobiotics, regulation by cytokines and hormones and alterations during disease states, as well as sex, age and others (Zanger and Schwab 2013). Genetic polymorphisms play a major role for the function of CYP2D6 and CYP2C19 and lead to distinct pharmacogenetic phenotypes termed poor (PM, no active alleles), intermediate (IM), extensive (EM, basic genotype) and ultrarapid metabolizers (UM).

Co-medication and other xenobiotics are another important determinant that has been found to affect the pharmacokinetics of drugs. Fluoxetine, fluvoxamine, paroxetine, bupropion, duloxetine, moclobemide and multiple other drugs were identified as potent inhibitors of distinct CYP enzymes. To a lesser degree, but also clinically relevant, carbamazepine, compounds in St. John's wort and other drugs were found to enhance the expression of CYP3A4. Marked pharmacokinetic drug-drug interactions can result when combining such inhibitors or inducers with drugs that are metabolized by inhibited or induced enzymes (victim drugs). The escalating use of prescribed drugs has led to polypharmacy as a "normal" condition of pharmacotherapy, in psychiatry as well as in other disciplines (Guthrie et al. 2015), especially in elderly patients.

Modern TDM uses the above-mentioned psychopharmacology knowledge gained during the last 40 years in practice for the best possible pharmacotherapy of individual patients. It thus enhances patient care and patient safety. Modern pharmacovigilance, which is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO 2002; EMA 2014), also aims to enhance patient care and patient safety in relation to the use of medicines. Spontaneous reporting of suspected adverse drug reactions (ADRs) has long been the cornerstone of pharmacovigilance worldwide for the identification of early signals of problems of safety related to the use of medicines. However, data generated from spontaneous reporting systems are often fragmentary. They are of limited use for the evaluation of observed events. Spontaneously reported adverse drug reactions are therefore considered as a hint that must be followed by systematic studies. Since TDM supervises pharmacotherapy under everyday conditions and thus aims to prevent safety problems related to the use of medicines (Haen 2011; Jaquenoud-Sirot et al. 2006), TDM and pharmacovigilance thus have the same primary aims. When applied appropriately, i.e. as recommended in the consensus guidelines for TDM in psychiatry, collected information is more complete and better structured (Baumann et al. 2004; Hiemke et al. 2011) than reports in the pharmacovigilance programs. TDM is therefore potentially a highly suitable tool and source for pharmacovigilance.

6.2 Monitoring of Plasma Concentrations to Guide and Supervise Psychopharmacotherapy

The benefits of monitoring of plasma concentrations regarding the optimization of pharmacotherapy can only be obtained if the method is adequately integrated into the clinical treatment process. The TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) issued best practice guidelines for TDM in psychiatry in 2004 (Baumann et al. 2004) which were updated in 2011 (Hiemke et al. 2011).

6.2.1 Therapeutic Reference Range and Laboratory Alert Level

TDM is based on the assumption that there is a relationship between plasma concentrations and clinical effects, i.e. therapeutic improvement, side effects and adverse effects (Hefner et al. 2013). It also assumes that there is a plasma concentration range of the drug which is characterized by maximal effectiveness and maximal safety, the "therapeutic reference ranges" (often called "therapeutic window"). The therapeutic reference range is a key target value to perform TDM.

The therapeutic reference ranges reported in the AGNP guideline define ranges of medication concentrations which specify a lower limit below which a drug-induced therapeutic response is relatively unlikely to occur and an upper limit above which tolerability decreases or above which it is relatively unlikely that therapeutic improvement may be still enhanced. It is an orienting, population-based range which may not necessarily be applicable to all patients. Individual patients, e.g. patients under drug combinations, may show optimal therapeutic response under a drug concentration that differs from the therapeutic reference range. The therapeutic reference ranges as recommended by the TDM group of the AGNP for antidepressant, antipsychotic and mood-stabilizing drugs are given in Table 6.1. They were evidence based and derived from the literature by a structured review process. For only 15 neuropsychiatric drugs, therapeutic reference ranges based on randomized clinical trials were found in the literature. For most drugs, reference ranges were obtained from studies with therapeutically effective doses.

If prospective or retrospective studies on the therapeutic reference range are lacking, the drug concentration that is expected under steady-state conditions (Css) can be calculated for the given dose as follows:

$$\mathrm{Css} = \mathrm{DD} / \mathrm{CLt}$$

The calculation is based on the direct correlation of the daily dose (DD, constant dose per day under steady state) to its blood concentration Css, with the total clearance of the drug (CLt) being the correlation coefficient:

$$\mathrm{DD} \times F / \tau = \mathrm{Css} \times \mathrm{CLt}$$

Table 6.1 Therapeutic reference ranges and laboratory alert levels of antidepressant, antipsychotic and mood-stabilizing drugs in blood plasma or serum used for therapeutic drug monitoring (TDM)-guided pharmacotherapy

Drug and active metabolite	Therapeutic reference range	Laboratory alert level	Comment
Antidepressant drugs			
Amitriptyline plus nortriptyline	80–200 ng/mL	300 ng/mL	Elevated concentration in PM of CYP2D6
Bupropion plus hydroxybupropion	225–1,500 ng/mL	2,000 ng/mL	Bupropion is unstable at room temperature; reference range and alert level refer to hydroxybupropion only
Citalopram	50–110 ng/mL	220 ng/mL	Elevated concentration in PM of CYP2C19
Clomipramine plus norclomipramine	230–450 ng/mL	450 ng/mL	Elevated concentration in PM of CYP2D6 and CYP2C19
Desipramine	100–300 ng/mL	300 ng/mL	Elevated concentration in PM of CYP2D6
Desvenlafaxine	100–400 ng/mL	600 ng/mL	Elevated concentration in PM of CYP2C19
Doxepin plus nordoxepin	50–150 ng/mL	300 ng/mL	Elevated concentration in PM of CYP2D6 or CYP2C19
Duloxetine	30–120 ng/mL	240 ng/mL	Lower concentration in smokers than in nonsmokers, moderate inhibitor of CYP2D6
Escitalopram	15–80 ng/mL	160 ng/mL	Higher concentration in PM of CYP2C19
Fluoxetine plus norfluoxetine	120–500 ng/mL	1,000 ng/mL	Long elimination half-life of norfluoxetine (mean 14 days) and long-lasting inhibition of CYP2D6
Fluvoxamine	60–230 ng/mL	500 ng/mL	Inhibitor of CYP1A2 and CYP2C19
Imipramine plus desipramine	175–300 ng/mL	300 ng/mL	Elevated concentration in PM of CYP2D6
Maprotiline	75–130 ng/mL	220 ng/mL	Active metabolite N-desmethylmaprotiline
Mianserine	15–70 ng/mL	140 ng/mL	
Milnacipran	50–110 ng/mL	220 ng/mL	No phase I metabolism
Mirtazapine	30–80 ng/mL	160 ng/mL	
Moclobemide	300–1,000 ng/mL	2,000 ng/mL	Inhibitor of CYP2C19 and CYP2D6

Nortriptyline	70–170 ng/mL	300 ng/mL	Elevated concentration in PM of CYP2D6
Paroxetine	30–60 ng/mL	120 ng/mL	Inhibitor of CYP2D6
Reboxetine	60–350 ng/mL	700 ng/mL	
Sertraline	10–150 ng/mL	300 ng/mL	
Tianeptin	30–80 ng/mL	160 ng/mL	
Tranylcypromin	≤50 ng/mL	100 ng/mL	Irreversible inhibition of monoamine oxidase (MAO); drug actions correlate with MAO activity but not with drug concentration in blood
Trazodone	700–1,000 ng/mL	1,200 ng/mL	
Trimipramine	150–300 ng/mL	600 ng/mL	Active metabolites
Venlafaxine plus O-desmethylvenlafaxine	100–400 ng/mL	800 ng/mL	Elevated concentration of venlafaxine in PM of CYP2D6 or CYP2C19
Vortioxetine	10–60 ng/mL	120 ng/mL	Elevated concentration in PM of CYP2D6
Antipsychotic drugs			
Amisulpride	100–320 ng/mL	640 ng/mL	
Aripiprazole	150–500 ng/mL	1,000 ng/mL	Active metabolite dehydroaripiprazole
Asenapine	2–5 ng/mL	10 ng/mL	
Benperidol	1–10 ng/mL	20 ng/mL	Higher levels may be required in patients under long-term high-dose therapy due to adaptive changes
Bromperidol	12–15 ng/mL	30 ng/mL	
Chlorpromazine	30–300 ng/mL	600 ng/mL	
Chlorprothixene	20–300 ng/mL	400 ng/mL	
Clozapine	350–600 ng/mL	1,000 ng/mL	Major metabolite N-desmethylclozapine
Flupenthixol	0.5–5 ng/mL (cis-Isomer)	15 ng/mL	
Fluphenazine	1–10 ng/mL	15 ng/mL	
Fluspirilen	0.1–2.2 ng/mL	4.4 ng/mL	

(continued)

Table 6.1 (continued)

Drug and active metabolite	Therapeutic reference range	Laboratory alert level	Comment
Haloperidol	1–10 ng/mL	15 ng/mL	Higher levels can be tolerated in patients under long-term high-dose therapy due to adaptive changes
Iloperidone	5–10 ng/ml	20 ng/ml	
Levomepromazine	30–160 ng/mL	320 ng/mL	Inhibitor of CYP2D6
Lurasidone	40–120 ng/mL	240 ng/mL	
Melperone	30–100 ng/mL	200 ng/mL	Inhibitor of CYP2D6
Olanzapine	20–80 ng/mL	100 ng/mL	Under olanzapine pamoate, patients exhibited a postinjection syndrome when drug concentrations exceeded 100 ng/mL
Paliperidone	20–60 ng/mL	120 ng/mL	Paliperidone = 9-hydroxyrisperidone
Perazine	100–230 ng/mL	460 ng/mL	
Perphenazine	0.6–2.4 ng/mL	5 ng/mL	
Pimozide	15–20 ng/mL	20 ng/mL	
Pipamperone	100–400 ng/mL	500 ng/mL	
Prothipendyl	5–10 ng/mL	20 ng/mL	
Quetiapine	100–500 ng/mL	1,000 ng/mL	When the patient has taken the extended release (XR) formulation in the evening and blood was withdrawn in the morning, plasma concentrations are by mean twofold higher than trough levels
Risperidone plus 9-hydroxyrisperidone	20–60 ng/mL	120 ng/mL	Elevated concentration of risperidone in PM of CYP2D6
Sertindole	50–100 ng/mL	200 ng/mL	Active metabolite dehydrosertindole (concentration at therapeutic doses 40–60 ng/mL)
Sulpiride	200–1,000 ng/mL	1,000 ng/mL	Renal elimination
Thioridazine	100–200 ng/mL	400 ng/mL	Contraindicated in poor metabolizers of CYP2D6, elevated concentration
Ziprasidone	50–200 ng/mL	400 ng/mL	The drug should be taken with a meal; otherwise absorption is reduced and plasma concentration will be lower than expected

Zotepine	10–150 ng/mL	300 ng/mL	
Zuclopentixol	4–50 ng/mL	100 ng/mL	
Mood-stabilizing drugs			
Carbamazepine	4–10 µg/mL	20 µg/mL	Active 10,11-epoxide metabolite contributes to clinical effects
Lamotrigine	3–14 µg/mL	30 µg/mL	So far no specific reference range for mood-stabilizing effect; valproate increases elimination half-life to 48–70 h
Lithium	0.5–1.2 mmol/l	1.2 mmol/l	Renal elimination
	(4–8 µg/mL)	(8 µg/mL)	
Valproic acid	50–100 µg/mL	120 µg/mL	In individual cases, 120 µg/mL is also tolerated in acute mania

Values given are those recommended in the AGNP consensus guidelines for TDM in psychiatry (Hiemke et al. 2011)
CYP cytochrome P450, *PM* poor metabolizer

with DD as dose (mg), F as bioavailability and τ as dosing interval (h). Based on this information, it is possible to calculate the plasma concentration of a drug that may be expected in blood under a defined dose (Haen et al. 2008).

In addition to the therapeutic reference range and especially with regard to safety aspects, the so-called laboratory alert level is another relevant target value for TDM-guided drug therapies. For most psychotropic drugs, plasma concentrations with an increased risk of toxicity are normally much higher than the upper threshold levels of the therapeutic reference ranges shown in Table 6.1. In the TDM guidelines (Hiemke et al. 2011), a "laboratory alert level" mostly above the upper plasma concentration limit of the therapeutic reference range was defined as follows: "The "laboratory alert levels" (Table 6.1) indicate drug concentrations that cause the laboratory to feedback immediately to the prescribing physician. The alert levels are based on reports on intolerance or intoxications and plasma concentration measurements. In most cases, however, it was arbitrarily defined as a plasma concentration that is twofold higher than the upper limit of the therapeutic reference range. The laboratory alert should lead to dose reduction when the patient exhibits signs of intolerance or toxicity. When the high drug concentration is well tolerated by the patient and if dose reduction bears the risk of symptom exacerbation, the dose should remain unchanged. The clinical decision, especially in case of unchanged dose, needs to be documented in the medical file.

6.2.2 TDM Request

TDM should only be requested when there is evidence that the result will provide an answer to a specific question. Typical indications are shown in Fig. 6.3.

TDM requests must include a completed request form, especially when information is to be used for pharmacovigilance issues. An adequate interpretation of the results is essential to support clinical decision making. The form should contain the following:

- Patient name or code
- Demographic data
- Diagnosis
- Medication including co-medications
- Reason for the request
- Commercial and the generic name of the drug and its dose
- Galenic formulation
- Time of the last change of the dose
- Time of blood withdrawal

Moreover,

- A brief clinical rating score for evaluation of therapeutic improvement
- A brief side effect rating score

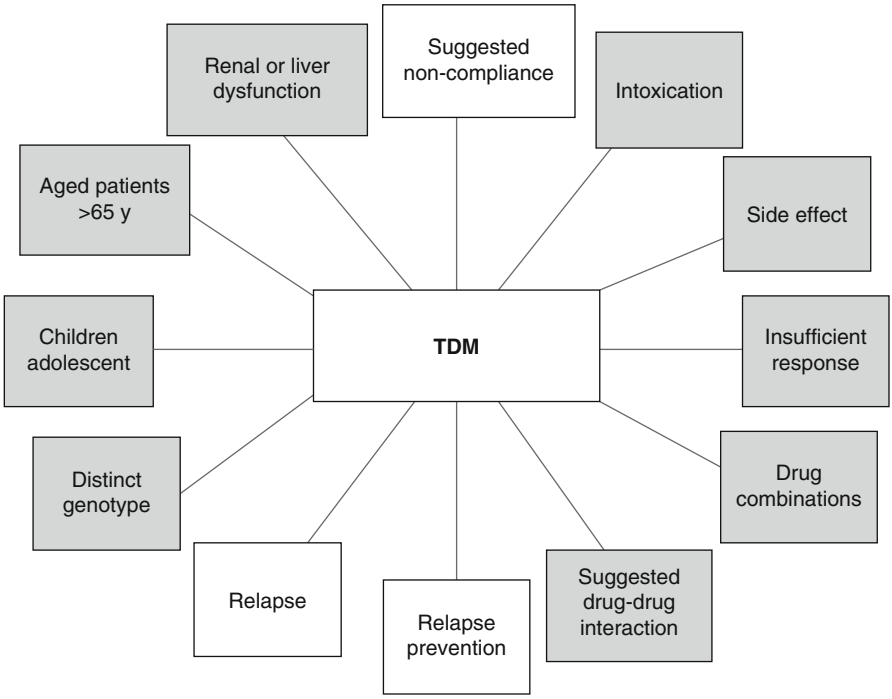

Fig. 6.3 Typical indications to request therapeutic drug monitoring (TDM). Indications related to pharmacovigilance are marked in grey

should be on the request form (Hiemke et al. 2011).

For objective symptom rating, the clinical global impression (CGI) scale, which measures severity of illness and therapeutic improvement (Guy 1976), is useful. For safety purposes, the summary form of the UKU scale (Lingjærde et al. 1987) is useful to evaluate the occurrence and severity of side effects.

A brief comment on the clinical situation must also be given for interpretation of the results.

6.2.3 Blood Sample Collection, Storage and Shipment

Generally, TDM is carried out in plasma or serum samples. There is no consensus whether plasma or serum should be preferred. The few available comparisons indicate that values obtained from serum or plasma can be used interchangeably. Analysis of drugs in other materials such as urine, spinal fluid, tears, hairs or maternal milk has not been introduced for TDM purposes, and no validated data are available which deal with therapeutic concentrations. Saliva offers the advantage of non-invasive collection.

With few exceptions, TDM relies on trough steady-state plasma concentrations. One exception is the indication "side effects". When they occur, it is useful to know if they can be attributed to elevated drug concentration and if the dose may be reduced without loss of efficacy. For concentration measurements under steady state, blood should be collected after four to five drug elimination half-lives after the start of or change of dosage. For most psychotropic drugs, elimination half-lives vary between 12 and 36 h. Notable exceptions are quetiapine, trazodone or venlafaxine, which display elimination half-lives around 6 h. Fluoxetine and aripiprazole have longer elimination half-lives. In clinical practice, the appropriate sampling time for most psychoactive drugs is 1 week after stable daily dosing and immediately before ingestion of the morning dose, which usually is 12–16 h (or 24 h if the drug is given once daily in the morning) after the last medication. It is always recommended to indicate exactly the time of administration of the last dose for interpretation.

With few exceptions, serum or plasma samples can be stored in the dark (at 4 °C) for at least 24 h, and most drug samples can be sent without freezing. An exception is bupropion. Blood serum or plasma must be frozen after blood withdrawal. Olanzapine must also be stored frozen (−20 °C) if not analysed within 72 h.

6.2.4 Laboratory Measurements

Selective and sensitive analytical methods for the quantitative evaluation of drugs and their metabolites (analytes) are essential for the successful conduct of TDM. Methods must be validated. Fundamental parameters for validation include (1) inaccuracy, (2) imprecision, (3) selectivity, (4) sensitivity, (5) reproducibility and (6) stability.

For psychoactive drugs, high-performance liquid chromatography (HPLC), in combination with suitable detection methods or liquid chromatography coupled with mass spectroscopy (LC-MS) especially tandem MS (LC-MS/MS) methods are preferred. They are most sensitive and selective and can be used without time-consuming sample preparation. Many compounds can be analysed simultaneously. In case of suspected intoxications, TDM methods should enable drug analysis within 1–2 h. For this purpose, automated methods are advantageous.

The laboratory should not only analyse the drug but also its active metabolites. The determination of metabolites that do not contribute to the overall clinical effect can also be useful to monitor drug adherence of the patient, to get information on his/her capacity to metabolize drugs or to interpret drug-drug interactions when drugs are involved exhibiting enzyme-inhibiting or enzyme-inducing properties. Within the therapeutic reference range, intraday and interday precision should not exceed 15 % (coefficient of variation), and accuracy should not deviate more than 15 % from the nominal value. To ensure quality and reliability of plasma concentrations assays, internal and external quality control procedures are mandatory.

6.2.5 *Reporting of Results*

Reporting of results should contain the following information:

- Concentration of the psychoactive drug as well as that of metabolites contributing to the therapeutic action
- Reference range
- Interpretation and pharmacologic advice

The results should be available for decision making within a clinically meaningful time. A 24 h TDM service is desirable; 48 h is sufficient in most cases. In case of suspected intoxications, a few hours of service is necessary. To assist rapid intervention in patients at risk for toxicity or loss of tolerability, prompt information (phone call) of the treating physician is required when the laboratory measures drug concentrations above the "laboratory alert level".

Expert interpretation of a drug concentration measurement and the adequate use of the information are essentials to ensure the full clinical benefit of TDM. Reporting of results with inclusion of dose recommendations and other comments must be guided by the best available evidence. Diagnosis and drug dose are important for interpretation, since they permit a judgement on whether a result is plausible or not. For the interpretation of the results, it should not only be considered whether the plasma concentration of the drug is within the "therapeutic reference range". It must also be considered if the drug plasma concentration is consistent with the dose. A plasma concentration may be outside the therapeutic reference range, just because a low or high dose was taken. Often it is necessary to deal with pharmacokinetic properties such as metabolic pathways, enzymes involved and substrate and inhibitor properties of all drugs taken by the patient for interpretation of the results. Supportive information is given in the TDM guidelines (Hiemke et al. 2011).

Any drug concentration outside its dose-related reference range should alert the TDM laboratory to actively look for non-average pharmacokinetic drug disposition of the patient, drug-drug-interactions, gene polymorphisms that give rise to poor or ultra rapid metabolism, altered function of the excretion organs liver and kidneys, age and/or disease-related changes in the patient's pharmacokinetics, compliance (adherence) problems, a nonsteady state and even signal interference from other medications that the patient may not have declared to the prescribing physician (e.g. St. John's wort) in the laboratory analysis.

Plasma concentrations must be interpreted with the clinical presentation in mind. Recommendations on dosage changes constitute the most frequent advice. Other information which could be of help for the physician are those related to genetic polymorphisms, risks of pharmacokinetic interactions in the case of polypragmasy and pharmacokinetic properties of the drug in patients belonging to a "special population", e.g. elderly patients, or patients with hepatic or renal insufficiency.

Since interpretation of TDM results may be complex, training in clinical psychopharmacology and pharmacokinetics is essential. Regular conferences with discussion of the interpretation of real cases are most helpful for learning. It is also recommended that junior psychiatrists interpret the results under supervision of an expert.

6.3 Computerized Data Entry Ordering and Reporting Systems for Therapeutic Drug Monitoring

Documented feedback to questionnaires indicates that clinicians often do not want to put clinical information on the form (Vuille et al. 1991). Moreover, the filled-in information is often not accurate. Therefore, it is advantageous to use computerized physician order entry and reporting of results (Bates 1998; Haen 2011), especially when TDM is to be used for pharmacovigilance research. This technology guides the ordering physician to give the relevant information required for interpretation in a comfortable way. Actual laboratory information systems are so far of limited use for TDM. They collect, record, organize and archive laboratory results. However, they do not have access to information that is required for interpretation of TDM results. Pharmacokinetic, pharmacodynamic and marketing characteristics of all drugs taken by the patient must be considered.

This can be made available by modern information technology: Konbest is a web-based laboratory information management system (LIMS) for TDM-laboratories (see www.konbest.de). Konbest consists of a server, a web client, the software for local hospital servers (electronic patient chart, clinic information system, laboratory information system LIS) and expansive pharmacological databases. The server hosts the following pharmacological databases:

- A database for pharmacokinetic characteristics of drugs
- A database for metabolic pathways of drugs
- A database for composition of commercial drug products
- A database for guidelines of pharmacotherapy
- The implementation of the database www.psiac.de for drug-drug-interactions

The web client coordinates the data flow from hospital to laboratory and allows interpretation by clinical pharmacological experts via the Internet. A server at hand for the treating physician stores personalized patient data (demographic data, diagnosis, clinical status as assessed by clinical global impression, CGI scale, medication and clinical variables), checks the medication for potential drug-drug interactions using a drug interaction database, exports pseudonymized patient data to be sent to the TDM laboratory and reimports the analysis results together to combine this information with the personalized patient chart.

The Internet platform Konbest supports clinical pharmacological experts in setting up the clinical pharmacological report. Some parts of the report are created automatically; for other parts, text sequences are suggested to the clinical pharmacologist who has to choose one and adapt it to the particular case; a third part of the report cannot be created by the computer at all; it has to be entered via the clipboard into Konbest. Finally Konbest creates a pdf file that is send back to the treating physician as laboratory result report.

Konbest classifies the drug concentration according to these relations in a TDM 9-field-board (Haen 2011): In row 1, all drug concentrations are found that were influenced by an metabolic pathway induced by drug-drug interaction or by genetically fast metabolizers; in row 2, all drug concentrations are found that were

quantified in “normal” patients; in row 3, all drug concentrations are found that were influenced by an metabolic pathway inhibited by drug-drug interaction or by genetically slow metabolizers.

TDM software like Konbest not only supports the practice of TDM but also assembles multiple data on the pharmacotherapy under everyday clinical conditions. It thus builds up over time a mine that is suitable for research. Systematic collection of data on drug exposure, serum concentrations and clinical characteristics as well as outcomes can generate practice-based evidence. A German-Swiss-Austrian competence network for TDM in child and adolescent psychiatry used such approach (Taurines et al. 2013). They compiled a multicentre Internet-based data infrastructure to document and collect demographic, safety and efficacy data as well as blood concentrations of psychotropic drugs in children and adolescents (for further information, see www.tdm-kjp.com). More recently, a large multicenter clinical trial («TDM-VIGIL»), funded by the German Federal Institute for Drugs and Medical Devices, has begun to collect epidemiological prescription and safety data of psychotropic drugs in children and adolescents (Egberts et al. 2015).

6.4 Drug Level Monitoring for Pharmacovigilance

When using drug level monitoring for pharmacovigilance purposes, supervision of the medication can directly prevent the occurrence of adverse drug reactions. They can occur when drug concentrations are abnormally high. Typical reasons are drug-drug interactions when a critical drug combination that contains an inhibitor of a drug metabolizing enzyme is prescribed. Using TDM, the dose can be adapted. Other pharmacovigilance-related indications aiming to prevent problems of tolerability or adverse effects are treatment of old-aged patients, children or adolescent patients and patients with comorbid diseases. In these patients, pharmacokinetically relevant alterations of renal or liver function may occur. Another group of risk patients are those with CYP gene variants that give rise to abnormal drug concentrations. For such patients, the dose can be easily adapted by TDM when plasma levels are measured regularly to avoid critical drug concentrations that may lead to side effects or loss of action (Fig. 6.2).

When unwanted side effects occur unexpectedly, drug concentration measurement in the blood is useful for clarification. How to do this step by step is shown schematically in Fig. 6.4. The algorithm indicates the usefulness of drug monitoring in case of side effects, intoxications or relapses (Fig. 6.5).

When the drug concentration is within the recommended therapeutic reference range, evidence is given that a pharmacodynamic or a patient-specific problem. When the drug concentration is lower than expected, CYP-inducing comedication, heavy smoking or other factors can be relevant. The most frequent reason, however, is non-adherence to medication. When the latter can be excluded, the dose can be adapted or changed even if inducing co-medication is taken. For a few patients, an ultrarapid metabolizer status of CYP2D6 may be relevant. This must be considered

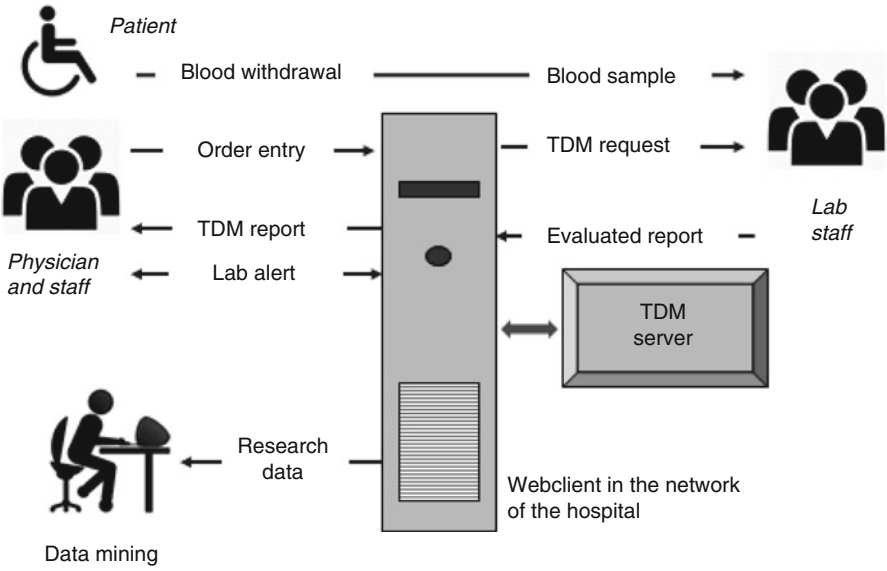

Fig. 6.4 Information technology (IT) supported therapeutic drug monitoring (TDM) to individually optimize pharmacotherapy of psychiatric patients. Computerized physician order entry and reporting of results support clinical decision making. Collected data can be used as a mine for retrospective analysis of pharmacotherapy and treatment outcomes under everyday clinical conditions

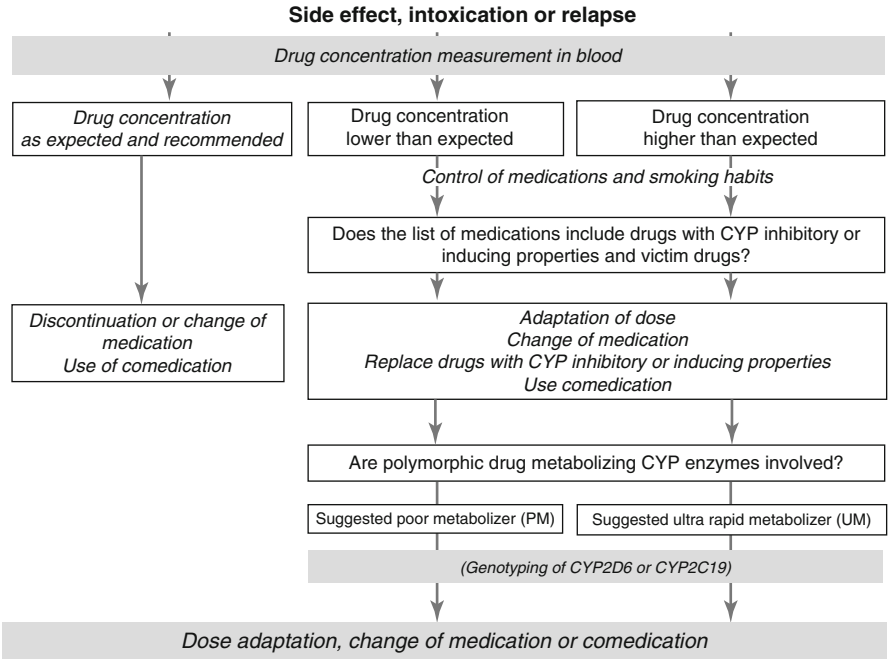

Fig. 6.5 Algorithm for the use of drug concentration measurement in the blood. In case of side effects, intoxications or relapses, it is advisable to measure drug concentrations for problem solving and for rationale clinical decision making

when the victim drug is a substrate of CYP2D6. For such cases, genotyping can be useful for clarification (Spina and de Leon 2015).

Case 1
A depressed male patient, aged 60 years, was treated for months with several antidepressant drugs without any clinical improvement. Other antidepressant drugs, especially those with noradrenaline reuptake inhibiting activity (doxepin and venlafaxine), were not tolerated. When prescribing escitalopram (up to 20 mg/day), the medication was well tolerated, but it did not lead to sufficient clinical improvement. Measuring the escitalopram concentration in blood revealed 10 ng/mL. This was below the therapeutic reference range of 15–80 ng/mL (Table 6.1). Dose increase up to 80 mg which was fourfold above the recommended maximal dose was required to attain therapeutic levels. Under these conditions, full remission was reached.

For this patient, plasma level monitoring could clarify an abnormally rapid elimination of escitalopram. CYP2C19 is the predominant enzyme involved in the degradation of escitalopram. High CYP2C19 activity could not be explained by CYP2C19 inducing medication or an abnormal genotype. Under TDM control, it was possible to apply supra-therapeutic doses and thus attain remission. Reasons for non-response or tolerability problems under other antidepressant medications remained obscure since plasma concentration measurement was not used for clarification.

Case 2
A schizophrenic male patient, aged 56 years and heavy smoker, was under stable daily medication with 10 mg olanzapine and 50 mg amitriptyline. Because of occurrence of psychotic symptoms, the olanzapine dose was increased to 20 mg. In parallel, an acute infection occurred which was associated with a severe cough. The patient stopped smoking and had soon a severe accident by bike (broken shoulder). In the intensive care unit, medication was discontinued. The consulting psychiatrist recommended TDM, and blood was taken 48 h after the last intake of olanzapine. Laboratory analysis revealed 113 ng/mL olanzapine which was above the upper threshold level of the reference range. Amitriptyline and nortriptyline were not detectable. Considering the elimination half-life, it was extrapolated that the concentration of olanzapine was above 300 ng/mL and thus above the laboratory alert level of 150 ng/mL. The accident could thus be explained as a drug-induced delirium. Suicidal ideations were not present.

For this patient, drug level measurement could clarify that the concentration of olanzapine in the blood had increased because of two reasons. The dose had been increased from 10 to 20 mg/day. Moreover, cessation of smoking decreased the activity of CYP1A2. CYP1A2 is relevant for olanzapine, and it is induced by smoking. The inducing effect of smoke was interrupted due to cessation of smoking.

6.5 Drug Level Monitoring for Detection and Characterization of Pharmacokinetic Drug-Drug Interactions

During the last 30 years of psychopharmacotherapy, the most important finding brought about by TDM with regard to pharmacovigilance was detection of drug-drug interactions. In a considerable number of cases supervised by TDM clinically relevant drug-drug interactions were found. Representative examples are given in Table 6.2.

Using TDM, it was recognized that most new antidepressants are strong inhibitors of CYPs. Fluoxetine, paroxetine, duloxetine and bupropion inhibit CYP2D6; fluvoxamine inhibits CYP1A2 and CYP2C19; moclobemide CYP2C19 and CYP2D6; and nefazodone CYP3A4. For all these drugs, their inhibitory potential was unknown when the drugs were introduced on the market. Testing of CYP inhibitory and inducing properties of drugs in the early clinical phase of drug development has therefore become obligatory for drug development.

Observations on drug-drug interactions gave rise to multiple prospective studies to verify the case report-based findings on drug-drug interactions and to quantify the magnitude of inhibitory or inducing properties of drugs. Thus drug-drug interactions were studied prospectively between fluvoxamine and imipramine (Spina et al. 1992, 1993b), fluvoxamine or fluoxetine and carbamazepine (Spina et al. 1993a, 1998), fluoxetine or fluvoxamine and tricyclic antidepressant and antipsychotic drugs (Vandel et al. 1995), phenobarbital and desipramine Spina et al. (1996), fluvoxamine and clozapine (Szegedi et al. 1995; Wetzel et al. 1998), fluvoxamine and clomipramine (Szegedi et al. 1996), ketoconazole and carbamazepine (Spina et al. 1997), paroxetine or sertraline and clozapine (Spina et al. 2000b), moclobemide and dextromethorphan (Härtter et al. 1998), risperidone with carbamazepine and valproate (Spina et al. 2000a), fluoxetine or paroxetine and risperidone (Spina et al. 2001a, 2002), reboxetine and clozapine or risperidone (Spina et al. 2001b), fluvoxamine and olanzapine (Hiemke et al. 2002), sertraline and risperidone (Spina et al. 2004), lamotrigine and clozapine, olanzapine or risperidone (Spina et al. 2006), and valproate and olanzapine (Spina et al. 2009).

Drug-drug interactions identified by case reports should always be verified, since a single case does not allow generalization of the finding. The best way of verification is a prospective, well-controlled clinical trial as mentioned above. When case reports, however, found severe adverse event by a drug combination, prospective studies can be ethically problematic. Then it is advantageous to conduct retrospective analysis using collected TDM data especially when computerized data entry ordering and reporting systems for TDM. When large TDM databases are available, it is possible to analyse drug-drug interactions retrospectively. Examples for publications that used this approach are summarized in Table 6.3.

TDM databases can be most informative for pharmacovigilance. So far such databases are rare. Actual routine laboratory software is not suitable. Clinical data on diagnoses, psychopathology or side effects or complete information on

Table 6.2 Drug-drug interactions identified by TDM in single cases

Inhibitory or inducing drug	Victim drug	Effect	Suggested mechanism	Reference
Fluvoxamine	Imipramine	Dramatic increase of imipramine and desipramine plasma concentration and side effects	Inhibition of CYP1A2, CYP2C19	Spina et al. (1992)
Fluvoxamine	Clozapine	Increase of clozapine plasma concentration, side effects, improved tolerability after dose reduction	Inhibition of CYP1A2 and CYP219	Hiemke et al. (1994)
				Szegedi et al. (1996)
Fluvoxamine	Methadone	40–100 % increase of methadone plasma concentration	Inhibition of methadone clearance	Bertschy et al. (1994)
Fluvoxamine	Trimipramine	Increase of trimipramine plasma concentration	Inhibition of CYP2C19 and CYP1A2	Seifritz et al. (1994)
Fluvoxamine	Clomipramine	Increase of clomipramine plasma concentration, improved response	Inhibition of CYP1A2 and CYP2C19	Conus et al. (1996)
Fluoxetine	Methadone	Moderate increase of methadone plasma concentration	Inhibition of CYP2D6 and CYP3A4	Bertschy et al. (1996)
Oxybutynin	Clomipramine	Decreased plasma concentrations of clomipramine and norclomipramine	Induction of CYP3A4	Grözinger et al. (1999)
Efavirenz	Methadone	Decrease of methadone plasma concentration, withdrawal symptoms	Induction of CYP2B6	Marzolini et al. (2000)
Mianserine	Venlafaxine	Increase of venlafaxine plasma concentration	Inhibition of CYP2D6	Eap et al. (2000)
Propofol				
Thioridazine				
Fluoxetine	Tramadol	Increased plasma concentration, serotonin syndrome	Inhibition of CYP2D6	Lange-Asschenfeldt et al. (2002)
Terbinafine	Amitriptyline	Prolonged increase of amitriptyline plasma concentrations, anticholinergic side effects	Inhibition of CYP2D6	Castberg et al. (2005)
Fluoxetine	Venlafaxine	Increase of venlafaxine plasma concentration and side effects	Inhibition of CYP2D6	Gerbaulet et al. (2012)
Cotrimoxazole	Venlafaxine	Increase of venlafaxine and side effects (tremor)	Inhibition of CYP2C9 in a PM of CYP2C19	Geber et al. (2013)
Melperone	Nortriptyline	Increase of nortriptyline plasma concentration, side effects	Inhibition of CYP2D6	Hefner et al. (2014)

Table 6.3 Drug-drug interactions identified and characterized by retrospective analysis of TDM data

Inhibitory or inducing drug	Victim drug	Effect	Suggested mechanism	Reference
Fluvoxamine	Clozapine	Increase of clozapine plasma concentration, occurrence of side effects	Inhibition of CYP1A2 and CYP219	Jerling et al. (1994b)
Levomepromazine, perphenazine, thioridazine	Amitriptyline	Increase of amitriptyline and plasma concentration, occurrence of side effects	Inhibition of CYP1A2 and CYP219	Jerling et al. (1994a)
Valproate Carbamazepine	Risperidone	Decrease of risperidone active moiety plasma concentration	Induction of CYP3A4	Spina et al. (2000a, b)
Lamotrigine Lorazepam Mirtazapine Oxcarbazepine Topiramate Valproate	Olanzapine	No effect on olanzapine plasma concentration		Botts et al. (2008)
Valproate	Clozapine	Decrease of clozapine plasma concentration	Induction of clozapine metabolism	Diaz et al. (2014)
Esomeprazole Lansoprazole Omeprazole Pansoprazole	Escitalopram Citalopram Sertraline	Increase of escitalopram and citalopram but not of sertraline concentration by omeprazole and esomeprazole	Inhibition of CYP2C19	Gjestadt et al. (2015)

prescribed drugs and doses are mostly missing. Nevertheless, when information is restricted to plasma concentrations, dose and co-medication, it is possible to evaluate at least pharmacokinetic aspects. Only few institutions have access to TDM data mines, and when available, they often do not use their databases for research. Examples for TDM studies that used the data mining approach are shown in Table 6.3.

6.6 Drug Level Monitoring in Risk Patients

Another example for the usefulness of TDM data mines and pharmacovigilance is psychiatric risk patients. Pregnant or breastfeeding patients, children or adolescent patients, individuals with intellectual disabilities, elderly patients, especially patients aged above 75 years, patients with co-morbid diseases or patients in

forensic psychiatry are generally excluded from clinical trials. Individuals with intellectual disabilities or patients in forensic psychiatry clinical trials are not allowed. For such patients, many psychoactive drugs are not approved for use. Therefore TDM is highly recommended for these patients (Hiemke et al. 2011). For pregnant or breastfeeding women, TDM aims to minimize the risk of relapse on the mother's side and, at the same time, to minimize risks associated with drug exposure of the foetus or the child. Moreover, pharmacokinetics and pharmacodynamics change during development. Ageing involves progressive impairments of the functional reserve of multiple organs, especially renal excretion, and body composition changes significantly. Hepatic clearance can be reduced by up to 30 % with phase I reactions being more likely to be impaired than phase II reactions.

To raise data on the effectiveness and tolerability of psychoactive drugs in these patients TDM is most useful. First results are available for children and adolescent psychiatric patients (Cherma et al. 2011; Taurines et al. 2013; Egberts et al. 2011, 2015). For old-aged patients the medication with citalopram and/or venlafaxine was analysed (Sigurdsson et al. 2014; Unterecker et al. 2012; Wenzel-Seifert et al. 2014). Old-aged patients exhibited a higher risk for adverse reactions under citalopram (Wenzel-Seifert et al. 2014), and a 42 % higher dose-adjusted plasma concentration was found for venlafaxine (Sigurdsson et al. 2014). Castberg and Spigset (2008) analysed data in a high-security forensic unit and found higher doses in forensic patients than in a control group. The dose-related plasma concentrations were significantly lower for olanzapine but higher for quetiapine in the forensic patients than in the control group. Pfuhlmann and co-workers used TDM data in conjunction with routine laboratory data (Pfuhlmann et al. 2009). They could thus show for clozapine that patients with abnormally high levels of serum levels had significantly more often pathological C reactive protein (CRP) levels, a common laboratory parameter indicating signs of inflammation. Logistic regression analysis revealed CRP elevation as the most relevant predictive factor for an increase of clozapine serum levels.

Overall the number of publications that used the data mining approach is so far limited. The rapid development of information technology and the broader use of TDM in the future will certainly have stimulating effects on such efforts.

6.7 Conclusion and Perspective

The common objectives of TDM and pharmacovigilance are supervision of medication in everyday clinical practice and improvement of tolerability and safety of medications. When TDM is used appropriately and more frequently than so far, treatment efficiency and safety of psychotropic medication will improve. TDM has the potential to become a highly suitable tool for pharmacovigilance. Computerized drug monitoring will gather valid information on clinical interventions and outcomes. In conjunction with computerized decision support systems, it will be able to analyse treatment strategies and outcomes. In psychiatry, there is an urgent need

for perfection of treatment available and a need for studies analysing treatment under everyday conditions, especially for aged patients and other risk patients who require pharmacotherapy but are normally excluded from clinical trials. Commercial laboratory software is actually not suitable for TDM and pharmacovigilance. Effective packages are on the way to become available (e.g. www.konbest.de). Information technology systems can support knowledge-based optimal drug dosing and clinical decision making in a user-friendly way and thereby build up a platform suitable for health-care research on drug treatment, especially for pharmacovigilance research.

References

Åsberg M, Crönholm B, Sjöqvist F, Tuck D (1971) Relationship between plasma level and therapeutic effect of nortriptyline. Br Med J 3(5770):331–334

Bates DW (1998) Improving the use of therapeutic drug monitoring. Ther Drug Monit 20:550–555

Baumann P, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, Kuss HJ, Laux G, Müller-Oerlinghausen B, Rao ML, Riederer P, Zernig G (2004) Arbeitsge-meinschaft fur neuropsychopharmakologie und pharmakopsychiatrie. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 37(6):243–265

Bertschy G, Baumann P, Eap CB, Baettig D (1994) Probable metabolic interaction between methadone and fluvoxamine in addict patients. Ther Drug Monit 16(1):42–45

Bertschy G, Eap CB, Powell K, Baumann P (1996) Fluoxetine addition to methadone in addicts: pharmacokinetic aspects. Ther Drug Monit 18(5):570–572

Botts S, Diaz FJ, Santoro V, Spina E, Muscatello MR, Cogollo M, Castro FE, de Leon J (2008) Estimating the effects of co-medications on plasma olanzapine concentrations by using a mixed model. Prog Neuropsychopharmacol Biol Psychiatry 32(6):1453–1458

Castberg I, Spigset O (2008) Prescribing patterns and the use of therapeutic drug monitoring of psychotropic medication in a psychiatric high-security unit. Ther Drug Monit 30(5):597–603

Castberg I, Helle J, Aamo TO (2005) Prolonged pharmacokinetic drug interaction between terbinafine and amitriptyline. Ther Drug Monit 27(5):680–682

Chermá MD, Ahlner J, Bengtsson F, Gustafsson PA (2011) Antidepressant drugs in children and adolescents: analytical and demographic data in a naturalistic, clinical study. J Clin Psychopharmacol 31(1):98–102

Conus P, Bondolfi G, Eap CB, Macciardi F, Baumann P (1996) Pharmacokinetic fluvoxamine-clomipramine interaction with favorable therapeutic consequences in therapy-resistant depressive patient. Pharmacopsychiatry 29(3):108–110

Diaz FJ, Eap CB, Ansermot N, Crettol S, Spina E, de Leon J (2014) Can valproic acid be an inducer of clozapine metabolism? Pharmacopsychiatry 47(3):89–96

Eap CB, Bertel-Laubscher R, Zullino D, Amey M, Baumann P (2000) Marked increase of venlafaxine enantiomer concentrations as a consequence of metabolic interactions: a case report. Pharmacopsychiatry 33(3):112–115

Egberts KM, Mehler-Wex C, Gerlach M (2011) Therapeutic drug monitoring in child and adolescent psychiatry. Pharmacopsychiatry 44(6):249–253

Egberts K, Karwautz A, Plener PL, Mehler-Wex C, Kölch M, Dang SY, Taurines R, Romanos M, Gerlach M (2015) Pharmacovigilance in child and adolescent psychiatry. Z Kinder Jugendpsychiatr Psychother 43(1):21–28

EMA (2014) Guideline on good pharmacovigilance practices http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf

Fry DE, Marks V (1971) Value of plasma-lithium monitoring. Lancet 1(7705):886–888

Geber C, Ostad Haji E, Schlicht K, Hiemke C, Tadić A (2013) Severe tremor after cotrimoxazole-induced elevation of venlafaxine serum concentrations in a patient with major depressive disorder. Ther Drug Monit 35(3):279–282

Gerbaulet M, Engel A, Hiemke C, Dahmen N (2012) High venlafaxine serum levels after prior fluoxetine medication. J Clin Psychopharmacol 32(2):295–297

Gjestad C, Westin AA, Skogvoll E, Spigset O (2015) Effect of proton pump inhibitors on the serum concentrations of the selective serotonin reuptake inhibitorscitalopram, escitalopram, and sertraline. Ther Drug Monit 37(1):90–97

Grözinger M, Härtter S, Hiemke C, Röschke J (1999) Oxybutynin enhances themetabolism of clomipramine and dextrorphan possibly by induction of a cytochrome P450 isoenzyme. J Clin Psychopharmacol 19(3):287–289

Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T (2015) The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Med 13(1):74 [Epub ahead of print]

Guy W (1976) Early clinical drug evaluation unit (ECDEU) assessment manual for psychopharmacology. Revised. NIMH publication (DHEW publ No ADM 76-338). National Institute of Mental Health, Bethesda, p 217–222

Haen E (2011) Therapeutic drug monitoring in pharmacovigilance and pharmacotherapy safety. Pharmacopsychiatry 44(6):254–258

Haen E, Greiner C, Bader W, Wittmann M (2008) Expanding therapeutic reference ranges using dose-related reference ranges. Nervenarzt 79(5):558–566

Härtter S, Dingemanse J, Baier D, Ziegler G, Hiemke C (1998) Inhibition of dextromethorphan metabolism by moclobemide. Psychopharmacology (Berl) 135(1):22–26

Hefner G, Laib AK, Sigurdsson H, Hohner M, Hiemke C (2013) The value of drug and metabolite concentration in blood as a biomarker of psychopharmacological therapy. Int Rev Psychiatry 25(5):494–508

Hefner G, Geschke K, Hiemke C (2014) Severe adverse drug events under combination of nortriptyline and melperone due to pharmacokinetic interaction. J Clin Psychopharmacol 34(3): 394–396

Hiemke C, Weigmann H, Härtter S, Dahmen N, Wetzel H, Müller H (1994) Elevated levels of clozapine in serum after addition of fluvoxamine. J Clin Psychopharmacol 14(4):279–281

Hiemke C, Peled A, Jabarin M, Hadjez J, Weigmann H, Härtter S, Modai I, Ritsner M, Silver H (2002) Fluvoxamine augmentation of olanzapine in chronic schizophrenia: pharmacokinetic interactions and clinical effects. J Clin Psychopharmacol 22(5):502–506

Hiemke C, Dragicevic A, Gründer G, Hätter S, Sachse J, Vernaleken I, Müller MJ (2004) Therapeutic monitoring of new antipsychotic drugs. Ther Drug Monit 26(2):156–160

Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, Egberts K, Fric M, Gerlach M, Greiner C, Gründer G, Haen E, Havemann-Reinecke U, Jaquenoud Sirot E, Kirchherr H, Laux G, Lutz UC, Messer T, Müller MJ, Pfuhlmann B, Rambeck B, Riederer P, Schoppek B, Stingl J, Uhr M, Ulrich S, Waschgler R, Zernig G (2011) AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry 44(6): 195–235

Jaquenoud Sirot E, van der Velden JW, Rentsch K, Eap CB, Baumann P (2006) Therapeutic drug monitoring and pharmacogenetic tests as tools in pharmacovigilance. Drug Saf 29(9): 735–768

Jerling M, Bertilsson L, Sjöqvist F (1994a) The use of therapeutic drug monitoring data to document kinetic drug interactions: an example with amitriptyline and nortriptyline. Ther Drug Monit 16(1):1–12

Jerling M, Lindström L, Bondesson U, Bertilsson L (1994b) Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. Ther Drug Monit 16(4):368–374

Lange-Asschenfeldt C, Weigmann H, Hiemke C, Mann K (2002) Serotonin syndrome as a result of fluoxetine in a patient with tramadol abuse: plasma level-correlated symptomatology. J Clin Psychopharmacol 22(4):440–441

Lingjærde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K (1987) The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 334:1–100

Marzolini C, Troillet N, Telenti A, Baumann P, Decosterd LA, Eap CB (2000) Efavirenz decreases methadone blood concentrations. AIDS 14(9):1291–1292

Ostad Haji E, Hiemke C, Pfuhlmann B (2012) Therapeutic drug monitoring for antidepressant drug treatment. Curr Pharm Des 18(36):5818–5827

Pfuhlmann B, Hiemke C, Unterecker S, Burger R, Schmidtke A, Riederer P, Deckert J, Jabs B (2009) Toxic clozapine serum levels during inflammatory reactions. J Clin Psychopharmacol 29(4):392–394

Preskorn SH, Fast GA (1991) Therapeutic drug monitoring for antidepressants: efficacy, safety, and cost effectiveness. J Clin Psychiatry 52(Suppl):23–33

Preskorn SH, Fast GA (1992) Tricyclic antidepressant-induced seizures and plasma drug concentration. J Clin Psychiatry 53(5):160–162

Seifritz E, Holsboer-Trachsler E, Hemmeter U, Eap CB, Baumann P (1994) Increased trimipramine plasma levels during fluvoxamine comedication. Eur Neuropsychopharmacol 4(1):15–20

Sigurdsson HP, Hefner G, Ben-Omar N, Köstlbacher A, Wenzel-Seifert K, Hiemke C, Haen E (2014) Steady-state serum concentrations of venlafaxine in patients with late-life depression. Impact of age, sex and BMI. J Neural Transm [Epub ahead of print] PubMed

Simpson GM, Cooper TA (1978) Clozapine plasma levels and convulsions. Am J Psychiatry 135(1):99–100

Sjöqvist F, Bertilsson L, Asberg M (1980) Monitoring tricyclic antidepressants. Ther Drug Monit 2(1):85–93

Spina E, de Leon J (2015) Clinical applications of CYP genotyping in psychiatry. J Neural Transm 122(1):5–28

Spina E, Campo GM, Avenoso A, Pollicino MA, Caputi AP (1992) Interaction between fluvoxamine and imipramine/desipramine in four patients. Ther Drug Monit 14(3):194–196

Spina E, Avenoso A, Pollicino AM, Caputi AP, Fazio A, Pisani F (1993a) Carbamazepine coadministration with fluoxetine or fluvoxamine. Ther Drug Monit 15(3):247–250

Spina E, Pollicino AM, Avenoso A, Campo GM, Perucca E, Caputi AP (1993b) Effect of fluvoxamine on the pharmacokinetics of imipramine and desipramine in healthy subjects. Ther Drug Monit 15(3):243–246

Spina E, Avenoso A, Campo GM, Caputi AP, Perucca E (1996) Phenobarbital induces the 2-hydroxylation of desipramine. Ther Drug Monit 18(1):60–64

Spina E, Arena D, Scordo MG, Fazio A, Pisani F, Perucca E (1997) Elevation of plasma carbamazepine concentrations by ketoconazole in patients with epilepsy. Ther Drug Monit 19(5):535–538

Spina E, Avenoso A, Facciolà G, Fabrazzo M, Monteleone P, Maj M, Perucca E, Caputi AP (1998) Effect of fluoxetine on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenia. Int Clin Psychopharmacol 13(3):141–145

Spina E, Avenoso A, Facciolà G, Salemi M, Scordo MG, Giacobello T, Madia AG, Perucca E (2000a) Plasma concentrations of risperidone and 9-hydroxyrisperidone: effect of comedication with carbamazepine or valproate. Ther Drug Monit 22(4):481–485

Spina E, Avenoso A, Salemi M, Facciolá G, Scordo MG, Ancione M, Madia A (2000b) Plasma concentrations of clozapine and its major metabolites during combined treatment with paroxetine or sertraline. Pharmacopsychiatry 33(6):213–217

Spina E, Avenoso A, Facciolà G, Scordo MG, Ancione M, Madia A (2001a) Plasmaconcentrations of risperidone and 9-hydroxyrisperidone during combined treatment with paroxetine. Ther Drug Monit 23(3):223–227

Spina E, Avenoso A, Scordo MG, Ancione M, Madia A, Levita A (2001b) No effect ofreboxetine on plasma concentrations of clozapine, risperidone, and their activemetabolites. Ther Drug Monit 23(6):675–678

Spina E, Avenoso A, Scordo MG, Ancione M, Madia A, Gatti G, Perucca E (2002) Inhibition of risperidone metabolism by fluoxetine in patients with schizophrenia: a clinically relevant pharmacokinetic drug interaction. J Clin Psychopharmacol 22(4):419–423

Spina E, D'Arrigo C, Migliardi G, Morgante L, Zoccali R, Ancione M, Madia A (2004) Plasma risperidone concentrations during combined treatment with sertraline. Ther Drug Monit 26(4):386–390

Spina E, D'Arrigo C, Migliardi G, Santoro V, Muscatello MR, Micò U, D'Amico G, Perucca E (2006) Effect of adjunctive lamotrigine treatment on the plasma concentrations of clozapine, risperidone and olanzapine in patients with schizophrenia or bipolar disorder. Ther Drug Monit 28(5):599–602

Spina E, D'Arrigo C, Santoro V, Muscatello MR, Pandolfo G, Zoccali R, Diaz FJ, de Leon J (2009) Effect of valproate on olanzapine plasma concentrations in patients with bipolar or schizoaffective disorder. Ther Drug Monit 31(6):758–763

Szegedi A, Wiesner J, Hiemke C (1995) Improved efficacy and fewer side effects under clozapine treatment after addition of fluvoxamine. J Clin Psychopharmacol 15(2):141–143

Szegedi A, Wetzel H, Leal M, Härtter S, Hiemke C (1996) Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety, and tolerability data. J Clin Psychiatry 57(6):257–264

Taurines R, Burger R, Wewetzer C, Pfuhlmann B, Mehler-Wex C, Gerlach M, Egberts K (2013) The relation between dosage, serum concentrations, and clinical outcome in children and adolescents treated with sertraline: a naturalistic study. Ther Drug Monit 35(1):84–91

Touw DJ, Neef C, Thomson AH, Vinks AA (2005) Cost-effectiveness of Therapeutic Drug Monitoring Committee of the International Association for Therapeutic Drug Monitoring and Clinical Toxicology. Cost-effectiveness of therapeutic drug monitoring: a systematic review. Ther Drug Monit 27(1):10–17

Unterecker S, Hiemke C, Greiner C, Haen E, Jabs B, Deckert J, Pfuhlmann B (2012) The effect of age, sex, smoking and co-medication on serum levels of venlafaxine and O-desmethylvenlafaxine under naturalistic conditions. Pharmacopsychiatry 45(6):229–235

Vandel S, Bertschy G, Baumann P, Bouquet S, Bonin B, Francois T, Sechter D, Bizouard P (1995) Fluvoxamine and fluoxetine: interaction studies with amitriptyline, clomipramine and neuroleptics in phenotyped patients. Pharmacol Res 31(6):347–353

Vuille F, Amey M, Baumann P (1991) Use of plasma level monitoring in clinical practice. Towards an analysis of clinical utility. Pharmacopsychiatry 24:190–195

Wenzel-Seifert K, Brandl R, Hiemke C, Haen E (2014) Influence of concomitant medications on the total clearance and the risk for supra-therapeutic plasma concentrations of Citalopram. A population-based cohort study. Pharmacopsychiatry 47(7):239–244

Wetzel H, Anghelescu I, Szegedi A, Wiesner J, Weigmann H, Härter S, Hiemke C (1998) Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. J Clin Psychopharmacol 18(1):2–9

World Health Organization (WHO) (2002) The importance of pharmacovigilance: safety monitoring of medicinal products. WHO, Genève

Zanger UM, Schwab M (2013) Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther 138(1): 103–141

Zanger UM, Klein K, Thomas M, Rieger JK, Tremmel R, Kandel BA, Klein M, Magdy T (2014) Genetics, epigenetics, and regulation of drug-metabolizing cytochrome p450 enzymes. Clin Pharmacol Ther 95(3):258–261

Chapter 7
The Role of Pharmacogenetics in Pharmacovigilance of Psychotropic Drugs

Alessandro Serretti and Chiara Fabbri

Abstract Compliance to psychotropic medications is often reduced by the emergence of unwanted side effects, and rare life-threatening adverse events to these drugs require strict systems of surveillance. Genetic factors are hypothesized to contribute significantly to the susceptibility of adverse drug reactions (ADRs). Indeed, about 50 % of ADRs in central nervous system disorders may be attributed to pharmacogenomic factors.

Some genotype tests such as HLA-B*1502 when using carbamazepine in populations of Asian descent aid in the prevention of Stevens-Johnson syndrome. This in addition to testing for *CYP2D6* genotypes when using pimozide is already recommended for use in clinical practice. *HLA-DQB1* testing for the susceptibility to clozapine-induced agranulocytosis and *CYP2D6* genotyping in case of polypharmacy could be recommended in the near future, at least in patients with nongenetic risk factors. The most promising findings for future clinical applications include the association between *HTR2C*, *MC4R*, *leptin* genes, and antipsychotic-induced metabolic side effects; *DRD2*, *HTR2A*, *CYP2D6*, *HSPG2*, and *ZFPM2* genes and antipsychotic-induced movement disorders; *SLC6A4*, *HTR2A*, and genes coding for cytochrome P450 isoenzymes and the overall risk of antidepressant-induced ADRs.

Given the preliminary results supporting improved outcomes (including improved tolerability) in case of pharmacogenetic testing and possible cost/benefit ratio improvement, clinical indications for genotyping are expected to increase in the near future.

Keywords Psychotropic drug • Antidepressant • Antipsychotic • Adverse drug reaction • Side effect • Gene • Polymorphism • Pharmacogenetic • Pharmacogenomic • Genotyping

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7.1 Introduction

7.1.1 The Genetic Contribution to Psychotropic Drug-Induced Side Effects

Neuropsychiatric disorders account for 19 % of disability-adjusted life years (DALYs) in Europe, representing the second most frequent cause of disability after cardiovascular diseases (WHO 2004). Psychotropic medications are not less effective than other drugs used in general medicine (Leucht et al. 2012), but treatments tailored to the individual are lacking and compliance to psychotropic drugs is often low due to stigma and also due to the issue of unwanted side effects. For example, treatment nonadherence occurs at a rate between 12 % and 64 % among individuals with bipolar disorder, with consequent increase in the likelihood of relapse and reduction of quality of life (Leclerc et al. 2013).

When considering psychotropic medications, one of the most relevant categories of adverse drug reactions (ADRs) is represented by metabolic ADRs. Patients with severe psychiatric disorders have twice the risk of obesity compared to the general population (Dickerson et al. 2006) and a higher risk of dyslipidemia, glucose intolerance, and type II diabetes. Consequently, cardiovascular diseases represent a main cause of mortality in patients with severe psychiatric diseases (Osborn et al. 2007), making metabolic ADRs in this population a significant health issue. Extrapyramidal side effects (EPS) and drug-induced sexual dysfunction are further critical ADRs due to their high incidence and heavy impact on quality of life. EPS are among the most frequent side effects reported by patients with schizophrenia (almost 60 % of patients), followed by sedation and weight gain (~50 % of patients for each) (Millier et al. 2014). Sexual dysfunction is reported by almost 30 % of patients with schizophrenia, and over 45 % of patients with depression may experience this side effect associated with antidepressant drugs (Baldwin and Foong 2013). In recent years, the issue of antidepressant-induced suicidal ideation also emerged, and efforts have been make to identify risk factors. Finally, some rare but potentially life-threatening ADRs are due to immune-mediated cutaneous hypersensitivity reactions such as carbamazepine- and lamotrigine-induced Stevens-Johnson syndrome (SJS), clozapine-induced agranulocytosis (CIA), and antipsychotic/antidepressant-induced cardiac arrhythmia.

Genetic polymorphisms are hypothesized to play a relevant role in determining the susceptibility to ADRs. It is estimated that genetics account for 20–95 % of variability in drug disposition and pharmacodynamics and about 50 % of adverse drug reactions (ADRs) in the central nervous system (CNS) disorders might be attributed to pharmacogenomic factors (Cacabelos et al. 2012). Twin studies indicate that genetic polymorphisms contribute 60–80 % of the variance observed in antipsychotic-induced weight gain (Gebhardt et al. 2010).

Some clinical applications of pharmacogenetics are already available or will probably be available in the near future (Table 7.1). Such pharmacogenetic data could guide drug choice and/or dose titration. Figure 7.1 represents a schema of current clinical-based and future genotype-clinical-based treatment choice.

Table 7.1 Recommended genotyping test for the prevention of severe psychotropic-induced adverse reactions (ADRs) and promising genes/polymorphisms for clinical application in the near future

Gene	Polymorphism(s)	Drug/drug class	Type of ADR	Comment on evidence
HLA-B	HLA-B*1502	Carbamazepine	Stevens-Johnson syndrome	Recommended in Asian ancestry
CYP2D6	Partially or totally inactive alleles	Pimozide	Arrhythmia	Recommended for doses >4 mg/day in adults and >0.05 mg/kg/day in children
CYP2D6	Partially or totally inactive alleles	Polypharmacy	Overall risk of ADRs	High evidence, probably will be recommended
POLG	A467T, W748S	Valproate	Liver toxicity	Recommended in children/adolescents
CPS1	rs1047891		Hyperammonemia	Recommended in case of suspected urea cycle disorder
HLA-DQB1	6672G>C	Clozapine	Agranulocytosis	Probably will be recommended in the near future
HLA-B	158T			Promising
HTR2C	−759C/T	Antipsychotics	Metabolic ADRs	Promising
MC4R	rs489693			Promising
Leptin	−2548A/G			Promising
CNR1	rs806378, rs1049353			Promising
HTR2A	rs6311, rs6313	Antidepressants	Overall tolerability	Promising
SLC6A4	5-HTTLPR, rs25531			Promising
DRD2	rs1800497	Antipsychotics	Tardive dyskinesia	Promising
HTR2A	102CC, −1438GG			Promising
CYP2D6	Partially or totally inactive alleles			Promising
HSPG2	rs2445142		Parkinsonism	Promising
ZFPM2	rs12678719			Promising

7.1.2 Pharmacogenetics in Focus

Approximately 0.5 % of the DNA sequence is responsible for phenotype (i.e., somatic) differences among humans. This difference consists in di-, tri-, and tetranucleotide repeats (satellite sequences) and large variants >1 kbp due to deletions, insertions, or duplications (copy number variants, CNV) and nucleotide substitutions. Over three million substitutions distinguish the individual genome, and over 80 % of them are in the form of single-nucleotide substitution polymorphism (SNP). Therefore, it has been estimated that SNPs account for over 80 % of the variability between humans,

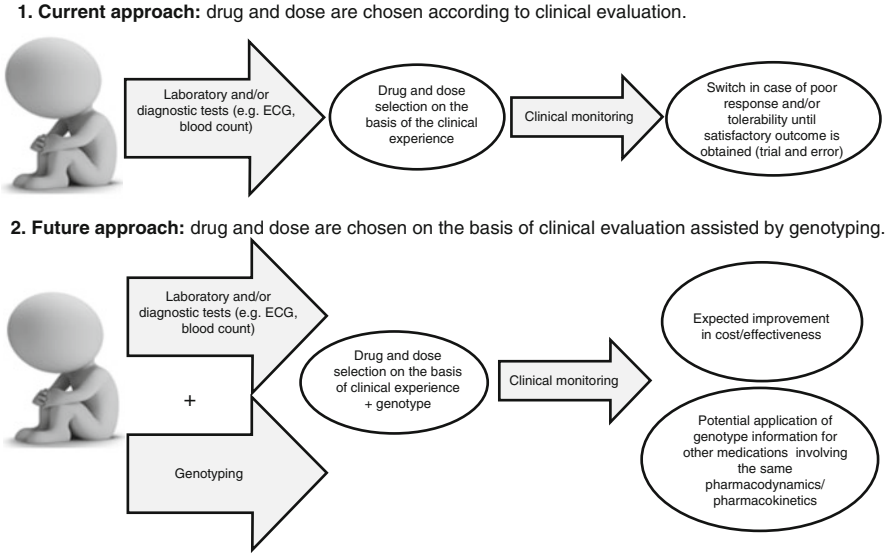

Fig. 7.1 Schematic description of the current approach in the choice of psychotropic medications (*1*) and expected future approach based on both clinical judgment and genotype information (*2*)

including liability to ADRs (Roberts et al. 2010). The Human Genome Project (HGP), which started in 1990 and was completed in 2003, with further analysis still being published, has made possible to determine the sequence of chemical base pairs which make up DNA and to identify and map the approximately 20,000–25,000 genes of the human genome from both a physical standpoint and functional standpoint.

The largest part of available data regarding the pharmacogenetics of ADRs has been obtained through candidate gene studies. Candidate genes are selected on the basis of their biological role and polymorphisms on the basis of their functional role (i.e., a known impact on gene function resulting in a variation in the level/function of the product), tagging properties (linkage disequilibrium with near variants), or position (in regulatory regions). In the last decade, genome-wide association studies (GWAS) were introduced and have rapidly expanded, since they provide hundreds of thousands of variants, thanks to the array technology without the need of any a priori hypothesis. Obviously, GWAS have some limitations (in particular the limited covering of genetic polymorphisms provided by the currently available platforms and the common difficulty in explaining the biological meaning of findings).

7.2 Pharmacogenetics of Antidepressant-Induced Side Effects

Antidepressant drugs are among the most frequently prescribed drugs worldwide. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are usually better tolerated than first-generation

antidepressants (tricyclic antidepressants or TCAs; inhibitors of monoamino oxidase or MAOIs). Nevertheless, some patients require treatment with the latter group of antidepressants or are genetically predisposed to develop idiosyncratic ADRs at therapeutic dosages (an abnormal effect due to polymorphisms in metabolic enzymes or target molecules) or to have an increased risk of overdose from drug with a well-defined and wide therapeutic index. Some patients are at higher risk of severe ADRs because of medical comorbidities, concomitant medications, and/or old age. Finally, the issue of treatment-induced suicidal ideation (TESI) when prescribing antidepressants led regulatory authorities to issue warnings to clinicians (US Food and Drug Administration 2006). Pharmacogenetics can provide clinically useful information on the safe use of antidepressant drugs, especially in patients at increased risk of ADRs due to individual, pharmacological, and/or environmental factors.

7.2.1 Treatment-Emergent Suicidal Behavior (TESI)

Family studies support a genetic contribution to suicidal behavior (SB) (Brent and Mann 2005). Candidate gene studies were focused especially on serotonin-related genes since low central nervous system (CNS) serotonin (5-HT) turnover was demonstrated in SB (Mann 2003). Consistently, the association of SB with variants in the serotonin transporter gene (*SLC6A4*) (Li and He 2007) and the tryptophan hydroxylase 1 gene (*TPH1* that codes for the rate-limiting enzyme responsible for 5-HT biosynthesis) (Bellivier et al. 2004) was supported at meta-analytic level. The noradrenergic system and especially the alpha 2A-adrenergic receptor gene (*ADRA2A*) have also been implicated in SB (Escriba et al. 2004; Sequeira et al. 2004) with an effect that may be higher in patients treated with noradrenergic antidepressants and in males (Perroud et al. 2009). The noradrenergic system is implicated in the modulation of aggressive and impulsive behaviors, and enhanced noradrenergic activity may have a role in treatment-emergent suicidal behavior (TESI). Thus, the enhanced activity or hypersensitivity of *ADRA2A* receptors may be associated with higher suicidal ideation during treatment with noradrenergic antidepressants.

Other candidate gene studies suggested the involvement of brain-derived neurotrophic factor gene (*BDNF*) and the gene coding for its receptor, the neurotrophic tyrosine kinase receptor type 2 (*NTRK2*) (Perroud et al. 2008). These genes are involved in the regulation and growth of 5-HT neurons and are mediators of neural plasticity in response to acute and chronic stress. The cyclic adenosine monophosphate (cAMP) response element binding (*CREB1*) protein gene is involved in the regulation of *BDNF* expression, and it has also been associated with TESI (Perlis et al. 2007).

In addition to dysregulation in the monoaminergic and neurotrophic systems, the hypothalamic-pituitary-adrenal (HPA) axis and inflammatory pathways have been also proposed as modulators of TESI. Indeed, altered sensitivity to glucocorticoids

and increase in proinflammatory cytokines were demonstrated in depression and particularly in suicide victims. BDNF and 5-HT positively modulate neurogenesis in the hippocampus (a pivotal area involved in depression pathogenesis), and the hippocampus in turn regulates HPA axis function and response to stress. In depressed subjects, hippocampal atrophy (due to reduced cell proliferation, cell survival, and cell differentiation) promotes impaired regulation of HPA axis activity (Mahar et al. 2014). FK506-binding protein 5 (*FKBP5*) gene, which codes for a protein that decreases the sensitivity of the glucocorticoid receptor to the effect of corticosteroids, was suggested as a modulator of TESI (Mandelli and Serretti 2013).

The role of glutamate in modulating mood and antidepressant response has been increasingly recognized, due to observations that existing antidepressants modulate various glutamatergic pathways. Disrupted glutamatergic-noradrenergic interactions at the level of the stress-sensitive locus coeruleus (LC) were demonstrated in depression and suicide victims (Chandley et al. 2014). Accordingly, polymorphisms in glutamate receptor genes *GRIK2* and *GRIA3* were associated with TESI during SSRI treatment (Laje et al. 2007).

Genome-wide association studies (GWAS) did not report the above genes among their top findings but outlined other genes that may involved in TESI. Associations were found for genetic variants within the loci encoding papilin (*PAPLN*) and IL-28 α-receptor (*IL28RA*) genes (Laje et al. 2009) and in the vicinity of the guanine deaminase (*GDA*) gene (Perroud et al. 2012). *IL28RA* encodes a cytokine receptor, while papilin is involved in the regulation of extracellular matrix remodeling, a process that affects the release of bioactive fragments that function as immune modulators (Korpos et al. 2009). The involvement of these genes in TESI is therefore consistent with the inflammation theory of depression and SB. On the other hand, *GDA* encodes an enzyme responsible for the hydrolytic deamination of guanine and is probably involved in microtubule assembly. No clear biological rationale links this gene to TESI. A recent development of GWAS is based on multimarker analyses given the hypothesis that multiple genetic variants contribute to complex phenotypes such as TESI. A cluster of 79 SNPs demonstrated a 94 % probability of predicting the nonoccurrence of TESI (negative predictive value), even with only a 48 % probability of correctly identifying TESI (positive predictive value) (Menke et al. 2012), but with no confirmation of this finding so far.

Given the complex and multifactorial pathogenesis of TESI, it seems unlikely that genotyping could be able to prevent it adequately.

7.2.2 Cardiovascular Side Effects

Tricyclic antidepressants (TCAs) have a higher risk of cardiovascular side effects compared to other antidepressants, even in patients with no previous cardiovascular disease (Pacher and Kecskemeti 2004). The most common among such side effects is the slowing of intraventricular conduction, manifested by prolonged PR, QRS, and QT intervals on the standard ECG, and orthostatic hypotension. TCAs have

been demonstrated to exert I/A class antiarrhythmic effects and antinoradrenergic and anticholinergic effects that are responsible for their cardiovascular ADRs.

The identification of genetic polymorphisms predicting the risk of intraventricular conduction alterations induced by antidepressants could help clinicians to prevent life-threatening side effects. So far, a number of genes have been associated with arrhythmia: *SCN5A*, *SCN4B*, *CACNL1AC*, *KCNH2*, *KCNQ1*, *KCNE1*, *ANK2*, *ALG10*, *KCNJ2*, *KCNE2*, *RYR2*, *KCND3*, *KCND2*, *ACE*, *NOS1AP*, *CASQ2*, and *Rad* (Drago et al. 2008). These genes are good candidates for the definition of a genetic proarrhythmic profile, but evidence is still lacking for antidepressant drugs.

Changes in systemic blood pressure are possible especially during treatment with antidepressants that affect the activity of the noradrenergic system (norepinephrine (NE) reuptake, transport, and elimination from the synapse). Blood pressure changes are mediated through the autonomic nervous system in part by the neurotransmitter NE. Selective NE transporter (NET) blockade creates a phenotype that resembles idiopathic orthostatic intolerance (Schroeder et al. 2002), but the gene encoding this transporter (*SLC6A2*) was very marginally associated with blood pressure changes during treatment with duloxetine (an SNRI antidepressant drug). Other noradrenergic genes (*ADRB2*, coding for the adrenergic beta 2 receptor, and *COMT*, encoding the main enzyme involved in NE metabolism) do not apparently play a role in the risk of blood pressure changes during treatment with duloxetine (Fijal et al. 2013). In addition, 5-HT binding to the serotonin-2A receptor has been associated with vasoconstriction and hypertension, and *HTR2A* gene has consistently been associated with essential hypertension in women (Liolitsa et al. 2001). Nevertheless, evidence suggesting an effect of this gene on blood pressure increase during treatment with duloxetine appears limited (Fijal et al. 2013).

The SSRIs fluoxetine and paroxetine demonstrated a relatively high receptor affinity for adrenergic beta receptors in vitro, suggesting an increased propensity of affecting cardiovascular parameters compared to other SSRIs. Interestingly, a polymorphism in the gene encoding the adrenergic beta 1 receptor (*ADRB1*) was found to modulate blood pressure and heart rate values in patients treated with these antidepressants (Thomas et al. 2010), but the potential clinical impact of this appears to be limited.

Finally, a group of clinically relevant side effects affecting the cardiovascular system are hemorrhagic complications, whose risk is increased during treatment with SSRI antidepressants, especially in some at-risk conditions (e.g., concomitant treatment with anticoagulant or antiaggregant drugs and surgery). 5-HT is a strong vasoconstrictor and a relatively weak platelet activator. At rest, 5-HT is stored in platelets, but after platelet activation, it is released into the circulation, together with other aggregating factors such as adenosine diphosphate (ADP) and adrenaline, and it acts as a stimulus for platelet aggregation. The 5-HT transporter is present on platelet surface and is necessary to transport 5-HT into the platelet, since platelets themselves do not produce 5-HT but are dependent on its uptake from the blood. Thus, blockade of the 5-HT transporter with an SSRI leads to a lower concentration of 5-HT in the platelet. Given this mechanisms, *SLC6A4* gene (encoding the 5-HT transporter) appears to be an optimal candidate for affecting the risk of bleeding

during SSRI treatment. An insertion/deletion polymorphism (named 5-HTTLPR) in the promoter region of *SLC6A4* showing two variant alleles (a short (S) allele and a long (L) allele) has been particularly studied since the S variant is associated with a nearly 50 % reduction in basal expression of the 5-HT transporter (Heils et al. 1996). Despite the interesting functional impact of this polymorphism, the available knowledge does not suggest any major impact of this variant on platelet function (Abdelmalik et al. 2008; Hougardy et al. 2008).

In conclusion, no genetic variants are known to significantly affect the risk of cardiovascular side effects during antidepressant treatment, but very few studies were focused on this topic. The identification of polymorphisms affecting the risk of proarrhythmic effects appears to be the most relevant issue under the clinical point of view.

7.2.3 Weight Gain, Sexual Dysfunction, and Other Side Effects

Sexual dysfunction, weight gain, and gastrointestinal side effects (dry mouth, constipation, diarrhea, and nausea) are the most frequent side effects induced by antidepressant drugs and thus the most frequently responsible for early treatment discontinuation. On the other hand, antidepressant-related hyponatremia is a relatively rare but potentially fatal antidepressant-induced ADR.

Some polymorphisms (5-HTTLPR, rs25531, intron 2 VNTR, or STin2) of the 5-HT transporter gene (*SLC6A4*) have been repeatedly investigated for association with the overall risk of antidepressant-induced side effects. Available evidence mainly suggests that carriers of the 5-HTTLPR/rs25531 short alleles show lower treatment tolerability while STin2 probably does not exert a significant influence on this phenotype (Garfield et al. 2014; Fabbri et al. 2013). *HTR1A* rs6295 and *HTR2A* rs6311/rs6313 are also promising variants that contribute to individual antidepressant tolerability (Fabbri et al. 2013; Garfield et al. 2014).

Weight gain is a quite common side effect of treatment with antidepressant drugs. Genes pertaining to the serotonergic system have been particularly investigated in relation to this ADR, since 5-HT has been implicated in the control of eating behavior and body weight by hypothalamic serotonergic receptor mechanisms (De Vry and Schreiber 2000). *HTR2C* gene (coding for 5-HT2C receptor) was proposed as a modulator of the risk of weight gain during both antidepressant and antipsychotic therapies (Altar et al. 2013). The stimulation of hypothalamic 5-HT2C receptors leads to a behaviorally specific hypophagic effect by accelerating satiety processes (De Vry and Schreiber 2000), providing a biological rationale that supports the pharmacogenetic finding.

Catechol-O-methyltransferase (*COMT*) and tryptophan hydroxylase type I (*TPH1*) encode pivotal enzymes in the catabolism and synthesis of 5-HT, respectively. *COMT* rs4680 and *TPH1* rs18532 were demonstrated to modulate the risk of weight gain during antidepressant treatment independently from age and gender (Secher et al. 2009). *GNB3* (that encodes the β3 subunit of the G protein complex)

is involved in the downstream signaling cascade following monoamine receptor activation. A functional polymorphism in this gene (C825T) was associated with the improvement of neurovegetative symptoms of depression during treatment, and the TT genotype was found to be a predictor of greater weight gain during treatment with nortriptyline (a drug of the TCA class) (Keers et al. 2011).

ADRA2A gene (encoding adrenergic α2 receptor) is a primary target of mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA). Mirtazapine is more likely to cause weight gain or increased appetite compared to SSRIs or SNRIs (Watanabe et al. 2011; Lee et al. 2009); thus the effect of *ADRA2A*-1291C/G polymorphism on the risk of weight gain during treatment with this antidepressant should be investigated further.

Sexual dysfunction in patients with major depression may be triggered or exacerbated by treatment with antidepressants (especially SSRIs, TCAs, and venlafaxine), with a prevalence of up to 50–70 % (Fava and Rankin 2002). Serotonergic, dopaminergic, noradrenergic, and glutamatergic systems are those primarily hypothesized to be involved in the pathogenesis of this ADR. In general, reduction of 5-HT function facilitates, whereas enhancement inhibits, sexual behavior, with the 5-HT transporter, 5-HT1A, 5-HT1B, 5-HT2A/B, and 5-HT7 receptors being the primary molecular players involved (Olivier et al. 2011). Furthermore, the blockade of 5-HT transporters may decrease the concentrations of dopamine and noradrenaline in the mesolimbic system by activating serotonin 5-HT2C receptors (Strohmaier et al. 2011); these two neurotransmitters play a role in the modulation of sexual arousal and sexual motivation. Indeed, dopamine antagonists inhibit copulation among male rats, whereas agonists have the opposite (facilitating) effect. Similar effects were demonstrated also for glutamate antagonists and agonists, respectively (Dominguez et al. 2006; Dominguez and Hull 2005).

The promoter polymorphism 5-HTTLPR rs25531 of the 5-HT transporter gene (*SLC6A4*) has been investigated as predictor of antidepressant-induced sexual dysfunction. Results suggested a higher risk in high-expressing genotypes (long alleles) of the polymorphism (Garfield et al. 2014), and the effect appears to be dependent on age (Strohmaier et al. 2011). *HTR1A* and *HTR2A* genes may also contribute to the development of this ADR (Garfield et al. 2014; Bishop et al. 2006).

Consistently with the involvement of glutamate in the modulation of sexual behavior, in SSRI-treated patients, multiple genes encoding glutamatergic receptors were associated with a decrease in libido (*GRIA3* and *GRIK2*), difficulty achieving orgasm (*GRIA1*), and difficulty developing an erection (*GRIN3A*) (Perlis et al. 2009). Currently, no data are available on the contribution of polymorphisms in noradrenergic and dopaminergic genes to the risk of antidepressant-induced sexual dysfunction.

Gastrointestinal ADRs are sometimes disabling side effects that usually emerge in the initial phases of antidepressant treatment. Variants in genes belonging to the serotonergic system were the most studied in relation to these ADRs, since 80 % of the body 5-HT stores are located in enterochromaffin cells of the gut and serotonin plays a central role in the regulation of motility and secreting activity of the gastrointestinal tract. *HTR3B* gene was associated with paroxetine-induced gastrointestinal side effects (Tanaka et al. 2008; Sugai et al. 2006), and *HTR2A* was shown to

exert a synergistic effect with *CYP2D6* gene polymorphisms in the prediction of fluvoxamine-induced gastrointestinal side effects (Suzuki et al. 2006). *CYP2D6* gene was associated also with venlafaxine (a SNRI)-induced gastrointestinal ADRs (Shams et al. 2006) and with broad antidepressant-induced ADRs (Rau et al. 2004). Polymorphisms in genes encoding cytochrome P450 enzymes (CYP450) are responsible for variations in drug metabolizing rapidity, including antidepressant drugs. Consequently, genetic variations in CYP450 genes could influence the occurrence of several ADRs, including the risk of overdose; this issue is discussed in the section "Toxicity from Overdose." P-glycoprotein (P-gp), an ATP-driven efflux pump that regulates the uptake of drugs through organ barriers, is another protein influencing the pharmacokinetics of antidepressants through the regulation of drug distribution in the body. Polymorphisms in the gene coding for this transporting protein (*ABCB1*) may influence gastrointestinal complaints and sexual side effects during antidepressant therapy (de Klerk et al. 2013).

Hyponatremia is a potentially fatal side effect of antidepressant drugs. It occurs in one in 200 elderly patients per year receiving fluoxetine and paroxetine, two commonly used SSRIs (Wilkinson et al. 1999). There is little pharmacogenetic evidence with regard to this ADR, but lower mean serum sodium concentrations were shown to be present in *CYP2D6* poor metabolizers (PMs) in comparison with *CYP2D6* extensive metabolizers (EMs). As a result, *CYP2D6* PMs might be at increased risk of developing hyponatremia (Kwadijk-de Gijsel et al. 2009).

GWAS did not outlined particularly interesting findings for any of the above ADRs, but different genes were proposed as putative candidates compared to candidate gene studies. *SACM1L* (coding for the phosphatidylinositide phosphatase SAC1) gene was associated with bupropion-induced sexual dysfunction, even though this antidepressant is not commonly responsible for this ADR, resulting in limited clinical utility. SAC1 is an integral membrane protein of the endoplasmic reticulum and the Golgi apparatus that plays a direct role in growth factor signaling; thus alterations in the activity of this enzyme may lead to disruptions in the cellular secretory machinery and hormone-neurotransmitter secretion, with possible consequences on sexual functioning (Clark et al. 2012). A later extension of the study by Clark et al. suggested that *EMID2* (EMI domain containing 2) gene may affect SSRI-induced vision/hearing side effects, *LAMA1* (laminin, alpha 1) gene and the rs16965962 SNP (in a gene desert on chromosome 7) may influence overall SSRI tolerability, while *AOX2P* gene may be related with dizziness. *EMID2* encodes the protein collagen α-1 chain that is involved in the regulation of corneal collagen fibrillogenesis (Rada et al. 1993). On the other hand, for *LAMA1* and *AOX2P*, it is not so easy to hypothesize a biological rationale explaining the reported GWAS findings.

7.2.4 Toxicity from Overdose

The risk of overdose from antidepressant drugs was reduced significantly after the introduction of SSRIs and SNRIs compared to earlier antidepressants (TCAs and MAOIs). Despite the reduction of life-threatening reactions, 5-HT toxicity can still

result from serotonin excess in the CNS from serotonergic drugs. Serotonin syndrome is a potentially life-threatening condition characterized by myoclonus, hyperreflexia, sweating, shivering, incoordination, and mental status changes. Furthermore, the risk of cardiac arrhythmia is another potentially fatal manifestation following overdose especially from TCAs but possibly also from venlafaxine and IMAOs.

The genetic variants that were hypothesized to influence the risk and severity of overdose symptoms are mainly those in genes coding for CYP450 enzymes and P-glycoprotein (P-gp) gene (*ABCB1*), the products of which are involved in the distribution and metabolism of antidepressant drugs.

CYP2D6 and *CYP2C19* encode the P450 isoenzymes that are mostly involved in antidepressant metabolism. The level of CYP enzyme activity is dependent on genetic polymorphisms and allows the distinction of different metabolizing groups. The wild-type genotype results in extensive metabolizers (EM), while the intermediate metabolizer (IM) is characterized by the presence of one wild-type allele plus a partially or totally defective allele. Poor metabolizers (PMs) have a combination of two partially or totally defective alleles, and the ultrarapid metabolizer (UM) category exists only for *CYP2D6* and is usually due to multiple copies of normal alleles.

The available evidence suggests that *CYP2D6* PMs have lower tolerance to TCAs as well as to venlafaxine (a SNRI drug), whereas they have an average tolerance to other antidepressants. Based on literature, *CYP2D6* PMs are expected to have a concentration-to-dose ratio (C:D ratio) of 4–6 for TCAs, whereas CYP2D6 EMs are expected to have a C:D ratio of 0.5–1.5. Dose adjustments for different metabolizing groups were calculated, even if prospective validations should be performed before routine clinical application (Porcelli et al. 2011). Polypharmacy is likely to represent a valid indication for *CYP2D6* genotyping to minimize the risk of toxicity from drug-drug interactions in PMs (Laje 2013).

Finally, P-gp limits drug uptake into key organs such as the brain, and fatal intoxication from venlafaxine overdose was associated with C1236T and C3435T polymorphisms in *ABCB1* gene (Karlsson et al. 2013).

7.3 Pharmacogenetics of Antipsychotic-Induced Side Effects

Antipsychotic drugs are the mainstay of treatment for schizophrenia and related disorder and have improved schizophrenia prognosis significantly since their introduction in the 1950s. In recent years, the use of second-generation antipsychotics (SGAPs) has been indicated also for the treatment of several phases of bipolar disorder or augmentation in major depressive disorder with benefits being seen especially in more severe cases. Both first-generation antipsychotics (FGAPs) and SGAPs carry the risk of severe and sometimes debilitating ADRs, whose clinical relevance has been increased in proportion with the expansion of their clinical use in terms of increasing indications and treatment duration.

7.3.1 Antipsychotic-Induced Weight Gain

Weight gain is a major health problem encountered during treatment with antipsychotics especially SGAPs due to a high risk of obesity and other metabolic conditions (Dickerson et al. 2006). Weight gain is associated with significant variability among individuals, and genetic factors play an important role, estimated to be around 60–80 % through twin and family studies (Gebhardt et al. 2010). Given that cardiovascular disease is the primary cause of excess of mortality among severe psychiatric diseases (Osborn et al. 2007), the identification of genetic predictors of antipsychotic metabolic ADRs could be a turning point in the treatment of schizophrenia and bipolar disorder.

Several pharmacogenetic studies have investigated the genes that could influence antipsychotic-induced weight gain (AIWG), with focus mainly on homeostatic regulators expressed in hypothalamic areas that belong to the complex network that regulates appetite and satiety.

The most replicated pharmacogenetic association is the serotonergic receptor 5-HTC2 (*HTR2C*) gene that is responsible for 5-HT central anorexigenic action on the hypothalamic nuclei. Consistently, antagonists of 5-HTC2 receptors, such as clozapine and olanzapine, promote appetite increase (Bonhaus et al. 1997). Carriers of the minor T allele of the promoter polymorphism −759C/T appear to be protected from substantial gain in weight (Sicard et al. 2010).

Leptin and melanocortin receptor 4 (*MC4R*) are other essential components of one of the most important hypothalamic satiety signals. Leptin is mainly synthesized in the adipocytes of white adipose tissue and activates leptin receptors in the arcuate nucleus of the hypothalamus, resulting in a feeling of satiety. The *leptin-2548A*/G polymorphism may interact with the *HTR2C* −759C/T variant in affecting AIWG (Reynolds 2012). Neurons of the arcuate nucleus also express *MC4R*, activation of which decreases food intake while elevating energy utilization (Fani et al. 2014). This gene has been consistently associated with AIWG by four independent studies (Shams and Muller 2014).

Cannabinoid receptor 1 (*CNR1*) gene and the fatty acid amide hydrolase (*FAAH*) gene have been suggested as genetic factors involved in AIWG (Shams and Muller 2014), consistently with the observation that they play an important role in the mediation of leptin anorexigenic action. Some SNPs within *CNR1* in particular provided encouraging findings.

Other candidate genes provided less convincing evidence for an association with AIWG, among them being ghrelin (*GHRL*) and neuropeptide Y (*NPY*), which act as antagonists of the leptin-induced satiety signal, other hypothalamic neuroendocrine regulators (*FTO* and *PMCH* genes), and histamine receptor 1 (*HRH1* gene, consistently to the observation that central histaminergic transmission contributes to the modulation of the motivational aspect of appetite and physical activity (Torrealba et al. 2012)). The T allele of *GNB3*C825T polymorphism was considered to be particularly interesting since it is associated with a G protein β3 splice variant and previously described associated with obesity in several ethnic groups. Nevertheless, the available evidence mainly does not support the involvement of this variant in AIWG (Souza et al. 2008). Furthermore, polymorphisms in AMP-activated protein kinase (*AMPK* gene, a central molecule integrating nutrient and hormonal signals to

maintain energy homeostasis), relaxin-3 (*RLN3*, a member of the insulin/relaxin pathway) and its receptors (*RXFP3* and *RXFP4*), tumor necrosis factor-α (*TNF-a*, a proinflammatory cytokine), and methylenetetrahydrofolate reductase (encoded by *MTHFR*, involved in nuclear methylation and gene expression regulation) were suggested to modulate AIWG (Muller et al. 2013; Kao and Muller 2013).

A GWAS was aimed to identify genetic risk factors for metabolic side effects in patients treated with psychopharmacological medications (Athanasiu et al. 2012). SNP rs7838490 (8q21.3 region) was associated with BMI alterations, while rs11615724 (12q21) was associated with the effect of medications on decreasing HDL-C levels. Both markers are in intergenic regions. rs7838490 is located upstream of the gene matrix metalloproteinase 16 (*MMP16*), and it may regulate the expression of *MMP16* and affect tumor necrosis factor receptor superfamily, member 1A (*sTNFRSF1A*), which may be involved in lipid regulation.

7.3.2 Antipsychotic-Induced Extrapyramidal Side Effects

The greater part of pharmacogenetic studies focused on genetic risk factors of antipsychotic-induced tardive dyskinesia, the most severe among extrapyramidal side effects (EPS) due to its tendency to persist over time, its treatment resistance, and its high frequency (around 20 % of patients after prolonged treatment (Kane et al. 1988)). Genes are hypothesized to be a relevant factor in the risk of tardive dyskinesia, as suggested by increased risk of tardive dyskinesia in affected families (Muller et al. 2013). Genes that influence the pharmacokinetics, pharmacodynamics, and oxidative stress associated with antipsychotics have been studied for tardive dyskinesia risk. In particular, the gene coding for the dopamine receptor 2 (*DRD2*), one of the main targets of antipsychotics (especially for those drugs with a higher risk of inducing this ADR), was suggested to be involved in the risk of this EPS by various independent studies (especially the Taq1A polymorphism or rs1800497). The minor (T) Taq1A allele has been associated with a 40 % reduction in striatal D2 receptor density (according to in vitro assays and in vivo imaging studies); this allele appears to be protective against tardive dyskinesia (Lencz and Malhotra 2009). *DRD2* may also be implicated in the risk of akathisia, even though only preliminary evidence is available (Muller et al. 2013). A functional missense mutation in dopamine 3 receptor (*DRD3*, another target of antipsychotics) gene (ser9gly or rs6280) has been suggested to modulate the risk of tardive dyskinesia, but meta-analytic results did not support this hypothesis (Tsai et al. 2010). 5-HT2A receptor (*HTR2A*) gene is a target of atypical antipsychotics, and it has been implicated in their reduced extrapyramidal side effect profile (Meltzer 2012). *HTR2A* gene has also been associated with tardive dyskinesia susceptibility by several candidate gene studies (Segman et al. 2001; Gunes et al. 2007; Wilffert et al. 2009).

The highly polymorphic gene *CYP2D6* is responsible for the hepatic metabolism of several commonly prescribed antipsychotics. *CYP2D6* poor metabolizer status (homozygosity for null alleles) or intermediate metabolizer status (null allele heterozygosity) were associated with 1.64- and 1.43-fold greater odds of developing tardive dyskinesia on the basis of literature meta-analysis (Patsopoulos et al. 2005).

Other genes were investigated in relation to antipsychotic-induced EPS, among which were the glutamate receptor *GRIN2A*, *BDNF*, *TNF-a* (Muller et al. 2013), and *SOD2* (Lencz and Malhotra 2009). *SOD2* encodes for manganese superoxide dismutase, a mitochondrial enzyme involved in oxidative metabolism. *SOD2* and *TNF-a* may be involved in the risk of tardive dyskinesia through neuron oxidative stress.

GWAS results shed light on the potential contribution of different genes to antipsychotic-induced tardive dyskinesia. In particular, the gamma-aminobutyric acid (GABA) receptor signaling pathway (especially *SLC6A11*, *GABRB2*, and *GABRG3* genes) may be involved in genetic susceptibility to treatment-resistant tardive dyskinesia in Asian populations (Inada et al. 2008). On the other hand, the involvement of *HSPG2* gene (coding for the heparan sulfate proteoglycan 2) was suggested by independent GWAS on both Asian (Syu et al. 2010) and Caucasian (Greenbaum et al. 2012a) populations, thus representing the strongest candidate outlined by GWAS. This pharmacogenomic finding was supported by an increase in *HSPG2* expression in subjects with lower risk of developing tardive dyskinesia, which may exert a protective effect via a cholinergic or basic fibroblast growth factor (FGF2)-mediated neuroprotective mechanism.

Some data are available also for other types of EPS. A GWAS investigating antipsychotic-induced Parkinsonism (Alkelai et al. 2009) has been replicated (Greenbaum et al. 2012b) supporting a role of the rs12678719 SNP in the zinc finger protein multitype 2 (*ZFPM2*) gene, especially in patients of African ancestry. The risk allele (G) was associated with lower FP-CIT uptake, which is indicative of a higher degree of nigrostriatal terminal degeneration, in Parkinson disease subjects as assessed by SPECT (Greenbaum et al. 2012b). Interestingly, another gene coding for a zinc finger protein (*ZNF202*) was associated with the development of abnormal movements during antipsychotic treatment (Aberg et al. 2010). The *ZNF202* is a transcriptional repressor controlling, among other genes, *PLP1*, which is the major protein expressed in myelin. Mutations in *PLP1* can determine the development of parkinsonism (Willard and Riordan 1985).

7.3.3 Neuroleptic Malignant Syndrome, Clozapine-Induced Agranulocytosis, and Antipsychotic-Induced QT Prolongation

Neuroleptic malignant syndrome (NMS) is a severe complication of treatment with antipsychotic drugs. Initial reports of familial clustering of NMS have suggested a genetic basis. As a result, some pharmacogenetic case-control association studies were performed in Japanese populations which were mainly focused on *CYP2D6* and *DRD2* polymorphisms, though with inconsistent findings (Ferentinos and Dikeos 2012). Further pharmacogenetic studies should be performed to elucidate the genetic contribution to NMS.

Clozapine-induced agranulocytosis (CIA) is a rare (incidence 0.8 %) but potentially fatal ADR of clozapine, which limits its use in treatment-resistant schizophrenia. Several pharmacogenetic case-control studies focused on CIA have produced

inconsistent findings, mainly regarding the major histocompatibility complex (MHC) region (including human leukocyte antigen (HLA) class I, II, and III loci and some non-HLA genes), as well as a few non-MHC genes. HLA-DQB1 polymorphisms have been the ones most consistently associated with CIA (Ferentinos and Dikeos 2012; Goldstein et al. 2014). Among them, a SNP (6672G>C) was found to confer a 16.9 times increased risk of CIA. A commercial test using this variant was marketed in 2007, but its clinical application is limited by its low sensitivity and low predictive validity (Ferentinos and Dikeos 2012).

The risk of sudden death for patients receiving antipsychotics has been estimated to be 2.4 times the risk of untreated controls (Ray et al. 2001). This increased risk is partly attributable to antipsychotic drugs causing QT prolongation (e.g., pimozide, thioridazine, sertindole, and haloperidol). Genetic research on the QT interval has initially identified several rare variants which cause congenital Mendelian QT syndromes (long QT and short QT syndromes), both increasing the risk of syncope and sudden death by predisposing to torsades de pointes and atrial fibrillation, respectively (Hedley et al. 2009). Some of these rare mutations have been found in patients with medication-induced QT prolongation; however, only 5–15 % of persons experiencing drug-induced torsades de pointes carry a mutation in one of the genes associated with hereditary long QT syndrome (Paulussen et al. 2004).

Two recent GWAS of antipsychotic-induced QT prolongation have identified potentially involved polymorphisms in several genes, including those coding for ceramide kinase-like protein (*CERKL*), solute carrier organic anion transporter 3A1 (*SLCO3A1*), paladin (*PALLD*), solute carrier family 22, member 23 (*SLC22A23*), nucleotide-binding protein-like (*NUBPL*) gene, and nitric oxide synthase 1 adaptor protein (*NOS1AP*) gene (the most frequently replicated candidate gene for QT-interval variation in the general population) (Ferentinos and Dikeos 2012). These findings suggest that some of the genes mediating antipsychotic-induced QT prolongation are unique, whereas others partially overlap with the genes affecting normal QT-interval variation.

Finally, given that pimozide is one of the highest-risk antipsychotics regarding proarrhythmic effects, the impact of *CYP2D6* (the CYP450 isoform mainly involved in its metabolism) genotype on pimozide exposure was investigated. Dose-ranging analyses revealed *CYP2D6* poor metabolizers should not receive more than 4 mg daily to avoid plasma concentrations in excess of those observed in extensive metabolizer and intermediate metabolizer receiving 10 mg daily. Thus, *CYP2D6* genotyping is now recommended in the pimozide product label before exceeding 4 mg of pimozide daily in adults or 0.05 mg/kg/day in children (Rogers et al. 2012).

7.3.4 Prolactin Elevation

Few pharmacogenetic studies have investigated this frequent antipsychotic side effect, occurring in 80–90 % of all female subjects treated with the highest-risk drugs, i.e., risperidone, amisulpride, and sulpiride (Peuskens et al. 2014), and the conclusions from such studies is unclear. Dopamine D2 receptor gene (*DRD2*) is an

attractive candidate, given that dopamine 2 antagonism plays an important role in the increase in prolactin via the tuberoinfundibular pathway. The *DRD2*Taq1A polymorphism was associated with increased risk for hyperprolactinemia by four independent studies, but conflicting negative results also exist (Lencz and Malhotra 2009). The gene coding for the cytochrome P450 2D6 (*CYP2D6*) enzyme is another interesting candidate explaining variation in prolactin levels after treatment with antipsychotic medications. *CYP2D6* metabolizer status was associated with plasma levels of different antipsychotic drugs such as risperidone, but no clear evidence of an impact on this side effect has been demonstrated (Novalbos et al. 2010).

7.4 Pharmacogenetics of Mood Stabilizer-Induced Side Effects

Mood stabilizers are used primarily in the treatment of bipolar disorders (for both acute phase and prophylaxis), but other clinical indications include the augmentation of antidepressant treatment in unipolar depression and the treatment of symptoms such as impulsivity in severe personality disorders. Some of them (e.g., valproate, carbamazepine, and lamotrigine) are also indicated for the treatment of some types of seizure disorders. The most frequent and potentially severe side effects of these medications are psychological/neurological (hypersomnia, sedation, retardation, tremors), endocrine/metabolic (body weight gain and metabolic dysfunction, kidney and thyroid dysfunction for lithium, hyperammonemia for valproate), gastrointestinal (nausea, abdominal pain, diarrhea, and hepatic dysfunction for valproate), hematologic (leucopenia, anemia, thrombocytopenia), and teratogenic. Immune-mediated cutaneous hypersensitivity reactions are the most common idiosyncratic reactions to antiepileptic drugs such as carbamazepine and lamotrigine. These ADRs include a risk of potentially life-threatening Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-related rash with eosinophilia and systemic symptoms (DRESS). Unfortunately, fewer pharmacogenetic data are available for mood stabilizers compared to antipsychotics and antidepressants.

7.4.1 Lithium- and Valproate-Induced Side Effects

Few and mainly negative pharmacogenetic findings are available for lithium-related ADRs (e.g., Zill et al. 2003). Lithium has been linked to the development of primary hyperparathyroidism and parathyroid tumors (Dwight et al. 2002). The majority of lithium-associated parathyroid tumors were reported to be independent of classical chromosomal alterations associated with this type of cancer (Dwight et al. 2002), suggesting a potential specific genetic susceptibility. In any case, few data are available to indicate an increased risk linked to specific genetic mutations.

Regarding valproate-induced ADRs, a missense polymorphism in carbamoyl phosphate synthase 1 (*CPS1*) gene (4217C>A or rs1047891) was suggested to

increase the risk and severity of hyperammonemia, even if drug plasmatic levels are within the therapeutic range (Bezinover et al. 2011; Janicki et al. 2013). In the Japanese population on the other hand, the association between rs1047891 and hyperammonemia may not be present (Inoue et al. 2014).

Valproate-induced liver impairment was related to mitochondrial DNA depletion and mutations in *POLG* gene that codes for the mitochondrial DNA polymerase gamma in pediatric patients (Pronicka et al. 2011; Saneto et al. 2010). Thus, *POLG* gene testing has been recommended in children/adolescents since they are particularly at risk of developing valproate-induced liver toxicity (FDA 2013a). The involvement of *POLG* mutations in the pathogenesis of this ADR was suggested also by in vitro experiments on human cell lines (Stewart et al. 2010). Other genes that may be involved in the risk of valproate hepatotoxicity are those responsible for the metabolism of the drug. The principal pathways of valproate metabolism involved glucuronidation and β-oxidation and cytochrome P450 system. Glutathione S-transferases (GSTs) comprise a supergene family of enzymes that catalyze the inactivation of a variety of endogenous and exogenous products. Polymorphisms in *GSTM1* and *GSTT1* genes were suggested to be potential predictors of increase in serum gamma-glutamyltransferase in patients treated with valproate, but these are not necessarily markers of valproate-induced liver toxicity (Franciotta et al. 2009). In rare cases, valproic acid can be metabolized to the active and hepatotoxic metabolite, 4-ene-valproic acid, but it is not yet clear whether genetic variants of the involved enzyme (*CYP2C9*) are responsible for this problem (Klotz 2007). Superoxide dismutase 2 (coded by the *SOD2* gene) plays a critical role in the detoxification of mitochondrial reactive oxygen species, and SNPrs4880 (Val16Ala) was suggested as a modulator of valproate-induced elevation of gamma-glutamyltransferase (γ-GT, a hepatic and biliary enzyme) (Ogusu et al. 2014).

Twin studies suggest that genetic factors have an influence on the weight change induced by valproate (Klein et al. 2005). The C825T variation of *GNB3* gene was associated with higher plasma total cholesterol, triglyceride, leptin levels, and body mass index in bipolar patients treated with valproate, suggesting that T allele carriers at this locus may have a lower risk of metabolic ADRs during valproate treatment (Chang et al. 2010). The same variant in *GNB3* was also associated with weight gain during treatment with nortriptyline (see paragraph 2.3) and proposed as a modulator of AIWG (see paragraph 3.1). Unfortunately, no other pharmacogenetic data exist for metabolic ADRs during mood stabilizer treatment.

7.4.2 Carbamazepine- and Lamotrigine-Induced Hypersensitivity Reactions

Severe hypersensitivity reactions (cutaneous or systemic) to carbamazepine and lamotrigine have a frequency that ranges between 1 and 10 per 10,000 new users (Zaccara et al. 2007). The risk of developing this type of ADR was initially associated with a genetic polymorphism in the promoter region of the proinflammatory cytokine tumor necrosis factor-alpha (*TNF-a*) and with variants in genes coding for

heat shock protein-70 isoforms (Franciotta et al. 2009). These associations were nevertheless not independently replicated. A breakthrough came in 2004 when a 100 % prevalence of carbamazepine-induced SJS was reported among Han Chinese carriers of the human leukocyte antigen HLA-B*1502 allele, compared with a frequency of this allele of only 3 % among carbamazepine-tolerant patients (Chung et al. 2004). Further case-control studies in Hong Kong Chinese and Thai populations confirmed the strong association of HLA-B*1502 with carbamazepine-induced SJS or TEN, but not with carbamazepine-induced maculopapular rash or DRESS. Ethnicity appears to play an important role in the association, since studies in Caucasians and in Japanese failed to identify any relationship between HLA-B*1502 status and SJS or TEN (Franciotta et al. 2009). On the basis of these data, the US Food and Drug Administration (FDA) recommended that patients with ancestry from areas in which HLA-B*1502 is present (China, Thailand, Malaysia, Indonesia, the Philippines, Taiwan, and Vietnam) should be screened for this allele before starting treatment with carbamazepine. Given that over 90 % of drug-induced SJS/TEN occur within 2 months of starting treatment, patients who have been taking carbamazepine for at least a few months without developing severe cutaneous reactions are at low risk of developing SJS or TEN during continuation of treatment, even if they carry the HLA-B*1502 allele (FDA 2013b).

Although much attention has been focused on HLA-B*1502, other HLA genotypes were investigated as potential predictors of cutaneous reactions. In a Chinese population, maculopapular reactions to carbamazepine were associated with SNPs in the HLA-E region and with the HLA-A*3101 allele, whereas DRESS was associated with polymorphisms in motilin (*MLN*) gene that is located in the MHC class II terminal region (Hung et al. 2006). In Caucasians, the HLA-B*0702 allele has been found to be potentially protective against severe carbamazepine-induced hypersensitivity, while the HLA-B*38 allele was identified as a possible risk factor for lamotrigine-induced SJS or TEN (Franciotta et al. 2009).

7.5 Conclusion

Current knowledge of the genetic factors involved in the risk of adverse drug reactions (ADRs) during treatment with psychotropic drugs is often not univocal, and clinical applications are still rare. Twin and family studies indicate a genetic contribution of about 50 % to the overall risk of ADRs in CNS disorders (Cacabelos et al. 2012) and a contribution varying from 60 % to 80 % for a clinically relevant ADR such as antipsychotic-induced weight gain (Gebhardt et al. 2010). As with other complex phenotypes, pharmacogenetic studies often failed to detect polymorphisms with the expected effect sizes, possibly due to confounders such as gene-gene or gene-environment interactions, heterogeneity in ancestry, and age. Despite a number of preliminary/unconfirmed findings, some pharmacogenetic findings are quite promising for future clinical applications, and a limited number have been already recommended for use in clinical practice (Table 7.1). Testing for HLA-B*1502

when using carbamazepine in Asian populations to prevent Stevens-Johnson syndrome, *CYP2D6* when using pimozide, *POLG* in children/adolescents treated with valproate, and *CPS1* before prescribing valproate in case of suspected urea cycle disorder is included in the latter group.

The first studies evaluating the benefits of clinical pharmacogenetic testing were performed, with promising results. Preliminary estimates in a simulated trial indicated that *SLC6A4* genetic testing may improve antidepressant tolerability in terms of quality-adjusted life weeks and incremental cost/effectiveness ratio in patients suffering from at least two depressive episodes (Serretti et al. 2011). In patients with depressive/anxiety disorders treated with antidepressant or antipsychotic drugs, a genetic test (GeneSight) for variations in cytochrome P450 genes (*CYP2D6*, *CYP2C19*, *CYP2C9*, and *CYP1A2*), serotonin transporter gene (*SLC6A4*), and serotonin 2A receptor gene (*5HTR2A*) was used to distinguish between them in three categories according to the predicted outcome. Patients that were classified in the "red" group (medication status "use with caution and frequent monitoring") had 69 % more total health care visits, 67 % more general medical visits, over threefold more medical absence days, and over fourfold more disability claims than subjects taking drugs categorized in the "green" group ("use as directed") or "yellow" group ("use with caution"). The result is attributable to increased side effects and poor outcome in the "red" group (Winner et al. 2013).

A better definition of relevant genes and polymorphisms with the subsequent production of targeted genetic chips represents a fundamental step for future developments in this field. Evidence regarding genetic test cost/benefit ratio and specific clinical indications for genotyping should be provided through randomized trials. The benefit deriving from genotype information to guide the choice of different medications prescribed to the patient lifelong should be considered.

On the basis of the results provided by existing studies and current clinical applications for a number of commercialized drugs (pharmacogenetic test information is currently included in over 200 drug labels among those approved in the United States (Ikediobi et al. 2009)), indications to genotyping are expected to increase in the psychiatric field in the next years.

References

Abdelmalik N, Ruhe HG, Barwari K, van den Dool EJ, Meijers JC, Middeldorp S, Buller HR, Schene AH, Kamphuisen PW (2008) Effect of the selective serotonin reuptake inhibitor paroxetine on platelet function is modified by a SLC6A4 serotonin transporter polymorphism. J Thromb Haemost JTH 6(12):2168–2174. doi:10.1111/j.1538-7836.2008.03196.x

Aberg K, Adkins DE, Bukszar J, Webb BT, Caroff SN, Miller DD, Sebat J, Stroup S, Fanous AH, Vladimirov VI, McClay JL, Lieberman JA, Sullivan PF, van den Oord EJ (2010) Genomewide association study of movement-related adverse antipsychotic effects. Biol Psychiatry 67(3):279–282. doi:10.1016/j.biopsych.2009.08.036

Alkelai A, Greenbaum L, Rigbi A, Kanyas K, Lerer B (2009) Genome-wide association study of antipsychotic-induced parkinsonism severity among schizophrenia patients. Psychopharmacology (Berl) 206(3):491–499. doi:10.1007/s00213-009-1627-z

Altar CA, Hornberger J, Shewade A, Cruz V, Garrison J, Mrazek D (2013) Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy. Int Rev Psychiatry 25(5):509–533. doi:10.3109/09540261.2013.825579

Athanasiu L, Brown AA, Birkenaes AB, Mattingsdal M, Agartz I, Melle I, Steen VM, Andreassen OA, Djurovic S (2012) Genome-wide association study identifies genetic loci associated with body mass index and high density lipoprotein-cholesterol levels during psychopharmacological treatment – a cross-sectional naturalistic study. Psychiatry Res 197(3):327–336. doi:10.1016/j.psychres.2011.12.036

Baldwin DS, Foong T (2013) Antidepressant drugs and sexual dysfunction. Br J Psychiatry J Ment Sci 202:396–397. doi:10.1192/bjp.bp.112.110650

Bellivier F, Chaste P, Malafosse A (2004) Association between the TPH gene A218C polymorphism and suicidal behavior: a meta-analysis. Am J Med Genet B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet 124B(1):87–91. doi:10.1002/ajmg.b.20015

Bezinover D, Postula M, Donahue K, Bentzen B, McInerney J, Janicki PK (2011) Perioperative exacerbation of valproic acid-associated hyperammonemia: a clinical and genetic analysis. Anesth Analg 113(4):858–861. doi:10.1213/ANE.0b013e318228a001

Bishop JR, Moline J, Ellingrod VL, Schultz SK, Clayton AH (2006) Serotonin 2A–1438 G/A and G-protein Beta3 subunit C825T polymorphisms in patients with depression and SSRI-associated sexual side-effects. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 31(10):2281–2288. doi:10.1038/sj.npp.1301090

Bonhaus DW, Weinhardt KK, Taylor M, DeSouza A, McNeeley PM, Szczepanski K, Fontana DJ, Trinh J, Rocha CL, Dawson MW, Flippin LA, Eglen RM (1997) RS-102221: a novel high affinity and selective, 5-HT2C receptor antagonist. Neuropharmacology 36(4–5):621–629

Brent DA, Mann JJ (2005) Family genetic studies, suicide, and suicidal behavior. Am J Med Genet C Semin Med Genet 133C(1):13–24. doi:10.1002/ajmg.c.30042

Cacabelos R, Martinez-Bouza R, Carril JC, Fernandez-Novoa L, Lombardi V, Carrera I, Corzo L, McKay A (2012) Genomics and pharmacogenomics of brain disorders. Curr Pharm Biotechnol 13(5):674–725

Chandley MJ, Szebeni A, Szebeni K, Crawford JD, Stockmeier CA, Turecki G, Kostrzewa RM, Ordway GA (2014) Elevated gene expression of glutamate receptors in noradrenergic neurons from the locus coeruleus in major depression. Int J Neuropsychopharmacol/Off Sci J Coll Int Neuropsychopharmacol 17(10):1569–1578. doi:10.1017/S1461145714000662

Chang HH, Gean PW, Chou CH, Yang YK, Tsai HC, Lu RB, Chen PS (2010) C825T polymorphism of the GNB3 gene on valproate-related metabolic abnormalities in bipolar disorder patients. J Clin Psychopharmacol 30(5):512–517. doi:10.1097/JCP.0b013e3181f03f50

Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT (2004) Medical genetics: a marker for Stevens-Johnson syndrome. Nature 428(6982):486. doi:10.1038/428486a

Clark SL, Adkins DE, Aberg K, Hettema JM, McClay JL, Souza RP, van den Oord EJ (2012) Pharmacogenomic study of side-effects for antidepressant treatment options in STAR*D. Psychol Med 42(6):1151–1162. doi:10.1017/S003329171100239X

de Klerk OL, Nolte IM, Bet PM, Bosker FJ, Snieder H, den Boer JA, Bruggeman R, Hoogendijk WJ, Penninx BW (2013) ABCB1 gene variants influence tolerance to selective serotonin reuptake inhibitors in a large sample of Dutch cases with major depressive disorder. Pharmacogenomics J 13(4):349–353. doi:10.1038/tpj.2012.16

De Vry J, Schreiber R (2000) Effects of selected serotonin 5-HT(1) and 5-HT(2) receptor agonists on feeding behavior: possible mechanisms of action. Neurosci Biobehav Rev 24(3): 341–353

Dickerson FB, Brown CH, Kreyenbuhl JA, Fang L, Goldberg RW, Wohlheiter K, Dixon LB (2006) Obesity among individuals with serious mental illness. Acta Psychiatr Scand 113(4):306–313. doi:10.1111/j.1600-0447.2005.00637.x

Dominguez JM, Hull EM (2005) Dopamine, the medial preoptic area, and male sexual behavior. Physiol Behav 86(3):356–368. doi:10.1016/j.physbeh.2005.08.006

Dominguez JM, Gil M, Hull EM (2006) Preoptic glutamate facilitates male sexual behavior. J Neurosci Off J Soc Neurosci 26(6):1699–1703. doi:10.1523/JNEUROSCI.4176-05.2006

Drago A, De Ponti F, Boriani G, De Ronchi D, Serretti A (2008) Strategy for a genetic assessment of antipsychotic and antidepressant-related proarrhythmia. Curr Med Chem 15(24): 2472–2517

Dwight T, Kytola S, Teh BT, Theodosopoulos G, Richardson AL, Philips J, Twigg S, Delbridge L, Marsh DJ, Nelson AE, Larsson C, Robinson BG (2002) Genetic analysis of lithium-associated parathyroid tumors. Eur J Endocrinol/Eur Fed Endocr Soc 146(5):619–627

Escriba PV, Ozaita A, Garcia-Sevilla JA (2004) Increased mRNA expression of alpha2A-adrenoceptors, serotonin receptors and mu-opioid receptors in the brains of suicide victims. Neuropsychopharm Off Publ Am Coll Neuropsychopharm 29(8):1512–1521. doi:10.1038/sj.npp.1300459

Fabbri C, Di Girolamo G, Serretti A (2013) Pharmacogenetics of antidepressant drugs: an update after almost 20 years of research. Am J Med Genet B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet 162B(6):487–520. doi:10.1002/ajmg.b.32184

Fani L, Bak S, Delhanty P, van Rossum EF, van den Akker EL (2014) The melanocortin-4 receptor as target for obesity treatment: a systematic review of emerging pharmacological therapeutic options. Int J Obes (Lond) 38(2):163–169. doi:10.1038/ijo.2013.80

Fava M, Rankin M (2002) Sexual functioning and SSRIs. J Clin Psychiatry 63(Suppl 5):13–16; discussion 23–15

FDA (2013a) FDA label for valproic acid and OTC, POLG. https://www.pharmgkb.org/label/PA166104825. Accessed 14 Dec 2014

FDA (2013b) Information for healthcare professionals: dangerous or even fatal skin reactions – carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm. Accessed 11 Dec 2014

Ferentinos P, Dikeos D (2012) Genetic correlates of medical comorbidity associated with schizophrenia and treatment with antipsychotics. Curr Opin Psychiatry 25(5):381–390. doi:10.1097/YCO.0b013e3283568537

Fijal BA, Kohler J, Ostbye K, Ahl J, Houston JP (2013) Association of candidate gene polymorphisms with diastolic blood pressure change in patients treated with duloxetine. Psychiatry Res 206(2–3):313–314. doi:10.1016/j.psychres.2012.10.019

Franciotta D, Kwan P, Perucca E (2009) Genetic basis for idiosyncratic reactions to antiepileptic drugs. Curr Opin Neurol 22(2):144–149. doi:10.1097/WCO.0b013e328328f276

Garfield LD, Dixon D, Nowotny P, Lotrich FE, Pollock BG, Kristjansson SD, Dore PM, Lenze EJ (2014) Common selective serotonin reuptake inhibitor side effects in older adults associated with genetic polymorphisms in the serotonin transporter and receptors: data from a randomized controlled trial. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry 22(10):971–979. doi:10.1016/j.jagp.2013.07.003

Gebhardt S, Theisen FM, Haberhausen M, Heinzel-Gutenbrunner M, Wehmeier PM, Krieg JC, Kuhnau W, Schmidtke J, Remschmidt H, Hebebrand J (2010) Body weight gain induced by atypical antipsychotics: an extension of the monozygotic twin and sib pair study. J Clin Pharm Ther 35(2):207–211. doi:10.1111/j.1365-2710.2009.01084.x

Goldstein JI, Jarskog LF, Hilliard C, Alfirevic A, Duncan L, Fourches D, Huang H, Lek M, Neale BM, Ripke S, Shianna K, Szatkiewicz JP, Tropsha A, van den Oord EJ, Cascorbi I, Dettling M, Gazit E, Goff DC, Holden AL, Kelly DL, Malhotra AK, Nielsen J, Pirmohamed M, Rujescu D, Werge T, Levy DL, Josiassen RC, Kennedy JL, Lieberman JA, Daly MJ, Sullivan PF (2014) Clozapine-induced agranulocytosis is associated with rare HLA-DQB1 and HLA-B alleles. Nat Commun 5:4757. doi:10.1038/ncomms5757

Greenbaum L, Alkelai A, Zozulinsky P, Kohn Y, Lerer B (2012a) Support for association of HSPG2 with tardive dyskinesia in Caucasian populations. Pharmacogenomics J 12(6):513–520. doi:10.1038/tpj.2011.32

Greenbaum L, Smith RC, Lorberboym M, Alkelai A, Zozulinsky P, Lifschytz T, Kohn Y, Djaldetti R, Lerer B (2012b) Association of the ZFPM2 gene with antipsychotic-induced parkinsonism in schizophrenia patients. Psychopharmacology (Berl) 220(3):519–528. doi:10.1007/s00213-011-2499-6

Gunes A, Scordo MG, Jaanson P, Dahl ML (2007) Serotonin and dopamine receptor gene polymorphisms and the risk of extrapyramidal side effects in perphenazine-treated schizophrenic patients. Psychopharmacology (Berl) 190(4):479–484. doi:10.1007/s00213-006-0622-x

Hedley PL, Jorgensen P, Schlamowitz S, Wangari R, Moolman-Smook J, Brink PA, Kanters JK, Corfield VA, Christiansen M (2009) The genetic basis of long QT and short QT syndromes: a mutation update. Hum Mutat 30(11):1486–1511. doi:10.1002/humu.21106

Heils A, Teufel A, Petri S, Stöber G, Riederer P, Bengel D, Lesch P (1996) Allelic variation of human serotonin transporter gene expression. J Neurochem 66(6):2621–2624

Hougardy DM, Egberts TC, van der Graaf F, Brenninkmeijer VJ, Derijks LJ (2008) Serotonin transporter polymorphism and bleeding time during SSRI therapy. Br J Clin Pharmacol 65(5):761–766. doi:10.1111/j.1365-2125.2008.03098.x

Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, Hu SL, Wu MT, Chen GS, Wong TW, Hsiao PF, Chen WH, Shih HY, Fang WH, Wei CY, Lou YH, Huang YL, Lin JJ, Chen YT (2006) Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics 16(4):297–306. doi:10.1097/01.fpc.0000199500.46842.4a

Ikediobi ON, Shin J, Nussbaum RL, Phillips KA, Translational UCf, Policy Research on Personalized M, Walsh JM, Ladabaum U, Marshall D (2009) Addressing the challenges of the clinical application of pharmacogenetic testing. Clin Pharmacol Ther 86(1):28–31. doi:10.1038/clpt.2009.30

Inada T, Koga M, Ishiguro H, Horiuchi Y, Syu A, Yoshio T, Takahashi N, Ozaki N, Arinami T (2008) Pathway-based association analysis of genome-wide screening data suggest that genes associated with the gamma-aminobutyric acid receptor signaling pathway are involved in neuroleptic-induced, treatment-resistant tardive dyskinesia. Pharmacogenet Genomics 18(4):317–323. doi:10.1097/FPC.0b013e3282f70492

Inoue K, Suzuki E, Takahashi T, Yamamoto Y, Yazawa R, Takahashi Y, Imai K, Miyakawa K, Inoue Y, Tsuji D, Hayashi H, Itoh K (2014) 4217C>A polymorphism in carbamoyl-phosphate synthase 1 gene may not associate with hyperammonemia development during valproic acid-based therapy. Epilepsy Res 108(6):1046–1051. doi:10.1016/j.eplepsyres.2014.04.008

Janicki PK, Bezinover D, Postula M, Thompson RS, Acharya J, Acharya V, McNew C, Bowman JD, Kurkowska-Jastrzebska I, Mirowska-Guzel D (2013) Increased occurrence of Valproic acid-induced hyperammonemia in carriers of T1405N polymorphism in carbamoyl phosphate synthetase 1 gene. ISRN Neurol 2013:261497. doi:10.1155/2013/261497

Kane JM, Woerner M, Lieberman J (1988) Tardive dyskinesia: prevalence, incidence, and risk factors. J Clin Psychopharmacol 8(4 Suppl):52S–56S

Kao AC, Muller DJ (2013) Genetics of antipsychotic-induced weight gain: update and current perspectives. Pharmacogenomics 14(16):2067–2083. doi:10.2217/pgs.13.207

Karlsson L, Green H, Zackrisson AL, Bengtsson F, Jakobsen Falk I, Carlsson B, Ahlner J, Kugelberg FC (2013) ABCB1 gene polymorphisms are associated with fatal intoxications involving venlafaxine but not citalopram. Int J Leg Med 127(3):579–586. doi:10.1007/s00414-013-0849-0

Keers R, Bonvicini C, Scassellati C, Uher R, Placentino A, Giovannini C, Rietschel M, Henigsberg N, Kozel D, Mors O, Maier W, Hauser J, Souery D, Mendlewicz J, Schmal C, Zobel A, Larsen ER, Szczepankiewicz A, Kovacic Z, Elkin A, Craig I, McGuffin P, Farmer AE, Aitchison KJ, Gennarelli M (2011) Variation in GNB3 predicts response and adverse reactions to antidepressants. J Psychopharmacol 25(7):867–874. doi:10.1177/0269881110376683

Klein KM, Hamer HM, Reis J, Schmidtke J, Oertel WH, Theisen FM, Hebebrand J, Rosenow F (2005) Weight change in monozygotic twins treated with valproate. Obes Res 13(8):1330–1334. doi:10.1038/oby.2005.161

Klotz U (2007) The role of pharmacogenetics in the metabolism of antiepileptic drugs: pharmacokinetic and therapeutic implications. Clin Pharmacokinet 46(4):271–279. doi:10.2165/00003088-200746040-00001

Korpos E, Wu C, Sorokin L (2009) Multiple roles of the extracellular matrix in inflammation. Curr Pharm Des 15(12):1349–1357

Kwadijk-de Gijsel S, Bijl MJ, Visser LE, van Schaik RH, Hofman A, Vulto AG, van Gelder T, Ch Stricker BH (2009) Variation in the CYP2D6 gene is associated with a lower serum sodium concentration in patients on antidepressants. Br J Clin Pharmacol 68(2):221–225. doi:10.1111/j.1365-2125.2009.03448.x

Laje G (2013) Pharmacogenetics of mood disorders: what clinicians need to know. CNS Spectr 18(5):272–284. doi:10.1017/S1092852913000278

Laje G, Paddock S, Manji H, Rush AJ, Wilson AF, Charney D, McMahon FJ (2007) Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. Am J Psychiatry 164(10):1530–1538. doi:10.1176/appi.ajp.2007.06122018

Laje G, Allen AS, Akula N, Manji H, John Rush A, McMahon FJ (2009) Genome-wide association study of suicidal ideation emerging during citalopram treatment of depressed outpatients. Pharmacogenet Genomics 19(9):666–674. doi:10.1097/FPC.0b013e32832e4bcd

Leclerc E, Mansur RB, Brietzke E (2013) Determinants of adherence to treatment in bipolar disorder: a comprehensive review. J Affect Disord 149(1–3):247–252. doi:10.1016/j.jad.2013.01.036

Lee HY, Kang RH, Paik JW, Jeong YJ, Chang HS, Han SW, Lee MS (2009) Association of the adrenergic alpha 2a receptor – 1291C/G polymorphism with weight change and treatment response to mirtazapine in patients with major depressive disorder. Brain Res 1262:1–6. doi:10.1016/j.brainres.2009.01.013

Lencz T, Malhotra AK (2009) Pharmacogenetics of antipsychotic-induced side effects. Dialogues Clin Neurosci 11(4):405–415

Leucht S, Hierl S, Kissling W, Dold M, Davis JM (2012) Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry J Ment Sci 200(2):97–106. doi:10.1192/bjp.bp.111.096594

Li D, He L (2007) Meta-analysis supports association between serotonin transporter (5-HTT) and suicidal behavior. Mol Psychiatry 12(1):47–54. doi:10.1038/sj.mp.4001890

Liolitsa D, Powell JF, Prince M, Lovestone S (2001) Association study of the 5-HT(2A) receptor gene polymorphism, T102C and essential hypertension. J Hum Hypertens 15(5):335–339. doi:10.1038/sj.jhh.1001177

Mahar I, Bambico FR, Mechawar N, Nobrega JN (2014) Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. Neurosci Biobehav Rev 38:173–192. doi:10.1016/j.neubiorev.2013.11.009

Mandelli L, Serretti A (2013) Gene environment interaction studies in depression and suicidal behavior: an update. Neurosci Biobehav Rev 37(10 Pt 1):2375–2397. doi:10.1016/j.neubiorev.2013.07.011

Mann JJ (2003) Neurobiology of suicidal behaviour. Nat Rev Neurosci 4(10):819–828. doi:10.1038/nrn1220

Meltzer HY (2012) Serotonergic mechanisms as targets for existing and novel antipsychotics. Handb Exp Pharmacol 212:87–124. doi:10.1007/978-3-642-25761-2_4

Menke A, Domschke K, Czamara D, Klengel T, Hennings J, Lucae S, Baune BT, Arolt V, Muller-Myhsok B, Holsboer F, Binder EB (2012) Genome-wide association study of antidepressant treatment-emergent suicidal ideation. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 37(3):797–807. doi:10.1038/npp.2011.257

Millier A, Amri I, Boyer L, Auquier P, Toumi M (2014) Utility decrements associated with side effects in schizophrenia. J Med Econ 17:853–861. doi:10.3111/13696998.2014.964405, 1–9

Muller DJ, Chowdhury NI, Zai CC (2013) The pharmacogenetics of antipsychotic-induced adverse events. Curr Opin Psychiatry 26(2):144–150. doi:10.1097/YCO.0b013e32835dc9da

Novalbos J, Lopez-Rodriguez R, Roman M, Gallego-Sandin S, Ochoa D, Abad-Santos F (2010) Effects of CYP2D6 genotype on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. J Clin Psychopharmacol 30(5):504–511. doi:10.1097/JCP.0b013e3181ee84c7

Ogusu N, Saruwatari J, Nakashima H, Noai M, Nishimura M, Deguchi M, Oniki K, Yasui-Furukori N, Kaneko S, Ishitsu T, Nakagaswa K (2014) Impact of the superoxide dismutase 2 Val16Ala polymorphism on the relationship between Valproic acid exposure and elevation of gamma-

glutamyltransferase in patients with epilepsy: a population pharmacokinetic-pharmacodynamic analysis. PLoS One 9(11):e111066. doi:10.1371/journal.pone.0111066

Olivier B, Chan JS, Snoeren EM, Olivier JD, Veening JG, Vinkers CH, Waldinger MD, Oosting RS (2011) Differences in sexual behaviour in male and female rodents: role of serotonin. Curr Top Behav Neurosci 8:15–36. doi:10.1007/7854_2010_116

Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB (2007) Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's general practice research database. Arch Gen Psychiatry 64(2):242–249. doi:10.1001/archpsyc.64.2.242

Pacher P, Kecskemeti V (2004) Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? Curr Pharm Des 10(20):2463–2475

Patsopoulos NA, Ntzani EE, Zintzaras E, Ioannidis JP (2005) CYP2D6 polymorphisms and the risk of tardive dyskinesia in schizophrenia: a meta-analysis. Pharmacogenet Genomics 15(3):151–158

Paulussen AD, Gilissen RA, Armstrong M, Doevendans PA, Verhasselt P, Smeets HJ, Schulze-Bahr E, Haverkamp W, Breithardt G, Cohen N, Aerssens J (2004) Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. J Mol Med 82(3):182–188. doi:10.1007/s00109-003-0522-z

Perlis RH, Purcell S, Fava M, Fagerness J, Rush AJ, Trivedi MH, Smoller JW (2007) Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR*D study. Arch Gen Psychiatry 64(6):689–697. doi:10.1001/archpsyc.64.6.689

Perlis RH, Laje G, Smoller JW, Fava M, Rush AJ, McMahon FJ (2009) Genetic and clinical predictors of sexual dysfunction in citalopram-treated depressed patients. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 34(7):1819–1828. doi:10.1038/npp.2009.4

Perroud N, Courtet P, Vincze I, Jaussent I, Jollant F, Bellivier F, Leboyer M, Baud P, Buresi C, Malafosse A (2008) Interaction between BDNF Val66Met and childhood trauma on adult's violent suicide attempt. Genes Brain Behav 7(3):314–322. doi:10.1111/j.1601-183X.2007.00354.x

Perroud N, Aitchison KJ, Uher R, Smith R, Huezo-Diaz P, Marusic A, Maier W, Mors O, Placentino A, Henigsberg N, Rietschel M, Hauser J, Souery D, Kapelski P, Bonvicini C, Zobel A, Jorgensen L, Petrovic A, Kalember P, Schulze TG, Gupta B, Gray J, Lewis CM, Farmer AE, McGuffin P, Craig I (2009) Genetic predictors of increase in suicidal ideation during antidepressant treatment in the GENDEP project. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 34(12):2517–2528. doi:10.1038/npp.2009.81

Perroud N, Uher R, Ng MY, Guipponi M, Hauser J, Henigsberg N, Maier W, Mors O, Gennarelli M, Rietschel M, Souery D, Dernovsek MZ, Stamp AS, Lathrop M, Farmer A, Breen G, Aitchison KJ, Lewis CM, Craig IW, McGuffin P (2012) Genome-wide association study of increasing suicidal ideation during antidepressant treatment in the GENDEP project. Pharmacogenomics J 12(1):68–77. doi:10.1038/tpj.2010.70

Peuskens J, Pani L, Detraux J, De Hert M (2014) The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs 28(5):421–453. doi:10.1007/s40263-014-0157-3

Porcelli S, Fabbri C, Spina E, Serretti A, De Ronchi D (2011) Genetic polymorphisms of cytochrome P450 enzymes and antidepressant metabolism. Expert Opin Drug Metab Toxicol 7(9):1101–1115. doi:10.1517/17425255.2011.597740

Pronicka E, Weglewska-Jurkiewicz A, Pronicki M, Sykut-Cegielska J, Kowalski P, Pajdowska M, Jankowska I, Kotulska K, Kalicinski P, Jakobkiewicz-Banecka J, Wegrzyn G (2011) Drug-resistant epilepsia and fulminant valproate liver toxicity. Alpers-Huttenlocher syndrome in two children confirmed post mortem by identification of p.W748S mutation in POLG gene. Med Sci Monit Int Med J Exp Clin Res 17(4):CR203–CR209

Rada JA, Cornuet PK, Hassell JR (1993) Regulation of corneal collagen fibrillogenesis in vitro by corneal proteoglycan (lumican and decorin) core proteins. Exp Eye Res 56(6):635–648. doi:10.1006/exer.1993.1081

Rau T, Wohlleben G, Wuttke H, Thuerauf N, Lunkenheimer J, Lanczik M, Eschenhagen T (2004) CYP2D6 genotype: impact on adverse effects and nonresponse during treatment with antidepressants-a pilot study. Clin Pharmacol Ther 75(5):386–393. doi:10.1016/j.clpt.2003.12.015

Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT (2001) Antipsychotics and the risk of sudden cardiac death. Arch Gen Psychiatry 58(12):1161–1167

Reynolds GP (2012) Pharmacogenetic aspects of antipsychotic drug-induced weight gain – a critical review. Clin Psychopharmacol Neurosci Off Sci J Korean Coll Neuropsychopharmacol 10(2):71–77. doi:10.9758/cpn.2012.10.2.71

Roberts R, Wells GA, Stewart AF, Dandona S, Chen L (2010) The genome-wide association study – a new era for common polygenic disorders. J Cardiovasc Transl Res 3(3):173–182. doi:10.1007/s12265-010-9178-6

Rogers HL, Bhattaram A, Zineh I, Gobburu J, Mathis M, Laughren TP, Pacanowski M (2012) CYP2D6 genotype information to guide pimozide treatment in adult and pediatric patients: basis for the U.S. Food and Drug Administration's new dosing recommendations. J Clin Psychiatry 73(9):1187–1190. doi:10.4088/JCP.11m07572

Saneto RP, Lee IC, Koenig MK, Bao X, Weng SW, Naviaux RK, Wong LJ (2010) POLG DNA testing as an emerging standard of care before instituting valproic acid therapy for pediatric seizure disorders. Seizure 19(3):140–146. doi:10.1016/j.seizure.2010.01.002

Schroeder C, Tank J, Boschmann M, Diedrich A, Sharma AM, Biaggioni I, Luft FC, Jordan J (2002) Selective norepinephrine reuptake inhibition as a human model of orthostatic intolerance. Circulation 105(3):347–353

Secher A, Bukh J, Bock C, Koefoed P, Rasmussen HB, Werge T, Kessing LV, Mellerup E (2009) Antidepressive-drug-induced bodyweight gain is associated with polymorphisms in genes coding for COMT and TPH1. Int Clin Psychopharmacol 24(4):199–203. doi:10.1097/YIC.0b013e32832d6be2

Segman RH, Heresco-Levy U, Finkel B, Goltser T, Shalem R, Schlafman M, Dorevitch A, Yakir A, Greenberg D, Lerner A, Lerer B (2001) Association between the serotonin 2A receptor gene and tardive dyskinesia in chronic schizophrenia. Mol Psychiatry 6(2):225–229. doi:10.1038/sj.mp.4000842

Sequeira A, Mamdani F, Lalovic A, Anguelova M, Lesage A, Seguin M, Chawky N, Desautels A, Turecki G (2004) Alpha 2A adrenergic receptor gene and suicide. Psychiatry Res 125(2):87–93. doi:10.1016/j.psychres.2003.12.002

Serretti A, Olgiati P, Bajo E, Bigelli M, De Ronchi D (2011) A model to incorporate genetic testing (5-HTTLPR) in pharmacological treatment of major depressive disorders. World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry 12(7):501–515. doi:10.3109/15622975.2011.572998

Shams TA, Muller DJ (2014) Antipsychotic induced weight gain: genetics, epigenetics, and biomarkers reviewed. Curr Psychiatry Rep 16(10):473. doi:10.1007/s11920-014-0473-9

Shams ME, Arneth B, Hiemke C, Dragicevic A, Muller MJ, Kaiser R, Lackner K, Hartter S (2006) CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. J Clin Pharm Ther 31(5):493–502. doi:10.1111/j.1365-2710.2006.00763.x

Sicard MN, Zai CC, Tiwari AK, Souza RP, Meltzer HY, Lieberman JA, Kennedy JL, Muller DJ (2010) Polymorphisms of the HTR2C gene and antipsychotic-induced weight gain: an update and meta-analysis. Pharmacogenomics 11(11):1561–1571. doi:10.2217/pgs.10.123

Souza RP, De Luca V, Muscettola G, Rosa DV, de Bartolomeis A, Romano Silva M, Kennedy JL (2008) Association of antipsychotic induced weight gain and body mass index with GNB3 gene: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 32(8):1848–1853. doi:10.1016/j.pnpbp.2008.08.014

Stewart JD, Horvath R, Baruffini E, Ferrero I, Bulst S, Watkins PB, Fontana RJ, Day CP, Chinnery PF (2010) Polymerase gamma gene POLG determines the risk of sodium valproate-induced liver toxicity. Hepatology 52(5):1791–1796. doi:10.1002/hep.23891

Strohmaier J, Wust S, Uher R, Henigsberg N, Mors O, Hauser J, Souery D, Zobel A, Dernovsek MZ, Streit F, Schmal C, Kozel D, Placentino A, Farmer A, McGuffin P, Aitchison KJ, Rietschel M (2011) Sexual dysfunction during treatment with serotonergic and noradrenergic

antidepressants: clinical description and the role of the 5-HTTLPR. World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry 12(7):528–538. doi:10.3109/15622975.2011.559270
Sugai T, Suzuki Y, Sawamura K, Fukui N, Inoue Y, Someya T (2006) The effect of 5-hydroxytryptamine 3A and 3B receptor genes on nausea induced by paroxetine. Pharmacogenomics J 6(5):351–356
Suzuki Y, Sawamura K, Someya T (2006) Polymorphisms in the 5-hydroxytryptamine 2A receptor and CytochromeP4502D6 genes synergistically predict fluvoxamine-induced side effects in japanese depressed patients. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 31(4):825–831. doi:10.1038/sj.npp.1300919
Syu A, Ishiguro H, Inada T, Horiuchi Y, Tanaka S, Ishikawa M, Arai M, Itokawa M, Niizato K, Iritani S, Ozaki N, Takahashi M, Kakita A, Takahashi H, Nawa H, Keino-Masu K, Arikawa-Hirasawa E, Arinami T (2010) Association of the HSPG2 gene with neuroleptic-induced tardive dyskinesia. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 35(5):1155–1164. doi:10.1038/npp.2009.220
Tanaka M, Kobayashi D, Murakami Y, Ozaki N, Suzuki T, Iwata N, Haraguchi K, Ieiri I, Kinukawa N, Hosoi M, Ohtani H, Sawada Y, Mine K (2008) Genetic polymorphisms in the 5-hydroxytryptamine type 3B receptor gene and paroxetine-induced nausea. Int J Neuropsychopharmacol/Off Sci J Coll Int Neuropsychopharm 11(2):261–267
Thomas KL, Ellingrod VL, Bishop JR, Keiser MJ (2010) A pilot study of the pharmacodynamic impact of SSRI drug selection and beta-1 receptor genotype (ADRB1) on cardiac vital signs in depressed patients: a novel pharmacogenetic approach. Psychopharmacol Bull 43(1):11–22
Torrealba F, Riveros ME, Contreras M, Valdes JL (2012) Histamine and motivation. Front Syst Neurosci 6:51. doi:10.3389/fnsys.2012.00051
Tsai HT, North KE, West SL, Poole C (2010) The DRD3 rs6280 polymorphism and prevalence of tardive dyskinesia: a meta-analysis. Am J Med Genet B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet 153B(1):57–66. doi:10.1002/ajmg.b.30946
US Food and Drug Administration (2006) Clinical review: relationship between antidepressant drugs and suicidality in adults. http://www.fda.gov/
Watanabe N, Omori IM, Nakagawa A, Cipriani A, Barbui C, Churchill R, Furukawa TA (2011) Mirtazapine versus other antidepressive agents for depression. Cochrane Database Syst Rev (12):CD006528. doi:10.1002/14651858.CD006528.pub2
WHO (2004) Mental Health. http://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/data-and-statistics
Wilffert B, Al Hadithy AF, Sing VJ, Matroos G, Hoek HW, van Os J, Bruggeman R, Brouwers JR, van Harten PN (2009) The role of dopamine D3, 5-HT2A and 5-HT2C receptor variants as pharmacogenetic determinants in tardive dyskinesia in African-Caribbean patients under chronic antipsychotic treatment: Curacao extrapyramidal syndromes study IX. J Psychopharmacol 23(6):652–659. doi:10.1177/0269881108091594
Wilkinson TJ, Begg EJ, Winter AC, Sainsbury R (1999) Incidence and risk factors for hyponatraemia following treatment with fluoxetine or paroxetine in elderly people. Br J Clin Pharmacol 47(2):211–217
Willard HF, Riordan JR (1985) Assignment of the gene for myelin proteolipid protein to the X chromosome: implications for X-linked myelin disorders. Science 230(4728):940–942
Winner J, Allen JD, Altar CA, Spahic-Mihajlovic A (2013) Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl Psychiatry 3:e242. doi:10.1038/tp.2013.2
Zaccara G, Franciotta D, Perucca E (2007) Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia 48(7):1223–1244. doi:10.1111/j.1528-1167.2007.01041.x
Zill P, Malitas PN, Bondy B, Engel R, Boufidou F, Behrens S, Alevizos BE, Nikolaou CK, Christodoulou GN (2003) Analysis of polymorphisms in the alpha-subunit of the olfactory G-protein Golf in lithium-treated bipolar patients. Psychiatr Genet 13(2):65–69. doi:10.1097/01.ypg.0000057881.80011.45

Part II
Pharmacovigilance of Specific Psychotropic Drug Classes

Chapter 8
Safety and Tolerability of Antidepressants

Chris Manson, Robert Gordon, and David Baldwin

Abstract Problems abound when assessing the comparative acceptability and safety of antidepressant drugs. The findings of double-blind randomised placebo- and comparator-controlled trials provide a reasonable impression of the relative tolerability of antidepressants in short-term treatment, but less is confidently known about their relative acceptability and safety in long-term treatment. The findings of randomised controlled trials which are conducted in homogenous and largely physically healthy samples of trial participants do not necessarily generalise well into the mixed and highly comorbid groups of depressed patients seen in real-world clinical settings. Furthermore, many of the reported adverse effects of antidepressants include reduced sexual desire, emotional indifference, and 'activation' – which can make it hard to distinguish the adverse effects of treatment from persistent or emerging symptoms of the underlying condition. The quality of many reports of possible adverse drug reactions with antidepressants is poor and this further hinders the accurate assessment of comparative tolerability and potential toxicity. Certain antidepressant classes are prescribed preferentially to particular groups of patients with comorbid physical illnesses, whose presence hinders the interpretation of tolerability events in pharmacoepidemiological studies. These problems are addressed through discussing the role of mixed treatment comparisons in assessing the acceptability of antidepressant treatment, are highlighted by referring to methodological challenges in research into sexual dysfunction and emotional indifference during treatment with selective serotonin reuptake inhibitors, are illustrated by considering the quality of case reports of adverse reactions relating to hepatic function with serotonin-noradrenaline reuptake inhibitors, and are further considered when reviewing pharmacoepidemiological data on antidepressant tolerability in elderly patients.

Keywords Antidepressant • Tolerability • Safety • Pharmacovigilance • Elderly

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8.1 Introduction

Pharmacotherapy, especially in the form of 'second-generation antidepressants' such as selective serotonin reuptake inhibitors (SSRIs), has become the mainstay first-line choice of medical management for many mood and anxiety disorders. This widespread use of antidepressants remains the source of some controversy. Double-blind randomised placebo-controlled and comparator-controlled trials provide a reasonable impression of their absolute and relative short-term tolerability, but less is confidently known about the relative long-term acceptability and safety of differing antidepressants. Furthermore randomised controlled trials are typically conducted in homogenous groups of generally physically healthy participants, who do not fully represent the more heterogeneous and highly comorbid groups of depressed patients in routine clinical practice.

Reported adverse effects of antidepressants often relate to largely subjective psychological experiences such as reduced sexual desire, emotional indifference, and 'activation', which makes the task of distinguishing these experiences from persistent or emerging symptoms of the underlying condition a difficult one. Another hindrance in assessing the adverse effects of antidepressants lies in the poor quality of many of the reports of their comparative tolerability and potential toxicity.

Current difficulties in assessing the safety of antidepressant drugs are considered through a discussion of the role of mixed treatment comparisons in assessing acceptability of antidepressant medications, are highlighted through the example of methodological challenges in research into 'treatment-emergent' sexual dysfunction and emotional indifference with SSRIs, and are illustrated through the examples of reported associations of antidepressants with attempted suicide, hepatic dysfunction, persistent pulmonary hypertension, and an increased risk of adverse outcomes in elderly patients.

8.2 The Range of Antidepressant Drugs

Antidepressants were first introduced in the 1950s and came to gradually be the first-line medical treatment for patients with moderate to severe depression (Excellence National Institute for Health and Clinical 2009). There are four main classes, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-noradrenaline reuptake inhibitor (SNRIs), and a group of other antidepressants with differing pharmacological properties, such as the noradrenaline and specific serotonergic antidepressant (NASSA) mirtazapine, the selective noradrenaline reuptake inhibitor reboxetine, and the melatonin agonist and serotonin receptor antagonist agomelatine. In addition to their principal use in treating patients with unipolar depressive disorders, antidepressants are also used to treat patients with anxiety disorders, obsessive-compulsive disorder, post-traumatic stress disorder, and other conditions including chronic pain.

'Second-generation' antidepressants include SSRIs, SNRIs, and others that selectively target neurotransmitters, as their primary mechanism of action. Some of these are available as both immediate-release and extended-release formulations

(Nussbaumer et al. 2014). The clinical rationale for extended-release formulations is to improve patients adherence to prescribed drug regimens because of the need for less frequent administration (once a day to once a week) (De Vane 2003); they may also have better overall tolerability through reduced fluctuations of plasma drug concentrations with lower plasma peaks (Nussbaumer et al. 2014). However, critics argue that the availability of extended-release formulations represents little more than a pharmaceutical industry marketing strategy, without improved benefits for patients but with substantially higher costs (Huskamp 2006). A recent systematic review and meta-analysis suggested there are no clear differences between the two approaches to drug formulation (Nussbaumer et al. 2014).

8.3 Relative Efficacy and Tolerability

The SSRI zimeldine was developed with the intention of it being superior in tolerability and having greater safety in overdose when compared to its TCA predecessors. However, it was associated with a 'hypersensitivity syndrome', symptoms of which included fever and myalgia (Nilsson 1983). Thirteen cases of drug reactions resembling Guillain-Barre syndrome had been reported by 1985 and the drug was withdrawn the same year (Fagius et al. 1985). Fortunately this has not been associated with other SSRIs. An early meta-analysis of randomised controlled trials with SSRIs (with the exception of fluvoxamine) indicated that the proportion of patients withdrawing from treatment due to adverse effects was significantly lower than the proportion treated with a TCA (with the exception of dosulepin [dothiepin]) (Anderson 2000). The SSRI class is currently the most widely recommended first-line pharmacological treatment for patients with major (unipolar) depression or anxiety disorders, based on their efficacy, tolerability, safety, and acquisition cost.

Until recently, relatively little was known about whether certain SSRIs were more efficacious or better tolerated than other newer antidepressants. Whether newer antidepressants such as the SNRIs, reboxetine, and mirtazapine perform better in terms of efficacy and side effect profile than existing SSRIs was also uncertain. However meta-analyses, sometimes utilising 'mixed treatment comparisons' based on network meta-analysis suggest that some newer drugs – for example, mirtazapine and escitalopram – are more efficacious than their comparators, while others are better tolerated – for example, escitalopram and sertraline (Cipriani et al. 2009; Nutt 2009). The SNRI reboxetine has disadvantages in both efficacy and tolerability, leading some to argue for it not to be used as a first-line treatment for patients with depression and some to suggest it should be withdrawn (Eyding et al. 2010).

Meta-analyses typically focus on overall efficacy (the proportion of patients responding to treatment or who go into symptomatic remission) and overall tolerability (the proportion of patients withdrawing due to adverse effects). However, some meta-analyses have examined the relative incidence of particular adverse effects: for example, Gartlehner and colleagues found that the SNRI venlafaxine is more strongly associated with the risks of nausea and vomiting, the SSRI sertraline with diarrhoea, mirtazapine with weight gain and trazodone with somnolence. They also found that there is a lower incidence of emergent sexual

dysfunction in patients treated with the predominantly dopaminergic antidepressant drug bupropion, when compared to other second-generation antidepressants (Gartlehner et al. 2011). Most published meta-analyses have been primarily concerned with the relative risks and benefits of SSRIs and other newer antidepressants in the acute treatment of patients with major (unipolar) depression, but some are now emerging which focus on treatment of other conditions such as generalised anxiety disorder (Baldwin et al. 2011).

8.4 Treatment Emergent Sexual Dysfunction

Depressed patients often experience lowered sexual interest and difficulty in achieving sexual satisfaction but many antidepressants are associated with 'treatment-emergent' sexual dysfunction (i.e. worsening of pre-existing difficulties or development of new problems during treatment). Sexual dysfunction is associated with worsening of mood and diminished self-esteem and is detrimental to interpersonal relationships (Williams et al. 2006, 2010). Meta-analyses and randomised controlled trials indicate that some antidepressants may be less likely to be associated with treatment-emergent sexual dysfunction than others. For example, Chiesa and Serretti suggest that agomelatine, bupropion, moclobemide, mirtazapine, and nefazodone were no different to placebo in associated treatment-emergent sexual difficulties (Serretti and Chiesa 2009). Mirtazapine may be less likely to cause sexual dysfunction (Serretti and Chiesa 2009) including delayed ejaculation (Taylor et al. 2013). The latter is a less common side effect with bupropion than with SSRI treatment, and bupropion is often used in the management of patients with SSRI-associated sexual dysfunction. However the long-term clinical relevance of these statistically significant differences seen between drugs in acute treatment studies is uncertain (Reichenpfader et al. 2014). It is often the case that a reduction in the severity of depressive symptoms is followed by an improvement in sexual function and satisfaction, even though patients are taking antidepressant drugs that can affect sexual function adversely (Baldwin et al. 2008, 2006).

8.5 Differentiating Depressive Symptoms from Adverse Emotional Effects

Emotional indifference, increased 'nervousness', and worsening of suicidal thoughts and images are all known to be potential adverse effects of antidepressant treatment. However, these experiences can also be symptoms of the underlying condition being treated, making it hard to distinguish adverse effects from worsening depression. Loss of interest and a reduced capacity for pleasure and reward (anhedonia) are cardinal depressive symptoms, but antidepressants themselves can sometimes reduce emotional responsiveness, increase apathy, and induce a state of 'psychic indifference'. A qualitative study of individuals being treated with SSRIs

found that problems such as emotional detachment and reductions in both positive and negative emotions were not uncommon (Price et al. 2009). Assessing indifference is difficult due to the presence of depressive symptoms as well as a lack of standardised methods. Previous scales and questionnaires have some weaknesses, but the Oxford Questionnaire on Emotional Side Effects of Antidepressants appears to have robust psychometric properties (Price et al. 2012) and in a randomised controlled trial was able to differentiate between the emotional effects of the SSRI escitalopram and the novel antidepressant agomelatine (Corruble et al. 2013).

Similar problems arise when assessing increased 'nervousness', worsened anxiety, increased agitation, and suicidal ideation during antidepressant treatment. The potential adverse effect of increased nervousness with SSRI treatment was recognised a few years after they became available for clinical use (Baldwin et al. 1991). Randomised controlled clinical trials suggest that SSRIs are often associated with a transient worsening of anxiety symptoms (Baldwin et al. 1999). However, the 'jitteriness syndrome', thought to be associated with the early stages of antidepressant treatment, is poorly characterised and its exact frequency (and optimal management) is unknown (Sinclair et al. 2009). An early prescription-event monitoring survey suggested an incidence of approximately 1 %, but this may represent significant underreporting.

'Discontinuation' symptoms are not uncommon when antidepressant treatment is withdrawn, either abruptly or when slowly tapered. Symptoms typically peak in the first week and then lessen over time. The risk of discontinuation syndromes differs between antidepressants but predicting which patients will be affected is challenging. The recommended withdrawal method is slow and stepwise (tapered), but its value is yet to be established through double-blind staggered discontinuation design studies (Baldwin et al. 2007). As with emotional indifference and suicidal thoughts and images, it is challenging to distinguish between pharmacological discontinuation symptoms and symptoms arising from an early relapse of anxiety and depression. This is compounded by the fact that the most widely used instrument for assessing withdrawal symptoms (the Discontinuation-Emergent Signs and Symptoms Scale) (Rosenbaum et al. 1998) has 43 items, only 10 of which are uncommon in untreated depressed patients.

8.6 Antidepressant Drugs and Suicidal Thoughts, Images, and Behaviour

Meta-analyses suggest that the incidence of suicidality does not markedly differ between classes of antidepressant: for example, a meta-analysis of 372 randomised double-blind placebo-controlled trials, involving almost 100,000 patients found 'little difference' between drugs, although it found a greater risk of suicidality in patients younger than 25 years (Stone et al. 2009). This is supported by the findings of a systematic review of suicide attempts during observational studies of patients being treated with SSRIs, which found them to be protective against both attempted and completed suicide in older adults (Barbui et al. 2009).

Research findings suggesting a potential link between antidepressants and suicide risk in young people have engendered much controversy. However, the evidence on antidepressants and suicide risk is inconsistent (Kaizar et al. 2006; Leckman and King 2007; Simon 2006) (See Table 8.1). During 2003–2004 the Food and Drug Administration (FDA) in the United States issued health advisory warnings stating that children and adolescents were at increased risk of suicidality (ideation and behaviour) and soon after made it a requirement that a safety warning be placed on the labels of all antidepressant drugs, this warning later being extended to include young adults. The reasoning behind the FDA decisions is contentious (Klein 2006): it appears based on an FDA-solicited meta-analysis, which showed a relative risk for 'suicidality' of 1.95 (95 % confidence interval 1.28–2.98) for young people taking antidepressants compared with those given placebo (Hammad et al. 2006). However, the trials included within the meta-analysis were not designed to estimate suicidality risk (Klein 2006; Hammad et al. 2006) and the majority of the reported adverse events involved suicidal thoughts and images and did not represent attempted or completed suicide (Klein 2006; Hammad et al. 2006; Baldessarini et al. 2006). Despite the evidence being inconclusive, the FDA advisories and boxed warning attracted much media coverage, leading to safety alarms in clinicians and young patients and their parents (Lu et al. 2014).

Treating young depressed people with antidepressant drugs can be effective in terms of improved mood (March et al. 2004, 2007; Gibbons et al. 2012) but the relationship between suicidal behaviour and antidepressant use is complex, and studies have produced inconsistent results (Lu et al. 2014). Pre-existing suicidality may be the reason for deciding to treat a depressed patient with an antidepressant, and suicidal risk is usually reduced with effective treatment (Simon 2006). Managing suicidality in this way may be associated with different risks in adults and in young people (Gibbons et al. 2012). In adolescents and young adults, antidepressants may lead to short-term increases in suicidality (Hammad et al. 2006; Jick et al. 2004; FDA 2004). Studies undertaken since the FDA warnings have revealed substantial reductions in the numbers of young people being treated with antidepressants (Libby et al. 2007, 2009); this effect is also seen in older adults, who were not included within the warnings (Valuck et al. 2007).

There were also an associated decline in diagnoses of depression in both children and adults (Libby et al. 2007, 2009; Valuck et al. 2007), but no increase in the use of alternative approaches in young people nor in the degree to which patients were monitored, despite this being an explicit part of the warning (Libby et al. 2007, 2009; Pamer et al. 2010).

A large-scale long-term quasi-experimental study by Lu and colleagues (2014) investigated whether there were changes in nationwide 'suicidality' following the FDA warnings, the study cohorts comprising approximately 1.1 million adolescents, 1.4 million young adults, and 5 million older adults. They found an abrupt decline (31 %) in the previously upward trend of adolescent antidepressant use during the second year after the warnings, but a simultaneous sharp increase in psychotropic drug poisonings (21.7 %) (a validated measure of suicide attempts), particularly amongst males; there was also a significant relative increase of 13.9 % in drug poisonings amongst adolescents. In younger adults there was a reversal of the upward trend in antidepressant use in the second year following the warnings

and a simultaneous increase in psychotropic drug poisonings (33.7 %): in older adults, there was an observed relative reduction of 14.5 % in antidepressant use, but no significant increase in psychotropic drug poisonings.

Contrary to the well-meaning intention of the regulatory warnings, the net effect may have been to increase suicides, by leaving young people without effective antidepressant treatment. Similar findings have been observed in Sweden, where Isacsson and colleagues assessed trends in antidepressant use by comparing prescription records and post-mortem toxicology for all suicides in the 10–19 year age group during the periods 1992–2003 (baseline) and 2004–2010 (after the warning). They found that suicide increased over five consecutive years (by 60.5 %) and that the increases occurred amongst individuals who were not undergoing antidepressant treatment (Isacsson et al. 2014). The findings from both the American and Swedish studies therefore reveal the potential for both intended and unintended outcomes following widely publicised warnings.

8.7 Antidepressants and Hepatic Dysfunction

Certain antidepressants become associated with particular adverse effects, sometimes without justification. An example is the TCA lofepramine, which became linked to potential hepatotoxicity during the first few years of its launch; the first reported case was in October 1987 (Macphee et al. 1987) and a further 57 reports had been received by the UK Committee on Safety of Medicines 2 months later. A case report featuring withdrawal of lofepramine and exposure to the metabolite desipramine implicated the 'parent drug' (i.e. lofepramine) as being responsible for hepatotoxicity (Lack et al. 1990). However, a subsequent case series involving elderly patients revealed that the effects of lofepramine on hepatic function were only transient (Kelly et al. 1993), and a further investigation demonstrated that there was no difference between lofepramine and placebo in the incidence of abnormal liver function tests (Tan et al. 1994). No further published reports about hepatic dysfunction with the drug have appeared.

There is much variability in the quality of case reporting of adverse drug reactions; a systematic review of all case reports published in a single psychopharmacology journal over 25 years found that only 7 out of 40 reports of presumed adverse reactions were deemed sufficiently robust for ascribing possible or probable causality (with no correlation between the quality of the report and its impact as assessed by citations) (Talat et al. 2013). Similarly, presumed hepatic reactions to SNRI antidepressants (primarily duloxetine and venlafaxine) have been reported 17 times between 1999 and 2012; but only two reports involved re-exposure, only two investigated possible 'dose-response' relationships, and only three confirmed presumed hepatic reactions with a biopsy (Pradeep et al. 2004). High likely causality scores were only seen in reports of acute hepatitis in patients treated with venlafaxine (Pradeep et al. 2004), of asymptomatic transaminitis in a patient with known Gilbert's syndrome treated with venlafaxine (Phillips et al. 2006), and of acute hepatitis attributed to venlafaxine in a patient who was also taking five other medications, and who had recently stopped a phytomedicine (Feinberg 2010).

Findings from clinical trials and pharmacoepidemiological studies of duloxetine suggest that the incidence of elevated liver function test results in patients without hepatic disease is generally low (being somewhat higher in patients with known liver pathology) and not significantly greater than when treated with placebo (Wernicke et al. 2008a). In a large pharmacoepidemiological investigation based on 1.55 million years of patient exposure, there were 406 reported cases of duloxetine-associated hepatic problems, equating to a cumulative reporting rate of 0.008 % for all hepatic events and a risk of severe hepatic injury in 0.7/100,000 exposed person-years (Wernicke et al. 2008b). However, independent analysis of the FDA adverse event reporting system, and of the i3 Aperio (health insurance) database, suggests that the reporting of hepatic events with duloxetine may be disproportionately greater, when compared to other antidepressants (Strombom et al. 2008).

The novel antidepressant agomelatine has been shown to be hepato-protective against paracetamol-induced liver damage in rats (Karakus et al. 2013). However in human studies, elevated AST and/or ALT levels were seen in 1.4 % of patients taking 25 mg per day, and 2.5 % of patients prescribed 50 mg per day. Agomelatine is therefore contraindicated in patients with pre-existing hepatic disease, and regular monitoring (at baseline and at weeks 3, 12, and 24 of treatment) of hepatic function is required (McAllister-Williams et al. 2010). One case of fulminant hepatic failure in a patient with pre-existing fatty liver disease has been described (Gruz et al. 2014), and the German regulatory agency BfArm has received 58 cases of 'hepatotoxic adverse drug reactions' (Gahr et al. 2013), emphasising the need for further research into the effects of agomelatine on hepatic function.

8.8 SSRIs and Persistent Pulmonary Hypertension

Prenatal exposure to antidepressant drugs has been suggested to be associated with a number of adverse effects in the newborn infant, and several variables need to be considered when deciding whether or not to treat a depressed pregnant woman. One potential adverse effect that should be considered is persistent pulmonary hypertension of the newborn (Kieler et al. 2012), (see Table 8.3 and Table 8.4) a relatively rare condition (with an estimated prevalence of 1.9 per 1,000 live births) (Walsh-Sukys et al. 2000), in which pulmonary vasculature in the infant fails to 'relax' resulting in poor oxygenation (Grigoriadis et al. 2014). Symptoms range in severity from mild respiratory distress to hypoxia which requires urgent intensive medical care (Jong et al. 2012). Study findings suggesting an association between maternal use of SSRIs during pregnancy and persistent pulmonary hypertension in the newborn led both Health Canada and the FDA to issue advice to clinicians alerting them to the potential adverse effect (FDA US 2012). However more recent findings have been inconsistent (Occhiogrosso et al. 2012), with some studies reporting no association (Andrade et al. 2009; Wilson et al. 2011), others some association (Kieler et al. 2012; Chambers et al. 2006), and others indicating differential effects depending on the stage of the pregnancy when exposure occurred (Kieler et al. 2012; Chambers et al. 2006) (See Table 8.2). The FDA has stated, 'given the conflicting

Table 8.1 Hazard ratios for six adverse outcomes by antidepressant class and adjusted for confounders (Coupland et al. 2011)

		Antidepressant class adjusted hazard ratio (95 % CI)			
		SSRIs	TCAs	Others	Not taking antidepressants
Adverse outcomes	All-cause mortality	1.54 (1.48–1.59)	1.16 (1.10–1.22)	1.66 (1.56–1.77)	1.00
	Attempted suicide/ self-harm	2.16 (1.71–2.71)	1.70 (1.28–2.25)	5.16 (3.90–6.83)	1.00
	Myocardial infarction	1.15 (1.04–1.27)	1.09 (0.96–1.23)	1.04 (0.85–1.27)	1.00
	Stroke/transient ischaemic attack	1.17 (1.10–1.26)	1.02 (0.93–1.11)	1.37 (1.22–1.55)	1.00
	Falls	1.66 (1.58–1.73)	1.30 (1.23–1.38)	1.39 (1.28–1.52)	1.00
	Fracture	1.58 (1.48–1.68)	1.26 (1.16–1.37)	1.64 (1.46–1.84)	1.00

The * simply refers to the fact that all figures are adjusted vales for age, sex etc. Adjusted for sex, age (5 year bands), year, severity of depression, depression before age 65, smoking status, Townsend deprivation score, coronary heart disease, diabetes, hypertension, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, epilepsy/seizures, statins, nonsteroidal anti-inflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, and hypnotics/anxiolytics; all outcomes except stroke/transient ischaemic attack also adjusted for stroke/transient ischaemic attack at baseline; fracture outcome also adjusted for falls at baseline

Table 8.2 Hazard ratios for five adverse outcomes by antidepressant class and adjusted for confounders (Coupland et al. 2011)

		Antidepressant class adjusted hazard ratio (95 % CI)			
		SSRIs	TCAs	Others	Not taking antidepressants
Adverse outcomes	Upper gastrointestinal bleeding	1.22 (1.07–1.40)	1.29 (1.10–1.51)	1.37 (1.08–1.74)	1.00
	Epilepsy/seizures	1.83 (1.49–2.26)	1.02 (0.76–1.38)	2.24 (1.60–3.15)	1.00
	Road traffic accidents	0.89 (0.70–1.13)	0.86 (0.64–1.15)	0.67 (0.39–1.14)	1.00
	Adverse drug reactions	1.16 (0.98–1.37)	1.06 (0.86–1.29)	0.95 (1.68–1.34)	1.00
	Hyponatraemia	1.52 (1.33–1.75)	1.05 (0.87–1.27)	1.28 (0.98–1.67)	1.00

*Adjusted for sex, age (5 year bands), year, severity of depression, depression before age 65, smoking status, Townsend deprivation score, coronary heart disease, stroke/transient ischaemic attack, diabetes, hypertension, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, nonsteroidal anti-inflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, hypnotics/anxiolytics; all outcomes except epilepsy/seizures also adjusted for epilepsy/seizures at baseline

results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy' and persistent pulmonary hypertension in the newborn (FDA 2012).

Risk factors for persistent pulmonary hypertension (Grigoriadis et al. 2014) include certain congenital malformations, premature birth, meconium aspiration, maternal obesity, and caesarean section delivery (Occhiogrosso et al. 2012; Koren and Nordeng 2012a, b), but many of the studies of SSRIs did not exclude or control for other known risk factors and more than one risk factor may be a prerequisite for developing the condition (Occhiogrosso et al. 2012; Galbally et al. 2012). In a systematic review and meta-analysis of the associations between SSRI treatment and persistent pulmonary hypertension, Grigoriadis and colleagues found an increased risk if exposure to SSRIs occurred in late (but not early) pregnancy: study design, congenital malformation, and meconium aspiration were not significant effect modifiers, but the possible moderating effects of caesarean section, preterm birth, and maternal obesity could not be examined (Grigoriadis et al. 2014). There was a statistically significantly pooled odds ratio of 2.5 for exposure to SSRIs in late pregnancy, though the absolute risk is low; between 286 and 351 women in late gestation would have to be treated with an SSRI for there to be one additional case of persistent pulmonary hypertension in a new born baby. Therefore the meta-analysis indicates that less than 1 infant in 100 will develop persistent pulmonary hypertension following prenatal exposure to SSRIs. Although this is a serious condition with death rates between 5 % and 10 % when associated with other conditions (such as congenital malformations, meconium aspiration, sepsis, and idiopathic disease), it can be managed successfully (Koran and Nodding 2012). The mortality of infants with persistent pulmonary hypertension who have been exposed to SSRI is not established, though one study suggests 9.1 % (3 out of 33 infants) of the infants who were exposed to an SSRI died, whereas 9.5 % (183 of 1,935 infants) who were not exposed to an SSRI died (Kieler et al. 2012); however the disparity in group size makes this finding hard to interpret.

8.9 Adverse Outcomes in Elderly Patients

Depression is common in older people with around 10–15 % of those living in the community being affected by depressive symptoms (McDougall et al. 2007; Beekman et al. 1999). Adverse drug events are more common in elderly patients, due to higher rates of comorbid illness, age-related physiological changes, and polypharmacy (Cadieux 1999). Despite this they are underrepresented in randomised controlled trials, as these typically exclude older people and those with comorbid conditions (Giron et al. 2005). Several observational studies have investigated adverse outcome associated with antidepressants (Reid and Barbui 2010), though few have been dedicated specifically to an older population.

This paucity of data led Coupland and colleagues to undertake a large cohort study of antidepressant use in older people (aged 65 years and older), involving a

Table 8.3 Exposure to SSRIs in gestational week 20 or later and risk of PPH of the newborn (Kieler et al. 2012)

		Number of infants with PPH of the newborn (per 1,000)		Adjusted* odds ratio (95 % CI)
		Not exposed	Exposed	
Drug	Any SSRI	1899 (1.2)	33 (3.0)	2.1 (1.5–3.0)
	Fluoxetine	1952 (1.2)	9 (2.7)	2.0 (1.0–3.8)
	Citalopram	1936 (1.2)	11 (3.3)	2.3 (1.2–4.1)
	Paroxetine	1959 (1.2)	5 (3.9)	2.8 (1.2–6.7)
	Sertraline	1949 (1.2)	10 (3.5)	2.3 (1.3–4.4)
	Escitalopram	1966 (1.2)	1 (1.8)	1.3 (0.2–9.5)

Table 8.4 Exposure to SSRIs before gestational week 8 or later and risk of PPH of the newborn (Kieler et al. 2012)

		Number of infants with PPH of the newborn (per 1,000)		Adjusted[a] odds ratio (95 % CI)
		Not exposed	Exposed	
Drug	Any SSRI	1899 (1.2)	32 (1.9)	1.4 (1.0–2.0)
	Fluoxetine	1952 (1.2)	7 (1.8)	1.3 (0.6–2.8)
	Citalopram	1936 (1.2)	17 (2.5)	1.8 (1.1–3.0)
	Paroxetine	1959 (1.2)	4 (1.7)	1.3 (0.5–3.5)
	Sertraline	1949 (1.2)	9 (2.7)	1.9 (1.0–3.6)
	Escitalopram	1966 (1.2)	1 (0.4)	0.3 (0.0–2.2)

[a]Adjusted for maternal age, dispensed nonsteroidal anti-inflammatory drugs and antidiabetes drugs, pre-eclampsia, chronic diseases during pregnancy, country of birth, birth year, level of delivery hospital, and birth order

total of 60,746 UK patients. The most commonly prescribed antidepressant drugs were SSRIs (54.7 % of prescriptions), followed by TCAs (31.6 % of prescriptions), other antidepressants (13.5 %), and MAOIs (0.2 %) (Coupland et al. 2011); the latter were excluded from analyses due to the small number of prescriptions. All classes of antidepressant were associated with significantly increased risks of all-cause mortality, nonfatal self-harm, falls, fractures, and upper gastrointestinal bleeding, compared with patient groups not taking antidepressants: SSRIs and the group of 'other' antidepressants were associated with greater risks of stroke and/or transient ischaemic attack and of epilepsy/seizures, and SSRIs were also associated with increased risk of myocardial infarction and hyponatraemia (Coupland et al. 2011) (see Tables 8.1 and 8.2).

Associations with seven adverse outcomes differed significantly between drug classes. SSRIs were associated with significantly higher rates of all-cause mortality, stroke/transient ischaemic attack, falls, fracture, epilepsy/seizures, and hyponatraemia. No significant difference was found for nonfatal self-harm. The group of 'other' antidepressants had significantly higher rates for all-cause mortality, nonfatal self-harm, stroke/transient ischaemic attack, fracture, and epilepsy/seizures when compared with TCAs. No significant difference was found for falls or hyponatraemia.

TCAs prescriptions were not associated with significantly higher rates of adverse outcomes than either SSRIs or the group of 'other' antidepressants.

When individual antidepressant drugs were examined, trazodone was found to be associated with the highest adjusted hazard ratio for all-cause mortality and one of the highest risks for nonfatal self-harm. Mirtazapine had the highest adjusted hazard ratio for nonfatal self-harm and one of the highest risks for all-cause mortality and stroke/ischaemic attack. Venlafaxine had higher hazard ratios for stroke/transient ischaemic attack, fracture, and epilepsy/seizures and is one of the highest associations with all-cause mortality and nonfatal self-harm. The SSRI citalopram had the highest association with falls, although risks were similar amongst all the SSRIs (Coupland et al. 2011). Three SSRIs (citalopram, escitalopram, and fluoxetine) were associated with significantly increased risks of hyponatraemia. The TCAs amitriptyline and dosulepin had the lowest associated risk for many adverse outcomes (Coupland et al. 2011). Significant trend was found in analyses of dosage relationships with TCAs and SSRIs for all-cause mortality, falls, and epilepsy/seizures. A significant dose relationship was also seen with TCAs and fracture. Previous evidence has suggested that low-dose TCAs may be similar to higher doses of TCAs in depressive symptom reduction (NICE 2009; Furukawa et al. 2003). Adverse outcomes were most likely during the first 28 days of use and again in the first 28 days after stopping treatment (Coupland et al. 2011): adverse events in the first 28 days of prescription could be due to depression being most severe, and increased risk after stopping treatment could be due to the onset of supervening illness, or admission to hospital or residential homes, rather than treatment withdrawal (Coupland et al. 2011).

Data such as these are hard to interpret. The effectiveness of the differing antidepressant classes in relieving depressive symptoms is not described. Given the association of depressive illness with chronic physical ill health, it should be expected that populations prescribed with antidepressant drugs will have increased mortality. The known association of TCAs with problems such as seizures and cardiac arrhythmias may lead doctors to avoid prescribing them in patients with epilepsy and cardiac disease, with a preference for SSRIs, which therefore become associated with these conditions.

8.10 Conclusion

A detailed analysis of ten drug information resources for the SSRI fluoxetine found a median of 74.5 reported possible adverse drug reactions (Tan et al. 2014). However, a recent population survey found that 9 of the 20 most commonly everyday symptoms in the general population are also listed as 'adverse drug reactions' in more than half of drug information documents (Petrie et al. 2014): so the misattribution of everyday symptoms to possible adverse effects of prescribed medication must be common in clinical settings (Tan et al. 2014). Frequently reported everyday symptoms include fatigue, sleeping problems, irritability, difficulty concentrating,

anxiety, depression, and agitation (Petrie et al. 2014), all common in depressed patients and all of which are also listed as potential adverse drug reactions with frequently prescribed medications (Tan et al. 2014). The routine provision of long lists of possible side effects of medication may increase the expectancy of unwanted treatment-emergent effects (Faasse and Petrie 2013), as informing individuals of possible symptoms increases the likelihood of those symptoms being reported (Myers et al. 1987); in randomised placebo-controlled trials with antidepressants, participants who receive placebo often report adverse events which are remarkably similar in nature to those seen with active drugs (Rief et al. 2009).

As such, careful communication of accurate information about potential adverse effects of pharmacological treatment is needed in the management of patients with chronic diseases, such as depression and anxiety disorders (Colloca and Finniss 2012). It makes sense to provide information on both the absolute and relative risks of the most important potential side effects, with the greatest emphasis being given to data from randomised controlled trials (Tan et al. 2014). However the quality of reporting of data from randomised controlled trials is highly variable (Ioannidis 2009; Zorzela et al. 2014); and observational studies tend to underestimate the risk of rare but serious adverse reactions (Papanikolau et al. 2006) and overestimate the risk of common but less important reactions (de Lange et al. 2008). It has been argued that simply listing the possible adverse effects of medication is probably unhelpful: rather, efforts should be made to contextualise the potential risks and benefits of intervention by considering the patient, the treatment being offered and the underlying condition being treated (Tan et al. 2014). In the pharmacological treatment of depressive illness, the need to provide understandable information about the anticipated beneficial effects and possible adverse effects of antidepressant medication has to be balanced with the imperative to encourage patients to accept potentially life-saving treatment, often for many years.

References

Administration Food and Drugs (2004) Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Paediatric Advisory Committee

Administration Food and Drug (2012) FDA drug and safety communication: selective serotonin inhibitor (SSRI) antidepressant use during pregnancy and reports of a rare heart and lung condition in newborn babies. www.fda.gov/Drugs/DrugSafety/ucm283375.htm

Administration US Food and Drug (2012) Public health advisory: treatment challenges of depression in pregnancy and the possibility of persistent pulmonary hypertension in newborns

Anderson IM (2000) Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord 58(1):19–36

Andrade SE, McPhillips H, Loren D, Raebel MA, Lane K, Livingston J et al (2009) Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf 18(3):246–252

Baldessarini RJ, Pompili M, Tondo L (2006) Suicidal risk in antidepressant drug trials. Arch Gen Psychiatry 63(3):246–248

Baldwin D, Fineberg N, Montgomery S (1991) Fluoxetine, fluvoxamine and extrapyramidal tract disorders. Int Clin Psychopharmacol 6(1):51–58
Baldwin D, Bobes J, Stein DJ, Scharwachter I, Faure M (1999) Paroxetine in social phobia/social anxiety disorder. Randomised, double-blind, placebo-controlled study. Paroxetine Study Group. Br J Psychiatry 175:120–126
Baldwin D, Bridgman K, Buis C (2006) Resolution of sexual dysfunction during double-blind treatment of major depression with reboxetine or paroxetine. J Psychopharmacol 20(1):91–96
Baldwin DS, Montgomery SA, Nil R, Lader M (2007) Discontinuation symptoms in depression and anxiety disorders. Int J Neuropsychopharmacol 10(1):73–84
Baldwin D, Moreno RA, Briley M (2008) Resolution of sexual dysfunction during acute treatment of major depression with milnacipran. Hum Psychopharmacol 23(6):527–532
Baldwin D, Woods R, Lawson R, Taylor D (2011) Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ 342:d1199
Barbui C, Esposito E, Cipriani A (2009) Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. CMAJ: Can Med Assoc J Assoc Med Can 180(3):291–297
Beekman AT, Copeland JR, Prince MJ (1999) Review of community prevalence of depression in later life. Br J Psychiatry J Ment Sci 174:307–311
Board Royal College of Psychiatrists' Public Education Editorial (2012) In: Psychiatrists RCo (ed) Antidepressants. Royal College of Psychiatrists, London
Cadieux RJ (1999) Antidepressant drug interactions in the elderly. Understanding the P-450 system is half the battle in reducing risks. Postgrad Med 106(6):231–232, 37–40, 45–49
Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL et al (2006) Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 354(6):579–587
Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R et al (2009) Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 373(9665):746–758
Colloca L, Finniss D (2012) Nocebo effects, patient-clinician communication, and therapeutic outcomes. JAMA 307(6):567–568
Corruble E, de Bodinat C, Belaidi C, Goodwin GM (2013) Agomelatine study group. Efficacy of agomelatine and escitalopram on depression, subjective sleep and emotional experiences in patients with major depressive disorder: a 24-wk randomized, controlled, double-blind trial. Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacologicum 16(10): 2219–2234
Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J (2011) Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 343:d4551
de Langen J, van Hunsel F, Passier A, de Jong-van den Berg L, van Grootheest K (2008) Adverse drug reaction reporting by patients in the Netherlands-three years of experience. Drug Saf 31(6):515–524
DeVane CL (2003) Immediate-release versus controlled-release formulations: pharmacokinetics of newer antidepressants in relation to nausea. J Clin Psychiatry 64(Suppl 18):14–19
Excellence National Institute for Health and Clinical (2009) Depression: the treatment and management of depression in adults (update) (National Clinical Practice Guideline 90): NICE
Eyding D, Lelgemann M, Grouven U, Harter M, Kromp M, Kaiser T et al (2010) Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 341:c4737
Faasse K, Petrie KJ (2013) The nocebo effect: patient expectations and medication side effects. Postgrad Med J 89(1055):540–546
Fagius J, Osterman PO, Siden A, Wiholm BE (1985) Guillain-barre syndrome following zimeldine treatment. J Neurol Neurosurg Psychiatry 48(1):65–69
Feinberg SS (2010) Correction of venlafaxine- and duloxetine-induced transaminase elevations with desvenlafaxine in a patient with Gilbert's syndrome. CNS Spectr 15(1):53–55

Furukawa T, McGuire H, Barbui C (2003) Low dosage tricyclic antidepressants for depression. Cochrane Database Syst Rev (3):CD003197

Gahr M, Freudenmann RW, Connemann BJ, Hiemke C, Schonfeldt-Lecuona C (2013) Agomelatine and hepatotoxicity: implications of cumulated data derived from spontaneous reports of adverse drug reactions. Pharmacopsychiatry 46(6):214–220

Galbally M, Gentile S, Lewis AJ (2012) Further findings linking SSRIs during pregnancy and persistent pulmonary hypertension of the newborn: clinical implications. CNS Drugs 26(10):813–822

Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux L, Van Noord M et al (2011) Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an update meta-analysis. Ann Intern Med 155(11):772–785

Gibbons RD, Brown CH, Hur K, Davis J, Mann JJ (2012) Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. Arch Gen Psychiatry 69(6):580–587

Giron MS, Fastbom J, Winblad B (2005) Clinical trials of potential antidepressants: to what extent are the elderly represented: a review. Int J Geriatr Psychiatry 20(3):201–217

Grigoriadis S, Vonderporten EH, Mamisashvili L, Tomlinson G, Dennis CL, Koren G et al (2014) Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis. BMJ 348:f6932

Gruz F, Raffa S, Santucci C, Papale RM, Videla MG, Fernandez MG et al (2014) Agomelatine: fulminant liver failure in a patient with fatty liver. Gastroenterol Hepatol 37(2):92–94

Hammad TA, Laughren T, Racoosin J (2006) Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 63(3):332–339

Huskamp HA (2006) Prices, profits, and innovation: examining criticisms of new psychotropic drugs' value. Health Aff 25(3):635–646

Ioannidis John PA (2009) Adverse events in randomized trials neglected, restricted, distorted, and silenced. Arch Intern Med 169(19):1737–1739

Isacsson G, Ahlner J (2014) Antidepressants and the risk of suicide in young persons-prescription trends and toxicological analyses. Acta Psychiatr Scand 129(4):296–302

Jick H, Kaye JA, Jick SS (2004) Antidepressants and the risk of suicidal behaviors. JAMA J Am Med Assoc 292(3):338–343

Jong GW, Einarson T, Koren G, Einarson A (2012) Antidepressant use in pregnancy and persistent pulmonary hypertension of the newborn (PPHN): a systematic review. Reprod Toxicol 34(3):293–297

Kaizar EE, Greenhouse JB, Seltman H, Kelleher K (2006) Do antidepressants cause suicidality in children? A Bayesian meta-analysis. Clin Trials 3(2):73–90; discussion 91–98

Karakus E, Halici Z, Albayrak A, Polat B, Bayir Y, Kiki I et al (2013) Agomelatine: an antidepressant with new potent hepatoprotective effects on paracetamol-induced liver damage in rats. Hum Exp Toxicol 32(8):846–857

Kelly C, Roche S, Naguib M, Webb S, Roberts M, Pitt B (1993) A prospective evaluation of the hepatotoxicity of lofepramine in the elderly. Int Clin Psychopharmacol 8(2):83–86

Kieler H, Artama M, Engeland A, Ericsson O, Furu K, Gissler M et al (2012) Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ 344:d8012

Klein DF (2006) The flawed basis for FDA post-marketing safety decisions: the example of antidepressants and children. Neuropsychopharmacol: Off Pub Am Coll Neuropsychopharmacol 31(4):689–699

Koren G, Nordeng H (2012a) Antidepressant use during pregnancy: the benefit-risk ratio. Am J Obstet Gynecol 207(3):157–163

Koren G, Nordeng H (2012b) SSRIs and persistent pulmonary hypertension of the newborn. BMJ 344:d7642

Lack SJ, Baldwin DS, Montgomery SA (1990) Lofepramine, desipramine and abnormal tests of liver function: a case report. Int Clin Psychopharmacol 5(3):185–190

Leckman JF, King RA (2007) A developmental perspective on the controversy surrounding the use of SSRIs to treat pediatric depression. Am J Psychiatry 164(9):1304–1306
Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ (2007) Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry 164(6):884–891
Libby AM, Orton HD, Valuck RJ (2009) Persisting decline in depression treatment after FDA warnings. Arch Gen Psychiatry 66(6):633–639
Lu CY, Zhang F, Lakoma MD, Madden JM, Rusinak D, Penfold RB et al (2014) Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. BMJ 348:g3596
Macphee GJA, Roberts MA, McKean CE (1987) Drug points: association of lofepramine with abnormal liver function in elderly patients. BMJ 295(6604): 1001
March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J et al (2004) Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. JAMA 292(7): 807–820
March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J et al (2007) The Treatment for Adolescents with Depression Study (TADS): long-term effectiveness and safety outcomes. Arch Gen Psychiatry 64(10):1132–1143
McAllister-Williams RH, Baldwin DS, Haddad PM, Bazire S (2010) The use of antidepressants in clinical practice: focus on agomelatine. Hum Psychopharmacol 25(2):95–102
McDougall FA, Matthews FE, Kvaal K, Dewey ME, Brayne C (2007) Prevalence and symptomatology of depression in older people living in institutions in England and Wales. Age Ageing 36(5):562–568
Myers MG, Cairns JA, Singer J (1987) The consent form as a possible cause of side-effects. Clin Pharmacol Ther 42(3):250–253, <Go to ISI>://WOS:A1987K208900003
Nilsson BS (1983) Adverse reactions in connection with zimeldine treatment – a review. Acta Psychiatr Scand Suppl 308:115–119
Nussbaumer B, Morgan LC, Reichenpfader U, Greenblatt A, Hansen RA, Van Noord M et al (2014) Comparative efficacy and risk of harms of immediate- versus extended-release second-generation antidepressants: a systematic review with network meta-analysis. CNS Drugs 28(8):699–712
Nutt DJ (2009) Prescribing antidepressants post Cipriani et al. J Psychopharmacol 23(8):865–866
Occhiogrosso M, Omran SS, Altemus M (2012) Persistent pulmonary hypertension of the newborn and selective serotonin reuptake inhibitors: lessons from clinical and translational studies. Am J Psychiatry 169(2):134–140
Pamer CA, Hammad TA, Wu YT, Kaplan S, Rochester G, Governale L et al (2010) Changes in US antidepressant and antipsychotic prescription patterns during a period of FDA actions. Pharmacoepidemiol Drug Saf 19(2):158–174
Papanikolaou PN, Christidi GD, Ioannidis JPA (2006) Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. Can Med Assoc J 174(5): 635–641
Petrie KJ, Faasse K, Crichton F, Grey A. (2014) How common are symptoms? Evidence from a New Zealand national telephone survey. BMJ Open. 4(6):e005374. doi:10.1136/bmjopen-2014-005374.
Phillips BB, Digmann RR, Beck MG (2006) Hepatitis associated with low-dose venlafaxine for postmenopausal vasomotor symptoms. Ann Pharmacother 40(2):323–327
Pradeep RJ, Victor G, Iby N, Kurpad SS, Galgali RB, Srinivasan K (2004) Venlafaxine induced hepatitis. J Assoc Physicians India 52:340
Price J, Cole V, Goodwin GM (2009) Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study. Br J Psychiatry J Ment Sci 195(3):211–217

Price J, Cole V, Doll H, Goodwin GM (2012) The Oxford questionnaire on the emotional side-effects of antidepressants (OQuESA): development, validity, reliability and sensitivity to change. J Affect Disord 140(1):66–74

Reichenpfader U, Gartlehner G, Morgan LC, Greenblatt A, Nussbaumer B, Hansen RA et al (2014) Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta- analysis. Drug Saf: Int J Med Toxicol Drug Experience 37(1):19–31

Reid S, Barbui C (2010) Long term treatment of depression with selective serotonin reuptake inhibitors and newer antidepressants. BMJ 340:c1468

Rief W, Nestoriuc Y, von Lilienfeld-Toal A, Dogan I, Schreiber F, Hofmann SG et al (2009) Differences in adverse effect reporting in Placebo Groups in SSRI and tricyclic antidepressant trials a systematic review and meta-analysis. Drug Saf 32(11):1041–1056

Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB (1998) Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 44(2): 77–87

Serretti A, Chiesa A (2009) Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol 29(3):259–266

Simon GE (2006) The antidepressant quandary – considering suicide risk when treating adolescent depression. N Engl J Med 355(26):2722–2723

Sinclair LI, Christmas DM, Hood SD, Potokar JP, Robertson A, Isaac A et al (2009) Antidepressant-induced jitteriness/anxiety syndrome: systematic review. Br J Psychiatry J Ment Sci 194(6):483–490

Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A et al (2009) Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 339:b2880

Strombom I, Wernicke JF, Seeger J, D'Souza DN, Acharya N (2008) Hepatic effects of duloxetine-III: analysis of hepatic events using external data sources. Curr Drug Saf 3(2):154–162

Talat B, Mayers A, Baldwin DS (2013) Quality of case reports of adverse drug reactions with psychotropic drugs: a 25-year review. Hum Psychopharmacol 28(5):413–420

Tan RS, Barlow RJ, Abel C, Reddy S, Palmer AJ, Fletcher AE et al (1994) The effect of low dose lofepramine in depressed elderly patients in general medical wards. Br J Clin Pharmacol 37(4):321–324

Tan K, Petrie KJ, Faasse K, Bolland MJ, Grey A (2014) Unhelpful information about adverse drug reactions. BMJ 349:g5019

Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K (2013) Strategies for managing sexual dysfunction induced by antidepressant medication. Cochrane Database Syst Rev (5):CD003382

Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ (2007) Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry 164(8):1198–1205

Waldinger MD, Zwinderman AH, Olivier B (2003) Antidepressants and ejaculation: a double-blind, randomized, fixed-dose study with mirtazapine and paroxetine. J Clin Psychopharmacol 23:467–470

Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK et al (2000) Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics 105(1 Pt 1):14–20

Wernicke J, Acharya N, Strombom I, Gahimer JL, D'Souza DN, DiPietro N et al (2008a) Hepatic effects of duloxetine-II: spontaneous reports and epidemiology of hepatic events. Curr Drug Saf 3(2):143–153

Wernicke J, Pangallo B, Wang F, Murray I, Henck JW, Knadler MP et al (2008b) Hepatic effects of duloxetine-I: non-clinical and clinical trial data. Curr Drug Saf 3(2):132–142

Williams VS, Baldwin DS, Hogue SL, Fehnel SE, Hollis KA, Edin HM (2006) Estimating the prevalence and impact of antidepressant-induced sexual dysfunction in 2 European countries: a cross-sectional patient survey. J Clin Psychiatry 67(2):204–210

Williams VS, Edin HM, Hogue SL, Fehnel SE, Baldwin DS (2010) Prevalence and impact of antidepressant-associated sexual dysfunction in three European countries: replication in a cross-sectional patient survey. J Psychopharmacol 24(4):489–496

Wilson KL, Zelig CM, Harvey JP, Cunningham BS, Dolinsky BM, Napolitano PG (2011) Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. Am J Perinatol 28(1):19–24

Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A et al (2014) Quality of reporting in systematic reviews of adverse events: systematic review. BMJ 2014:348

Chapter 9
Safety and Tolerability of Antipsychotics

Michael W. Jann and William K. Kennedy

Abstract Antipsychotics are commonly used to treat schizophrenia, bipolar disorders, depression, and other conditions where psychotic symptoms occur. Antipsychotics are classified as typical first-generation agents (FGAs) or atypical second-generation agents (SGAs). Regulatory agencies have approved their usage in the adult population 18–65 years. However, these agents are prescribed "off-label" for children and adolescents. Antipsychotics have special warnings for use in the elderly patients with dementia-related psychosis that includes an increased risk for fatalities and cerebrovascular events. Extrapyramidal side effects (EPS) and tardive dyskinesia are a risk with all antipsychotic classes. Even though antipsychotics can lower seizure threshold, clozapine is the most commonly known for this adverse effect. The metabolic syndrome associated with the SGAs is well known, and olanzapine most commonly produces weight gain and lipid changes. Thioridazine and mesoridazine have a "black box" FDA warning due to QTc prolongation and risk for torsades de pointes. Hematologic disorders such as agranulocytosis are associated with clozapine and specific guidelines for patient monitoring are established. Both FGAs and SGAs are known to produce elevations from baseline prolactin levels with risperidone and paliperidone. Aripiprazole was reported to have the least effects on plasma prolactin levels. Neuroleptic malignant syndrome is an acute medical emergency, and antipsychotic therapy must immediately cease and the patient treated in the hospital.

Keywords Antipsychotics • Safety • Tolerability • Dementia • Elderly • Adverse effects

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9.1 Introduction

Antipsychotics are the mainstay therapeutic treatment for a variety of psychiatric conditions including schizophrenia, bipolar disorders, and others associated diseases. These psychiatric disorders have acute episodes of psychotic symptoms requiring immediate therapy. However, usage of antipsychotics often requires chronic disease management as these conditions are long-term debilitating diseases. With the exception of clozapine, all other antipsychotics were found to be equally effective agents (Perel and Jann 2006). Adverse side effects of antipsychotics are associated with their pharmacologic actions at various receptors located in the central nervous system (CNS) and periphery displayed in Table 9.1 (Richelson 1999, 2010; Richelson and Sounder 2000). Pharmacovigilance detects, assesses, and attempts to understand the adverse effects of medications so that preventative measures can be employed to maximize their outcomes and tolerability. The adverse side effect profiles of 15 antipsychotic agents (both first generation and second generation) were compared using meta-analysis from over 200 clinical trials and provided an overall profile of each agent relative to the other antipsychotics with six parameters (e.g., all-cause discontinuation) so that policy decision-makers can formulate practice guidelines (Rajkumar and Melvin 2014). From the practical perspective, patients typically experience more than one adverse effect at any particular time during treatment with different levels of severity (Perel and Jann 2006). These types of studies focus on the adult population, and antipsychotics are used in all age groups from the geriatric population to children and adolescents including during pregnancy. It is beyond the scope of this chapter to fully investigate and present studies that have assessed the adverse events associated with the antipsychotics as several topics themselves can be an individual chapter such as the metabolic syndrome. References are included with a summary of their impact on health systems, and this chapter will center on the various adverse side effects reported with antipsychotics that influence regulatory agencies and policy makers (Rajkumar and Melvin 2014; Piparva et al. 2011).

9.2 Specific Populations

9.2.1 Elderly

Unless the patient has an existing diagnosis for schizophrenia or bipolar disorders, antipsychotic use in the elderly is “off-label” by the regulatory agencies. Antipsychotics are commonly used in the elderly and present a different set of issues compared to the adult population as polypathology, polypharmacy, potential drug-drug interactions, and age-related pharmacokinetic and pharmacodynamics are important variables in selecting the drug dosages. Due to these multiple variables, antipsychotics doses are generally lower in the elderly versus the adult group (Gareri et al. 2003). The adverse event profile for the antipsychotic drugs in the elderly

Table 9.1 Summary of the antipsychotic receptor pharmacology and adverse side-effect profile

Drug	D2	5HT2A	M	H1	Alpha-1	Adverse side-effect association
Reference compound						
Spiperone	4	–	–	–	–	EPS, tardive dyskinesia, prolactin
Ketanserin	–	4	–	–	–	Rhabdomyolysis
3-quinuclidinyl-4-iodobenzilate (QNB)	–	–	4		–	Anticholinergic, memory impairment, ↑ narrow angle, glaucoma, sinus tachycardia, blurred vision
Pyrilamine	–	–	–	4	–	Sedation and weight gain
Prazosin	–	–	–	–	4	Cardiovascular, orthostatic hypotension
First-generation typical antipsychotics						
Chlorpromazine	3	2	2	3	3	
Fluphenazine	4	2	1	2	2	
Haloperidol	3	3	0	1	1	
Loxapine	3	2	1	2	2	
Mesoridazine	3	3	1	3	2	
Perphenazine	4	3	0	3	2	
Thioridazine	3	3	2	2	3	
Second-generation typical antipsychotics						
Aripiprazole	4	3	0	2	1	
Asenapine	3	3	0	2	3	
Clozapine	1	4	3	4	2	
Iloperidone	3	4	0	2	4	
Lurasidone	3	3	0	0	4	
Olanzapine	2	3	2	4	1	
Paliperidone	3	3	0	3	2	
Quetiapine	1	2	0	2	2	
Risperidone	3	4	0	3	3	
Ziprasidone	3	4	0	2	1	

0 = negligible, 1 = low, 2 = moderate, 3 = moderate high, 4 = high, reference compound; *EPS* extrapyramidal side effects
D2 = dopamine receptor subtype, 5Ht2A = serotoninergic receptor subtype 2A, M = muscarinic receptor, H1 = histamine receptor subtype 1, Alpha-1 = alpha adrenergic receptor subtype 1

differs than the adult population with specific patient warnings such as regarding their use for dementia-related psychosis and potential for cerebrovascular disorders.

9.2.2 Children and Adolescents

Most antipsychotic drugs prescribed for children are also "off-label" that include use in aggression and irritability in patients with autism, conduct disorders, and pervasive developmental disorders with an increasing frequency (Schneider et al. 2014). Antipsychotic use in clinical practice especially in young children as early as

2 years of age presents on-going challenges to healthcare systems. The overall adverse side-effect profile of antipsychotics in children and adolescents does not substantially differ from the adult population, but due to the earlier exposure to these drugs, the long-term risks and benefits must be taken into consideration by prescribers. Database systems have been set up to monitor antipsychotic adverse events in the children and adolescent population. Compared to other medications, it was reported from the FDA Adverse Event Reporting System (FAERS) that the atypical agents aripiprazole, risperidone, and quetiapine were among the top 20 medications with adverse events (Lee et al. 2014). Some countries have established nationwide antipsychotic safety monitoring programs for children and adolescents to provide system-wide safety information for clinicians (Harrison-Woolrych et al. 2007; Rani et al. 2009; Palanca-Maresca et al. 2014).

9.2.3 Pregnancy

Antipsychotic use in pregnant women continues, and information from the Tennessee Medicaid program reported use of the typical first-generation agents (FGAs) decreased while prescribing of the atypical second-generation agents (SGAs) has increased (Epstein et al. 2013). For the FGAs, the incidence of use decreased from 7.77 to 0.99 per 1,000 pregnancies between 1995 and 2005. In contrast, SGAs use increased from 1.73 to 16.52 per 1,000 pregnancies between 2000 and 2005. The specific warnings for atypical antipsychotic use during pregnancy were possible risk of abnormal muscle movements and withdrawal symptoms described for the mother and infant.

9.2.4 Dementia-Related Psychosis Fatality

Psychosis associated with Alzheimer's disease (PAD) forms part of the behavioral and psychological symptoms of dementia (BPSD) that include hallucinations, delusions, agitation, paranoia, combativeness, or depression (Madhusoodanan et al. 2007). Delirium was reported to be the third most common cause of psychosis in the elderly characterized by thought disturbance, poverty of thinking, irrationality, and usually visual hallucinations (Jeste and Finkel 2000). Major depression was reported to be the second most common diagnosis in the elderly accounting for most of the psychosis in this population (Kyonmen and Whitfield 2009). Depression-related psychosis is typically characterized by themes of somatic troubles, persecution, guilt, and poor self-esteem. While regulatory agencies have yet to recognize BPSD as a disease, the diagnostic criteria for the concept of PAD could be acknowledged (Madhusoodanan et al. 2007; Jeste and Finkel 2000). Yet, these patients can present the clinician with a complex, multifactorial, and fluctuating nature of psychotic symptoms (Kyonmen and Whitfield 2009; Devanand 2013).

In April 2005, the FDA issued a "black box" warning for the SGAs and for the FGAs in June 2008 indicating an increased risk for death in persons with dementia

(Kalapatapu and Schimming 2009). Data reported by the FDA noted a relative risk (RR) ratio of 1.47 and 1.68 for the SGAs and FGAs, respectively (US Food and Drug Administration 2014). A large meta-analysis study with 15 placebo-controlled clinical trials 10–12 weeks of duration treated with the atypical antipsychotics in patients with dementia reported an increased odds ratio (OR) of 1.54 [95 % C.I. 1.06–2.23, $p=0.02$] for death that was similar to the FDA findings with a number needed to harm (NNH) = 87 (Schneider et al. 2005). A later systematic review and meta-analysis evaluated adverse events and divided the patients into two categories: elderly patients with dementia and all other nonelderly adult patients (Simoni-Wastila et al. 2009). This study examined the combined adverse events that included cardiovascular symptoms, edema, and vasodilatation. Risperidone (2.10, 95 % C.I. 1.38–3.22) and olanzapine (2.30, 95 % C.I. 1.08–5.61) was found to have a higher OR compared to placebo for these combined symptoms. Quetiapine and aripiprazole were found not associated with cardiovascular outcomes. However, when antipsychotics were examined in an outpatient population in patients with probable Alzheimer's disease for an extended time period (mean of 4.3 years), the presence of antipsychotic drugs was found not to increase the risk of death using time-dependent sensitive models (Lopez et al. 2013). It was reported that nursing home admission and death were more frequent in patients treated with FGAs than SGAs. But, both FGAs and SGAs were not associated with nursing home admission or time to death when including covariate factors such as diabetes, hypertension, pre-existing heart disease, and cognitive and demographic variables.

The efficacy of SGAs in patients with PAD ($N=423$) was assessed with olanzapine, quetiapine, and risperidone, and the main outcomes were discontinuation of treatment for any reason and the number of patients with at least a minimal improvement on the Clinical Global Impression of Change (CIBIC) at 12 weeks (Schneider et al. 2006). Significant differences were not found between the SGAs, and improvement based upon CIBIC scores was found with olanzapine 32 %, quetiapine 26 %, and risperidone 29 % compared to placebo 21 % ($p=0.22$). Patients treated with SGAs had a higher discontinuation rate due to intolerability ($p=0.009$). The study reported that the overall adverse events offset the efficacy from SGAs. While the risk of fatality was not an outcome, these results pose difficult questions for the use of SGAs in elderly patients with dementia that display PAD or BPSD (Maher et al. 2011). The American College of Neuropsychopharmacology (ACNP) White Paper noted that the two most common causes for deaths were due to cardiovascular disease or infections in this population (Jeste et al. 2008). Also noted that besides psychosis and agitation commonly occurring in patients with dementia, these symptoms lead to significant caregiver distress and accelerated patient placement into the nursing home environment. Finally, regulatory agencies have not yet "approved" any medications for the treatment of patients with PAD or BSPD.

Clinicians face unusual challenges in risk management when prescribing antipsychotics in this patient population. Risk management procedures recommended are to avoid unnecessary medications, balancing acute versus long-term risks, informed consent from the patient and family members, and documentation in the medical records (Jeste et al. 2008; Recupero and Rainey 2007). The ACNP White Paper recommended these 11 steps: (1) determine the etiology of psychotic symptoms, (2) general treatment considerations, (3) shared decision-making, (4) identify

specific target symptoms for treatment, (5) pharmacotherapy selection, (6) dose, (7) monitor for efficacy, (8) monitoring for safety, (9) educate patient and caregivers, (10) know when to discontinue or switch pharmacotherapy, and (11) coordinate care among the treatment team and family members (Jeste et al. 2008).

9.2.4.1 Cerebrovascular Warning

The FDA black box warning for SGAs in 2003 of increased fatality in patients with dementia-related psychosis coincided with the cerebrovascular warning (US Food and Drug Administration 2003). Cerebrovascular adverse events (CVAEs) were specifically noted for olanzapine, aripiprazole, and risperidone which included strokes, transient ischemic events, and other undetermined events thought to be vascular in origin. Whether or not the increased risk of fatality and CVAEs risk have similar mechanisms or are interrelated remains unknown, but the overall death rate was not overly represented by the CVAEs (Nelson 2005). The risk for CVAEs is higher among patients with vascular dementia, vascular disease, or risk factors for stroke. Added to the pathophysiology are potential drug-induced orthostatic hypotension and oversedation as both events could result in falls and aspiration pneumonia. A cohort study compared the OR of CVAEs between FGAs and SGAs in patients with dementia aged 65 years or older (Laredo et al. 2011). The OR for FGAs was reported to be 1.16 [95 % C.I. 1.07–1.27], whereas the OR for the atypical agents was 0.62 [95 % C.I. 0.53–0.72]. The results of this study indicate that FGAs have a slightly higher risk for CVAEs but substantially and that SGAs appear to be safe. A large systematic meta-analysis reported that the SGAs were associated with an increased risk of stroke (pooled OR, 3.12 [95 % C.I. 1.32–8.21]) and determined the NNH = 53. The optimal approach to care is that each patient who needs an antipsychotic drug must be carefully assessed with both short-term and long-term risks and benefits. The ACNP White Paper included the CVAE assessment and noted significant limitations of employing randomized clinical trial data and attempting to determine long-term patient outcome with adverse events (Jeste et al. 2008). The identical 11 steps for patient assessment and treatment with SGAs in consideration of the CVAEs possibility were recommended in the patients with dementia-related psychosis.

9.3 Specific Adverse Events

9.3.1 Extrapyramidal Side Effects (EPS) and Tardive Dyskinesia (TD)

The advent of the SGAs was viewed as a major improvement in the pharmacotherapy of psychotic disorders as a lower incidence of extrapyramidal side effects (EPS, dystonia, pseudoparkinson's, and akathisia) was found compared to the first-generation agents (Divac et al. 2014; Peluso et al. 2012). Although not entirely

EPS-free, the use of adjunctive anticholinergic medications was 30-fold lower among the patients treated with the atypical antipsychotics (Peluso et al. 2012). CLZ had the reported lowest EPS odds ratio (OR) of 0.3 [95 % C.I. 0.12–0.62], and lurasidone had the highest for the SGAs with an OR of 2.46 [95 % C.I. 155–3.72] (Leucht et al. 2013). In comparison to the FGAs, the OR for chlorpromazine and haloperidol was 2.65 [95 % C.I. 1.33–4.76] and 4.76 [95 % C.I. 3.70–6.04], respectively (Leucht et al. 2013). A 17-year experience of drug-induced Parkinsonism from a regional pharmacovigilance center reported that antipsychotics had the highest incidence compared to all other drugs reported to cause this adverse event (49 % versus miscellaneous drugs 28.7 % and antidepressants 8.0 %) (Bondon-Guitton et al. 2011). Although other medications can cause EPS, antipsychotics (both SGAs and FGAs) are likeliest agents when compared to other medication classes.

A systematic review of long-term studies investigating the annual incidence of tardive dyskinesia (TD) reported a rate of 3.9 % for the SGAs and 5.5 % for the FGAs (Correll and Schenk 2008). Two risk factors were identified possibly associated with an increased risk of TD – mood disorders and age (Keck et al. 2000). The observed rate of TD from a 15-year time period of atypical use on patients with mood or anxiety disorder was 5.9 % from a retrospective chart review of 268 patients (Coplan et al. 2013). The mean length of treatment for TD occurrence was 28.7 months (range 1–83 months) and average chlorpromazine equivalent dose was 350 mg (range 67–969 mg) and symptoms resolved in all but one patient when antipsychotics were discontinued. Most patients (90.9 %) consented to a second treatment with an atypical antipsychotic and did not reexperience TD. The risk of TD with FGAs was found to be three to five times higher in patients >55 years than younger patients (Woerner et al. 1998). Two large studies in elderly patients with risperidone and olanzapine reported TD rates comparable to the adult population, but either drug had an equal or lower incidence than FGAs (Woerner et al. 2011; Kinon et al. 2014). Careful patient monitoring for EPS and early detection of TD in all patients are recommended with FGAs and SGAs.

9.3.2 Seizures

Patients with schizophrenia may be more prone to seizures than the general population (Hyde and Weinberger 1997). Psychotropic drugs and especially antipsychotics and some selected antidepressants reduce seizure threshold with a reported range of 0.1–1.5 % in patients with psychiatric disorders versus the general population of 0.07–0.09 % with therapeutic doses (Devinsky et al. 1991). Dose-dependent and rapid dose increase were factors reported with clozapine and chlorpromazine that can lower seizure threshold. The overall incidence of seizures reported with CLZ daily doses were <300 mg 1.0 %, 300–600 mg 2.7 %, and >600 mg 4.4 % (Devinsky and Pacia 1994). Tonic-clonic seizures were most often noted, but myoclonic seizures can also occur (Pacia and Devinsky 1994). The FDA analysis of seizure incidence from the atypical antipsychotic clinical trial data reported a standard incidence

ratio (SIR) of 2.05 for all antipsychotics, whereas the SIR for CLZ was found to be 9.50 (Pisani et al. 2002). The Spanish Pharmacovigilance network reported a higher reporting odds ratio (ROR) with the SGAs versus the FGAs of 3.2 [95 % C.I. 2.21–4.63] with the highest incidence with CLZ (94/169 of the total number of convulsions with SGAs) (Alper et al. 2007). Whether or not atypical agents possess a higher seizure induction compared to first-generation agents should be further evaluated (Lertxundi et al. 2013).

9.3.3 Metabolic Syndrome (MetS)

The MetS associated with SGAs is well known and associated with increased weight gain, diabetes, and hyperlipidemia (Bak et al. 2014). The MetS definition includes the presence of at least three of five parameters – blood pressure >130/85, fasting blood glucose (FBS) >110 mg/dL, fasting triglycerides >150 mg/dL, HDL <40 mg/dL (men) or <50 mg/dL (women), waist circumference >102 cm (men) or >88 cm (women) (Ganguli and Strassnig 2011). The prevalence of MetS in the general population was estimated to be about 23 % compared to a higher incidence of 35–37 % in patients with psychiatric disorders treated with SGAs (Newcomer and Hennekens 2007; Kagal et al. 2012). The FDA in 2003 issued a warning regarding hyperglycemia and diabetes and recommended monitoring fasting blood glucose in patients with diabetic risk factors, symptoms of hyperglycemia, or diabetes (Mittal et al. 2013). The consensus panel a year later from the American Diabetic Association (ADA), American Psychiatric Association (APA), and the Mount Sinai Summit panel recommended monitoring weight, glucose, or glycosylated hemoglobin and lipids every 12 weeks. Blood pressure was included every 12 weeks while body weight monitoring every 4 weeks and waist circumference annually (ADA et al. 2004).

Weight gain is among the strongest factors leading to the MetS (Papanastasiou 2013). Data from the antipsychotic registration clinical trials reported the risk for clinically significant weight gain (≥7 % than baseline) was about ten times greater for olanzapine compared to placebo. Ziprasidone, aripiprazole, and paliperidone were only about twice the risk of placebo. Data reported on weight gain associated with SGAs from highest to lowest were olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, and paliperidone (Leucht et al. 2013). From the comparative study with the FGAs and SGAs, the latest SGA lurasidone had a low SMD (0.10, 95 % C.I. −0.02–0.21) for weight gain and was about equal to the SMD for ziprasidone (0.10, 95 % C.I. −0.02–0.22) and haloperidol (0.09, 95 % C.I. −0.00–0.17) in producing weight gain. Asenapine SMD (0.23, 95 % C.I. 0.07–0.39) was slightly greater than aripiprazole (0.17, 95 % C.I. 0.05–0.28) but less than paliperidone (0.38, 95 % C.I. 0.27–0.48). The iloperidone SMD (0.62, 95 % C.I. 0.49–0.74) was above chlorpromazine (0.55, 95 % C.I. 0.34–0.76) and slightly less than clozapine (0.65, 95 % C.I. 0.31–0.99). Clozapine was slightly lower than olanzapine (0.74, 95 % C.I. 0.67–0.81) in weight gain, and both agents are well known to cause MetS

(Leucht et al. 2013). The underlying pathophysiology for antipsychotics to cause weight gain is complex but thought to involve genetic variables that include the 5HT2C receptor system and leptin promoter gene variants MTHFR and MC4R genes. Additional factors reported were HRH1, BDNF, NPY, CNR1, GHRL, FTO, and the AMPK gene (Kao and Muller 2013). Further research remains underway to determine biological mechanisms that influence antipsychotic-induced weight gain.

As the monitoring parameters for MetS in patients treated with SGAs were recommended, implementation remains challenging for healthcare systems. A large VA retrospective cohort study ($N = 12{,}009$) evaluated practices for monitoring MetS from antipsychotics between April 2008 and March 2009 (Kumra et al. 2008). Weight, glucose or Hb1Ac, and LDL cholesterol were monitored within 30 days of antipsychotic therapy initiation (baseline) and every 60–120 days afterward. This study reported that weight was the most frequently monitored. Patients without a schizophrenia diagnosis were less likely to be monitored. Antipsychotics with lowest MetS risk were more likely to have weight monitored versus the higher-risk agents at baseline. Whereas, patients taking antipsychotics with a moderate MetS risk were more likely to have baseline glucose and LDL compared to low- and high-risk antipsychotics. The study concluded that improvements are needed and should be applied to all patients regardless of the antipsychotic agent being prescribed.

Another factor associated with antipsychotic-induced weight gain and MetS was age (Papanastasiou 2013). This finding can have significant impact as the antipsychotics are used in the elderly population. Antipsychotics can also cause weight gain in children and adolescents (Kumra et al. 2008; Kranzler and Cohen 2013). No appreciable differences were reported between men and women (Papanastasiou 2013). Waist size was found to be a useful factor in predicting MetS with a sensitivity of 79.4 % and specificity of 78.8 % with the highest rate found with CLZ (Mitchell et al. 2013). Hospitalized patients with various psychiatric disorders were evaluated for MetS in which weight gain and BMI were strongly associated (Centorrino et al. 2012). Risk of MetS was also greater with polytherapy (defined as >2 antipsychotics or one plus adjunctive mood stabilizer) (Centorrino et al. 2012). Factors reported to be associated with MetS were sex, ethnicity, and martial and living status where patients with schizophrenia can develop quickly even within 6 weeks of antipsychotic treatment (Papanastasiou 2013).

As the landscape of MetS associated with FGAs and SGAs became evident for clinicians and monitoring parameters established, the issue of prediabetes emerged given that patients with serious mental illnesses had increased incidences of MetS compared to the general population. The ADA in January 2010 published the prediabetes criteria that includes impaired FBG (>125 mg/dL) or impaired glucose tolerance (140–199 mg/dL 2 h after 75 g of glucose) or Hb1Ac in the range of 5.7 %–6.4 % (ADA 2010). Abdominal obesity, hypertension, dyslipidemia, decreased HDL, and or increased triglycerides are other factors that are associated with prediabetes. From 2003 to 2007, patients ($N = 783$) without a history of type 1 or type 2 diabetes admitted to a psychiatric facility treated with antipsychotics were assessed for metabolic screening (Manu et al. 2012). Using the ADA 2010 criteria for prediabetes, 413 (52.8 %) subjects had normal glucose, while 290 (37.0 %) were

identified as prediabetic. Newly diagnosed diabetes was found among 80 patients (10.2 %). Prediabetes diagnosis was established by using one criteria in 209 patients (72.1 %), 71 patients (24.5 %) had two criteria, and only 10 patients (3.4 %) fulfilled all three criteria. An abnormal Hb1Ac identified 120 of the 290 (41.4 %) of the prediabetic patients when used as the sole criteria. When FBS and/or Hb1Ac was used with the glucose tolerance test, 89.7 % of prediabetic patients were identified. FGA and SGA use was evaluated among all patients. CLZ and olanzapine had the highest incidence of prediabetes and diabetes, while the other SGAs and FGAs had about an equal incidence.

MetS associated with antipsychotic treatment is an important component when clinicians prescribe these medications when treating patients with various psychiatric conditions. The consequences of patients with prediabetes and then those who develop diabetes present significant challenges in antipsychotic drug therapy and lifestyle management in balancing the risks and benefits of short-term and long-term use. MetS can lead to other significant diseases like cardiovascular, cerebrovascular, ophthalmologic, and renal impairment with an increased morbidity and mortality resulting in significant healthcare expenditures (Riordan et al. 2011).

9.3.4 Cardiovascular

9.3.4.1 Torsades de Pointes (TdP)

A meta-analysis review of 15 antipsychotics revealed that the lowest OR occurred with lurasidone −0.10 [95 % C.I. −0.21–0.01], a modest OR with ziprasidone of 0.41 [95 % C.I. 0.31–0.51], and the highest OR with sertindole 0.90 [95 % C.I. 0.76–1.02]. Other SGA agents had OR between lurasidone and ziprasidone. Sertindole and amisulpride had the highest OR; however, these two agents are not available in the USA (Leucht et al. 2013). From the historical perspective, in 1996, sertindole was under development in the USA, but due to prolonged QTc interval and association with 12 sudden unexplained deaths, the FDA did not grant approval. TdP is a malignant ventricular arrhythmia associated with syncope and sudden death. The primary form of TdP occurs from congenital courses either familial or sporadic. The secondary TdP form is usually drug-induced (Beach et al. 2013). From an electrical cardiovascular pathophysiological approach, the heart rate is inversely related to the QT interval and can be viewed upon an ECG. The "c" in the QTc accounts for a "correction" intended to remove the heart rate as a confounding variable. The Bazett formula is the most method QTc = QT/square root of the R-R interval (Beach et al. 2013). Clinicians should be concerned when the QTc interval is between 450 and 500 ms, and >500 ms has increased risk of developing TdP.

The risk factors for TdP include women, elderly age, electrolyte imbalance, previous history of heart disease, metabolic disorders, stroke, and medications (Beach et al. 2013; Vieweg 2003). As the elderly population is included, the link with deaths associated with dementia-related psychosis and cerebrovascular with TdP is

plausible but not directly associated. Elderly patient assessment for antipsychotic therapy recommendations include ECG, chest x-ray, stress test, and echocardiogram (Narang et al. 2010). The echocardiogram may be considered optional, but periodic ECG monitoring is recommended on an individual patient basis.

The antipsychotics with the highest TdP risk are thioridazine and mesoridazine which have FDA "black box" warnings. Other agents in the high-risk group are droperidol, pimozide, and intravenous (IV) haloperidol (Meyer-Massetti et al. 2011). The remaining antipsychotics range from mild to moderate and little or no risk. Ziprasidone's drug development led to an established protocol for antipsychotic investigations to assess QTc prolongation and possible TdP including the use of drug-drug interaction studies with metabolic CYP inhibitors (Glassman and Bigger 2001). It was found that ziprasidone produced a modest QTc prolongation of 6–10 ms, whereas sertindole and thioridazine prolonged QTc intervals by 20–22 ms and 30 ms, respectively. Although a modest QTc prolongation occurs with ziprasidone, it has a low association with TdP. In contrast, both thioridazine and IV haloperidol are associated with significant QTc prolongation and possible TdP (Glassman and Bigger 2001). All other antipsychotics have less than a moderate association with QTc prolongation and TdP.

The results over a 7-year time period from 2004 to 2010 of reports from the FDA FAERS identified 37 different antipsychotics with a reported odds ratio (ROR) examining cardiovascular adverse events (Poluzzi et al. 2013). Cardiac arrhythmias were detected in 4,794 cases, and three agents with the highest ROR are amisulpride, cyamemazine, and olanzapine. The olanzapine finding was surprising as other pharmacovigilance studies were not able to separate this agent from other SGAs in association with prolonged QTc intervals, TdP, or cardiac arrhythmias (Manu et al. 2011; Ozeki et al. 2010). The risk of sudden cardiac death and antipsychotics in a Medicaid and dual eligible Medicare-Medicaid population of 459,614 patients from five different states reported that haloperidol and chlorpromazine had less favorable profiles. Among the SGAs, risperidone, quetiapine, and olanzapine had lower risks of sudden death (Leonard et al. 2013).

9.3.4.2 Myocarditis

Myocarditis is an uncommon but potentially life-threatening condition. Clozapine (CLZ) has been known to cause myocarditis with the total number of cases that exceeds all other antipsychotics combined together (Coulter et al. 2001). The total number of cases reported from this study for myocarditis from CLZ was 231 cases versus 89 cases from all other antipsychotics. The incidence of CLZ-induced myocarditis ranges between 1 in 1,000 and 1 in 10,000 patients with 213 cases (including 50 fatalities) that occurred in the first 2 months of therapy (Berardis et al. 2012). CLZ dose was an independent factor. Recommendations for myocarditis detection includes weekly ECGs, C-reactive protein (CRP), and troponin laboratory testing matched with vital signs and clinical symptomatology for the first 4 weeks of CLZ therapy (Berardis et al. 2012; Munshi et al. 2014). Afterward, vital signs and clinical

symptoms can be closely followed for the next few months. If the patient's heart rate becomes ≥120 bpm or increases by >30 bpm with symptoms of shortness of breath, chest pain, cough, and myalgia, laboratory CRP and troponin should be obtained and if needed a cardiology consult.

9.3.5 Hematologic

Hematological disorders have been associated with both the FGAs and SGAs that include leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and anemia (Flanagan and Dunk 2008). Drug-induced neutropenia usually occurs after 1–2 weeks of treatment and agranulocytosis typically appears 3–4 weeks with the exception of CLZ (Nooijen et al. 2011). Of all the antipsychotics, CLZ is the most well recognized for hematological adverse events and extensively studied. The CLZ-induced agranulocytosis is estimated to occur at 1:10,000 with the weekly complete blood count (CBC) monitored for the first 18 weeks and then every 2 weeks afterward. In the USA, CBC occurs weekly for the first 6 weeks and then every 2 weeks (Cohen et al. 2012). Regulatory agencies required CBC monitoring programs when CLZ was prescribed. The mechanism for CLZ-induced agranulocytosis remains unknown, but formation of a nitrenium cation metabolite from the flavin-containing monoxygenase-3 (FMO3) is suggested to be the initial step for hematological toxicity (Flanagan and Dunk 2008; Nooijen et al. 2011). A strong genetic component is noted with the HLA-DQB1 haplotype that may allow for identifying a patient subset at exceptionally high risk (5.1 % positive predictive value). This finding also occurs with carbamazepine especially patients of Jewish ethnicity in which biomarkers HLA-B38, DR4, and DQw3 provide a positive signal for potential CLZ-induced agranulocytosis (Flanagan and Dunk 2008). Any CLZ-treated patient that develops a fever or infection such as laryngitis should be immediately evaluated for possible agranulocytosis and consider immediate medication discontinuation.

The incidence of CLZ-induced agranulocytosis varied from 3.8 % to 8 % from four studies that included 130,133 patients. The mortality rate was 0.1–0.3 % and case-fatality rate was 2.2–4.2 % (Cohen et al. 2012). The Australian monitoring program reported 209 cases of CLZ-induced white blood cell deficiency (WBCD) between 2006 and 2010. The program reported with CLZ from 1993 to 2011; 141 cases of CLZ-induced agranulocytosis were recorded (Cohen and Monden 2013). With US data, the incidence of CLZ-induced agranulocytosis was reported to dramatically decrease after 18 weeks from 3.39–6.93/1,000 patient-years to 0.37–0.40/100 patient-years; agranulocytosis can still occur even years after CLZ initiation with a recommendation for quarterly CBC monitoring beyond the initial 18 weeks (Drew 2013). Treatment for CLZ-induced agranulocytosis includes supportive therapy, use of antibiotics, and GM-CSF or G-CSF (Flanagan and Dunk 2008). The use of antibiotics significantly lowered the mortality of almost 80 to 5–10 % in Western countries (Nooijen et al. 2011).

9.3.6 Prolactin-Related Adverse Events

Hyperprolactinemia (HPRL) is a well-known common adverse event from antipsychotics since the 1970s. The standardized mean difference (SMD) on prolactin effects for the various agents reported the lowest with aripiprazole 0.22 [95 % C.I. −0.46–0.03] and the highest with paliperidone 1.30 [95 % C.I. 1.08–1.51]. Haloperidol and chlorpromazine were registered at 0.70 [95 % C.I. 0.56–0.85] (-) and 0.16 [95 % C.I. −0.48–0.8], respectively (Leucht et al. 2013). A comprehensive article on antipsychotic-induced HPRL was recently published (Peuskens et al. 2014). Antipsychotic-induced HPRL was associated with dopamine receptor subtype 2 (D2) antagonism at the anterior pituitary gland with changes in serum prolactin concentrations the same between adults and children and adolescents. HPRL increases are dose related but for RIS and paliperidone, and a small dose increase may lead to a profound impact compared to other antipsychotics. As D2 receptor antagonism is associated with HPRL, other endocrine effects are also included such as galactorrhea, amenorrhea, and gynecomastia (Peuskens et al. 2014). Data mining from the FDA Adverse Event Reporting System (AERS) for these endocrine problems associated with antipsychotics was conducted for the time period between January 1968 and May 2005 (Szarfman et al. 2006). A total of 1,530 cases of endocrine problems were reported, and risperidone accounted for the vast majority of these adverse events (1,247 cases, 81.5 %). The total number of pituitary tumors was 77 case reports, and risperidone had the vast majority with 54 cases (70 %). As a group, SGAs cause a lesser elevation in prolactin levels than FGAs except RIS and paliperidone with a class warning for this condition included in their regulatory labeling (Peuskens et al. 2014). HPRL may be associated with sexual dysfunction; however, matching clinical symptoms and ruling out other medical conditions and medications (besides the antipsychotics) need to be included in patient assessment.

9.3.7 Neuroleptic Malignant Syndrome (NMS)

NMS is a rare and idiosyncratic reaction reported with both FGAs and SGAs reported to occur between 0.02 % and 0.25 % of patients (Trollor et al. 2012; Zarrouf and Bhanot 2007; Guanci et al. 2012). Diagnosis of NMS consists of hyperthermia (>100.4 °F or 38 °C on at least two occasions), muscle rigidity, and two of following symptoms: diaphoresis, dysphagia, incontinence, altered consciousness, hypertension (≥25 % above baseline), mutism, labile blood pressure (≥20 mmHg diastolic; ≥ 25 mmHg systolic), creatine kinase (CK) increase (>4 times the upper normal limit), tachypnea (≥50 % above baseline), and tremor or tachycardia (≥25 % above baseline) (Guanci et al. 2012). NMS from antipsychotics was recognized since the late 1970s (Gurrera et al. 2011). The Australian Adverse Drug Reaction Advisory Committee (ADRAC) identified 208 NMS cases from both FGAs ($N=43$) and SGAs ($N=165$) from April 1994 to September 2010 (Trollor et al. 2012). The

overall mortality rate was 5.8 % which is below the 10 % from the historical large-case series (Caroff 1980). The SGA mortality rate was 3.0 % and lower than the 16.3 % with the FGAs (Trollor et al. 2012). CLZ-induced NMS had less muscle rigidity than other antipsychotics and could be related to its pharmacologic profile of weak D2 but potent 5-HT receptor binding affinity (Trollor et al. 2012). The antipsychotic NMS adverse effect statement is found in the regulatory literature as a class warning. Additional factors reported that can increase NMS risk were use of polypharmacy (>2 antipsychotics) and rapid dose escalation (Su et al. 2014; Langan et al. 2012). NMS symptom duration was reported to be about 7–10 days and longer when depot antipsychotics are involved. The time period for NMS onset was found to be 16 % in the first 24 h of antipsychotics therapy, 66 % within the first week, and all cases by 30 days (Caroff and Mann 1988). NMS treatment involves the supportive therapy, use of benzodiazepines, dopamine agonists, and dantrolene (Caroff and Mann 1993).

9.3.8 Rhabdomyolysis (Rhab) and Acute Kidney Injury (AKI)

Rhab ensues from damaged skeletal muscle fiber breakdown that results in the release of toxic products from myocytes into the systemic circulation. The mechanism of antipsychotic-induced Rhab remains unknown (Packhard et al. 2014). Although Rhab is commonly associated with NMS (see Sect. 3.7), Rhab can occur independently of NMS. Besides in the adult population, Rhab was reported to occur in children and adolescents treated with antipsychotics, and only six cases of NMS occurred among the 26 Rhab reports (Star et al. 2012). Significant elevations in serum CK are often present in patients with Rhab with laboratory findings >5,000 IU/L (median 9,600 IU/L), whereas in NMS, the serum CK was lower and ranged from 500 to 3,000 IU/L (Melzter et al. 1996). Rhab and acute renal failure were noted to occur in case reports since in the 1980s it was initially associated with antipsychotic overdoses (Tam et al. 1980). However, later case reports included low to modest antipsychotic doses (Stephanie and Trenkwalder 2010). Clinical symptoms that preceded recognition of Rhab were muscle and abdominal pain, generalized weakness, and dark urine (Packhard et al. 2014). The pathophysiology of antipsychotic-induced Rhab may be associated with increased skeletal muscle membrane permeability involving the 5HT2A receptor antagonism (Packhard et al. 2014). Blockade of the 5HT2A receptor may impact glucose uptake in the skeletal muscle increasing CK permeability leading to the muscle breakdown. An alternative mechanism involves the D2 receptor system where excessive muscle stiffness and rigidity also lead to muscle breakdown. At this time, Rhab has been reported with each antipsychotic agent except the newer agents lurasidone, asenapine, and iloperidone as only time on the market for these agents will determine whether or not Rhab occurs. Two risk factors were identified as contributing to Rhab that included polytherapy (>2 antipsychotics) and dose as most of the reported cases took place with antipsychotic overdose situations (Packhard et al. 2014).

A large population-based, retrospective cohort study in the elderly (>65 years, $N = 97{,}777$) who received a prescription for a SGAs was matched with patients who did not receive this class of medication to examine the risk of AKI (Hwang et al. 2014). AKI is defined as a sudden loss of renal function and can be attributed to hypotension, acute urinary retention, and NMS or Rhab. Patients with an SGA prescription from June 2003 to December 2011 were included and followed for 90 days after the antipsychotic start date. The primary outcome was hospitalization with AKI. The secondary outcomes were known causes of AKI and all-cause mortality. AKI was defined as a median increase in serum creatinine level of 1.11 mg/dL (interquartile range of 0.49–2.26 mg/dL) at the time of hospitalization, by an absolute increase of serum creatinine level of 0.31 mg/dL or >50 % increase from baseline. Patients were matched with others who did not receive antipsychotic medications, and analysis was conducted where patients were coded for AKI presence and where possible included the serum creatinine values. The relative risk (RR) for hospitalization with AKI was 1.73 [95 % C.I. 1.55–1.92] for patients taking SGAs. In patients with information on serum creatinine levels, a higher risk for AKI was found in patients with SGA use with an RR of 1.70 [95 % C.I. 1.22–2.38]. The all-cause mortality was higher in patients taking SGAs than nonrecipients (6.8 % versus 3.1 %) which was similar to the randomized clinical trials reported by the FDA in 2005 (See Sect. 2.4). It was recommended that proactive patient clinical monitoring after SGA initiation with serum creatinine be included. If a patient complains of urinary difficulty, a bladder scan to detect urinary retention must be conducted. If AKI is suspected with SGAs, prompt drug discontinuation is suggested.

9.3.9 Gastrointestinal Hypomotility and Pancreatitis

FGAs and SGAs with highly potent anticholinergic pharmacologic properties are thought to be the mostly likely agents to induce GI hypomotility (Richelson 1999, 2010; Richelson and Sounder 2000). A pharmacovigilance study collected data from 1997 to 2006 and identified 27 GI hypomotility cases from FGAs and SGAs. Intestinal colitis was reported in 57 cases that included a variety of FGAs and SGAs with phenothiazines having the highest incidence of 33 cases. Other antipsychotics reported were: haloperidol 9 cases and CLZ 7 cases, and all other SGAs reported a total of 11 cases (Peyriere et al. 2009). Ischemic colitis occurred in 10 patients and 24 required surgery. Of the 27 cases, 14 fatalities were reported with 6 cases during surgery and only 6 patients fully recovered. Other concomitant medications with anticholinergic properties were found in 68.4 % of the patients. An analysis of 102 cases of CLZ-induced GI hypomotility (CIGH) was conducted with published reports from 1950 to 2007 (Palerm et al. 2008). The mortality rate was 27.4 % and mostly due to bowel resection surgery. The risk factors for GI hypomotility included high CLZ dose or serum concentrations, concomitant anticholinergic use, and prior history of GI disturbances. An additional pharmacologic mechanism for CIGH was suggested to include the serotonergic (5HT) system with the 5HT2, 5HT3, and

5HT7 receptor subtypes that influence GI smooth muscle, colon transit, and visceral sensation. As antipsychotic-induced GI hypomotility is a very rare but potentially fatal adverse event, clinicians need to be especially aware of a patient reporting constipation that continues unabated and when other drugs with anticholinergic activity are included in the patient's treatment.

Acute pancreatitis is another rare but potentially fatal adverse event due to antipsychotic and is listed in the USA Physician's Desk Reference (PDR) for CLZ, OLZ, and RIS (Hauben 2004; Koller et al. 2003; Kawabe and Ueno 2014). The laboratory tests that assist in diagnosis are increased serum levels of amylase and lipase with the clinical symptoms of GI pain, nausea, vomiting, and high fever. Most cases occurred within 6 months of treatment initiation but rare cases have been reported afterwards (Hauben 2004). The FDA Medwatch surveillance system had reported 192 cases of antipsychotic-induced pancreatitis with 22 fatalities (Koller et al. 2003). The antipsychotics reported and their occurrence were CLZ 40 %, OLZ 30 %, RIS 16 %, and haloperidol 12 %. Concomitant valproate use was found in 23 % of the cases with additional laboratory findings of hyperglycemia and metabolic acidosis. A data mining study using Bayesian analysis failed to detect a signal of disproportional of pancreatitis with these three atypical antipsychotics (Hauben 2004). Nevertheless, clinicians should be aware of this serious medical condition when prescribing antipsychotics.

9.4 Patient Safety Monitoring

Patients with psychotic symptoms pose a tremendous challenge for clinicians to provide short-term and long-term benefits while balancing risks and potential adverse side effects. Selection of antipsychotic agent is based upon the patient's history, medical conditions, and use of other concurrent medications to treat the medical conditions. The antipsychotic pharmacological profile shown in Table 9.1 provides a basic overall information regarding the extrapyramidal side effects, anticholinergics, sedation, and orthostatic hypotensive properties in which to monitor patients for these adverse effects. However, antipsychotics can have a wide spectrum of potential adverse events displayed in Table 9.2. Antipsychotic use in special populations that include the elderly, children, and adolescents must be carefully examined. In the elderly, the increased risk of fatalities and cerebrovascular events must be balanced with efficacy and appropriate documentation of the antipsychotic usage. The potential long-term consequences of antipsychotic treatment in children and adolescents can lead to an increased continuum of care to minimize potential adverse effects compared to the adult and elderly populations.

Clinical observations and early symptom detection of potential adverse effects with antipsychotics are foundational methods that minimize patient risk and increases safety. A comprehensive baseline laboratory assessment including ECGs should be included when antipsychotics are initiated. If clinicians wish to add a quantitative approach to patient monitoring for extrapyramidal side effects (e.g.,

pseudoparkinson's, akathisia, and tardive dyskinesia), the use of standardized patient rating scales can be periodically and systematically used (Simpson and Angus 1970; Barnes 1989; Guy 1976). Although specific guidelines for routine patient monitoring with rating scales have not been established for EPS, assessments every 3–6 months can be employed. Unlike EPS, specific recommendations and guidelines for monitoring patients regarding MetS have been established (See Sect. 3.3). ECG monitoring to reduce the risk of TdP and identify prolonged QTc intervals can be accomplished with consideration of incorporating patient's past medical history, age, and other medications known to increase QTc interval. If clozapine is selected for a patient, specific hematologic monitoring recommendations for <1 year are established. Long-term periodic CBC monitoring >1 year must continue with clozapine. Besides the CBC monitoring, clozapine-treated patients should be assessed for the potential of myocarditis and gastrointestinal colitis. The potential for NMS and pancreatitis can occur with any antipsychotic, and clinicians need to be vigilant in detecting early clinical symptoms.

A special notation needs to be presented regarding long-acting depot antipsychotic administration as a "black box" warning for postinjection delirium/sedation syndrome (PDSS) that regulatory agencies have required patients treated with

Table 9.2 Summary of adverse events and the associated clinical assessment and/or laboratory tests

Adverse event	Clinical assessment and/or laboratory tests
Dementia-related psychosis fatality	Clinical assessment of benefits versus risk
Cerebrovascular risk	Clinical assessment of benefits versus risk
Extrapyramidal side effects	Clinical observation
Pseudoparkinson's	Simpson-Angus Scale (SAS)
Akathisia	Barnes Akathisia Rating Scale (BARS)
Tardive dyskinesia	Abnormal Involuntary Movement Scale (AIMS)
Seizures	Clinical assessment of benefits versus risk – clozapine dose and rate of titration
Metabolic syndrome	Body weight, FBS, blood pressure, lipid profile, and waist circumference
Cardiovascular	Vital signs and clinical symptoms
Torsade de pointes	Electrocardiograph (ECG) monitoring; QTc <500 ms
Myocarditis	Clozapine-treated patients – ECGs, CRP, and troponin
Hematologic	Vital signs, fever, sore throat, and infection. Complete blood counts with differential – especially with clozapine-treated patients
Prolactin	Clinical symptoms and prolactin serum concentrations
Neuroleptic malignant syndrome	Hyperthermia (>38 °C), muscle rigidity, diaphoresis, dysphagia, hypertension, serum creatine kinase (>4 times upper limit), tachypnea, tremor, or tachycardia
Gastrointestinal colitis	Constipation – especially with clozapine-treated patients and use of other anticholinergic drugs
Pancreatitis	Hyperglycemia, serum amylase, metabolic acidosis

FBS fasting blood glucose, *CRP* C-reactive protein

olanzapine pamoate be observed for 3 h after each injection administration (Alphs et al. 2011). The PDSS symptoms include excessive sedation, altered consciousness, slurred speech, and lethargy in which the patient may need to be taken to a hospital's emergency department for close monitoring (Alphs et al. 2011; Detke et al. 2010). A 6-year multinational study ($N=931$ patients) who received depot olanzapine pamoate injections ($N=45{,}662$) noted 36 (0.08 %) PDSS occurrences in 35 patients. One patient experienced two events and no fatalities were reported. All patients recovered within 72 h postinjection. The PDSS events occurred at different ages and BMIs without any significant identifying factors (McDonnell et al. 2014). Thus, the recommendation for retaining the patient at the facility for 3 h remains intact as PDSS can occur at any injection in any patient while being treated with depot olanzapine pamoate injection. The PDSS has not been found with any other long-acting depot antipsychotic products and is recommended to avoid accidental injection into the blood vessel (Alphs et al. 2011; Novakovic et al. 2013).

9.5 Conclusions

FGAs and SGAs continue to be used in the management of patients with various psychiatric conditions. The use of these agents in the elderly are "off-label" as regulatory agencies have not yet recognized psychosis associated with Alzheimer's disease as a psychiatric or medical disorder. When antipsychotics are prescribed in children and adolescents, their usage has expanded in addition to the various psychiatric illnesses to include other disorders such as autism. Clinicians must always balance the benefits and risks when prescribing these agents especially in the elderly, children, and adolescents. Appropriate individual patient safety monitoring for potential adverse events should be implemented by clinicians taking into consideration each antipsychotic pharmacologic and safety profile while matching the patient characteristics. Pharmacovigilance surveillance studies and data can provide important information on specific adverse event features, patterns of clinical symptoms, severity of the events, and where applicable, fatality rates of various antipsychotic agents. Healthcare systems at the local, regional, or national levels may wish to employ patient safety monitoring programs for antipsychotics based upon pharmacovigilance studies.

References

Alper K, Schwartz KA, Kolts RL, Khan A (2007) Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approvals reports. Biol Psychiatry 62:345–354

Alphs L, Gopal S, Karcher K et al (2011) Are the long-acting intramuscular formulations of risperidone or paliperidone palmitate associated with post-injection delirium/sedation syndrome? An assessment of safety databases. Curr Drug 6:43–45

American Diabetes Association (2010) Standards of medical care in diabetes – 2010. Diabetes Care 33(Suppl 1):S11–S61
American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists et al (2004) Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 27:596–601
Bak M, Fransen A, Janssen J, van Os J, Drukker M (2014) Almost all antipsychotics result in weight gain: a meta-analysis. PLoS 9(4):e94112. doi:10.1371/journal.pone.0094112
Barnes TR (1989) A rating scale for drug-induced akathisia. Br J Psychiatry 154:672–676
Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC (2013) QTc prolongation, Torsades de Pointes, and psychotropic medications. Psychosomatics 54:1–13
Berardis D, Serroni N, Campanella D et al (2012) Update on the adverse effects of clozapine: focus on myocarditis. Curr Drug Saf 7:55–62
Bondon-Guitton E, Perez-Lloret SP, Bagheri H, Brefel C, Rascol O, Montastruc JL (2011) Drug-induced Parkinsonism: a review of 17 years' experience in a regional pharmacovigilance center in France. Mov Disord 26:2226–2231
Caroff SN (1980) The neuroleptic malignant syndrome. J Clin Psychiatry 41:79–83
Caroff SN, Mann SC (1988) Neuroleptic malignant syndrome. Psychopharmacol Bull 24:25–29
Caroff SN, Mann SC (1993) Neuroleptic malignant syndrome. Med Clin N Am 77:185–202
Centorrino F, Masters GA, Talamo A, Baldessarini RJ, Ongur D (2012) Metabolic syndrome in psychiatrically hospitalized patients treated with antipsychotics and other psychotropics. Hum Psychopharmacol 27:521–526
Cohen D, Monden M (2013) White blood cell monitoring during long-term clozapine treatment. Am J Psychiatry 170:366–369
Cohen D, Bogers JPA, van Dijk D, Bakker B, Schulte PFJ (2012) Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. J Clin Psychiatry 73:1307–1312
Coplan J, Gugger JJ, Tasleem H (2013) Tardive dyskinesia from atypical antipsychotic agents in patients with mood disorders in a clinical setting. J Affect Disord 150:868–871
Correll CU, Schenk EM (2008) Tardive dyskinesia and new antipsychotics. Curr Opin Psychiatry 21:151–156
Coulter DM, Bate A, Meyboom RHB, Lindquist M, Edwards IR (2001) Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. BMJ 322:1207–1209
Detke HC, McDonnell DP, Brunner E et al (2010) Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection: I. Analysis of cases. BMC Psychiatry 10:4
Devanand DP (2013) Psychosis, agitation, and antipsychotic treatment in dementia. Am J Psychiatry 170:957–958
Devinsky O, Pacia SV (1994) Seizures during clozapine therapy. J Clin Psychiatry 55(Suppl B):153–156
Devinsky O, Honigfeld G, Patin J (1991) Clozapine-related seizures. Neurology 41:369–371
Divac N, Prostran M, Jakovcevski I, Cerovac N (2014) Second-generation antipsychotics and extrapyramidal adverse effects. BioMed Res Int; http://dx.doi.org/10.1155/2014/656370
Drew L (2013) Clozapine and agranulocytosis. Aust Psychiatry 21:335–337
Epstein RA, Bobo WV, Shelton RC et al (2013) Increasing use of atypical antipsychotics and anticonvulsants during pregnancy. Pharmacoepidemiol Drug Saf 22:794–801
Flanagan RJ, Dunk L (2008) Haematological toxicity of drugs used in psychiatry. Hum Psychopharmacol Clin Exp 23:27–41
Ganguli R, Strassnig M (2011) Prevention of metabolic syndrome in serious mental illness. Psychiatr Clin N Am 34:109–125
Gareri P, De Fazio P, Stilo M, Ferrei G, De Sarro G (2003) Conventional and atypical antipsychotics in the elderly. Clin Drug Invest 23:287–322
Glassman AH, Bigger JT (2001) Antipsychotic drugs: prolonged QTc interval, Torsade de Pointes, and sudden death. Am J Psychiatry 158:1774–1782
Guanci N, Aggarwal R, Schleifer S (2012) Atypical neuroleptic malignant associated with iloperidone administration. Psychosomatics 53:603–604

Gurrera RJ, Caroff SN, Cohen A et al (2011) An international consensus study of neuroleptic malignant syndrome diagnostic criteria suing the Delphi method. J Clin Psychiatry 72:1222–1228

Guy W (1976) AIMS. Abnormal Involuntary Movement Scale. Early Clinical Drug Evaluation Unit (ECDEU). In: Rockville MD (ed) Assessment manual for psychopharmacology, vol 338. NIMH, DHHS No. ADM 91–338, pp 534–537

Harrison-Woolrych M, Garica-Quiroga J, Ashton J, Herbison P (2007) Safety and usage of atypical antipsychotic medicines in children. Drug Saf 30:569–579

Hauben M (2004) Application of an empiric Bayesian data mining algorithm to reports of pancreatitis associated atypical antipsychotics. Pharmacotherapy 24:1122–1129

Hwang YJ, Dixon SN, Reiss JP et al (2014) Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults. Ann Intern Med 161:242–248

Hyde TM, Weinberger DR (1997) Seizures and schizophrenia. Schizophrenia Bull 23:611–622

Jeste D, Finkel S (2000) Psychosis of Alzheimer's Disease and related: diagnostic for a distinct syndrome. Am J Geriatr Psychiatry 8:29–34

Jeste DV, Balzer D, Casey D et al (2008) ACNP white paper: update on the use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology 33:957–970

Kagal UA, Torgal SS, Patil NM, Malleshappa A (2012) Prevalence of the metabolic syndrome in schizophrenic patients receiving second-generation antipsychotic agents – a cross sectional study. J Pharm Pract 25:368–373

Kalapatapu RK, Schimming C (2009) Update on neuropsychiatric symptoms of dementia: antipsychotic use. Geriatrics 64:10–18

Kao AC, Muller DJ (2013) Genetics of antipsychotic-induced weight gain: update and current perspectives. Pharmacogenomics 14:2067–2083

Kawabe K, Ueno SC (2014) A case of acute pancreatitis associated with risperidone treatment. Clin Psychopharmacol Neurosci 12:67–68

Keck PE, McElroy SL, Stakowski SM, Soutullo CA (2000) Antipsychotics in the treatment of mood disorders and the risk of tardive dyskinesia. J Clin Psychiatry 61(Suppl 4):33–38

Kinon BJ, Kollack-Walker S, Jeste D et al (2015) Incidence of tardive dyskinesia in older adult patients treated with olanzapine or conventional antipsychotics. J Geriatr Psychiatry Neurol 28(1):67–79

Koller EA, Cross JT, Doraiswamy PM, Malozowski SN (2003) Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. Pharmacotherapy 23:1123–1130

Kranzler HN, Cohen SD (2013) Psychopharmacologic treatment of psychosis in children and adolescents: efficacy and management. Child Adolesc Psychiatry N Am 22:727–744

Kumra S, Oberstar JV, Sikich L et al (2008) Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. Schizopr Bull 34:60–71

Kyonmen HH, Whitfield TH (2009) Psychosis in the elderly. Am J Psychiatry 166:146–150

Langan J, Martin D, Shajahan P, Smith DJ (2012) Antipsychotic dose escalation as a trigger for neuroleptic malignant syndrome (NMS): literature review and case series report. BMC Psychiatry 12:214

Laredo L, Vargas E, Blasco AJ, Aguilar MD, Moreno A, Portoles A (2011) Risk of cerebrovascular accident associated with use of antipsychotics: population-based case-control study. JAGS 59:1182–1187

Lee WJ, Lee TA, Pickhard AS, Caskey RN, Schumock GT (2014) Drugs associated with adverse events in children and adolescents. Pharmacotherapy 34(9):918–926

Leonard CE, Freeman CP, Newcomb CW et al (2013) Antipsychotics and risk of sudden cardiac death and all-cause death: cohort studies in Medicaid and dually-eligible Medicaid-Medicare beneficiaries of five states. J Clin Exp Cardiol Suppl 10:1–9

Lertxundi U, Hernandez R, Medrano J, Domingo-Echaburu S, Garcia M, Aguirre C (2013) Antipsychotics and seizures: higher risk with atypicals? Seizure 22:141–153

Leucht S, Cipriani A, Spineli L et al (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382:951–962

Lopez OL, Becker JT, Chang YF et al (2013) The long-term effects of conventional and atypical antipsychotics in patients with probable Alzheimer's Disease. Am J Psychiatry 170:1051–1058

Madhusoodanan S, Shah P, Brenner R, Gupta S (2007) Pharmacological treatment of psychosis of Alzheimer's disease. CNS Drugs 21:101–115

Maher AR, Magione M, Bagley S et al (2011) Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults. JAMA 306:1359–1369

Manu P, Kane JM, Correll CU (2011) Sudden deaths in psychiatric patients. J Clin Psychiatry 72:936–941

Manu P, Corrll CU, van Winkel R, Wampers M, De Hert M (2012) Prediabetes in patients treated with antipsychotic drugs. J Clin Psychiatry 73:460–466

McDonnell DP, Landry J, Detke HC (2014) Long-term safety and efficacy of olanzapine long-acting injection in patients with schizophrenia or schizoaffective disorder: a 6-year, multinational, single-arm, open-label study. Int Clin Psychopharmacol 29(6):322–331

Melzter HY, Cola PA, Parsa M (1996) Marked elevations of serum creatine kinase activity associated with antipsychotic drug treatment. Neuropsychopharmacology 15:395–405

Meyer-Massetti C, Vaerini S, Ratz Bravo AE et al (2011) Comparative safety of antipsychotics in the WHO pharmacovigilance database: the haloperidol case. Int J Clin Pharm 33:806–814

Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M (2013) Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders – a systematic review and meta-analysis. Schizophr Bull 39:306–318

Mittal D, Li C, Williams JS, Viverito K, Landes RD, Owen RR (2013) Monitoring veterans for metabolic side effects when prescribing antipsychotics. Psychiatr Serv 64:28–35

Munshi TA, Volochniouk D, Hassan T, Mazhar N (2014) Clozapine-induced myocarditis: is mandatory monitoring warranted for its early recognition? Case Rep Psychiatry 20, 513108

Narang P, El-Refai M, Parlapalli R et al (2010) Antipsychotic drugs: sudden cardiac death among elderly patients. Psychiatry 7:25–29

Nelson JC (2005) Increased risk of cerebrovascular adverse events and death in elderly demented patients treated with atypical antipsychotics: what's a clinician to do? J Clin Psychiatry 66:1071

Newcomer JW, Hennekens CH (2007) Severe mental illness and risk of cardiovascular disease. JAMA 298:1794–1796

Nooijen PMM, Carvalho F, Flanagan RJ (2011) Haematological toxicity of clozapine and some other drugs used in psychiatry. Hum Psychopharmacol Clin Exp 26:112–119

Novakovic V, Adel T, Peselow E, Lindenmayer JP (2013) Long-acting injectable antipsychotics and the development of post injection delirium/sedation syndrome (PDSS). Clin Neuropharmacol 36:59–62

Ozeki Y, Fujii K, Kurimoto N et al (2010) QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 34:401–405

Pacia SV, Devinsky O (1994) Clozapine-induced seizures: experience with 5,629 patients. Neurology 44:2247–2249

Packhard K, Price P, Hanson A (2014) Antipsychotic use and risk of rhabdomyolysis. J Pharm Pract 27(5):501–512

Palanca-Maresca I, Ruiz-Antorian B, Centeno-Soto G et al (2014) SENTA: a systematic online monitoring registry for children and adolescents treated with antipsychotics. SpingerPlus 3:187

Palerm SE, McLean RM, Ellis PM, Harrison-Woolrych M (2008) Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. J Clin Psychiatry 69:759–769

Papanastasiou E (2013) The prevalence and mechanism of metabolic syndrome in schizophrenia: a review. Ther Adv Psychopharmacol 3:33–51

Peluso MJ, Lewis SW, Barnes TR, Jones PB (2012) Extrapyramidal motor side effects of first-generation and second-generation antipsychotic drugs. Br J Psychiatry 200:387–392

Perel JM, Jann MW (2006) Antipsychtoics. In: Burton ME, Shaw LM, Schentag JJ, Evans WE (eds) Applied pharmacokinetics and pharmacodynamics – principles of therapeutic drug monitoring, 4th ed. Lippincott Williams and Wilkins, Baltimore, pp 813–838

Peuskens J, Pani L, Detraux J, De Hert M (2014) The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs 28:421–453
Peyriere H, Roux C, Ferard C et al (2009) Antipsychotic-induced ischaemic colitis and gastrointestinal necrosis: a review of the French pharmacovigilance database. Pharmacoepidemiol Drug Saf 18:948–955
Piparva KG, Buch JG, Chandrani KV (2011) Analysis of adverse drug reactions of atypical antipsychotic drugs in psychiatry OPD. Indian J Psychol Med 33:153–157
Pisani F, Oteri G, Costa C, Di Raimondo G, Di Perri R (2002) Effects of psychotropic drugs on seizure threshold. Drug Saf 25:91–110
Poluzzi E, Raschi E, Kochi A et al (2013) Antipsychotics and torsadogenic risk: signals emerging from the US FDA adverse events reporting system database. Drug Saf 36:467–479
Rajkumar RP, Melvin G (2014) Pharmacovigilance for psychiatrists: an introduction. Ind J Psychiatry 56:176–181
Rani FA, Byrne PJ, Murray ML, Carter P, Wong ICK (2009) Paediatric atypical antipsychotic monitoring safety (PAMS) study. Drug Saf 32:325–333
Recupero PR, Rainey SE (2007) Managing risk when considering the use of atypical antipsychotics for elderly patients with dementia-related psychosis. J Psychiatr Pract 13:143–152
Richelson E (1999) Receptor pharmacology of neuroleptics: relation to clinical effects. J Clin Psychiatry 60(Suppl 10):5–14
Richelson E (2010) New antipsychotic drugs: how do their receptor-binding profiles compare? J Clin Psychiatry 71:1243–1244
Richelson E, Sounder T (2000) Binding of antipsychotic drugs to human brain receptors – focus on newer generation compounds. Life Sci 68:29–39
Riordan HJ, Antonini P, Murphy MF (2011) Atypical antipsychotics and metabolic syndrome in patients with schizophrenia: risk factors, monitoring, and healthcare implications. Am Health Drug Benefits 4:292–302
Schneider LSD, Dagerman KS, Insel P (2005) Risk of death with atypical antipsychotic drug treatment for dementia. JAMA 294:1934–1943
Schneider LS, Tariot PN, Dagerman KS et al (2006) Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. NEJM 355:1525–1538
Schneider C, Taylor D, Zalsman G, Frangou S, Kyriakopoulos M (2014) Antipsychotics use in children and adolescents: an on-going challenge in clinical practice. J Psychopharmacol 28:615–623
Simoni-Wastila L, Ryder PT, Qian J et al (2009) Association of antipsychotic use with hospital events and mortality among Medicare beneficiaries residing in long-term care facilities. Am J Geriatr Psychiatry 17:417–427
Simpson GM, Angus JW (1970) A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 212:11–19
Star K, Iessa N, Almandil NB et al (2012) Rhabdomyolysis reported for children and adolescents treated with antipsychotic medicines: a case series analysis. J Child Adolesc Psychopharmacol 22:440–451
Stephanie C, Trenkwalder C (2010) Rhabdomyolysis after low dose quetiapine in a patient with Parkinson's disease with drug-induced psychosis. A case report. Mov Disorder 25:790–791
Su YP, Chang CK, Hayes RD et al (2014) Retrospective chart review on exposure to psychotropic medications associated with neuroleptic malignant syndrome. Acta Psychiatr Scand 130:52–60
Szarfman A, Tonning JM, Levine J, Doraiswamy PM (2006) Atypical antipsychotics and pituitary tumors: a pharmacovigilance study. Pharmacotherapy 26:748–758
Tam CW, Olin BR, Ruiz AE (1980) Loxapine-associated rhabdomyolysis and acute renal failure. Arch Int Med 140:975–976
Trollor JN, Chen X, Chitty K, Sachdev PS (2012) Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. Br J Psychiatry 201:52–56
US Food and Drug Administration (2003) Safety alert – risperdal (risperidone) [on line]. Available at http://www.fda.gov/cder/drug/advisory/antipsychotics.htm. Accessed May 2014

US Food and Drug Administration (2014) FDA public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. Available at http://www.fda.gov/cder/drug/advisory/antipsychotics.htm. Accessed May 2014

Vieweg WV (2003) New generation antipsychotic drugs and QTc interval prolongation. Primary Care Companion J Clin Psychiatry 5:2–5, 215

Woerner MG, Alvir JMJ, Saltz BL, Lieberman JA, Kane JM (1998) Prospective study of tardive dyskinesia in the elderly: rates and risk factors. Am J Psychiatry 155:1521–1528

Woerner MG, Correll CU, Alvir JMJ, Greenwald B, Delman H, Kane JM (2011) Incidence of tardive dyskinesia with risperidone or olanzapine in the elderly: results from a 2-year, prospective study in antipsychotic-naïve patients. Neuropsychopharmacology 36:1738–1746

Zarrouf FA, Bhanot V (2007) Neuroleptic malignant syndrome: don't let your guard down yet. Curr Psychiatry 6:89–95

Chapter 10
Safety and Tolerability of Anxiolytics/ Sedative-Hypnotics

Vincenzo Arcoraci and Edoardo Spina

Abstract A variety of pharmacological agents are currently available for the treatment of anxiety disorders and insomnia. The adverse event profile of selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), first-line drugs for the treatment of many anxiety conditions, is discussed in Chap. 8. Benzodiazepines are still valuable in the management of anxiety disorders and transient insomnia. Tolerability and safety issued associated with benzodiazepines includes sedation, memory and psychomotor impairment and reduced driving performance. As stated in international guidelines, benzodiazepine treatment should be of short duration not exceeding 3 months, as continuous use of benzodiazepines can lead to abuse and dependence. In addition, recent findings suggest that long-term use of benzodiazepines in the elderly may increase the risk of developing Alzheimer's disease. Moreover, warnings released by European Medicines Agency (EMA) and Food and Drug Administration (FDA) advised that two benzodiazepines, tetrazepam and clobazam, may cause serious skin events, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Emerging evidence indicates that pregabalin, a pharmacological agent approved for the treatment of generalized anxiety disorder, also has the potential to lead to abuse and dependence. Recent data in elderly patients has highlighted potential safety concerns of non-benzodiazepine hypnotics, the so-called Z-drugs, including zolpidem, specifically with regard to effects on balance and memory and on fracture risk.

Keywords Anxiolytics • Sedative-hypnotics • Tolerability • Safety

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10.1 Introduction

A variety of agents and drug classes provide anxiolytic and sedative-hypnotic effects. Benzodiazepines are still among the most widely prescribed agents for the management of anxiety and insomnia. However, there is great concern regarding long-term use of benzodiazepines due to their potential for dependence and abuse as well as negative effects on memory and cognition (Lader 2014). Therefore, other drugs, which generally have fewer side effects and lower addiction potentials, have gradually replaced benzodiazepines. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are licenced for the treatment of many anxiety conditions such as generalised anxiety disorder, panic disorder, social phobia and obsessive-compulsive disorder. According to recent guidelines, these agents are first-line treatment for most types of anxiety disorders (Bandelow et al. 2012; Baldwin et al. 2014). The tolerability and safety profile of these agents are covered in Chap. 8. Buspirone, an azapirone acting on the serotonin system, has been available for nearly 30 years to treat generalised anxiety disorders and appears to be useful especially in patients who have not been previously on a benzodiazepine (Chessick et al. 2006). The antiepileptic and antineuropathic pain agent pregabalin has been also approved for the treatment of generalised anxiety disorder in the EU since 2006 (Frampton 2014). The non-benzodiazepine drugs zopiclone, eszopiclone (not licenced in the European Union), zolpidem and zaleplon, commonly known as Z-drugs, have been developed as hypnotics with improved pharmacokinetics and better tolerability profile in comparison to benzodiazepines, the traditional treatments for insomnia (Gunja 2013).

In this chapter, we will review the various adverse effects associated with the use of benzodiazepines, buspirone, pregabalin and non-benzodiazepine hypnotics.

10.2 Benzodiazepines

Benzodiazepines have been widely used in clinical practice for over five decades and continue to be among the most commonly prescribed agents to treat anxiety and insomnia (Greenblatt 2011). All benzodiazepines have anxiolytic, hypnotic, muscle relaxant, and anticonvulsant properties. The various compounds differ in their potency and efficacy with regard to each of the pharmacodynamic actions. All the effects of benzodiazepines are mediated by their interaction with specific binding sites (benzodiazepine receptors) located on the ionotropic GABA-A receptors, but distinct from GABA binding site. The binding of benzodiazepines to their receptors causes an allosteric modification of the GABA-A receptor that results in an enhanced neurotransmitter affinity for its receptor and an increased frequency of channel-opening events thereby leading to an increase in chloride ion conductance and inhibition of the action potential.

Benzodiazepines are generally viewed as safe and effective for short-term use, although cognitive impairment and paradoxical effects such as aggression or

behavioural disinhibition occasionally occur (Lader 2011). A minority of people can have paradoxical reactions such as worsened agitation or panic. Long-term use is controversial due to concerns about adverse psychological and physical effects, decreasing effectiveness, physical dependence and withdrawal. Due to adverse effects associated with the long-term use of benzodiazepines, withdrawal from benzodiazepines, in general, leads to improved physical and mental health. Elderly patients are at an increased risk of suffering from both short- and long-term adverse effects (Gould et al. 2014; Paquin et al. 2014).

10.2.1 Short-Term Effects

10.2.1.1 Sedation

Sedation is the most common subjective effect of benzodiazepines. Tolerance may develop within a few weeks of starting treatment, but some residual effects as increased alertness is reported by patients on stopping treatment with benzodiazepines (Curran et al. 2003). At higher doses, unsteadiness, slurring of speech and disorientation indicate over-sedation particularly when benzodiazepines are combined with alcohol (Lader 2014).

10.2.1.2 Psychomotor Impairment

Benzodiazepines generally have consistent psychomotor effects in short- and long-term use (Woods et al. 1992). They impair the performance of simple and more complex tasks. This effect is due to alteration in the speed of execution, because persons taking benzodiazepines tend to slow down in order to maintain accuracy of performance. Benzodiazepines also impair the performance of simple tasks requiring heightened attention. Despite the possible development of tolerance to effects such as sedation and impaired psychomotor performance, impaired performance of simple repetitive tasks may persist for periods of up to 1 year (Lader 2011). On the other hand, the ability to perform tests of attention may remain impaired after several years of treatment in long-term benzodiazepine users as compared to non-users.

10.2.1.3 Learning and Memory Impairment

The short-term use of benzodiazepines significantly impairs multiple areas of cognition, including learning and memory (Lader 2011). These cognitive effects are enhanced when benzodiazepines are taken concomitantly with alcohol. Memories formed before drug administration (retrograde memory) are not impaired, but the formation of new memories after benzodiazepine use (anterograde memory) can be significantly impaired by benzodiazepines. The more complex a memory is, e.g.

memory regarding high task complexity and delay in recall, the greater the effect of benzodiazepines on memory formation is expected to be. It should be noted that there are differences between the propensities of individual benzodiazepine drugs to impair memory formation. The majority of benzodiazepines do not affect implicit memory or priming, but lorazepam was found to impair these aspects of memory formation (Curran et al. 1994). After months or even years of stopping treatment, the effects of benzodiazepines on episodic memory may still be noticeable and were not reversed by the action of flumazenil, a GABA-A receptor antagonist (Gorenstein et al. 1994). Findings from a meta-analysis suggest that benzodiazepine users perform worse on most of cognitive tasks assigned, in particular those requiring the use of verbal memory, compared to non-users (Barker et al. 2004). It should be noted however that the studies included in the meta-analysis were very diverse with respect to length of use, dosage and diagnosis.

10.2.1.4 Falls and Hip Fractures

The use of benzodiazepines, as well as other sedative drugs, is often associated with falls and hip fractures, particularly in elderly patients (Ray et al 1989). Due to increased sedation and cognitive/psychomotor impairment, benzodiazepines increase the likelihood of falls, which are commonly the cause of hip fracture, a devastating event in the life of an older person.

An early meta-analysis of observational epidemiological studies found that use of benzodiazepines was associated with a 50 % increased risk of falling (Leipzig et al. 1999). A more recent Bayesian meta-analysis has substantially confirmed this finding (Woolcott et al. 2009). Cumming and Le Couteur (2003) provided a detailed review of epidemiological studies on the relationship between the use of benzodiazepines and the risk of hip fracture. The results of these studies were somewhat inconsistent, and this was almost entirely explained by research design. The studies that did not find an association between the increased risk of hip fracture and the use of benzodiazepines were nearly all hospital-based case-control studies. These types of studies are susceptible to confounding due to the difficulty of finding a suitable control group. Apart from the hospital-based case-control studies, all of the remaining seven studies included in the meta-analysis found that benzodiazepines use was associated with an increased risk of hip fracture, except one. No evidence was found to support a differential risk of hip fracture associated with short- or long-acting benzodiazepines. The use of higher benzodiazepine doses and the incident use of benzodiazepines were associated with the highest risk of hip fracture. Some preliminary evidence was found that benzodiazepines which are substrates for oxidation in the liver may be associated with a higher risk of hip fracture in the oldest old.

A recent meta-analysis including 25 studies (19 case-control studies and 6 cohort studies) investigated the association between use of benzodiazepines and risk of fractures (Xing et al. 2014). In general, the meta-analysis indicated that benzodiazepine use was associated with a significantly increased risk of fracture (relative risk (RR) = 1.25; 95 % confidence intervals (CI), 1.17–1.34; $p < 0.001$). A higher fracture

risk associated with benzodiazepine use was observed in persons ≥65 years old (RR = 1.26; 95 % CI, 1.15–1.38; $p<0.001$). When only hip fractures were considered the outcome of interest, the risk ratio increased to 1.35. A subgroup meta-analyses did not find any significant association between long-acting benzodiazepine use and risk of fractures (RR = 1.21; 95 % CI, 0.95–1.54; $p=0.12$). Adjusting for publication bias, the association between benzodiazepine use and the risk of fracture remained but was slightly weaker (RR = 1.21; 95 % CI, 1.13–1.30) and significant. The results of this meta-analysis demonstrated that the use of benzodiazepines, especially short-acting ones, is associated with a moderate and clinically significant increase in fracture risk.

In conclusion, evidence from pharmacoepidemiological studies strongly suggests that the use of benzodiazepines by elderly people increases their risk of hip fracture by up to half. Given the serious sequelae of hip fracture among older people (including the risk of death), the use of benzodiazepines in this population should be avoided and older persons already using benzodiazepines should have them tapered off.

10.2.1.5 Complex Skills and Driving

Sedation and impaired psychomotor function may influence the ability to drive or operate machinery (Leung 2011). Both simulated driving performance and actual driving ability can be impaired and accidents are more likely. Early epidemiological studies have confirmed that road traffic accidents involving injury or death are associated with the use of sedative drugs (Barbone et al. 1998), and this appeared to be related to dose, increased age and concomitant use of alcohol (Hemmelgarn et al. 1997). A systematic literature review has confirmed that exposure to benzodiazepine increases the risk of traffic accidents (Smink et al. 2010). In particular, the greater accident risk seems to be associated with the use of long half-life benzodiazepines, increasing dosages in the first few weeks of use. A meta-analysis of studies from 1966 to 2000 concluded that benzodiazepines were associated with a 60–80 % higher the risk of accidents (Dassanayake et al. 2011). The impaired ability to drive was often related to long plasma half-lives of hypnotics, with few exceptions. Daytime anxiolytics were found to impair driving independently of their half-lives. Alcohol significantly potentiates the detrimental effects of benzodiazepines on driving (Maxwell et al. 2010; Orriols et al. 2011).

10.2.1.6 Paradoxical Effects

Although benzodiazepines are traditionally prescribed as anxiolytic and sedating agents, they may cause paradoxical effects characterised by increased talkativeness, emotional release, excitement, excessive movement and even hostility, rage, aggression and violence (Mancuso et al. 2004). The patient may have complete or partial amnesia for the event. Paradoxical reactions to benzodiazepines are relatively

uncommon and occur in less than 1 % of patients. The pathophysiology behind these reactions is poorly defined. However, several risk factors such as age, genetic predisposition, alcoholism and psychiatric and/or personality disorders have been identified. Children and older patients are more likely to experience paradoxical reactions with benzodiazepines compared to other patients. It has been speculated that these patients may have a different pharmacodynamic response to benzodiazepines. However, the exact differences have not been specifically described in the literature. Some patients may have differences in the benzodiazepine-GABA-chloride receptor at the genetic level, such changes may result in an abnormal pharmacodynamic response. There are multiple allelic forms of benzodiazepine receptors, resulting in different affinities for benzodiazepine drugs. Alcohol has been found to increase the risk of benzodiazepine-associated violence and aggression (Daderman and Lidberg 1999). High-risk patients include those with borderline personality disorders, impulse control disorder, history of substance abuse and persistent alcohol problems (Mancuso et al. 2004). Disinhibition as a result of sedative drugs is related to the type of benzodiazepine used, the dose and the mode of administration (Bond 1998). Preoperative intravenous administration of high doses of high-potency benzodiazepines poses a particularly enhanced risk of disinhibition.

Paradoxical excitement is an unwanted effect which also has possible legal implications (Paton 2002). This disinhibition associated with benzodiazepines can produce increased anxiety, acute excitement and hyperactivity. Aggressive impulses may be triggered with the emergence of hostility and rage; criminal acts such as assault and rape have been recorded.

10.2.2 Long-Term Effects

10.2.2.1 Risk of Dementia

While the acute effects of benzodiazepines on memory and cognition are well documented, the possibility that they increase risk of dementia is still debated. Studies investigating the association between the use of benzodiazepines and cognitive decline or dementia in elderly patients have given conflicting results (Verdoux et al. 2005). Some found an increased risk of dementia or cognitive impairment in benzodiazepine users (Lagnaoui et al. 2002; Paterniti et al., 2002; Allard et al. 2003; Wu et al. 2009, 2011; Gallacher et al. 2012), whereas others were not conclusive or even reported a potential protective effect (Dealberto et al. 1997; Fastbom et al. 1998; Hanlon et al. 1998; Lagnaoui et al. 2009; Boeuf-Cazou et al. 2011). Such previous studies had many methodological shortcomings, and, in particular, the timing of exposure to benzodiazepines in relation to the outcome event allowed for the possibility of reverse causation. Moreover, it should be acknowledged that insomnia, depression and anxiety (the main indications for prescribing benzodiazepines) can be prodromal symptoms of dementia (Amieva et al. 2008).

Two recent studies by the same research group suggested that the use of benzodiazepines may increase the risk of developing dementia in the elderly (Bilioti de Gage et al. 2012, 2014). The first study evaluated the association between the use of benzodiazepines and incident dementia (Bilioti de Gage et al. 2012). This was a prospective, population-based study involving 1,063 men and women (mean age 78.2 years) who were free of dementia and did not start taking benzodiazepines until at least the third year of follow-up. During a 15-year follow-up, 253 incident cases of dementia were confirmed. New use of benzodiazepines was associated with an increased risk of dementia (multivariable adjusted hazard ratio 1.60, 95 % confidence interval 1.08–2.38). A secondary analysis consisted of the association between incident dementia and the initiation of benzodiazepines. The hazard ratio of incident benzodiazepine users was 1.46 (1.10–1.94). Results of a nested case-control study suggest that use of benzodiazepines at any time was associated with roughly a 50 % increase in the risk of dementia (adjusted odds ratio 1.55, 1.24–1.95) compared with non-users. Similar results were obtained for past users (odds ratio 1.56, 1.23–1.98) and recent users (1.48, 0.83–2.63), but findings were significant only for past users. The second study investigated the association between Alzheimer's disease and exposure to benzodiazepines starting at least 5 years before benzodiazepine use, considering both the dose-response relation and prodromes (anxiety, depression, insomnia) possibly related to treatment (Bilioti de Gage et al. 2014). This was a case-control study, based on the Quebec health insurance programme database (RAMQ), involving 1,796 people with a first diagnosis of Alzheimer's disease and followed up for at least 6 years before were matched with 7,184 controls on sex, age group and duration of follow-up. Both groups were randomly sampled from older people (age >66) living in the community in 2000–2009. The association between Alzheimer's disease and benzodiazepine use started at least 5 years before diagnosis was assessed by using multivariable conditional logistic regression. Exposure any time to benzodiazepines was first considered and then categorised according to the cumulative dose expressed as prescribed daily doses (1–90, 91–180, >180) and the drug elimination half-life. Benzodiazepine use was associated with Alzheimer's disease (adjusted odds ratio 1.51, 95 % confidence interval 1.36–1.69). No association was found for a cumulative dose <91 prescribed daily doses. The association increased with exposure density (1.32 (1.01–1.74) for 91–180 prescribed daily doses and 1.84 (1.62–2.08) for >180 prescribed daily doses) and with the drug half-life (1.43 (1.27–1.61) for short-acting drugs and 1.70 (1.46–1.98) for long-acting ones). Based on the findings of these studies, the authors suggest to avoid indiscriminate long-term and widespread use of benzodiazepine in general population.

The possible association between dementia and the use of benzodiazepines should nevertheless be viewed with caution and the above studies have prompted some criticism (Barbui et al. 2013; Kmietowicz 2014; Salzman and Shader 2015). While the above studies by Billioti de Gage et al. (2012, 2014) provide evidence in favour of such an association, such as an increase in risk with increasing duration of exposure and increasing benzodiazepine half-life, observational studies on the topic may be subject to confounding by indication in the case that the drugs were prescribed for anxiety and/or insomnia that were due to prodromal symptoms of

dementia (Barbui et al. 2013). In addition, the follow-up of 6 years may be considered relatively short to study a neurodegenerative disease such as Alzheimer's, which may take much longer to develop (Kmietowicz 2014). It was also pointed out that the cohort of patients under study may have had mild cognitive impairment although they did not have Alzheimer disease and that other factors which may be associated with memory impairment, such as alcohol use, were not controlled for (Salzman and Shader 2015).

In conclusion, findings on the risk of Alzheimer's disease with benzodiazepine use are thought provoking and suggest that these drugs may increase the risk of Alzheimer's disease, but such findings should be considered an indication of definitive causality, in particular given that observational studies are not the most suited study design to investigate causality.

10.2.2.2 Tolerance, Dependence and Withdrawal

The main problem associated with long-term use of benzodiazepines is the development of tolerance and dependence (Ashton 2005; O'Brien 2005; Lader 2011).

Tolerance can be defined as a reduced pharmacological response following repeated administration of the same drug dose. As a consequence, increasing doses are needed to produce the same response. Benzodiazepine tolerance develops at different rates and to different extents (Ashton 2005). Tolerance to hypnotic effects develops rapidly, within a few days or weeks of regular use. Although some subjects report continued efficacy of benzodiazepine hypnotics, clinical experience suggests that a considerable proportion of hypnotic users must gradually increase their dosage to maintain a given level of therapeutic response. Tolerance to the anticonvulsant and muscular relaxant effects of benzodiazepines also develops relatively quickly. On the other hand, tolerance to the anxiolytic effects develops more slowly, over a few months, and clinical experience shows that long-term use does little to control anxiety and may even aggravate it (Ashton 2005). There is also evidence of dosage escalation when benzodiazepines are used for their anxiolytic effect. In general, little tolerance develops to the amnesic other cognitive effects caused by benzodiazepines. Studies of long-term users have shown deficits in learning, memory, attention and visuospatial ability. A meta-analysis of 13 research studies that evaluated the effect on long-term use of benzodiazepines on cognitive function found that long-term benzodiazepine users had moderate-significant deficits for each of the 12 of the cognitive domains tested compared to controls (Barker et al. 2004).

According to the World Health Organization, dependence is defined as a strong compulsion to take a substance, difficulty in controlling its use, the development of tolerance and the presence of a withdrawal state. Withdrawal consists of a group of symptoms which occur on cessation or reduction of use of a psychoactive substance that has been used repeatedly, often for prolonged periods and/or in high doses (Lader 1987). Withdrawal may be accompanied with physiological disturbances. Withdrawal syndrome is one of the markers of dependence. Benzodiazepine discontinuation or an abrupt reduction in dose may result in rebound and/or withdrawal

syndrome, even after only 3–4 weeks of treatment. Rebound can be considered as the mildest form of withdrawal (Lader 2011). Rebound symptoms are the return of the symptoms for which the patient was treated but with a greater intensity than before. The most common phenomenon with benzodiazepines is the rebound of the hypnotic effect which is likely when stopping hypnotic benzodiazepines, particularly short-acting ones, even after only a few days or nights of use (Bonnet and Arand 1999). After stopping the hypnotic benzodiazepine, the insomnia can return in an exaggerated form, time to sleep onset is prolonged, sleep is more disturbed and it is shorter in duration. Rebound is generally short lived lasting a night or two, but can panic the patient into resuming the medication. Withdrawal is a more serious phenomenon, consisting in a characteristic grouping of signs and symptoms that occur when the benzodiazepine is stopped or the dose is reduced. Withdrawal often involves the onset of *new* symptoms not experienced previously by the patient. The occurrence of a withdrawal syndrome is the main indicator of physical dependence (Chouinard 2004). Withdrawal syndrome associated with benzodiazepine use is generally related to high dosage and long-term treatment. Withdrawal symptoms usually occur after 4–6 weeks of use, but only in about 15–30 % of patients (Lader 1998). Benzodiazepine withdrawal symptoms may be divided into common, less common and rare symptoms (Table 10.1). Severe symptoms usually occur as a result of abrupt or over-rapid withdrawal. Abrupt withdrawal can be dangerous; therefore, the dose of benzodiazepines should be gradually tapered off until they are discontinued. The symptoms of withdrawal usually subside in 2–4 weeks but can be prolonged. Withdrawal symptoms may occur even if the dose of benzodiazepines is reduced gradually, but symptoms tend to be less severe. Nevertheless, they may persist as a withdrawal syndrome for months after discontinuation of benzodiazepines. A prospective study by Vikander et al. (2010) identified four patterns of withdrawal symptoms over time: (1) a gradual decrease in symptom severity over 50 weeks, (2) an increase in the severity of symptoms at the beginning of dose tapering followed by a decrease in severity after tapering the dose off, (3) an increase

Table 10.1 Benzodiazepine withdrawal symptoms

Common	Less common	Rare
Anxiety	Muscle pain	Convulsions
Insomnia	Vomiting	Delirium
Dysphoria	Hyperacusis	Psychotic symptoms
Excitability	Photophobia	Delusions
Poor memory and concentration	Altered sensation	Hallucinations
Dizziness	Depersonalization	Mania
Gastrointestinal problems	Derealization	Depression
Palpitations		Suicidal ideation
Sweating		
Tremor		
Nausea		
Headache		

in the severity of symptoms 4 weeks after the cessation of benzodiazepine tapering, and (4) no change over 50 weeks.

10.2.2.3 Abuse

A clear distinction should be made between dependence and withdrawal from therapeutic or somewhat higher doses within the medical context and abuse of benzodiazepines in the context of recreational and illicit use (Lader 2014). Benzodiazepines are widely misused, although patterns vary from country to country and from region to region. One type takes the form of binges, say at weekends, another regular sustained high-dose usage. Some misusers keep to oral use, whereas others inject intravenously or sniff intranasally like with cocaine use. The abuse of benzodiazepines depends on their formulation, bioavailability and pharmacokinetics. Temazepam and flunitrazepam are known to be often misused. Although benzodiazepines may be misused alone, they may also be misused along with other drugs, for example, to potentiate the euphorigenic effects of opioids, lessen the impact following the effects of cocaine or interact in a complex way with amphetamines or other drugs of abuse. Drug abusers may turn to benzodiazepines if other drugs of abuse become scarce and expensive. The risks of benzodiazepine abuse such as viral infection or local tissue necrosis are well known and are associated with intravenous drug use. Overdose is a hazard, particularly in combination with other psychotropic drugs. Another danger is related to the potentiation of the depressant effects of alcohol by benzodiazepines. This has been associated with an increased likelihood of criminal acts, often accompanied by amnesia. The misuse of benzodiazepines is undoubtedly dangerous, and the potential for misuse should be a consideration when deciding to prescribe these drugs.

10.2.2.4 Mortality

Adverse effects of benzodiazepines are generally unpleasant but may not be severe; most adverse effects are reversible. However, recent data suggest that use of benzodiazepines may be associated with excess mortality (Charlson et al. 2009; Kripke et al. 2012). A systematic review has examined the risk of death associated with benzodiazepine use in studies published from 1990 onwards (Charlson et al. 2009). Data from six cohort and three registry studies indicate that regular users and illicit benzodiazepine users had a higher risk of mortality compared to non-users. A recent matched cohort study, based on electronic medical records and involving 10,529 people who received hypnotic agents (including both benzodiazepine and non-benzodiazepine hypnotics) and 23,676 controls with no hypnotic prescriptions, estimated the mortality risks, using proportional hazard regression models (Kripke et al. 2012). For patients prescribed 0.4–18, 18–132 and >132 pills/year, the hazard ratios were 3.60 (95 % CI 2.92, 4.44), 4.43 (3.67, 5.36) and 5.32 (4.50, 6.30), respectively. Thus, even occasional hypnotic users had over three times the

background risk of dying in 2.5 years. Selective prescription of hypnotics for ailing patients was ruled out as the main explanation. The presence of co-morbidities was associated with a significant increase in the risk of death among patients receiving hypnotics, but this accounted for only a small proportion of the excess risk.

10.2.2.5 Skin Reactions

Skin manifestations such as generalised reactions, contact dermatitis, photodermatitis and Stevens-Johnson syndrome are rarely associated with benzodiazepine treatment.

In April 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) issued a warning about tetrazepam, a benzodiazepine that has been used to treat painful muscle spasms (such as low-back pain and neck pain) and spasticity (excessive stiffness of muscles) in some European countries (European Medicines Agency 2013). The alert was prompted by the occurrence of life-threatening skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms syndrome), as described by the French National Agency for the Safety of Medicine and Health Products (Proy-Vega et al. 2014). After an assessment of available data on the risk of skin reactions, the PRAC concluded that tetrazepam is indeed associated with a low but increased risk of serious skin reactions compared to other benzodiazepines. The Coordination Group for Mutual Recognition and Decentralized Procedures of medicines for human use of the EMA agreed with the PRAC conclusion that the benefits of tetrazepam do not outweigh its risks, and on 29 May 2013, EMA adopted a final decision and suspended the marketing authorizations of tetrazepam across the European Union (EMA 2013). Proy-Vega et al. (2014) have recently commented on the clinical evidence leading to tetrazepam withdrawal, underlining the lack of randomised controlled clinical trials evaluating tetrazepam efficiency and safety. In their conclusion, they claim that 'it is very important to foster a strong interaction between pharmacovigilance agencies, scientific publications and health professionals, in order to improve and optimise exchange of knowledge on clinical cases of ADRs'.

In December 2013, the FDA released a warning that clobazam, a benzodiazepine medication approved as adjunctive therapy to treat seizures that accompany Lennox-Gastaut syndrome, may cause serious skin events, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP), and consequently approved changes to clobazam label and medication guide (FDA 2013a). The FDA identified 20 cases of severe skin reactions from its Adverse Event Reporting System database: all cases had resulted in hospitalisation, one case in blindness and one in death. These reactions can occur at any time during clobazam treatment, but the risk is greater during the first 8 weeks of treatment or when clobazam is stopped and then restarted. However, no comparative pharmacovigilance analysis was conducted for other anticonvulsant benzodiazepines, including clonazepam, clorazepate, diazepam and lorazepam.

10.3 Buspirone

Buspirone is an azapirone used in the treatment of generalised anxiety disorder. While the anxiolytic effects of benzodiazepines usually occur within a few days of therapy, buspirone requires chronic treatment for effectiveness (Chessick et al. 2006). Buspirone lacks the sedative, muscle relaxant and anticonvulsant properties of the benzodiazepines. The underlying mechanism of action of buspirone is not clear; however, it is thought that its anxiolytic effects are mediated through interactions with the serotonin $5HT_{1A}$ receptor, where it acts as a partial agonist (Loane and Politis 2012). The most common side effects of buspirone are dizziness, headache and light-headedness. Buspirone does not impair psychomotor performance or results in abuse, dependence or withdrawal. Like benzodiazepines, buspirone appears to be safe even when given in very high doses.

10.4 Pregabalin

Pregabalin is a pharmacological agent approved in many countries for the treatment of neuropathic pain, partial seizures and generalized anxiety disorder (Frampton 2014). Pregabalin is a structural analogue of GABA that neither interacts with GABA receptors nor alters GABA uptake or degradation. On the other hand, pregabalin binds to the $\alpha_2\delta$ (alpha-2-delta) subunit of the voltage-dependent calcium channel in the central nervous system so thus decreasing the release of neurotransmitters including glutamate and substance P. The most frequent adverse effects of pregabalin include dizziness, somnolence, dry mouth, peripheral oedema, blurred vision and weight gain (Zaccara et al. 2011).

Following its introduction, accumulating evidence from case reports, databases and a limited number of studies have suggested that pregabalin has the potential to cause abuse and dependence (Gahr et al. 2013). Schwan et al. (2010) analysed data from the Swedish national register of adverse drug reactions and concluded that pregabalin is likely to be associated with an abuse potential based on 16 positive reports. As a result, the prescribing information was changed and now states that cases of pregabalin abuse have been reported and patients with a previous history of psychotropic substance abuse should be monitored closely for signs of pregabalin abuse (Lyrica SPC). However, there is currently limited evidence on this topic. According to recent review articles (Baldwin et al. 2013; Frampton 2014; Schifano 2014), the potential for abuse of pregabalin is low, as its positive psychological effects are weak and not maintained over time. Moreover, unless stopped abruptly, pregabalin seems to carry a limited risk for physical dependence or withdrawal. In this respect, a recent study documented that gradual discontinuation of pregabalin after 4–24 weeks of treatment at a dose ranging from 150 to 600 mg/day was not associated with clinically significant withdrawal symptoms (Kasper et al. 2014).

Post-marketing surveillance studies are needed to identify risk factors for pregabalin abuse and dependence. The assessment of pregabalin's potential to cause addictive behaviours is also of particular clinical relevance as this agent is currently under evaluation for the treatment of benzodiazepine and alcohol dependence (Oulis and Konstantakopoulos 2012).

10.5 Non-benzodiazepine Hypnotics

Non-benzodiazepine hypnotics, the so-called Z-drugs, including zolpidem, zaleplon, zopiclone and eszopiclone, are a class of drugs structurally unrelated to benzodiazepines, but with a similar mechanism of action. These agents are agonists at the α_1 subunit of GABA-A receptors which mediate sedation. They have become preferred drugs for the treatment of insomnia, in particular among older adults, because of perceived improved safety profiles compared with traditional benzodiazepines. The most common adverse events of non-benzodiazepine hypnotics are drowsiness or fatigue, headache, nightmares and nausea or gastrointestinal disturbances. However, recent evidence in elderly patients over the age of 65 has highlighted potential safety concerns of these medications and zolpidem specifically with regard to effects on balance and memory and on fracture risk (Levy 2014).

On January 2013, the US FDA issued a warning recommending that the bedtime dose of zolpidem should be lowered based on new data showing that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Therefore, FDA required manufacturers of zolpidem products to lower the recommended initial dose for women from 10 to 5 mg for immediate-release products and from 12.5 to 6.25 mg for extended-release products (Food and Drug Administration 2013b). Driving simulation and laboratory studies had established a threshold of 50 ng/ml, above which zolpidem is associated with decreased alertness and increased risk of adverse events. A randomised, placebo-controlled trial has shown that a single 5 mg dose of zolpidem resulted in clinically significant balance and cognitive impairments upon awakening from sleep (Frey et al. 2011). In particular, 58 % of older adults (7/12) and 27 % of younger adults (3/11) tested had a loss of balance after taking zolpidem, whereas none of the same participants had a loss of balance during ten pre-sleep practice trials. A loss of balance after zolpidem use was marked and more common in older adults compared to placebo.

Early evidence of zolpidem-associated hip fracture in older adults (Wang et al. 2001) has recently been reinforced by findings from three studies (Finkle et al. 2011; Kang et al., 2012; Berry et al. 2013). In the first study (Finkle et al. 2011), zolpidem was found to have a similar risk of hip fractures compared with diazepam and lorazepam, but significantly lower compared with alprazolam. A second investigation found that fracture risk was significantly greater with zolpidem compared with traditional benzodiazepines (odds ratio [OR]: 1.72 vs. 1.00, respectively) (Kang et al. 2012). A sub-analysis of 135 patients aged 85 or older found an even more pronounced risk with zolpidem compared with benzodiazepines (OR: 4.48 vs. 1.13, respectively). A third

study utilised a nursing home population (Berry et al. 2013). Claims data were evaluated in residents who were prescribed zolpidem, eszopiclone or zaleplon during the 'hazard period' (within 30 days of a hip fracture) or during the 'control period' (60 days or longer before hip fracture). Residents who were prescribed a non-benzodiazepine during the hazard period were more likely to experience a hip fracture compared with residents prescribed a non-benzodiazepine during the control period (OR: 1.66).

Due to a lack of evidence on the optimal selection of zolpidem and other non-benzodiazepines in the elderly, it would be prudent to use these hypnotic agents sparingly and cautiously in older adults.

10.6 Conclusion

Benzodiazepines continue to be used in the management of patients with anxiety and insomnia. Based on cognitive and psychomotor impairment as well as abuse and dependence liability associated with benzodiazepines, clinicians must always balance the benefits and risks when prescribing these agents especially in the elderly. Other pharmacological agents used to treat anxiety disorders or insomnia, including pregabalin and non-benzodiazepine hypnotics, may share with benzodiazepines similar tolerability and safety issues. Pharmacovigilance surveillance studies can provide important information on specific adverse event features, patterns of clinical symptoms, severity of the events and, where applicable, fatality rates of various anxiolytics/sedative-hypnotics. Healthcare systems at the local, regional or national levels may wish to employ patient safety monitoring programmes for anxiolytics/sedative-hypnotics based upon pharmacovigilance studies.

References

Allard J, Artero S, Ritchie K (2003) Consumption of psychotropic medication in the elderly: a re-evaluation of its effect on cognitive performance. Int J Geriatr Psychiatry 18:874–878

Amieva H, Le Goff M, Millet X, Orgogozo JM, Peres K, Barberger-Gateau P, Jacqmin-Gadda H, Dartigues JF (2008) Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Ann Neurol 64:492–498

Ashton H (2005) The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry 18:249–255

Baldwin DS, Ajel K, Masdrakis VG, Nowak M, Rafiq R (2013) Pregabalin for the treatment of generalized anxiety disorder: an update. Neuropsychiatr Dis Treat 9:883–892

Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, Christmas DM, Davies S, Fineberg N, Lidbetter N, Malizia A, McCrone P, Nabarro D, O'Neill C, Scott J, van der Wee N, Wittchen HU (2014) Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol 28:403–439

Bandelow B, Sher L, Bunevicius R, Hollander E, Kasper S, Zohar J, Moller HJ, WFSBP Task Force on Mental Disorders in Primary Care, WFSBP Task Force on Anxiety Disorders, OCD and PTSD (2012) Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. Int J Psychiatry Clin Pract 16:77–84

Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352:1331–1336
Barbui C, Gastaldon C, Cipriani A (2013) Benzodiazepines and risk of dementia: true association or reverse causation? Epidemiol Psychiatry Sci 22:307–308
Barker MJ, Greenwood KM, Jackson M, Crowe SF (2004) Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs 18:37–48
Berry SD, Lee Y, Cai S, Dore DD (2013) Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents. JAMA Intern Med 173:754–761
Billioti de Gage S, Bégaud B, Bazin F, Verdoux H, Dartigues JF, Pérès K, Kurth T, Pariente A (2012) Benzodiazepine use and risk of dementia: prospective population based study. BMJ 345:e6231
Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, Pariente A, Bégaud B (2014) Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ 349:g5205
Boeuf-Cazou O, Bongue B, Ansiau D, Marquie JC, Lapeyre-Mestre M (2011) Impact of long-term benzodiazepine use on cognitive functioning in young adults: the VISAT cohort. Eur J Clin Pharmacol 67:1045–1052
Bond AJ (1998) Drug-induced behavioural disinhibition. Incidence, mechanisms and therapeutic implications. CNS Drugs 9:41–57
Bonnet MH, Arand DL (1999) The use of lorazepam TID for chronic insomnia. Int Clin Psychopharmacol 14:81–89
Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M (2009) A systematic review of research examining benzodiazepine-related mortality. Pharmacoepidemiol Drug Saf 18:93–103
Chessick CA, Allen MH, Thase M, Batista Miralha da Cunha AB, Kapczinski FF, de Lima MS, dos Santos Souza JJ (2006) Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev 3, CD006115
Chouinard G (2004) Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. J Clin Psychiatry 65(Suppl 5):7–12
Cumming RG, Le Couteur DG (2003) Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS Drugs 17:825–837
Curran HV, Bond A, O'Sullivan G, Bruce M, Marks I, Lelliot P, Shine P, Lader M (1994) Memory functions, alprazolam and exposure therapy: a controlled longitudinal trial of agoraphobia with panic disorder. Psychol Med 24:969–976
Curran HV, Collins R, Fletcher S, Kee SCY, Woods B, Iliffe S (2003) Older adults and withdrawal from benzodiazepine hypnotics in general practice: effects on cognitive function, sleep, mood and quality of life. Psychol Med 33:1223–1227
Daderman AM, Lidberg L (1999) Flunitrazepam (rohypnol) abuse in combination with alcohol causes premeditated, grievous violence in male juvenile offenders. J Am Acad Psychiatry Law 27:83–99
Dassanayake T, Michie P, Carter G, Jones A (2011) Effects of benzodiazepines, antidepressants and opioids on driving: a systematic review and meta-analysis of epidemiological and experimental evidence. Drug Saf 34:125–156
Dealberto MJ, McAvay GJ, Seeman T, Berkman L (1997) Psychotropic drug use and cognitive decline among older men and women. Int J Geriatr Psychiatry 12:567–574
European Medicine Agency (EMA). Recommendation to suspend tetrazepam-containing medicines endorsed by CMDh. EMA Drug Safety Communication (29 April 2013). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001777.jsp&mid=WC0b01ac058004d5c1. Accessed on 19 May 2015
Fastbom J, Forsell Y, Winblad B (1998) Benzodiazepines may have protective effects against Alzheimer disease. Alzheimer Dis Assoc Disord 12:14–17
Finkle WD, Der JS, Greenland S, Adams JL, Ridgeway G, Blaschke T, Wang Z, Dell RM, VanRiper KB (2011) Risk of fractures requiring hospitalization after an initial prescription for zolpidem, alprazolam, lorazepam, or diazepam in older adults. J Am Geriatr Soc 59:1883–1890
Food and Drug Administration (FDA) (2013a). FDA warns of serious skin reactions with the antiseizure drug Onfi (Clobazam) and has approved label changes. FDA Drug Safety Communication

(12 Dec 2013). Available from: http://www.fda.gov/Drugs/DrugSafety/ucm377204.htm. Accessed on: 19 May 2015
Food and Drug Administration (FDA) (2013b) Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem. FDA Drug Safety Communications (10 Jan 2013). Available from: http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm. Accessed on: 19 May 2015
Frampton JE (2014) Pregabalin: a review of its use in adults with generalized anxiety disorder. CNS Drugs 28:835–854
Frey DJ, Ortega JD, Wiseman C, Farley CT, Wright KP (2011) Influence of zolpidem and sleep inertia on balance and cognition during nighttime awakening: a randomized placebo-controlled trial. J Am Geriatr Soc 59:73–81
Gahr M, Freudenmann RW, Hiemke C, Kölle MA, Schönfeldt-Lecuona C (2013) Pregabalin abuse and dependence in Germany: results from a database query. Eur J Clin Pharmacol 2013:1335–1342
Gallacher J, Elwood P, Pickering J, Bayer A, Fish M, Ben-Shlomo Y (2012) Benzodiazepine use and risk of dementia: evidence from the Caerphilly Prospective Study (CaPS). J Epidemiol Community Health 66:869–873
Gorenstein C, Bernik MA, Pompeia S (1994) Differential acute psychomotor and cognitive effects of diazepam on longterm benzodiazepine users. Int Clin Psychopharmacol 9:145–153
Gould RL, Coulson MC, Patel N, Highton-Williamson E, Howard RJ (2014) Interventions for reducing benzodiazepine use in older people: meta-analysis of randomized controlled trials. Br J Psychiatry 204:98–107
Greenblatt DJ (2011) Psychotropic drug prescribing in the United States: extent, costs, and expenditures. J Clin Psychopharmacol 31:1–3
Gunja N (2013) The clinical & forensic toxicology of Z-drugs. J Med Toxicol 9:163–171
Hanlon JT, Horner RD, Schmader KE, Fillenbaum GG, Lewis IK, Wall WE Jr, Landerman LR, Pieper CF, Blazer DG, Cohen HJ (1998) Benzodiazepine use and cognitive function among community-dwelling elderly. Clin Pharmacol Ther 64:684–692
Hemmelgarn B, Suissa S, Huang A, Boivin JF, Pinard G (1997) Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA 278:27–31
Kang DY, Park S, Rhee CW, Kim YJ, Choi NK, Lee J, Park BJ (2012) Zolpidem use and risk of fracture in elderly insomnia patients. J Prev Med Public Health 45:219–226
Kasper S, Iglesias-García C, Schweizer E, Wilson J, DuBrava S, Prieto R, Pitman VW, Knapp L (2014) Pregabalin long-term treatment and assessment of discontinuation in patients with generalized anxiety disorder. Int J Neuropsychopharmacol 17:685–695
Kmietowicz Z (2014) Benzodiazepines may be linked to Alzheimer's disease, study finds. BMJ 349:g5555. doi:10.1136/bmj.g5555 (Published 10 September 2014)
Kripke DF, Langer RD, Kline LE (2012) Hypnotic association with mortality or cancer; a matched cohort study. BMJ Open 2, e000850
Lader M (1987) Long-term anxiolytic therapy: the issue of drug withdrawal. J Clin Psychiatry 48:12–16
Lader M (1998) Withdrawal reactions after stopping hypnotics in patients with insomnia. CNS Drugs 10:425–440
Lader M (2011) Benzodiazepines revisited—will we ever learn? Addiction 106:2086–2109. add_3563
Lader M (2014) Benzodiazepine harm: how can it be reduced? Br J Clin Pharmacol 77:295–301
Lagnaoui R, Begaud B, Moore N, Chaslerie A, Fourrier A, Letenneur L, Dartigues JF, Moride Y (2002) Benzodiazepine use and risk of dementia: a nested case-control study. J Clin Epidemiol 55:314–318
Lagnaoui R, Tournier M, Moride Y, Wolfson C, Ducruet T, Begaud B, Moore N (2009) The risk of cognitive impairment in older community-dwelling women after benzodiazepine use. Age Ageing 38:226–228
Leipzig RM, Cumming RG, Tinetti ME (1999) Drugs and falls in older people: a systematic review and meta-analysis. I: psychotropic drugs. J Am Geriatr Soc 47:30–39
Leung SY (2011) Benzodiazepines, opioids and driving: an overview of the experimental research. Drug Alcohol Rev 30:281–286

Levy HB (2014) Non-benzodiazepine hypnotics and older adults: what are we learning about zolpidem? Expert Rev Clin Pharmacol 7:5–8
Loane C, Politis M (2012) Buspirone: what is it all about? Brain Res 1461:111–118
Mancuso C, Tanzi MG, Gabay M (2004) Paradoxical reactions to benzodiazepines: literature review and treatment options. Pharmacotherapy 24:1177–1185
Maxwell HG, Dubois S, Weaver B, Bédard M (2010) The additive effects of alcohol and benzodiazepines on driving. Can J Public Health 101:353–357
O'Brien CP (2005) Benzodiazepine use, abuse, and dependence. J Clin Psychiatry 66(suppl 2):28–33
Orriols L, Philip P, Moore N, Castot A, Gadegbeku B, Delorme B, Mallaret M, Lagarde E (2011) Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. Clin Pharmacol Ther 89:595–601
Oulis P, Konstantakopoulos G (2012) Efficacy and safety of pregabalin in the treatment of alcohol and benzodiazepine dependence. Expert Opin Investig Drugs 21:1019–1029
Paquin AM, Zimmerman K, Rudolph L (2014) Risk versus risk: a review of benzodiazepine reduction in older adults. Exp Opin Drug Saf 13:919–934
Paterniti S, Dufouil C, Alperovitch A (2002) Long-term benzodiazepine use and cognitive decline in the elderly: the epidemiology of vascular aging study. J Clin Psychopharmacol 22: 285–293
Paton C (2002) Benzodiazepines and disinhibition: a review. Psychiatr Bull 26:460–462
Proy-Vega B, Aguirre C, de Groot P, Solis-Garcia del Pozo J, Jordan J (2014) On the clinical evidence leading to tetrazepam withdrawal. Exp Opin Drug Saf 13:705–712
Ray WA, Griffin MR, Downey W (1989) Benzodiazepines of long and short elimination half-life and risk of hip fracture. JAMA 262:3303–3307
Salzman C, Shader RI (2015) Benzodiazepine use and risk for Alzheimer disease. J Clin Psychopharmacol 35:1–3
Schifano F (2014) Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs 28:491–496
Schwan S, Sundström A, Stjernberg E, Hallberg E, Hallberg P (2010) A signal for an abuse liability for pregabalin–results from the Swedish spontaneous drug reaction reporting system. Eur J Clin Pharmacol 66:947–953
Smink BE, Egberts AC, Lusthof KJ, Uges DR, de Gier JJ (2010) The relationship between benzodiazepine use and traffic accidents: a systematic literature review. CNS Drugs 24:639–653
Verdoux H, Lagnaoui R, Begaud B (2005) Is benzodiazepine use a risk factor for cognitive decline and dementia? A literature review of epidemiological studies. Psychol Med 35:307–315
Vikander B, Koechling UM, Borg S, Tönne U, Hiltunen AJ (2010) Benzodiazepine tapering: a prospective study. Nord J Psychiatry 64:273–282
Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J (2001) Zolpidem use and hip fractures in older people. J Am Geriatr Soc 49:1685–1690
Woods JH, Katz JL, Winger G (1992) Benzodiazepine use, abuse and consequences. Pharmacol Rev 44:151–347
Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, Marra CA (2009) Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 169:1952–1960
Wu CS, Wang SC, Chang IS, Lin KM (2009) The association between dementia and long-term use of benzodiazepine in the elderly: nested case-control study using claims data. Am J Geriatr Psychiatry 17:614–620
Wu CS, Ting TT, Wang SC, Chang IS, Lin KM (2011) Effect of benzodiazepine discontinuation on dementia risk. Am J Geriatr Psychiatry 19:151–159
Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y (2014) Association between use of benzodiazepines and risk of fractures: a meta-analysis. Osteoporos Int 25:105–120
Zaccara G, Gangemi P, Perucca P, Specchio L (2011) The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. Epilepsia 52: 826–836

Chapter 11
Safety and Tolerability of Mood Stabilisers

Michele Fabrazzo and Alfonso Tortorella

Abstract Safety and tolerability of mood stabilisers are major clinical concerns when used in bipolar patients. Side effects of lithium and some antiepileptics have been reviewed in the context of a spontaneous reporting database over the last 10 years (FDA database and published reports). During pregnancy, antiepileptics show great concerns, and adverse events are all related to childbirth, whilst congenital abnormalities are not higher than previously estimated. Cutaneous adverse reactions are the most prevalent in children and adolescent. In adult lithium-treated patients, nephrotoxicity is still a major problem; the combination with carbamazepine and valproate can increase the risk of hypothyroidism. Hyperparathormonemia and hypercalcaemia are unrecognised and underappreciated adverse effects. Acute exacerbation of psoriasis is still a major problem, and the risk of skin reactions with eosinophilia and systemic symptoms is higher when mood stabilisers are used concomitantly; when associated with antipsychotics, the risk of pneumonia is possible (highest risk for olanzapine plus carbamazepine). A decrease in total body water and the decline of glomerular filtration rate represent the main lithium adverse effects in elderly patients. Long-term treatment is associated with impairment in immediate verbal learning and memory and creativity performance. Antiepileptics display significant adverse events (hyponatraemia, cardiac toxicity) and the risk of multiple drug-drug interactions is very high. Cumulative exposure to antipsychotics and mood stabilisers can be associated with vascular stiffness (elevated systolic blood pressure), hypertriglyceridaemia, insulin resistance and low HDL cholesterol. In light of the above considerations, clinicians should continuously and further assess risks and benefits of mood stabilisers when treating bipolar patients.

Keywords Mood stabilisers • Lithium • Safety • Tolerability • Bipolar disorder

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11.1 Introduction

Bipolar disorder (BD) is a dynamic illness that is amongst the top 30 causes of disability worldwide and is associated with a complex clinical picture characterised by dramatic changes in mood (typically manic/hypomanic episodes alternate with episodes of depression), energy, cognition and to multiple psychiatric/nonpsychiatric comorbidities (Strakowski et al. 2011). BD affects 3 % or more of the general population and ranks second only to unipolar depression as a cause of worldwide disability (Murray and Lopez 1997; Kupfer 2005).

In this chapter, we will review the various adverse side effects reported for lithium and some antiepileptic drugs (AEDs) indicated as mood stabilisers (sodium valproate, carbamazepine, oxcarbazepine and lamotrigine). The safety profile of lithium and individual AEDs will be considered in the context of a spontaneous reporting database over the last 10 years.

Taken in therapeutic doses, these drugs can cause a range of side effects that can be divided into five different groups: (1) common (greater than 10 %), (2) uncommon (between 1 and 10 %), (3) rare (between 0.1 and 1 %), (4) very rare (between 0.01 and 0.1 %) and (5) isolated reports (less than 0.01 %). Moreover, when assessing side effects of drugs, many variables can be considered, and the age of patients is one of the most important. We will therefore divide this chapter on the basis of the effects reported in different populations of patients.

11.2 Lithium Safety

Although they are rapidly outdated, all major evidence-based guidelines support the use of lithium as a first-line option for long-term maintenance treatment and prophylaxis of BD (Yatham et al. 2013; Pfennig et al. 2013; Goodwin 2009; Grunze et al. 2009). Lithium has been demonstrated to be a suitable first-line treatment in several clinical circumstances including acute manic/hypomanic episodes, relapse prevention, suicidal ideation and as an augmentation agent in the treatment of unipolar major depression (Fountoulakis et al. 2005; Baldessarini and Tondo 2008; Geddes et al. 2010).

Despite the fact that lithium is still considered the most important mood stabiliser, at least for maintaining long-term stability of BD patients (Müller-Oerlinghausen et al. 2002), it has also been described as the most underutilised treatment supported by solid evidence-based reports. The narrow therapeutic index necessitating regular monitoring of therapeutic concentrations (serum levels between 0.6 and 1.5 mEq/L) and concerns over a number of adverse effects are responsible for the underutilisation of lithium (Ferrier et al. 2006; McKnight et al. 2012). The most frequent adverse effects found in patients treated with lithium are (a) reduced urinary concentrating ability (polyuria, often accompanied by polydipsia) (Raja 2011), (b) hypothyroidism (Özerdem et al. 2014; Bauer et al. 2014) and

Table 11.1 Most common lithium adverse events reported to the FDA from 2004 to present

	Lithium N (%)
Therapeutic agent toxicity	601 (2.3 %)
Tremor	525 (2.01 %)
Drug interaction	477 (1.82 %)
Confusional state	337 (1.29 %)
Completed suicide	299 (1.14 %)
Drug ineffective	264 (1.01 %)
Acute renal failure	259 (0.99 %)
Neuroleptic malignant syndrome	253 (0.97 %)
Vomiting	241 (0.92 %)
Somnolence	240 (0.92 %)
Diarrhoea	222 (0.85 %)
Nausea	209 (0.8 %)
Depression	205 (0.78 %)
Mania	203 (0.78 %)
Drug toxicity	201 (0.77 %)
Agitation	195 (0.74 %)
Dysarthria	193 (0.74 %)
Suicide attempt	190 (0.73 %)
Fatigue	186 (0.71 %)
Dehydration	185 (0.71 %)

The percentage of each adverse event as a proportion of all adverse events is reported

hyperparathyroidism (Broome and Solorzano 2011), (c) weight gain (Torrent et al. 2008), (d) skin disorders (Jafferany 2008) and (e) risk of malformation and teratogenic effects (Dols et al. 2013; Galbally et al. 2010).

Given that lithium salts have been used therapeutically for almost 150 years and that John Cade reported highly successful results in ten manic patients who received the drug as early as 1949 (Cade 1949), it is not surprising that lithium features heavily in the majority of pharmacovigilance reports published in the past, when lithium was one of the few psychotropic drug available for the treatment of BD. Present reports, instead, are often the revival of data that was well established in the scientific literature of recent years. To update reports on lithium pharmacovigilance, we used the Food and Drug Administration (FDA) database, restricting our search from 2004 to 2014 (Table 11.1).

11.2.1 Pregnancy

Lithium has been assigned to pregnancy category D by the FDA. This category is assigned on the basis of prospective studies conducted in the 1990s (Jacobson et al. 1992). Despite these considerations, data regarding adverse effect of lithium treatment during pregnancy are controversial, in particular due to

conflicting findings regarding teratogenicity. In fact, some authors showed high incidences of teratogenic effects (Kallen and Tandberg 1983; Nora et al. 1974), even in the first reports carried out during the 1970s and the 1980s amongst newborn exposed to lithium, whereas this correlation was not reported in other studies (Schou et al. 1973).

The Registry of Lithium Babies was founded in 1968 in order to monitor the effects of lithium in infants who were prenatally exposed to the drug after several case reports of cardiovascular defects, in particular Ebstein's anomaly, amongst children born from mothers who were given lithium during the first trimester or throughout pregnancy (Weinstein and Goldfield 1975). In a retrospective study, including all the 225 cases of lithium babies of the registry, the same author reported 25 malformed infants (11.1 %). This rate consisted of 18 cardiovascular defects, 6 of which were Ebstein's anomaly (Weinstein 1980). In a second retrospective study, Källén and Tandberg (1983) reported 10.2 % neonatal deaths, 11.9 % malformations and 6.8 % heart defects in a group of 59 babies exposed to either lithium alone or in combination with other psychotropic drugs. As well as several retrospective studies showing the teratogenic effect of lithium, the two studies mentioned are based on voluntary reports and therefore associated with an overestimation of results due to the sample selection. These differences have become more marked through the years, mainly if we compare early reports with the more recent ones. Indeed, the top ten adverse events are all related to childbirth (premature, abortion, placental disorder, etc.), whilst congenital abnormalities are much rarer. Over the last few years, we have witnessed the complete reconsideration of the literature and the revision of the data published in the past.

In a meta-analysis by Yacobi and Ornoy (2008), the authors reviewed all the studies on teratogenic and embryotoxic effects associated with lithium treatment during pregnancy. In the conclusions, the authors stated that lithium therapy throughout pregnancy did not seem to increase the general rate of major anomalies and apparently added only a small risk of cardiovascular defects, notably Ebstein's anomaly. Similarly, a more recent meta-analysis concluded that the odds of lithium exposure in cases of Ebstein's anomaly were not significantly elevated (McKnight et al. 2012), even though the value of this assessment was limited by the small number of cases. Although the use of lithium in the first trimester of pregnancy should be avoided, it is fair to say that one cannot rule out completely the teratogenic potential of the drug and that the prevalence of this risk is not as high as previously estimated.

11.2.2 Children and Adolescents

Lithium is approved by FDA for the treatment of mania in children aged 12 years and above and is the first therapeutic option in the acute monotherapy for mania in this population. The early reports on paediatric lithium treatment were mainly based on adult studies (Prien et al. 1972), and for this reason, they had no specific

relevance to the topic. Even in later reports, the results were difficult to evaluate due to the small sample sizes or the methodological limitations.

More recently, a number of case reports, chart reviews and prospective studies have been published providing better insight into the tolerability of lithium treatment in young people. Unfortunately, the lack of definitive randomised controlled trials prevented an adequate assessment of the real efficacy and tolerability of lithium treatment in children and adolescents suffering from mania or mixed states.

For this reason, the FDA and the National Institute of Child Health and Human Development (NICHD) sponsored the Collaborative Lithium Trials (CoLT) to provide an evaluation of the acute and long-term effectiveness of lithium in paediatric bipolarity and characterise the short and long-term safety of lithium (Findling et al. 2008). The same authors have recently published a study evaluating lithium dose strategies and monitoring the potential treatment emergent adverse events (TEAEs) in 41 children and adolescents suffering from bipolar I disorder. The most commonly experienced TEAEs reported during the study were those repeatedly reported in adult patients (vomiting, upper abdominal pain, nausea, thirst, headache, dizziness). No patients experienced serious TEAEs (Findling et al. 2013).

11.2.3 Adults

11.2.3.1 Kidney

Lithium-induced nephrotoxicity is a form of chronic tubulointerstitial nephropathy known since lithium was introduced in the treatment of mood disorders and reported from the mid-1970s (Lindop and Padfield 1975). Renal complications associated with lithium treatment include (a) impairment of tubular function and urinary concentrating ability with polyuria and polydipsia and development of nephrogenic diabetes insipidus that may become irreversible in 15 % of patients after long-term lithium exposure and renal tubular acidosis, (b) chronic kidney disease secondary to tubulointerstitial nephritis and (c) infrequent and relatively mild renal insufficiency (Vestergaard and Schou 1981; Boton et al. 1987).

Early lithium reports established that lithium-induced nephropathy was usually characterised by tubulointerstitial nephritis with minimal glomerular involvement (Hansen 1981) and rare significant changes in glomerular filtration rate (GFR), even in presence of a long-term lithium usage (Jensen and Rickers 1984; DePaulo et al. 1986; Schou and Vestergaard 1988). More recently, several reports have clarified that a very high percentage of patients treated chronically with lithium have low GFR and that GFR monitoring is frequently neglected, with a risk of progression to end-stage renal disease (ESRD) (Bassilios et al. 2008; Janowsky et al. 2009). ESRD was considered an unlikely event in patients taking lithium, and only three case reports of lithium-induced ESRD were known in the world literature up to the early nineties (Von Knorring et al. 1990; Gitlin 1993). Since then, pharmacovigilance

reports have uncovered adverse events more accurately, and from 2004 to present, data recorded by FDA, despite small differences related to age and sex, detect rates around 0.1 % for the most severe adverse events such as renal impairment ($N=34$), acute renal failure ($N=132$), increased blood creatinine ($N=91$), renal failure ($N=60$) and haemodialysis ($N=68$).

The presence of renal damage induced by long-term lithium treatment in chronically treated patients was confirmed by Markowitz et al. (2000). Lithium-induced chronic renal disease is slowly progressive, and its rate of progression is related to the duration of lithium administration. Regular monitoring of estimated creatinine clearance is mandatory in long-term lithium-treated patients. A survey of lithium-induced ESRD conducted in France adds further information on this topic, demonstrating that lithium-related ESRD represents only 0.22 % of all causes of ESRD in France and that the rate of progression is related to the duration of lithium administration (Presne et al. 2003). Lepkifker et al. (2004) reported similar findings in a retrospective study showing that in long-term lithium therapy, dose reduction or discontinuation of lithium resulted in stabilisation of plasma creatinine levels and that about 20 % of long-term lithium developed renal insufficiency.

These results are slightly different from a large nationally representative sample, such as the Third National Health and Nutrition Examination Survey, estimating the prevalence and distribution of chronic kidney disease in the United States. The results of this survey show that the risk of ESRD, in lithium-treated patients, might be increased compared with healthy controls, but the absolute risk seems to be relatively low (0.53 % compared to 0.2 % of the general population) (Coresh et al. 2003). In contrast with these results, Bendz et al. (2010), reviewing the data of The Swedish Registry for Active Treatment of Uremia in two Swedish regions (2.7 million inhabitants), observed a substantially higher prevalence of lithium-induced ESRD in patients on renal replacement therapy.

McKnight et al. (2012), in a recent meta-analysis, clarified that GFR impairment secondary to lithium treatment is not clinically significant in most patients with a reduction ranging from 0 to 5 mL/min that represents only 5 % of the minimum normal GFR.

At the moment, two elements, strictly related, seem to be very important to prevent irreversible renal damage and glomerular failure in patients treated with lithium: the duration of lithium treatment and the age of treated patients (Bocchetta et al. 2013).

Pharmacovigilance reports emphasise that renal function must be carefully assessed in every patient starting lithium treatment. To minimise the risk of adverse events during treatment, assessment of renal function at least twice a year is mandatory. This assessment must provide (1) complete 24-h urine collection; (2) glomerular filtration rate either by 24-h creatinine clearance or estimated glomerular filtration rate; (3) in case of a chronic kidney disease, a nephrologist should be consulted before lithium treatment as long as the creatinine clearance is >40 mL/min and (4) the decision should be taken also on the basis of the patient's age and the duration of lithium treatment.

11.2.3.2 Thyroid Gland

Long-term treatment with lithium results in its accumulation in the thyroid with many effects on the physiology of the gland. The pathogenetic mechanism of lithium-induced hypothyroidism is manifold; lithium acts through five different mechanisms: (1) inhibition of thyroidal iodine uptake, (2) inhibition of iodotyrosine coupling, (3) changes of the thyroglobulin structure, (4) inhibition of thyroid hormone (thyroxine) secretion and (5) increase of TSH levels as a result of reduced availability of thyroxine (Berens et al. 1970; Burrow et al. 1971). Inhibition of thyroid hormone secretion associated with high rates of hypothyroidism and thyrotoxicosis is the result of these effects on the gland function (Bocchetta et al. 2001; Barclay et al. 1994).

Adverse events submitted to the FDA from 2004 to present have revealed 54 cases of hypothyroidism in adult patients treated with lithium and, although minor differences related to age and sex, rates are around 0.29 % of the total FDA reports.

Hypothyroidism is the most common thyroid disorder caused by lithium treatment. It is very difficult to evaluate its prevalence because records range from 3.3 to 35.4 %. Eight case-control studies reveal a prevalence of clinical and subclinical hypothyroidism of 9.2 % in patients treated with lithium compared with a prevalence in the general population comprised between 0.5 and 1 %. The risk of hypothyroidism increases about six times in patients taking lithium (OR = 5.78) (McKnight et al. 2012). The main risk factors for the onset of hypothyroidism in lithium-treated patients are female gender, age between 40 and 60 years, a personal or family history of thyroid disorders and the presence of autoantibodies (Malhi et al. 2012). The risk amongst women is greater than in men and in the general population and is related to the age of patients and the duration of treatment (Grandjean and Aubry 2009). However, it is important to stress that, irrespective of lithium treatment, patients with mood disorders show higher rates of thyroid abnormalities (hypothyroidism and hyperthyroidism) than the general population (Chakrabarti 2011).

Goitre is a clinical finding associated with lithium therapy, probably linked to the inhibition of thyroid hormone synthesis and release, determining an increase of TSH and a final thyroid enlargement. The prevalence of goitre is highly variable, ranging from 3.6 to 51 %. This variability is probably due to the presence of various geographic risk factors, specifically the reduced availability of iodine, the different duration of the exposure to lithium and different diagnostic methods (Kibirige et al. 2013). The presence of hypothyroidism or goitre is not a contraindication to lithium treatment; therefore, patients successfully treated should continue treatment, even in the presence of hypothyroidism, and compensate with a hormone replacement treatment.

Case reports of hyperthyroidism and thyrotoxicosis have been described in the literature since the 1970s (Rosser 1976). More recent studies clarified that it is a rare condition whose incidence is comparable to that of the general population (Vanderpump et al. 1995). Thyrotoxicosis occurs in the early stages of treatment and at a young age, especially in women.

11.2.3.3 Parathyroid Gland

Hyperparathormonemia and hypercalcaemia are unrecognised and underappreciated adverse effects of lithium treatment despite the evidence that in healthy volunteers a single dose of lithium (600 mg) is enough to induce a transient, and statistically significant, rise in the serum PTH (Seely et al. 1989) and a prevalence ranging from 6.3 to 50 % (Livingstone and Rampes 2006).

Health Canada has reviewed the available evidence and scientific literature concerning the association between lithium treatment and hypercalcaemia associated with hyperparathyroidism. Following this evaluation, Health Canada advised health professionals about the risk of hypercalcaemia/hyperparathyroidism associated with lithium treatment and the need of considering calcium and parathormone blood levels before starting lithium treatment and of repeating this evaluation every 6 months in order to reduce the risk of hypercalcaemia (www.healthycanadians.gc.ca).

Adverse events submitted to the FDA from 2004 to present have revealed 29 cases of hypothyroidism in adult patients treated with lithium, and, despite minor differences related to age and sex, rates are around 0.24 % of the total FDA reports (Table 11.1).

Saunders et al. (2009) reviewed the effect of lithium exposure on parathyroid cell function confirming that lithium causes hypercalcaemia and isolated hyperparathormonemia and the need of a screening of patients on chronic lithium therapy for hypercalcaemia. More recently, a meta-analysis identified 60 studies (14 case-control studies, 36 case reports, 6 cross-sectional studies) and a 10 % increase of calcium and parathormone (PTH) levels in patients treated with lithium. This adverse effect remains unrecognised by most psychiatrists with an underestimation of the long-term effects of hypercalcaemia and hyperparathyroidism (McKnight et al. 2012).

This evidence indicates that the assessment of serum calcium before and during lithium treatment is mandatory. Currently, only the clinical guideline of The International Society for Bipolar Disorders (ISBD) suggests this assessment before starting lithium treatment and, in the absence of clinical elements suggestive of impaired parathyroid function, a re-evaluation after 6 months and then annually (Pacchiarotti et al. 2013).

11.2.3.4 Skin

Potential skin changes associated with lithium treatment are generally limited, and the evidence supporting this association is restricted to descriptions of several case reports, retrospective studies and few case-control studies. There are only two recent randomised controlled trials comparing lithium with lamotrigine and placebo for 18 months. The combined analysis of the results of these two studies showed no significant difference in the prevalence of cutaneous adverse effects between patients given lithium and those given placebo (Goodwin et al. 2004). It is therefore

not clear whether lithium exposes them to a greater risk of developing cutaneous adverse effects in general. This statement is confirmed by the difficulty in assessing the real prevalence rates of this adverse effect. The few controlled studies on prevalence seem to suggest an increase of these adverse effects in patients treated with lithium, compared to the general population, ranging from 13.6 to 34 % in the study by Sarantidis et al. (1983) and from 25 to 45 % in the study by Chan et al. (2000).

The situation is slightly different for psoriasis since the presence of this skin disorder in lithium-treated patients is reported in several cases as de novo onset of psoriasis or as a marked worsening of a previously diagnosed disease (actually, reports are greater for acute exacerbation of a known disease).

There are only three case-control studies evaluating the prevalence of psoriasis in patients treated with lithium. The above-mentioned studies found a prevalence of 2.2 % in patients compared to 0 % in controls (Sarantidis and Waters 1983) and 6 % in patients compared to 0 % in controls (Chan et al. 2000). The third one is a large-scale epidemiological case-control study that found a small but significant increase in the risk of psoriasis in lithium-treated patients (Brauchli et al. 2009).

11.2.3.5 Weight Gain

The greater part of pharmacovigilance reports on lithium treatment-associated weight gain has been published in the 1970s and 1980s (Rockwell et al. 1983), and present reports are often the continuation of data well established in the scientific literature of recent years. Reports on adverse events submitted to the FDA from 2004 to present have revealed 93 cases of weight gain representing, despite minor differences related to age and sex, the 0.66 % of the total FDA reports.

11.2.3.6 Cognition

Bipolar patients display a persistent cognitive impairment in the different stages of the disease including euthymia. This impairment, evident in a range of neuropsychological tests including memory and executive functioning (Frangou et al. 2005), is present in unaffected first-degree relatives and is thought to be related to illness severity, specific neurodevelopmental features, medical co-morbidity and patient's lifestyle (Bourne et al. 2013).

Data in this area of research are highly controversial mainly due to the presence of numerous methodological problems which reduce their reliability. Lithium treatment is associated with mild impairment in psychomotor speed, verbal memory and psychomotor speed functioning without a clear positive effect on cognition (Pachet and Wisniewski 2003). In a recent study, Wingo et al. (2009) reviewed the results of 12 studies involving 276 lithium-treated bipolar patients. Long-term lithium treatment was associated with impairment in immediate verbal learning and memory and creative psychomotor performance with no evidence of cognitive improvements.

11.2.3.7 Elderly

Concerns about lithium adverse effects in older patients have led to both declining rates of lithium use and questions regarding the most useful approach to the use of lithium in this population.

Despite the lack of randomised placebo-controlled trials, it is assumed that lithium is as effective in the elderly as in the younger population for prophylaxis of affective disorders and for resistant unipolar depression (Bech 2006), but several concerns about neurotoxicity have led to questions about the effectiveness and safety of lithium in older bipolar patients.

The decrease in total body water and the decline of glomerular filtration rate are common amongst older persons, and in bipolar patients treated with lithium, this can result in a decrease in lithium clearance and increased serum level (Slater et al. 1984; Sproule et al. 2000). In a 2-year study of unipolar and bipolar out-patients (21–78 years) on long-term lithium treatment, Murray et al. (1983) found polydipsia/polyuria in 44 % of patients and hand tremor in 29 % of them. The prevalence and severity of the tremor tended to increase with age, but polydipsia/polyuria didn't. More recently, van Melick et al. (2013) evaluated 759 patients aged 40 or older and treated with lithium with at least 2 years follow-up in a retrospective study and assumed that age was not a determinant of serum lithium concentration instability and, above all, was not a reason not to initiate or to discontinue lithium therapy.

Lithium is a drug that continues to have a critical role in the treatment of bipolar disorder in the elderly. It becomes clear that, in the elderly more than in the young bipolar patients, lithium requires a careful evaluation in order to prevent adverse effects or toxicity. Lithium treatment in the elderly may be appropriate only after a clear evaluation of benefits and risks in each individual patient, and if the patient is monitored correctly, it is possible to avoid commonly reported adverse effects that can occur even at therapeutic dosages.

Guidelines for lithium concentrations in geriatric bipolar population are based on limited evidence, and a recent study recommends a low concentration range (0.5–0.6 mmol/L) for patients of 50 years and over (Wijeratne and Draper 2011).

11.3 Safety of Mood Stabilisers Other Than Lithium: Antiepileptic Drugs (AEDs)

In different studies, the proportion of patients with side effects from AED therapy ranged from less than 10 % to over 70 % depending on ascertainment methods, characteristics of the patients, AED dosage and duration of follow-up (Perucca et al. 2000).

The tolerability profiles of AEDs differ substantially from one drug to another, and it is not straightforward to establish which drug has the best one. However, the safety profile is often a determining factor in drug selection because efficacy rates shown by most AEDs are similar (Perucca and Meador 2005). Clinical trials have provided inconclusive information to evaluate the comparative risk-benefit ratio.

In addition, there is a lack of systematic pharmaco-epidemiological studies investigating adverse drug reactions (ADRs) to AEDs, which makes it difficult to accurately assess the incidence of anticonvulsant-related ADRs (Acharya et al. 2005; Wong and Lhatoo 2000). Moreover, clinical exposure to some of the newer drugs is still relatively limited, and experience shows that it may take many years for important adverse effects to be discovered, especially when they are rare (Perucca et al. 2000). We will therefore review the safety profile of individual AEDs in a spontaneous reporting database over the last 10 years with a particular attention to carbamazepine, oxcarbazepine, valproic acid and lamotrigine.

11.3.1 Pregnancy

A report by Tica et al. (2013) highlighted the possibility that phenobarbital (PH)/carbamazepine (CBZ) therapy during foetal organogenesis could induce sirenomelia by a synergistic teratogenic effect and supported the recommendation to use only one drug in pregnant epileptic or bipolar women. At birth, the newborn, delivered by an epileptic woman after 37 weeks of gestation, weighed 2.2 kg and presented with sirenomelia type II, with some of its "classic" features: oligohydramnios and absence of kidneys, bladder, rectum, uterus and a single umbilical artery. Some other "particularities" included the absence of Potter's face and no significant cardio-pulmonary abnormalities. The authors postulated that combined therapy with PH and CBZ (both strong enzyme inductors, especially PH) had potentiated their teratogenicity, by producing supplementary quantities of epoxides and/or other oxides, which accumulated in the foetal tissues who received in the first 4 months of pregnancy PH (0.1 g/day) and CBZ (0.4 g/day), followed only by PH 0.1 g/day, until delivery.

Another report presented an infant born with renal and cardiac malformations who developed a withdrawal syndrome and hyponatraemia following in utero exposure to oxcarbazepine. The infant was born at 35 weeks' gestation by urgent caesarean section to a mother in status epilepticus who had been treated with oxcarbazepine throughout her pregnancy. Evaluation for congenital anomalies identified mild aortic stenosis, a bicuspid aortic valve, patent foramen ovale, patent ductus arteriosus and severe left hydronephrosis due to left ureteropelvic junction stenosis. On the third day of life, the infant developed clinical signs of a withdrawal syndrome, which peaked on day 7 and resolved by day 12. Transient hyponatraemia resolved by day 8 of life. Follow-up showed normal development at 15 months (Rolnitsky et al. 2013).

The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs was studied in a prospective cohort of women with epilepsy and a control group of women without epilepsy. The children of this cohort were followed longitudinally until 6 years of age ($N=415$), and the analysis revealed an increase in risk for children exposed to monotherapy sodium valproate and in those exposed to polytherapy with sodium valproate compared to control children (4/214;

1.87 %). Autistic spectrum disorder was the most frequent diagnosis. No significant increase was found amongst children exposed to carbamazepine (1/50) or lamotrigine (2/30) (Bromley et al. 2013).

Valproate is associated with polycystic ovary syndrome as well as congenital malformations and developmental delays of infants who were prenatally exposed. In a study by Wisner et al. (2011), using New York State Medicaid Claims for Persons with Psychiatric Disorders, the authors concluded that over 20 % of childbearing-aged women receiving mood stabilisers were treated with valproate.

In women, according to FDA-reported side effects, the use of valproic acid during pregnancy led to spontaneous abortion in a different percentage, depending on the age of patients (0.1 %, 0.02 % and 0.04 %, respectively, for women's age of 10–19, 20–29 and 30–39 years). Intrauterine deaths were reported, instead, only in few cases (0.03 %). Carbamazepine and oxcarbazepine use during pregnancy was associated to spontaneous abortion only in 0.12 % and 0.16 %, respectively, of all treated patients. Lamotrigine, on the other hand, was reported to FDA to induce spontaneous abortion in 0.5 % of cases, with a peak of 0.12 % in women ageing from 20 to 29 years.

11.3.2 Children and Adolescents

Cutaneous adverse drug reactions (CADRs) are the most prevalent ADRs in hospitalised children, with an estimated rate of 2–3 % (Ross et al. 2007). An analysis of reports from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) included 326 CADR cases of which 214 (65.6 %) were severe and 112 (34.4 %) non-severe. Overall, carbamazepine ($N = 17$, 4.9 %) and lamotrigine ($N = 13$, 3.7 %) accounted for almost 9 % of all suspected medications (Castro-Pastrana et al. 2011).

A case-control study of severe cutaneous drug reactions (SCDR) with carbamazepine was reported by Chong et al. (2014). In recruited patients, HLA-B*1502 positivity increased the odds of carbamazepine-induced SCDR in children of Chinese and Malay ethnicity and they occurred within 2 weeks and at low doses. Stevens-Johnson Syndrome (SJS), on the other hand, was induced by oxcarbazepine, and HLA genotyping showed a HLA-B15 variant in this patient (HLA-B*1518/B*4001) (Lin et al. 2009). A 4-year-old girl with a life-threatening clinical course of drug rash with eosinophilia and systemic symptoms syndrome (DRESS) with massive pulmonary involvement was also reported by Irga et al. (2013).

The use of combined antiepileptic drugs can cause toxicity by affecting the clearance of the drugs, especially in children. A case with SJS triggered by the combination of clobazam, lamotrigine and valproic acid treatment was reported in a 4-year-old boy admitted to the hospital with a 3-day history of fever, oral mucosa ulcerations and skin lesions. The patient had been under the treatment of valproic acid (900 mg/day) for 3 years with the diagnosis of epilepsy. Because of the poor control of the seizures, lamotrigine (75 mg/day) had been added to the treatment 1 month before and clobazam (20 mg/day) 10 days before. Weintraub et al. (2005)

reported that valproic acid decreased lamotrigine clearance by approximately 60 % in a study with 570 patients. It has been reported that valproic acid may interfere with the metabolism of lamotrigine by inhibiting glucuronides, leading to increased blood levels of the drug, or resulting in accumulation of toxic metabolites of the drug. New AEDs (clobazam, etc.) are reported not to affect the clearance of lamotrigine significantly, but the skin lesions of SJS in the above patient appeared when clobazam was added to valproic acid and lamotrigine treatment. Therefore, it could be concluded that clobazam can affect the clearance of combined drugs. Adverse reactions have been reported in children co-treated with lamotrigine and valproate (Kocak et al. 2007; Levi et al. 2009). Sixty-three cases of interaction between lamotrigine and other drugs have been reported to FDA from 2004 to present.

In 2011, the US FDA informed the public that children born to mothers who take the anti-seizure medication sodium valproate or related products (valproic acid and divalproex sodium) during pregnancy have an increased risk of lower cognitive test scores than children exposed to other anti-seizure medications during pregnancy. This conclusion was based on the results of epidemiologic studies. The largest of these studies is a prospective cohort study conducted in the United States and United Kingdom (Meador et al. 2009). They found that children with prenatal exposure to valproate throughout pregnancy had lower Differential Ability Scale (DAS) scores at age 3 than children with prenatal exposure to the other evaluated antiepileptic drug monotherapy treatments: lamotrigine, carbamazepine and phenytoin. Although all of the available studies have methodological limitations, the weight of the evidence supports the conclusion that valproate exposure in utero causes subsequent adverse effects on cognitive development in offspring (Gaily et al. 2004; Adab et al. 2004).

The FDA reported that for AEDs, the most common side effects in children and adolescents (0–19 years of age) were represented by the following:

- Convulsions, exposure during pregnancy, foetal anticonvulsant syndrome, dysmorphism for valproic acid
- Atrial septal defect, aggressive behaviour, psychomotor hyperactivity, convulsions, pyrexia and rashes for lamotrigine
- Hypertelorism of orbit, micrognathia, drug rashes with eosinophilia and systemic symptoms, pyrexia, convulsions for carbamazepine

11.3.3 Adults

In a recent review, Dols et al. (2013) described the prevalence of neurological, gastrointestinal, metabolic, thyroid, dermatological, nephrogenic, cognitive, sexual, haematological, hepatogenic and teratogenic side effects of lithium, valproate, carbamazepine and lamotrigine and discussed their clinical management. The most common side effects reported to the FDA since 2004 are listed in Table 11.2.

Table 11.2 Most common carbamazepine, valproate and lamotrigine adverse events reported to the FDA from 2004 to present

	Carbamazepine	Valproate	Lamotrigine
Convulsions	642 (2.15 %)	455 (2.7 %)	993 (2.87 %)
Drug exposure during pregnancy	315 (1.06 %)	226 (1.34 %)	778 (2.25 %)
Rash	236 (0.79 %)	55 (0.33 %)	501 (1.45 %)
Completed suicide	304 (1.02 %)	–	480 (1.39 %)
Drug toxicity	234 (0.78 %)	87 (0.52 %)	466 (1.35 %)
Drug interaction	417 (1.4 %)	395 (2.34 %)	384 (1.11 %)
Pyrexia	397 (1.33 %)	163 (0.97 %)	373 (1.08 %)
Dizziness	223 (0.75 %)	65 (0.39 %)	311 (0.9 %)
Somnolence	288 (0.97 %)	195 (1.16 %)	278 (0.8 %)
Vomiting	221 (0.74 %)	133 (0.79 %)	270 (0.78 %)
Maternal drugs affecting foetus	98 (0.33 %)	46 (0.27 %)	257 (0.74 %)
Stevens-Johnson syndrome	221 (0.74 %)	56 (0.33 %)	230 (0.66 %)
Spontaneous abortion	–	58 (0.34 %)	179 (0.52 %)
Agitation	81 (0.27 %)	79 (0.47 %)	177 (0.51 %)
Confusional state	178 (0.6 %)	131 (0.78 %)	159 (0.46 %)
White blood cell count increased	–	43 (0.25 %)	128 (0.37 %)
Premature baby	–	–	74 (0.21 %)
Thrombocytopenia	80 (0.27 %)	127 (0.75 %)	–

For each event, the number of involved patients is indicated along with the percentage of the adverse events as a proportion of all reactions reported for the drug

Moreover, Gau et al. (2010) indicated that lithium, carbamazepine and valproate may dose dependently increase the risk of hypothyroidism with the increasing number of mood stabilisers used (the risk of hypothyroidism was more prominent when the combination included lithium and valproate).

The study by Gau et al. (2008) investigated the association between two mood stabilisers (carbamazepine and valproate) and other medications (including other anticonvulsants) and the risks of erythema multiforme (EM), SJS and toxic epidermal necrolysis (TEN) amongst patients with BD. Results showed that carbamazepine and valproate use significantly predicted EM, SJS or TEN. Other significant predictors for EM, SJS or TEN included other anticonvulsants (phenytoin, phenobarbital and lamotrigine). The most predictive exposures were carbamazepine, valproate, other anticonvulsants and acetaminophen. They also found that the combination of carbamazepine and acetaminophen further increased the risk for the occurrence of EM, SJS or TEN and that no interaction effect of age and sex was evident.

Matsuda et al. (2013) reported a case of drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) due to carbamazepine and associated with maculopapular eruptions and systemic skeletal muscle involvement. Sharma et al. (2013), on the other hand, reported the case of a patient with seizure who developed SJS and neuroleptic malignant syndrome (NMS) following administration of carbamazepine.

Hydzik et al. (2011) published the case of acute poisoning with carbamazepine and quetiapine, which resulted in cardiotoxic effects in the form of arrhythmias and conduction disorders of the heart. These symptoms disappeared spontaneously after resolution of the poisoning.

He et al. (2012) reported that the incidence of oxcarbazepine (OXC)-induced cutaneous drug reactions (cADRs) was low, and no severe reactions occurred although they observed that patients with a history of allergy were more susceptible to OXC-cADRs. Moreover, they did not find a significant association between HLA-B*1502 and OXC-maculopapular eruptions.

In a nationwide cohort of bipolar patients, Yang et al. (2013) highlighted that some drug combinations were associated with a dose-dependent increase in the risk of pneumonia. In particular, olanzapine plus carbamazepine had the highest risk, followed by clozapine and valproic acid, but lithium had a dose-dependent protective effect.

The use and safety profile of antiepileptic drugs in Italy was evaluated only for those associated with at least 30 reports by Iorio et al. (2007). Skin reactions were the most frequently reported ADRs, followed by haematological, general condition, hepatic and neurological and gastrointestinal adverse reactions. Lamotrigine and carbamazepine had the highest percentage of skin reactions (67 % and 60 %, respectively). Many haematological reactions were reported for each AED, but the highest percentage was related to valproic acid (25 %) which was associated also to the highest percentage of hepatic reactions (20 %).

SJS associated with single high dose of lamotrigine was reported in a 23-year-old female patient with idiopathic epilepsy and previously taking carbamazepine, valproic acid and lamotrigine until 1 week prior to referral. Following consultations with a range of clinicians, the patient was diagnosed with SJS related to lamotrigine based on her history and physical findings and on consideration of current consensus definitions of this condition (Kocak et al. 2007).

In addition, SJS after lamotrigine treatment was also reported in a 24-year-old man on lamotrigine (25 mg every other day for the first 2 weeks with the dose increased to 25 mg/day for the subsequent 2 weeks) for tonic-clonic seizures not adequately controlled with valproate (600 mg/day). The patient had been receiving valproate for 3 years without any other medications, whilst in the fourth week of titration therapy, he mistakenly took lamotrigine 200 mg at one time rather than 25 mg. A few hours later, high-grade fever (40 °C) and painful oral ulcerations involving much of the oropharynx developed (Famularo et al. 2005). Bicknell et al. (2012) reported a case of drug reaction with eosinophilia and systemic symptoms apparently precipitated by the associated use of lamotrigine and cyclobenzaprine.

Side effects are also related to non-adherence, but at a low level (Baldessarini et al. 2008; Jonsdottir et al. 2012). More than one-half of BD patients either discontinue pharmacotherapy or use it irregularly. Although rates of non-adherence do not necessarily differ between mood-stabilising medications, the predictors for non-adherence do. Moreover, adherence to one medication does not guarantee adherence to another, nor does adherence at one time-point ensure later adherence. Attitudes towards treatment affect adherence to medications as well as psychosocial

treatments and should be repeatedly monitored (Arvilommi et al. 2014). Some side effects have more impact on adherence than others, and in order of importance, weight gain, cognitive impairment and severity of depressive symptoms (as an outcome of medication) were most associated with non-adherence to medication (Johnson et al. 2007). Experts reported that sedative side effects of medications also contributed to non-adherence (Velligan et al. 2010).

Somnolence, sedation, fatigue, pyrexia and drug rashes were all reported to the FDA for carbamazepine (age ranging from 20 to 59 years); convulsions, vomiting, decreased platelet count, breast abscesses and rashes were those reported for lamotrigine whilst pyrexia, somnolence, drug interactions, thrombocytopenia and tremor for valproic acid.

11.3.4 Elderly

Descriptions of geriatric patients with BD tend to include an overview of cognitive impairment. However, the literature regarding cognitive test performance in this population is very limited.

Cognitive impairment in elderly (defined by the commonly accepted criterion of age ≥60 years) bipolar patients persists during euthymic state. At the moment, the aetiology of cognitive impairment is not well understood, although it has been associated with lithium and other mood stabilisers. The dosage of medications has been reported to influence the cognition of treated patients significantly, especially when affected by cardiovascular co-morbidities (Schouws et al. 2010). Other studies, on the other hand, have found no association between exposure to mood stabilisers (lamotrigine, valproate, lithium, carbamazepine all used at clinical therapeutic dosage) and any clinical or cognitive variables in the elderly (Martino et al. 2008).

The use of AEDs (mainly, valproic acid, carbamazepine and oxcarbazepine) in the management of behavioural and psychological symptoms in Alzheimer's disease and related dementias (ADRD) was reported by Dutcher et al. (2014) in a study where these medications were used in 3 % ($N=571$) of the all dementia patients. They observed a functional decline in activity of daily living (ADL) scores and a negative effect on cognition over time in most patients. In particular, female users of mood stabilisers declined most quickly, followed by male non-users, female non-users and male users thus suggesting a faster ADL decline in women but not in men when these drugs were used.

The treatment of behavioural and psychological symptoms in patients with dementia has included several different mood stabilisers. Amongst these medications, only carbamazepine demonstrated its efficacy in behavioural and psychological symptoms of dementia (BPSD) in controlled studies (Olin et al. 2001), but significant adverse events were reported (sedation, hyponatraemia, cardiac toxicity), and multiple drug-drug interactions occurred probably because this drug is a strong enzymatic inducer. Valproic acid showed some interesting results

in BPSD within a large number of open studies and case reports. However, amongst the five controlled studies that have been published (Pinheiro 2008), none confirmed its efficacy on these symptoms. Regarding its tolerability in the geriatric population, no notable major side effect was reported (haematologic and hepatic effects were not more frequent than in the general population), except for a possible over-sedation. Moreover, it appears that valproic acid could have neuroprotective effects, even if the contrary has also been observed. More studies need to be (and are being) conducted, notably on the potentially prophylactic effect of valproic acid in BPSD. Lamotrigine, which may potentially induce severe cutaneous side effects when administered with valproic acid, has shown its efficacy in BD, and two recent case reports seem to indicate some clinical relevance to BPSD. Oxcarbazepine, theoretically, could be an alternative to carbamazepine, which is, as previously mentioned, the only anticonvulsant proved to be of clinical benefit in BPSD. However, no clinical study has been published so far to support this hypothesis. This drug, although inducing severe and more frequent hyponatraemia than carbamazepine, is better tolerated than carbamazepine. Polypharmacotherapy and concomitant psychotropic drugs are also reported as risk factors for falls in long-term care setting for elderly patients (Baranzini et al. 2009; Landi et al. 2005).

Carbamazepine use was also associated with a nearly tenfold increase in severe cutaneous drug reactions in Korean elderly patients (Kim et al. 2013). This association was consistently high with SCARs in patients who received carbamazepine for neuropathic pain. On the other hand, other studies reported that elderly patients had a lower incidence of reported allergic skin reactions with mood-stabilising anticonvulsants (carbamazepine, lamotrigine and valproic acid), and the risk for other ADRs decreases significantly with age, in particular extrapyramidal motor system (EPMS) symptoms, galactorrhoea, weight gain and increased liver enzymes. In contrast, the risk of developing delirium increased with age, and the risk of developing oedema showed a corresponding trend (Greil et al. 2013).

Koda et al. (2012) reported the case of a 68-year-old woman with Alzheimer's disease developing renal dysfunction after starting carbamazepine for epilepsy: the autopsy found an acute tubulointerstitial nephritis with multiple organ involvement, including fatal adrenalitis.

Carbamazepine may have negative chronotropic and dromotropic effects on the cardiac conduction system (Ide and Kamijo 2007). Koutsampasopoulos et al. (2014) reported the case of an 82-year-old woman who was admitted in the hospital following a syncopal episode at home and that developed a cardiac syncope due to atrial tachycardia combined with complete atrioventricular block as a consequence of carbamazepine administration for trigeminal neuralgia.

Mood disorders substantially increase the risk of cardiovascular diseases, though the mechanisms are unclear. Chronicity of mood symptoms contribute to vasculopathy in a dose-dependent fashion. Fiedorowicz et al. (2012) reported that patients with more manic/hypomanic symptoms had poorer vascular endothelial function. Moreover, antipsychotic/mood stabiliser and antidepressant exposure were not

associated with flow-mediated dilation (FMD) or nitroglycerin-mediated vasodilation. Cumulative exposure to antipsychotics and mood stabilisers (in particular, valproic acid derivatives, lithium, carbamazepine and lamotrigine) was instead associated with vascular stiffness as shown by elevated aortic systolic augmentation pressure and total aortic systolic blood pressure. Valproic acid derivative exposure was also associated with hypertriglyceridaemia, insulin resistance and low HDL cholesterol.

The adverse events most commonly reported to the FDA for carbamazepine, from 2004 to present, were mainly those induced by drug interactions, hyponatraemia and pyrexia in patients older than 60 years lamotrigine induced decreased haemoglobin level, convulsions and myelodysplastic syndrome more frequently, whilst valproic acid was associated with confusional state, convulsions and drug interactions.

11.4 Conclusions

Several combinations of mood stabilisers appear to be safe and effective. Unfortunately, there is a conspicuous lack of data from randomised controlled trials regarding mood stabiliser combinations despite their widespread use, and only limited data from open-label studies are available for many such combinations. Combination therapy introduces considerations such as drug interactions and additional side effects. The interactions of combinations of mood stabilisers are sometimes complex, often very useful and potentially dangerous.

As discussed previously, combination therapy may also decrease compliance. One general rule that may reduce the risks of toxic drug interactions is to add medication to the patient's current regimen in modest doses and increase the dose slowly. This strategy of using low doses is particularly relevant for the elderly bipolar patients.

Currently, the most useful mood stabiliser combinations are the mixtures of anticonvulsants and lithium, particularly valproate plus lithium. Carbamazepine, lamotrigine and gabapentin have also been added to lithium and appear to be well tolerated. Moreover, combinations of anticonvulsants have been used successfully, although pharmacokinetic interactions may complicate this strategy, particularly when valproate and carbamazepine or valproate and lamotrigine combinations are used. Combinations of lithium or anticonvulsant mood stabilisers with standard or atypical antipsychotic agents and benzodiazepines have also been used relatively successfully. In particular, several second-generation antipsychotics have been approved for the management of BD (olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, asenapine, paliperidone).

Future research should clarify the mechanisms of action of the most widely used/ mood stabilisers as these are currently not well understood. This will give clinicians the possibility of using combinations of different mood stabilisers more rationally and improve clinical outcomes in treated patients.

References

Acharya NV, Pickering RM, Wilton LW et al (2005) The safety and effectiveness of newer antiepileptics: a comparative postmarketing cohort study. J Clin Pharmacol 45:385–393

Adab N, Kini U, Vinten J et al (2004) The longer-term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 75:1575–1583

Arvilommi P, Suominen K, Mantere O et al (2014) Predictors of adherence to psychopharmacological and psychosocial treatment in bipolar I or II disorders – an 18-month prospective study. J Affect Disord 155:110–117

Baldessarini RJ, Tondo L (2008) Lithium and suicidal risk. Bipolar Disord 10:114–115

Baldessarini RJ, Perry R, Pike J (2008) Factors associated with treatment non-adherence among US bipolar disorder patients. Hum Psychopharmacol Clin Exp 23:95–105

Baranzini F, Poloni N, Diurni M et al (2009) Polypharmacy and psychotropic drugs as risk factors for falls in long-term care setting for elderly patients in Lombardy. Recenti Prog Med 100:9–16

Barclay ML, Brownlie BE, Turner JG et al (1994) Lithium associated thyrotoxicosis: a report of 14 cases, with statistical analysis of incidence. Clin Endocrinol 40:759–764

Bassilios N, Martel P, Godard V et al (2008) Monitoring of glomerular filtration rate in lithium-treated outpatients—an ambulatory laboratory database surveillance. Nephrol Dial Transplant 23:562–565

Bauer M, Glenn T, Pilhatsch M et al (2014) Gender differences in thyroid system function: relevance to bipolar disorder and its treatment. Bipolar Disord 16(1):58–71

Bech P (2006) The full story of lithium (1918–2005). A tribute to Mogens Schou. Psychother Psychosom 75:265–269

Bendz H, Schön S, Attman PO et al (2010) Renal failure occurs in chronic lithium treatment but is uncommon. Kidney Int 77(3):219–224, Epub 2009 Nov 25

Berens SC, Wolff J, Murphy DL (1970) Lithium concentration by the thyroid. Endocrinology 87(5):1085–1087

Bicknell LT, Sanches M, Schatte DJ (2012) Erythema multiforme vs. DRESS syndrome associated with the combined use of lamotrigine and cyclobenzaprine: a case report. Int J Psychiatry Med 44(4):305–314

Bocchetta A, Mossa P, Velluzzi F et al (2001) Ten-year follow-up of thyroid function in lithium patients. J Clin Psychopharmacol 21:594–598

Bocchetta A, Ardau R, Carta P et al (2013) Duration of lithium treatment is a risk factor for reduced glomerular function: a cross-sectional study. BMC Med 11:33

Boton R, Gaviria M, Batlle DC (1987) Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium therapy. Am J Kidney Dis 10(5):329–345

Bourne C, Aydemir O, Balanza-Martinez V et al (2013) Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatr Scand 128(3):149–162

Brauchli YB, Jick SS, Curtin F et al (2009) Lithium, antipsychotics, and risk of psoriasis. J Clin Psychopharmacol 29(2):134–140. doi:10.1097/JCP.0b013e31819a4b7c

Bromley RL, Mawer GE, Briggs M et al (2013) The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. J Neurol Neurosurg Psychiatry 84(6):637–643

Broome JT, Solorzano CC (2011) Lithium use and primary hyperparathyroidism. Endocrinology 17(Suppl 1):31–35

Burrow GN, Burke WR, Himmelhoch JM et al (1971) Effect of lithium on thyroid function. J Clin Endocrinol Metab 32(5):647–652

Cade JF (1949) Lithium salts in the treatment of psychotic excitement. Med J Aust 2(10):349–352

Castro-Pastrana LI, Ghannadan R, Rieder MJ et al (2011) Cutaneous adverse drug reactions in children: an analysis of reports from the Canadian pharmacogenomics network for drug safety (CPNDS). J Popul Ther Clin Pharmacol 18(1):e106–e120

Chakrabarti S (2011) Thyroid functions and bipolar affective disorder. J Thyroid Res 2011:306–367
Chan HL, Wing Y, Su R et al (2000) A control study of the cutaneous side effects of chronic lithium therapy. J Affect Disord 57:107–113
Chong KW, Chan DW, Cheung YB et al (2014) Association of carbamazepine-induced severe cutaneous drug reactions and HLA-B*1502 allele status, and dose and treatment duration in paediatric neurology patients in Singapore. Arch Dis Child 99(6):581–584
Coresh J, Astor BC, Greene T et al (2003) Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 41:1–12
De Paulo J, Correa E, Sapir D (1986) Renal function and lithium: a longitudinal study. Am J Psychiatry 143:892–895
Dols A, Sienaert P, van Gerven H et al (2013) The prevalence and management of side effects of lithium and anticonvulsants as mood stabilizers in bipolar disorder from a clinical perspective: a review. Int Clin Psychopharmacol 28(6):287–296
Dutcher SK, Rattinger GB, Langenberg P et al (2014) Effect of medications on physical function and cognition in nursing home residents with dementia. J Am Geriatr Soc 62(6):1046–1055
Famularo G, De Simone C, Minisola G (2005) Stevens-Johnson syndrome associated with single high dose of lamotrigine in a patient taking valproate. Dermatol Online J 11(1):25
Ferrier N, Ferrier LJ, Macritchie KA (2006) Lithium therapy. Adv Psychiatry Treat 12:256–264
Fiedorowicz JG, Coryell WH, Rice JP et al (2012) Vasculopathy related to manic/hypomanic symptom burden and first generation antipsychotics in a sub-sample from the Collaborative Depression Study (CDS). Psychother Psychosom 81(4):235–243
Findling RL, Frazier JA, Kafantaris V et al (2008) The Collaborative Lithium Trials (CoLT): specific aims, methods, and implementation. Child Adolesc Psychiatry Ment Health 2(1):21
Findling RL, Kafantaris V, Pavuluri M et al (2013) Post-acute effectiveness of lithium in pediatric bipolar I disorder. Child Adolesc Psychopharmacol 23(2):80–90
Fountoulakis KN, Vieta E, Sanchez-Moreno J et al (2005) Treatment guidelines for bipolar disorder: a critical review. J Affect Disord 86(1):1–10
Frangou S, Donaldson S, Hadjulis M et al (2005) The Maudsley bipolar disorder project: executive dysfunction in bipolar disorder I and its clinical correlates. Biol Psychiatry 58:859–864
Gaily E, Kantola-Sorsa E, Hiilesmaa V et al (2004) Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 62:28–32
Galbally M, Roberts M, Buist A (2010) Perinatal psychotropic review group. Mood stabilizers in pregnancy: a systematic review. Aust N Z J Psychiatry 44(11):967–977. doi:10.3109/00048674.2010.506637
Gau SS, Chao PF, Lin YJ et al (2008) The association between carbamazepine and valproate and adverse cutaneous drug reactions in patients with bipolar disorder: a nested matched case-control study. J Clin Psychopharmacol 28(5):509–517
Gau CS, Chang CJ, Tsai FJ et al (2010) Association between mood stabilizers and hypothyroidism in patients with bipolar disorders: a nested, matched case-control study. Bipolar Disord 12(3):253–263. doi:10.1111/j.1399-5618.2010.00814.x
Geddes JR, Goodwin GM, Rendell J et al (2010) Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 375:385–395
Gitlin MJ (1993) Lithium-induced renal insufficiency. J Clin Psychopharmacol 13:276–279
Goodwin GM (2009) Evidence-based guidelines for treating bipolar disorder: revised second edition – recommendations from the British Association for Psychopharmacology. J Psychopharmacol 23(4):346–388
Goodwin GM, Bowden CL, Calabrese JR et al (2004) A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 65:432–441

Grandjean EM, Aubry JM (2009) Lithium: updated human knowledge using an evidence-based approach: part III: clinical safety. CNS Drugs 23:397–418
Greil W, Häberle A, Schuhmann T et al (2013) Age and adverse drug reactions from psychopharmacological treatment: data from the AMSP drug surveillance programme in Switzerland. Swiss Med Wkly 143:w13772
Grunze H, Vieta E, Goodwin GM et al (2009) The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J Biol Psychiatry 10(2):85–116
Hansen HE (1981) Renal toxicity of lithium. Drugs 22(6):461–476
He N, Min FL, Shi YW et al (2012) Cutaneous reactions induced by oxcarbazepine in Southern Han Chinese: incidence, features, risk factors and relation to HLA-B alleles. Seizure 21(8): 614–618
Hydzik P, Balicka-Slusarczyk B, Jastrzebski M (2011) Cardiologic interaction carbamazepine with atypical neuroleptics. Acute mixed carbamazepine and quetiapine intoxication-case report. Przegl Lek 68(8):499–502
Ide A, Kamijo Y (2007) Intermittent complete atrioventricular block after long term low-dose carbamazepine therapy with a serum concentration less than the therapeutic level. Intern Med 46:627–629
Iorio ML, Moretti U, Colcera S et al (2007) Use and safety profile of antiepileptic drugs in Italy. Eur J Clin Pharmacol 63:409–415. doi:10.1007/s00228-006-0236-6
Irga N, Kosiak W, Jaworski R et al (2013) Pediatrician! Do you know the symptoms of DRESS syndrome? A case report of a 4-year-old girl. Pediatr Emerg Care 29(4):504–507
Jacobson SJ, Jones K, Johnson K et al (1992) Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 339(8792):530–533
Jafferany M (2008) Lithium and skin: dermatologic manifestations of lithium therapy. Int J Dermatol 47(11):1101–1111
Janowsky DS, Soares J, Hatchm JP et al (2009) Lithium effect on renal glomerular function in individuals with intellectual disability. J Clin Psychopharmacol 29:296–299
Jensen S, Rickers H (1984) Glomerular filtration rate during lithium therapy. Acta Psychiatr Scand 70:235–238
Johnson FR, Ozdemir S, Manjunath R et al (2007) Factors that affect adherence to bipolar disorder treatments: a stated preference approach. Med Care 45(6):545–552
Jonsdottir H, Opjordsmoen S, Birkenaes AB et al (2012) Predictors of medication adherence in patients with schizophrenia and bipolar disorder. Acta Psychiatr Scand 127(1):23–33
Kallen B, Tandberg A (1983) Lithium and pregnancy. A cohort study on manic depressive women. Acta Psychiatr Scand 68:134–139
Källén B, Tandberg A (1983) Lithium and pregnancy. A cohort study on manic-depressive women. Acta Psychiatr Scand 68(2):134–139
Kibirige D, Luzinda K, Ssekitoleko R (2013) Spectrum of lithium induced thyroid abnormalities: a current perspective. Thyroid Res 6(1):3
Kim JY, Lee J, Ko YJ et al (2013) Multi-indication carbamazepine and the risk of severe cutaneous adverse drug reactions in Korean elderly patients: a Korean health insurance databased study. PLoS One 8(12). doi:10.1371/journal.pone.0083849
Kocak S, Girisgin SA, Gul M et al (2007) Stevens-Johnson syndrome due to concomitant use of lamotrigine and valproic acid. Am J Clin Dermatol 8(2):107–111
Koda R, Aoyagi R, Okazaki E et al (2012) Acute tubulointerstitial nephritis with multiple organ involvement including fatal adrenalitis: a case report with autopsy findings. Intern Med 51:2917–2922
Koutsampasopoulos K, Zotos A, Papaioannou K (2014) Carbamazepine induced atrial tachycardia with complete AV block. Hippokratia 18(2):185–186
Kupfer DJ (2005) The increasing medical burden in bipolar disorder. J Am Med Assoc 293:2528–2530

Landi F, Onder G, Cesari M et al (2005) Silver Network Home Care Study Group. Psychotropic medications and risk for falls among community-dwelling frail older people: an observational study. J Gerontol A Biol Sci Med Sci 60:622–626

Lepkifker E, Sverdlik A, Iancu I et al (2004) Renal insufficiency in long-term lithium treatment. J Clin Psychiatry 65:850–856

Levi N, Bastuji-Garin S, Mockenhaupt M et al (2009) Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis. Pediatrics 123(2):e297–e304

Lin LC, Lai PC, Yang SF et al (2009) Oxcarbazepine-induced Stevens-Johnson Syndrome: a case report. Kaohsiung J Med Sci 25(2):82–85

Lindop P, Padfield GL (1975) The renal pathology in a case of lithium-induced diabetes. J Clin Pathol 28:472–475

Livingstone C, Rampes H (2006) Lithium: a review of its metabolic adverse effects. J Psychopharmacol 20:347–355

Malhi GS, Tanious M, Das P et al (2012) The science and practice of lithium therapy. Aust N Z J Psychiatry 46:192–211

Markowitz GS, Radhakrishnan J, Kambham N et al (2000) Lithium nephrotoxicity: a progressive combined glomerular and tubulo-interstitial nephropathy. J Am Soc Nephrol 11: 1439–1448

Martino DJ, Igoa A, Marengo E et al (2008) Cognitive and motor features in elderly people with bipolar disorder. J Affect Disord 105:291–295

Matsuda H, Saito K, Takayanagi Y et al (2013) Pustular-type drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms due to carbamazepine with systemic muscle involvement. J Dermatol 40(2):118–122

McKnight RF, Adida M, Budge K et al (2012) Lithium toxicity profile: a systematic review and meta-analysis. Lancet 379:721–728

Meador K, Baker GA, Browning N et al (2009) Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 360:1597–1605

Müller-Oerlinghausen B, Berghöfer A, Bauer M (2002) Bipolar disorder. Lancet 359(9302):241–247

Murray CJ, Lopez AD (1997) Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 349:1436–1442

Murray N, Hopwood S, Balfour DJK et al (1983) The influence of age on lithium efficacy and side-effects in out-patients. Psychol Med 13:53–60

Nora JJ, Nora AH, Toews WH (1974) Letter: lithium, Ebstein's anomaly, and other congenital heart defects. Lancet 2:594–595

Olin JT, Fox LS, Pawluczyk S et al (2001) Pilot randomized trial of carbamazepine for behavioral symptoms in treatment-resistant outpatients with Alzheimer disease. Am J Geriatr Psychiatry 9(4):400–405

Özerdem A, Tunca Z, Çımrın D et al (2014) Female vulnerability for thyroid function abnormality in bipolar disorder: role of lithium treatment. Bipolar Disord 16(1):72–82

Pacchiarotti I, Bond DJ, Baldessarini RJ et al (2013) The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry 170(11):1249–1262

Pachet AK, Wisniewski AM (2003) The effects of lithium on cognition: an updated review. Psychopharmacology 170(3):225–234, Epub 2003 Sep 19

Perucca E, Meador KJ (2005) Adverse effects of antiepileptic drugs. Acta Neurol Scand 112(Suppl 181):30–35

Perucca E, Beghi E, Dulac O et al (2000) Assessing risk to benefit ratio in antiepileptic drug therapy. Epilepsy Res 41:107–139

Pfennig A, Bschor T, Falkai P et al (2013) The diagnosis and treatment of bipolar disorder: recommendations from the current S3 guideline. Dtsch Arztebl Int 110(6):92–100

Pinheiro D (2008) Anticonvulsant mood stabilizers in the treatment of behavioral and psychological symptoms of dementia (BPSD). Encéphale 34(4):409–415

Presne C, Fakhouri F, Noël LH et al (2003) Lithium-induced nephropathy: rate of progression and prognostic factors. Kidney Int 64(2):585–592
Prien RF, Caffey EM Jr, Klett CJ (1972) Comparison of lithium carbonate and chlorpromazine in the treatment of mania. Report of the Veteran Administration and National Institute of Mental Health Collaborative Study Group. Arch Gen Psychiatry 26(2):146–153
Raja M (2011) Lithium and kidney, 60 years later. Curr Drug Saf 6(5):291–303
Rockwell WJ, Ellinwood EH Jr, Trader DW (1983) Psychotropic drugs promoting weight gain: health risks and treatment implications. South Med J 76(11):1407–1412
Rolnitsky A, Merlob P, Klinger G (2013) In utero oxcarbazepine and a withdrawal syndrome, anomalies, and hyponatremia. Pediatr Neurol 48:466–468
Ross CJ, Carleton B, Warn D et al (2007) Genotypic approaches to therapy in children: a national active surveillance network (GATC) to study the pharmacogenomics of severe adverse drug reactions in children. Ann N Y Acad Sci 10:177–192
Rosser R (1976) Thyrotoxicosis and lithium. Br J Psychiatry 128(48):61–66
Sarantidis D, Waters BA (1983) A review and controlled-study of cutaneous conditions associated with lithium-carbonate. Br J Psychiatry 143:42–50
Saunders BD, Saunders EF, Gauger PG (2009) Lithium therapy and hyperparathyroidism: an evidence-based assessment. World J Surg 33(11):2314–2323
Schou M, Vestergaard P (1988) Prospective studies on a lithium cohort: II renal function. Water and electrolyte metabolism. Acta Psychiatr Scand 78:427–433
Schou M, Goldfield M, Weinstein MR et al (1973) Lithium and pregnancy, I: report from the Register of Lithium Babies. BMJ 2:135–136
Schouws SN, Stek ML, Comijs HC, Beekman AT (2010) Risk factors for cognitive impairment in elderly bipolar patients. J Affect Disord 25:330–335
Seely EW, Moore TJ, LeBoff MS et al (1989) A single dose of lithium carbonate acutely elevates intact parathyroid hormone levels in humans. Acta Endocrinol 121:174–176
Sharma B, Sannegowda RB, Gandhi P et al (2013) Combination of Steven-Johnson syndrome and neuroleptic malignant syndrome following carbamazepine therapy: a rare occurrence. BMJ Case Rep. doi:10.1136/bcr-2013-008908
Slater V, Milanes F, Talcott V et al (1984) Influence of age on lithium therapy. South Med J 77:153–154, 158
Sproule BA, Hardy BG, Shulman KI (2000) Differential pharmacokinetics of lithium in elderly patients. Drugs Aging 16:165–177
Strakowski SM, Fleck DE, Maj M (2011) Broadening the diagnosis of bipolar disorder: benefits vs. risks. World Psychiatry 10(3):181–186
Tica OS, Tica AA, Brailoiu CG et al (2013) Sirenomelia after phenobarbital and carbamazepine therapy in pregnancy. Birth Defects Res A Clin Mol Teratol 97(6):425–428
Torrent C, Amann B, Sánchez-Moreno J et al (2008) Weight gain in bipolar disorder: pharmacological treatment as a contributing factor. Acta Psychiatr Scand 118(1):4–18
van Melick EJ, Souverein PC, den Breeijen JH et al (2013) Age as a determinant of instability of serum lithium concentrations. Ther Drug Monit 35(5):643–648
Vanderpump MP, Tunbridge WM, French JM et al (1995) The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 43(1):55–68
Velligan DI, Weiden PJ, Sajatovic M et al (2010) Strategies for addressing adherence problems in patients with serious and persistent mental illness: recommendations from the expert consensus guidelines. J Psychiatr Pract 16(5):306–324
Vestergaard P, Schou M (1981) Kidney morphology and function in lithium-treated patients. Bibl Psychiatr 161:104–114
Von Knorring L, Wahlin A, Nystr K et al (1990) Uremia induced by long-term lithium treatment. Lithium 1:251–253
Weinstein MR (1980) Lithium treatment of women during pregnancy and in the post-delivery period. In: Johnson FN (ed) Handbook of lithium therapy. MTP, Lancaster, pp 421–429
Weinstein MR, Goldfield M (1975) Cardiovascular malformations with lithium use during pregnancy. Am J Psychiatry 132:529–531

Weintraub D, Buchsbaum R, Resor SR Jr et al (2005) Effect of antiepileptic drug comedication on lamotrigine clearance. Arch Neurol 62:1432–1436

Wijeratne C, Draper B (2011) Reformulation of current recommendations for target serum lithium concentration according to clinical indication, age and physical comorbidity. Aust N Z J Psychiatry 45(12):1026–1032

Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ (2009) Effects of lithium on cognitive performance: a meta-analysis. J Clin Psychiatry 70:1588–1597

Wisner KL, Leckman-Westin E, Finnerty M et al (2011) Valproate prescription prevalence among women of childbearing age. Psychiatr Serv 62(2):218–220

Wong IC, Lhatoo SD (2000) Adverse reactions to new anticonvulsant drugs. Drug Saf 23(1):35–56

Yacobi S, Ornoy A (2008) Is lithium a real teratogen? What can we conclude from the prospective versus retrospective studies? A review. Isr J Psychiatry Relat Sci 45(2):95–106

Yang SY, Liao YT, Liu HC et al (2013) Antipsychotic drugs, mood stabilizers, and risk of pneumonia in bipolar disorder: a nationwide case-control study. J Clin Psychiatry 74(1):e79–e86

Yatham LN, Kennedy SH, Parikh SV et al (2013) Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord 15:1–44

Chapter 12
Safety and Tolerability of Medications for ADHD

Antonio Clavenna and Maurizio Bonati

Abstract Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children and adolescents that comprises core symptoms of developmentally inappropriate levels of inattention and/or hyperactivity and impulsivity. Current drug treatment approaches for ADHD comprise stimulant medications (methylphenidate, amphetamines) and non-stimulant medications (atomoxetine, clonidine and guanfacine). Drugs for ADHD appear to be safe and well tolerated, and most of the adverse events observed in randomised clinical trials were mild and temporary. Stimulants and atomoxetine are associated with decreased appetite and gastrointestinal pain. An increased risk of insomnia exists for stimulants, while atomoxetine and alpha-2 agonists are associated with somnolence. Long-term safety is poorly evaluated. Concerns regarding cardiovascular and psychiatric adverse events have been raised by regulatory authorities in the last decade. However, there is currently no proven association between ADHD medications and an increased risk of these events, and their incidence is extremely low.

Keywords Attention deficit hyperactivity disorder • Amphetamines • Atomoxetine • Methylphenidate

12.1 Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children and adolescents that comprises core symptoms of developmentally inappropriate levels of inattention and/or hyperactivity and impulsivity (American Psychiatric Association 2013).

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The prevalence of ADHD is estimated to be approximately 7.2 % (95 % CI 6.7–7.8) in children and 5.0 % (95 % CI 4.1–6.2) in adults according to the results of 175 epidemiological studies, although wide differences were reported across geographical regions (Thomas et al. 2015; Willcutt 2012). Diagnostic criteria, study setting, size of population, study design and medical culture of patients as well as healthcare practitioners can affect these estimates (Thomas et al. 2015; Willcutt 2012).

Several drug therapies for the treatment of ADHD have been evaluated in randomised controlled trials.

Current drug treatment approaches for ADHD comprise stimulant medications (methylphenidate, amphetamines) and non-stimulant medications (atomoxetine and alpha-2 agonists clonidine and guanfacine).

Stimulants enhance the neurotransmission of dopamine and norepinephrine, atomoxetine selectively blocks the reuptake of norepinephrine, clonidine binds equally to α 2A-, α 2B-, and α 2C-adrenoceptors, while guanfacine binds preferentially to postsynaptic α 2A-adrenoceptors in the prefrontal cortex which have been implicated in attentional and organisational functions.

Differences exist between countries in the availability of ADHD medications. Atomoxetine, immediate and sustained-release formulations of methylphenidate, amphetamines, guanfacine and clonidine are registered in the USA. In Europe, only atomoxetine and methylphenidate are commercially available. Guanfacine and clonidine are not licensed for use in ADHD in Europe (extended release guanfacine was approved by European Commission in September 2015), while amphetamines are available only in some countries.

It is widely recognised that interventions in ADHD should be based on multimodal treatment combining psychosocial interventions with pharmacological therapies. There is a consensus on the treatment of ADHD in the international guidelines regarding the recommended use of psychostimulant drugs, particularly methylphenidate, as first-line treatment, with a documented efficacy in 80 % of children considering all psychostimulants as a class. Atomoxetine, although less effective than stimulants, may be recommended as an alternative to methylphenidate (American Academy of Pediatrics 2011; National Collaborating Centre for Mental Health 2008).

12.2 Safety of ADHD Medications

There is mounting evidence that many conditions exist concurrently with ADHD, and each modifies the overall clinical presentation and treatment response. About two-thirds of children with ADHD have comorbid learning disorders, other mental health or neurodevelopmental conditions and other nonpsychiatric disorders (Becker et al. 2012; Chen et al. 2013; Elia et al. 2008). These comorbid conditions should be considered together in order to broaden our understanding of the clinical picture and optimise treatment. The significance of this issue is underscored by the fact that a few disorders (e.g. oppositional defiant disorders and conduct disorders, depression and

anxiety disorders, bipolar disorders, tic disorders, obsessive compulsive disorders and autism spectrum disorders) are relatively common and genetically related, their occurrence is associated with more severe impairment, and they are often underdiagnosed (Gillberg et al. 2004). Moreover, the same disorder can be a comorbid condition occurring before the start of pharmacological treatment (e.g. tics, sleep disorders), as well as a drug side effect (Simpson et al. 2011). Thus, in clinical practice, in particular in psychiatry, it is a challenge to discriminate between an adverse drug reaction and an exacerbation of a disease. Not all the studies investigating the safety of drugs adequately address the prevention or minimisation of methodological bias, and these limitations should be taken into account when evaluating adverse events (AEs) reported for pharmacological treatments described in the following sections.

12.2.1 Findings from Clinical Trials

Since their approval, several issues have affected the use of ADHD medications, such as tolerability, the presence of comorbidities, potential substance abuse risk and lack of efficacy (Vaughan and Kratochvil 2012).

Hundreds of clinical studies have reported that ADHD drugs are generally well tolerated and that most of their adverse effects are mild and/or temporary (Aagaard and Hansen 2011; Cortese et al. 2013; Graham et al. 2011; Graham and Coghill 2008).

Several meta-analyses have addressed the safety of methylphenidate, atomoxetine and alpha-2 agonists in children with ADHD (Aagaard and Hansen 2010; Cheng et al. 2007; Hirota et al. 2014; Ruggiero et al. 2014; Schachter et al. 2001; Schwartz and Correll 2014).

According to the findings of clinical trials, irritability, crying, sleeping problems, daydreams and anxiety were the most frequent AEs reported for stimulant users. Decreased appetite and emotional disturbances were common AEs in children taking stimulants or atomoxetine. Headache and gastrointestinal pain were among the most frequent AEs reported for all ADHD medications, while somnolence and fatigue were more commonly reported with atomoxetine and alpha-2 agonists (Table 12.1).

When compared to placebo (Table 12.2), the short-term effects of lisdexamfetamine and immediate-release methylphenidate are decreased appetite (number needed to harm, NNH = 3 and 4, respectively) and insomnia (NNH = 8 and 7) (Coghill et al. 2014; Schachter et al. 2001), while atomoxetine was associated with significantly decreased appetite (NNH = 9), increased somnolence (NNH = 19) and abdominal pain (NNH = 23) (Cheng et al. 2007).

An increased odds ratio was found mainly for somnolence (NNH = 5), fatigue (NNH = 15), and sedation (NNH = 16) in guanfacine-treated patients (Ruggiero et al. 2014) and for somnolence (NNH = 4) and fatigue (NNH = 8) in patients treated with clonidine (Hirota et al. 2014).

Table 12.1 Adverse drug event reporting rates (%) by category

ADE	AMP (%) (5; 1,226)[a]	MPH (%) (16; 2,092)[a]	ATX (%) (21; 3,127)[a]	GUA (%) (6; 1,150)[a]	CLO (%) (1; 154)[a]
Irritability	7–82	1–80	2–12	6–7	8
Crying	76	2–71	1	–	–
Sleeping problems	70	9–64	–	–	–
Decreased appetite	28–59	3–56	3–50	7	–
Daydreams	62	30–62	–	–	–
Anxiety	68	5–61	–	–	–
Emotional disturbances	59	1–56	3–55[b]	–	4
Social withdrawal	64	27–59	–	–	–
Fingernail biting	40	22–45	–	–	–
Stomachache	40	4–32	5	–	–
Anorexia	17–25	3–15	9–35	–	–
Headache	12–30	2–33	4–28	17–27	–
Insomnia	17–28	2–44	3–19	4	4
Tics	26	1–28	31	–	–
Somnolence	5	1–2	4–36	27–51	35
Mood alteration	–	1–34	44	–	–
Dizziness	5–32	1–30	2–13	5–16	–
Gastrointestinal pain	11–19	4–19	5–47	6–14	–
Nightmares	28	16–21	–	–	6
Unusually happy	26	28	–	–	–
Fatigue	2	1–4	3–33	9–22	14
Dry mouth	5	12–24	–	6	3
Blood pressure changes	–	3–18	18	6	–
Nervousness	6	4–10	6–16	–	–
Changes in heart rate	–	12	11–19	–	–
Abnormal behavior	–	1–5	2–19	–	–
Depression	–	5	3–10	–	–

Data from Aagaard and Hansen (2011), Ruggiero et al. (2014) and Hirota et al. (2014). Only ADEs with rate ≥10 % for at least one medication were reported

AMP amphetamine, *MPH* methylphenidate, *ATX* atomoxetine, *GUA* guanfacine, *CLO* clonidine

[a]N of studies; N of children

[b]Emotional lability

12.2.2 Findings from Spontaneous Reporting

ADHD medications were among the drugs most commonly associated with spontaneously reported ADRs in pediatric populations (Blake et al. 2014; Hawcutt et al. 2012; Lee et al. 2014).

Methylphenidate was the most commonly suggested cause of spontaneously reported ADRs in the UK (covering 6 % of drug-related ADRs) (Hawcutt et al. 2012), and in the USA (5 %) (Lee et al. 2014) and the second most commonly

Table 12.2 Number needed to harm (NNH) estimated from RCTs

ADE	AMP	MPH	ATX	GUA	CLO
Discontinuation	26 (15–84)	–	50 (33–100)	15 (12–21)	5 (4–10)
≥1 AE	6 (4–10)	–	7 (5–13)	7 (5–10)	4 (2–50)
Decreased appetite	3 (3–4)	3 (2–5)	9 (7–12)	–	–
Insomnia	8 (6–10)	6 (4–12)	n.s.	–	–
Gastrointestinal pain	–	11 (6–83)	10 (8–14)	22 (14–48)	–
Somnolence	–	–	19 (12–44)	5 (3.5–4.9)	4 (3–5)
Fatigue	–	–	62 (38–182)	15 (11–21)	8 (5–15)
Headache	–	17 (10–71)	–	17 (10–52)	–
Irritability	19 (13–35)	–	–	33 (19–112)	–
Dizziness	39 (22–186)	20 (12–45)	53(33–131)	–	–
Vomiting	–	–	30 (16–171)	–	–

Data from Coghill et al. (2014), Schachter et al. (2001), Cheng et al. (2007), Ruggiero et al. (2014), Hirota et al. (2014). Confidence intervals (95 % CI) are reported under parenthesis
Abbreviations: ADE adverse drug event, *AMP* amphetamine (lisdexamfetamine), *MPH* methylphenidate, *ATX* atomoxetine, *GUA* guanfacine, *CLO* clonidine

suggested cause of ADRs in Europe (2 % of all the pediatric ADRs) (Blake et al. 2014).

Atomoxetine was the drug for which the second largest number of spontaneously reported ADRs was registered in the UK (Hawcutt et al. 2012).

ADHD medications accounted for 14 % of ADRs collected in the World Health Organization global individual case safety report database (VigiBase) during the 2005–2010 period occurring in children aged 2–11 years. ADRs concerned mainly decreased appetite, psychomotor hyperactivity, upper abdominal pain, aggression, somnolence and suicidal ideation (Star et al. 2011).

12.2.3 Regulatory Authorities' Warnings

Drug regulatory authorities raised several concerns about cardiovascular and psychiatric adverse drug reactions associated with ADHD medications in the last decade (Clavenna and Bonati 2009).

In the USA, the Food and Drug Administration (FDA) issued a black box warning for amphetamines (risk of serious cardiovascular events and risk of drug dependence), methylphenidate (risk of drug dependence), and atomoxetine (risk of suicidal ideation). Other related warnings not leading to a black box warning concerned psychiatric adverse events, effects on growth, heart rate and blood pressure (Table 12.3).

The most recent warning issued by the FDA concerned the risk of priapism in males treated with methylphenidate (Food and Drug Administration 2013). According to the FDA statement, this risk is also associated with atomoxetine and amphetamine use.

Table 12.3 Adverse drug events for ADHD medications that were highlighted in warnings issued by the Food and Drug Administration

MPH	AMP	ATX	GUA	CLO
Drug dependence[a]	Drug dependence[a]	Suicidal ideation[a]	Hypotension, bradycardia and syncope	Hypotension, bradycardia and syncope
Serious cardiovascular events	Serious cardiovascular events[a]	Serious cardiovascular events	Sedation and somnolence	Sedation and somnolence
↑ Blood pressure and heart rate	↑ Blood pressure and heart rate	↑ Blood pressure and heart rate	Cardiac conduction abnormalities	Cardiac conduction abnormalities
Psychiatric adverse events (psychosis, aggression, bipolar disorder)	Psychiatric adverse events (psychosis, aggression, bipolar disorder)	Psychiatric adverse events (psychosis, aggression, bipolar disorder)		
Long-term suppression of growth	Long-term suppression of growth	Long-term suppression of growth		
Priapism	Priapism	Priapism		
Seizures	Seizures	Severe liver injury		
Peripheral vasculopathy	Peripheral vasculopathy	Allergic events		
Visual disturbance	Visual disturbance	Urinary retention		
Potential for gastrointestinal obstruction	Potential for gastrointestinal obstruction			

[a]Black box warning
Abbreviations: MPH methylphenidate, *ATX* atomoxetine, *GUA* guanfacine, *CLO* clonidine

12.2.4 Adverse Events of Particular Concern

As stated above, despite the fact that most of AEs observed in clinical trials were mild and temporary, physicians should be aware of some uncommon severe events (e.g. cardiac AEs, psychiatric AEs, suicidal ideation) and on the potential impact of drug treatment on child growth and development.

Guidelines on this were published in 2011 by the European Network for Hyperkinetic Disorders regarding the management of clinically relevant adverse effects of ADHD medication (Graham et al. 2011).

The following paragraphs address the most relevant AEs that clinicians should be aware of and monitor when deciding on drug therapy for ADHD.

12.2.4.1 Sleep Disturbances

Sleep disturbances may be associated both with ADHD medication and with ADHD itself. Higher rates of sleep problems were reported by parents in a systematic review, but few of these were confirmed by objective sleep data (Cohen-Zion and Ancoli-Israel 2004; Cortese et al. 2009).

Studies on the relationship between psychostimulants and 'sleep disturbance' assessed with objective methods (e.g. polysomnography, actigraphy) reported inconsistent findings (Stein et al. 2012). The heterogeneity in results may be explained by several factors, including differences in the length of the trial, the dose of the drug and duration of exposure. It should be taken into account, however, that a meta-analysis of eight studies (393 patients) recording homogeneous actigraphic outcomes found that children taking methylphenidate had a decreased mean activity, a decreased total sleep time and a longer sleep latency compared with children taking placebo (De Crescenzo et al. 2014). A history of any sleep problems should therefore be taken before starting ADHD medication, and if this is a significant concern, then atomoxetine could be considered as the first choice. Sleep hygiene should be encouraged and a switch of medication should be considered when sleep problems persist after dose adjustment and dose scheduling of the original medication (Graham et al. 2011).

12.2.4.2 Growth

Treating ADHD children with stimulants generally results in a reduction in height and weight gain. A systematic analysis of psycho-stimulant effects in 18 studies found height and weight deficits. The height reduction was approximately 1 cm/year during the first 1–3 years of treatment, while the decrease of weight is estimated to be around 3 kg over a 3-year period (Faraone et al. 2008).

However, the number of children who fall below the fifth growth percentile did not increase. The initial effect of stimulants on growth appears to slow down over time, and final adult height does not seem to be affected (Biederman et al. 2010).

A longitudinal study monitoring 243 ADHD cases and 394 controls did not find an association between ADHD or treatment with stimulants and differences in magnitude of peak height velocity (PHV) during adolescence (Harstad et al. 2014). The mean age of PHV was slightly later in boys treated with stimulants (13.6 years in those treated with stimulants for at least 3 years versus 12.9 years in ADHD cases never receiving stimulants), but no correlation was found between treatment duration and change in height for age Z scores, and the adult height was not different in ADHD patients treated with stimulants compared with ADHD stimulant naive and controls (Harstad et al. 2014). A slower body mass index (BMI) growth in childhood was observed in children with ADHD and children undergoing stimulant treatment compared with untreated ADHD and non-ADHD (Schwartz et al. 2014). However, during adolescence, the rate of BMI increase was more rapid in the first

group, with BMIs eventually exceeding those of controls (Schwartz et al. 2014). With regard to atomoxetine, a meta-analysis of seven double blind placebo-controlled and six open-label studies found that height and weight at 24 months of treatment were 2.5 cm and 2.7 kg lower than the expected values (Kratochvil et al. 2006). Patient weight, height and body mass index should be monitored every 6 months, and a growth chart should be used (Graham et al. 2011; National Collaborating Centre for Mental Health 2008).

12.2.4.3 Tics

Psychostimulants increase dopamine levels and can therefore theoretically aggravate tic severity.

A meta-analysis including nine double-blind placebo-controlled trials evaluating the efficacy of medications in treatment of ADHD in patients with comorbid tic concluded that there is no evidence that methylphenidate worsens tic severity in the short-term, that supra-therapeutic doses of dextroamphetamine worsen tics and that atomoxetine improves tics (Bloch et al. 2009).

However, psychostimulants may exacerbate tics in individual cases. Since tics are common in childhood and tend to wax and wane spontaneously, an observation period of at least 3 months is needed before making a clinical decision. If tics are troublesome, clinicians should consider a dose reduction or drug substitution. If these measures are ineffective, an antipsychotic could be added to control tics (Graham et al. 2011).

12.2.4.4 Cardiac Adverse Events

In June 2009, the Food and Drug Administration issued a safety communication to warn health professionals about a possible association between stimulant medications and an increased risk of sudden deaths in healthy children. The alert was issued after the completion of a study funded by the FDA and the National Institute of Mental Health (NIMH) that compared the use of stimulant medications in 564 healthy children with a registration of sudden death and in 564 children who died as passengers in a motor vehicle accident. Stimulant use was reported by ten out of 564 children with sudden death versus two out of ten children in the control group (Gould et al. 2009). Due to the limitation of the study, the FDA was unable to evaluate the presence of a causal association. However, subsequent studies did not find an increased risk of cardiovascular events. In a cohort of 1,200,438 children and young adults aged 2–24 years, a total of 81 subjects had a serious cardiovascular event (3.1 per 100,000 person-years) including 33 sudden cardiac deaths (1.3 per 100,000 person-years). As compared with the nonusers, the adjusted rate of serious cardiovascular events did not differ significantly among current users of ADHD drugs (hazard ratio, HR 0.75; 95 % CI 0.31–1.85) or among former users (HR 1.03; 95 % CI 0.57–1.89) (Cooper et al. 2011). In a cohort of 241,417 incident ADHD medication

users, no statistically significant difference in the rate of validated sudden death or ventricular arrhythmia was found compared to nonusers (HR 1.60; 95 % CI 0.19–13.60) or all-cause death (HR 0.76; 95 % CI 0.52–1.12) (Schelleman et al. 2011). Similar findings, i.e. no increased risk of cardiovascular events, were also found in a study performed in the adult population (25–64 years) (Habel et al. 2011).

All stimulant medications and atomoxetine are reported to increase blood pressure. An average increase of 1–5 mmHg of blood pressure and an increase of ≤10 heart beats per minute have been observed with stimulants (Hammerness et al. 2015). An average increase of 1–4 mmHg of systolic pressure and 1–2 mmHg in diastolic pressure was observed.

An increase in blood pressure was observed with atomoxetine, with a standardised mean difference (SMD) of 0.27 mmHg (95 % CI 0.19–0.35) in diastolic blood pressure and 0.15 mmHg (95 % CI 0.06–0.23) in systolic blood pressure (Schwartz and Correll 2014). Elevation of blood pressure above the 95th percentile occurred in 6.8 % of patients (systolic) and 2.8 % (diastolic) treated with atomoxetine in comparison with 3 and 0.5 % patients treated with placebo (Hammerness et al. 2011; Wernicke et al. 2003). Immediate-release clonidine was associated with a significant SMD drop of 0.52 mmHg (95 % CI −0.15 to −0.89) in systolic blood pressure and an SMD of – 0.49 mmHg (95 % CI −0.02 to −0.097) in diastolic blood pressure.

Change in QTc interval showed no significant differences between alpha-2 agonists and placebo (SMD = 0.12, 95 % CI – 0.18–0.43). In a subgroup analyses, however, extended-release guanfacine significantly prolonged the QTc interval by a mean of 5.3 ms (95 % CI 2.7–7.9) compared to placebo (SMD = 0.33, 95 % CI 0.12–0.43) (Hirota et al. 2014). Pretreatment monitoring of pulse and blood pressure is recommended with any ADHD medication. Blood pressure should be measured prior to treatment and at each visit and converted to a percentile score using the appropriate chart. If BP is elevated and above the 95th percentile after at least three measurements, patients should be referred to a pediatric cardiologist. Moreover, before starting any ADHD drug treatment, family history of cardiac diseases and history of exercise syncope, undue breathlessness and any other cardiovascular symptoms should be assessed (Graham et al. 2011; National Collaborating Centre for Mental Health 2008). Routine electrocardiographic screening of ADHD patients prior to initiation of medication is not recommended (Graham et al. 2011; National Collaborating Centre for Mental Health 2008).

12.2.4.5 Suicide-Related Events

According to the available evidence, there is a relationship between the presence of ADHD itself and suicidal attempts (Impey and Heun 2012). Thus it is difficult to investigate if ADHD medications are associated with an increased risk of suicidal ideation. In September 2005, the US Food and Drug Administration (FDA) added a black box warning to the product labelling of atomoxetine. A meta-analysis of clinical trials observed that suicidal ideation was more frequently recorded

among children and adolescents treated with atomoxetine compared to those treated with placebo (0.37 %, 5/1,357 versus 0 % (0/851) respectively) with an NNH of 227 (Bangs et al. 2008). A subsequent meta-analysis did not find a statistically significant increased risk of suicidal behavior/ideation in children or adults treated with atomoxetine compared with placebo (RR 1.57; 95 % CI 0.53–4.71 and RR 0.96; 95 % CI 0.19–4.74, respectively) (Bangs et al. 2014) No completed suicide was reported, while nine out of 2,445 (0.37 %) children in the atomoxetine group had suicidal behavior/ideation. The analysis of data collected in the ADHD Italian register identified a total of seven cases of suicidal ideation or self-harming behaviour were reported among 971 children treated with atomoxetine. No cases were reported among 1,268 children receiving methylphenidate. The median time to event for the seven cases was 6 months after the first atomoxetine administration and 2 months after an increase in dosage (Capuano et al. 2014).

A study evaluating data from the Swedish national patient register found a greater rate of suicide-related events during treatment periods with ADHD medications than during nontreatment period (HR = 1.31; 95 % CI 1.19–1.44). On the contrary, no evidence of an increased risk was found when comparing the rates of suicide-related events for the same patients over different periods (HR = 0.89; 95 % CI 0.79–1.00) (Chen et al. 2014).

Although the evidence suggests minimal risk with atomoxetine treatment, patients should be appropriately monitored during treatment, in particular after dose increase (Graham et al. 2011).

12.2.4.6 Seizures

ADHD is a risk factor for seizures in children. The incidence of unprovoked seizures is two- to threefold greater in ADHD than non-ADHD children (Hesdorffer et al. 2004). Among children with epilepsy, ADHD is the most common psychopathological comorbidity (Dunn et al. 2009). Concern exists that ADHD medications may lower the seizure threshold. However, in ADHD patients without epilepsy, the risk of seizure did not differ among methylphenidate, atomoxetine and placebo (McAfee et al. 2008).

Adolescents with epilepsy are at increased risk for depression and suicidal ideation. During ADHD treatment, they should be monitored for the emergence of depression, irritability and suicidal ideation (Graham et al. 2011).

12.2.4.7 Psychosis

Psychotic symptoms are rarely associated with ADHD drug treatment. A review of 49 RCTs performed by the Food and Drug Association found 11 psychosis/mania events, with a rate per 100 person-years in the pooled active drug group of 1.48

(95 % CI 0.74–2.65 per 100 person-years) (Mosholder et al. 2009). Among all of the pediatric ADHD patients in placebo treatment groups, corresponding to 420 person-years of placebo exposure, there were no psychosis/mania adverse events. The highest rate of psychotic adverse events was observed with transdermal methylphenidate (13.2 per 100 person-years) followed by dexamfetamine (two per 100 person-years) (Mosholder et al. 2009).

A total of 865 unique post-marketing cases were spontaneously reported to manufacturers in the period 2000–2005. In the vast majority of cases, there was no previous history of a similar psychiatric condition reported. Many young children with hallucinations reported visual and/or tactile sensations of insects, snakes or worms. When the drug was discontinued, the psychosis/mania-type symptoms often resolved (Mosholder et al. 2009). According to the guidelines, caution is needed when prescribing ADHD drugs to children and adolescents with a past history of psychotic episodes or a family history of psychosis (Graham et al. 2011).

12.2.4.8 Risk for Substance Use Disorders (SUD)

Children with ADHD have been found to be at increased risk for developing SUDs (Zulauf et al. 2014).

Why SUD is linked to ADHD is still unclear. Different hypotheses have been developed: substances may be used as a kind of self-medication with the aim to decrease symptoms (e.g. depressed mood, insomnia); ADHD and SUD may share alterations in dopaminergic neurotransmission and abnormalities in reward circuitry (Cortese et al. 2013).

Concerns have been raised that ADHD medications, in particular stimulants, may be associated with an increased risk of SUD. However, this hypothesis is not supported by the available evidence.

A meta-analysis of 15 longitudinal studies (for a total of 2,565 subjects) did not find any increase or reduction of SUD risk associated with ADHD medication (Humphreys et al. 2013). Previously, meta-analysis of six studies suggested that psychostimulant therapy might be associated with a reduced risk of SUD. A 1.9-fold (95 % CI 1.1–3.6) reduction in risk for SUD in ADHD youths treated with stimulants compared with youths with no pharmacotherapy was estimated (Humphreys et al. 2013). Even if the risk of SUD was not proved, an increased risk of misuse/abuse of ADHD medications is reported. Data from a 10-year follow-up study reported a medication misuse in 22 % of ADHD children compared with 5 % of a group receiving psychotropic drugs for reasons other than ADHD (Wilens et al. 2006). Current use or previous substance abuse in the family could be a reason to closely monitor patient treated with ADHD medications or a relative contraindication for stimulant prescription. Atomoxetine or extended-release formulations of stimulants should be preferred in high-risk patients, since they are less prone to diversion (Graham et al. 2011).

12.3 Long-Term Safety

The majority of the clinical trials that monitored the occurrence of AEs in children and adolescents receiving drug treatment for ADHD were short term (Schachter et al. 2001; Schwartz and Correll 2014). In a systematic review of the literature (Clavenna and Bonati 2014), only six prospective studies were found evaluating the long-term safety of ADHD medications (Donnelly et al. 2009; Findling et al. 2009; Harfterkamp et al. 2013; Hoare et al. 2005; McGough et al. 2005; Wilens et al. 2005). These studies concerned atomoxetine (two studies, 802 patients), the osmotic controlled-released oral formulation of methylphenidate (two studies, 512 patients), the extended-release formulation of mixed amphetamine salts (one study, 568 patients) and transdermal methylphenidate (one study, 326 patients). All studies were open-label extension that followed patients previously enrolled in a total of 24 short-term randomised clinical trials, with a duration of treatment ranging from 1 to 18 weeks. Vital signs (e.g. heart rate, blood pressure), weight and height were monitored in four studies (Donnelly et al. 2009; Findling et al. 2009; Hoare et al. 2005; McGough et al. 2005). AEs were collected mainly through spontaneous reporting by patients and/or caregivers and in one study in combination with investigator queries. In four studies, investigators evaluated the severity of AEs and their relationship to drug treatment (Findling et al. 2009; Hoare et al. 2005; McGough et al. 2005; Wilens et al. 2005). Heterogeneity was found in the duration of follow-up (ranging between 1 and 4 years) and the way data were reported. The rate of discontinuation due to AEs was the only measure reported in all six studies (Table 12.4).

According to the long-term open-label extension studies, the rate of treatment-related AEs ranged from 58 to 78 %, and most of the AEs were mild or moderate in severity, with a range of 86–98 %. The rate of discontinuation due to AEs ranged from 8 to 25 % of the children (Table 12.4). The adverse events most commonly associated with therapy discontinuation were reported in five out of six studies. None of these AEs were reported in all the studies. Insomnia and abdominal pain were among the most common AEs leading to discontinuation in four studies. Weight loss (32 % of the children who discontinued) and decreased appetite (26 %) were the most common reasons for suspending extended-release amphetamine (McGough et al. 2005), tics (24 %) and decreased appetite (24 %) were the most common reasons for discontinuing osmotic controlled-released oral formulation of methylphenidate (Wilens et al. 2005), and upper abdominal pain (21 %) and emotional lability (17 %) were the most common AEs for atomoxetine discontinuation (Donnelly et al. 2009).

Most of the discontinuation occurred during the first year of treatment. The rate of discontinuation in patients treated with extended-release amphetamine was 7 % in the first quarter and 6 % in the second quarter. In the third and fourth quarters, it decreased to 2 %, after which it was <1 % (McGough et al. 2005). The discontinuation rate with osmotic controlled-released oral formulation of methylphenidate was 7 % in the first 12 months and 8 % after 24 months (Wilens et al. 2003, 2005). A total of 71 (4 %) out of 1,553 children receiving atomoxetine interrupted the

Table 12.4 Number of subjects (%) with at least one adverse event (AE) (Clavenna and Bonati 2014)

Drug	N. short-term CT[a]	N. children[b]	Age (years)	Duration (years)	% Cut-off for AE reporting	AEs		Treatment-related AEs		Discontinuation due to AEs
						Any	Serious	Any	Serious	
Atomoxetine	1	88	6–17	12 weeks	≥1	n.r.	2 (2)	n.r.	0	11 (25)
Atomoxetine	13	1,533 (508)[c]	6–17	≥4	≥10	n.r.	78 (15)[c]	n.r.	n.r.	71 (9)[c]
Atomoxetine	14	596	6–17		–					82 (14)
MAS XR	2	568 (284)	6–17	2	≥5	525 (92)	18 (3)	440 (78)	2 (<1)	84 (15)
MPH OROS	3	407 (229)	6–13	2	≥5	363 (89)	n.r.	282 (69)	n.r.	31 (8)
MPH OROS	1	101 (56)	6–16	1	≥2	76 (72)	n.r.	61 (58)	4 (4)	16 (15)
MPH OROS	4	508	6–16	1–2	–	439 (86)	–	343 (68)	–	47 (9)
Transdermal MPH	4	326	6–15	1	≥5	265 (81)	3 (1)	n.r.	0	29 (9)

CT controlled trial, *MAS XR* extended-release amphetamine, *OROS MPH* osmotic controlled-released oral formulation of methylphenidate (MPH), *n.r.* not reported

[a]Number of short-term clinical trials that originally enrolled children followed up by each open-label extension study

[b]Number of children followed up; number of children who were still on drug treatment at the end of the study period is reported under brackets

[c]Number of children treated for at least 4 years was considered as the denominator, with the exception of discontinuation, which was calculated using the 1,533 patients initially enrolled and treated for less than 3 years

therapy before 3 years had elapsed. The subsequent rate of discontinuation in those treated for ≥3 years and ≥4 years was 2 % (Donnelly et al. 2009).

Only for a few studies was it possible to compare the incidence of AEs over time. Harfterkamp et al. compared the rate of AEs during the first 8 weeks of treatment with atomoxetine (experimental phase) with the rate during the subsequent 12 weeks of treatment. A decrease in the rate across time was observed for all the AEs. In particular, a statistically significant reduction was found for nausea (from 13.6 to 1.1 %, $p=0.003$) and fatigue (from 18.2 to 6.8 %, $p=0.04$) (Harfterkamp et al. 2013). McGough et al. compared the percentage of the AEs reported with extended-release amphetamine in four periods, from months 1–6 to months 18–24. For all the AEs, the percentage of cases was highest in the first 6 months and decreased with time. In all, 58 % of the AEs were recorded during the first 4 months of therapy (McGough et al. 2005). In studies concerning osmotic controlled-released oral formulation of methylphenidate, the incidence of AEs increased from 42 to 89 % between the experimental phase (short-term) and the long-term open-label follow-up (24 months) (Wilens et al. 2005). No children had tics in the experimental phase, and no psychiatric AEs (e.g. aggravation reaction, anxiety, emotional lability and hostility) were reported in the short-term RCTs (Clavenna and Bonati 2014). An increase in the incidence of AEs was observed comparing short-term RCTs with the prospective open-label extension trial concerning transdermal methylphenidate (from 55 to 81 %). The percentage of children with decreased appetite was similar, the incidence of headache increased from 4 to 17 %, while the incidence of insomnia, vomiting and nausea decreased. Tics, affect lability and anorexia were reported only during short-term trials while abdominal pain and irritability only during the open-label extension phase. The incidence of the most common AEs observed in the short- and long-term periods is summarised in Fig. 12.1.

12.4 Conclusions

Drugs for ADHD seem to be safe and well tolerated. Decreased appetite, insomnia, headache and abdominal pain are the most common adverse events observed both in the short- and the long-term studies. Long-term safety and tolerability need to be further investigated. Few trials are available with different follow-up duration and criteria for defining and reporting adverse events. Many AEs are mild or moderate in severity, and the incidence of serious events is low. Although the medications for ADHD are generally well tolerated, with only mild or minor adverse effects in most cases, their rational use can be guaranteed by implementing and monitoring evidence-based practice. In this regard, recommendations regarding pretreatment screening and monitoring of adverse events issued by the National Institute for Health and Care Excellence (NICE) are reported in Box 12.1.

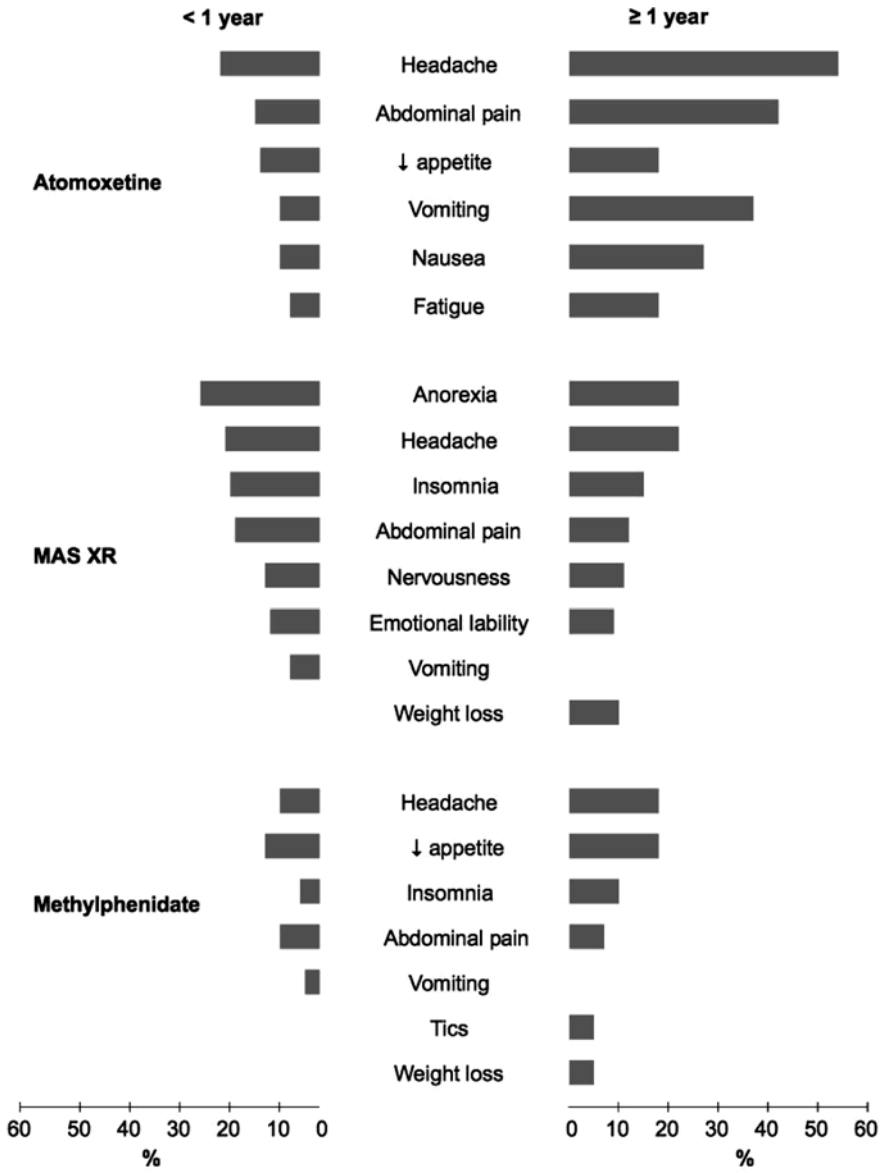

Fig. 12.1 Incidence (%) of the most common AEs in short versus long periods by drug. Incidence was calculated using all the monitored children as denominator (Clavenna and Bonati 2014). Abbreviations: *MAS XR* extended-release amphetamine

Box 12.1: National Institute for Health and Care Excellence (NICE) recommendations (National Collaborating Centre for Mental Health 2008)

Pre-drug treatment assessment

Before starting drug treatment, children and young people with ADHD should have a full pretreatment assessment, which should include:

- Full mental health and social assessment
- Full history and physical examination, including:
  - Assessment of history of exercise syncope, undue breathlessness and other cardiovascular symptoms
  - Heart rate and blood pressure (plotted on a centile chart)
  - Height and weight (plotted on a growth chart)
  - Family history of cardiac disease and examination of the cardiovascular system
- An electrocardiogram (ECG) if there is past medical or family history of serious cardiac disease, a history of sudden death in young family members or abnormal findings on cardiac examination
- Risk assessment for substance misuse and drug diversion (where the drug is passed on to others for nonprescription use).

Monitoring side effects

Healthcare professionals should consider using standard symptom and side effect rating scales throughout the course of treatment as an adjunct to clinical assessment for people with ADHD.

- In people taking methylphenidate, atomoxetine or dexamfetamine:
  - Height should be measured every 6 months in children and young people.
  - Weight should be measured 3 and 6 months after drug treatment has started and every 6 months thereafter in children, young people and adults.
  - Height and weight in children and young people should be plotted on a growth chart and reviewed by the healthcare professional responsible for treatment.
- If there is evidence of weight loss associated with drug treatment in adults with ADHD, healthcare professionals should consider monitoring body mass index and changing the drug if weight loss persists.
- Strategies to reduce weight loss in people with ADHD or manage decreased weight gain in children include:
  - Taking medication either with or after food, rather than before meals
  - Taking additional meals or snacks early in the morning or late in the evening when the stimulant effects of the drug have worn off
  - Obtaining dietary advice
  - Consuming high-calorie foods of good nutritional value

- If growth is significantly affected by drug treatment (i.e. the child or young person has not met the height expected for their age), the option of a planned break in treatment over school holidays should be considered to allow 'catch-up' growth to occur.
- In people with ADHD, heart rate and blood pressure should be monitored and recorded on a centile chart before and after each dose change and routinely every 3 months.
- For people taking methylphenidate, dexamfetamine and atomoxetine, routine blood tests and ECGs are not recommended unless there is a clinical indication.
- Liver damage is a rare and idiosyncratic adverse effect of atomoxetine, and routine liver function tests are not recommended.
- For children and young people taking methylphenidate and dexamfetamine, healthcare professionals and parents or carers should monitor changes in the potential for drug misuse and diversion, which may come with changes in circumstances and age. In these situations, modified-release methylphenidate or atomoxetine may be preferred.
- In young people and adults, sexual dysfunction (i.e. erectile and ejaculatory dysfunction) and dysmenorrhoea should be monitored as potential side effects of atomoxetine.
- People taking methylphenidate, dexamfetamine or atomoxetine who have sustained resting tachycardia, arrhythmia or systolic blood pressure greater than the 95th percentile (or a clinically significant increase) measured on two occasions should have their dose reduced and be referred to a paediatrician or adult physician.
- If psychotic symptoms (e.g. delusions and hallucinations) emerge in children, young people and adults after starting methylphenidate or dexamfetamine, the drug should be withdrawn and a full psychiatric assessment carried out. Atomoxetine should be considered as an alternative.
- If seizures are exacerbated in a child or young person with epilepsy, or de novo seizures emerge following the introduction of methylphenidate or atomoxetine, the drug should be discontinued immediately.
- If tics emerge in people taking methylphenidate or dexamfetamine, healthcare professionals should consider whether:
  - The tics are stimulant related (tics naturally wax and wane).
  - Tic-related impairment outweighs the benefits of ADHD treatment.
- If tics are stimulant related, reduce the dose of methylphenidate or dexamfetamine, consider changing to atomoxetine, or stop drug treatment.

Anxiety symptoms, including panic, may be precipitated by stimulants, particularly in adults with a history of coexisting anxiety. Where this is an issue, lower doses of the stimulant and/or combined treatment with an antidepressant used to treat anxiety can be used; switching to atomoxetine may be effective.

References

Aagaard L, Hansen EH (2010) Adverse drug reactions from psychotropic medicines in the paediatric population: analysis of reports to the Danish medicines agency over a decade. BMC Res Notes 3:176

Aagaard L, Hansen EH (2011) The occurrence of adverse drug reactions reported for attention deficit hyperactivity disorder (ADHD) medications in the pediatric population: a qualitative review of empirical studies. Neuropsychiatr Dis Treat 7:729–744

American Academy of Pediatrics (2011) ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 128:1007–1022

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5, 5th edn. American Psychiatric Publishing, Washington, DC

Bangs ME, Tauscher-Wisniewski S, Polzer J et al (2008) Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. J Am Acad Child Adolesc Psychiatry 47:209–218

Bangs ME, Wietecha LA, Wang S, Buchanan AS, Kelsey DK (2014) Meta-analysis of suicide-related behavior or ideation in child, adolescent, and adult patients treated with atomoxetine. J Child Adolesc Psychopharmacol 24:426–434

Becker SP, Luebbe AM, Langberg JM (2012) Co-occurring mental health problems and peer functioning among youth with attention-deficit/hyperactivity disorder: a review and recommendations for future research. Clin Child Fam Psychol Rev 15:279–302

Biederman J, Spencer TJ, Monuteaux MC, Faraone SV (2010) A naturalistic 10-year prospective study of height and weight in children with attention-deficit hyperactivity disorder grown up: sex and treatment effects. J Pediatr 157:635–640, 640

Blake KV, Zaccaria C, Domergue F et al (2014) Comparison between paediatric and adult suspected adverse drug reactions reported to the European medicines agency: implications for pharmacovigilance. Paediatr Drugs 16:309–319

Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF (2009) Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. J Am Acad Child Adolesc Psychiatry 48:884–893

Capuano A, Scavone C, Rafaniello C et al (2014) Atomoxetine in the treatment of attention deficit hyperactivity disorder and suicidal ideation. Expert Opin Drug Saf 13(Suppl 1):S69–S78

Chen MH, Su TP, Chen YS et al (2013) Asthma and attention-deficit/hyperactivity disorder: a nationwide population-based prospective cohort study. J Child Psychol Psychiatry 54:1208–1214

Chen Q, Sjolander A, Runeson B et al (2014) Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. BMJ 348:g3769

Cheng JY, Chen RY, Ko JS, Ng EM (2007) Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. Psychopharmacol (Berl) 194:197–209

Clavenna A, Bonati M (2009) Adverse drug reactions in childhood: a review of prospective studies and safety alerts. Arch Dis Child 94:724–728

Clavenna A, Bonati M (2014) Safety of medicines used for ADHD in children: a review of published prospective clinical trials. Arch Dis Child 99:866–872

Coghill DR, Caballero B, Sorooshian S, Civil R (2014) A systematic review of the safety of lisdexamfetamine dimesylate. CNS Drugs 28:497–511

Cohen-Zion M, Ancoli-Israel S (2004) Sleep in children with attention-deficit hyperactivity disorder (ADHD): a review of naturalistic and stimulant intervention studies. Sleep Med Rev 8:379–402

Cooper WO, Habel LA, Sox CM et al (2011) ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 365:1896–1904

Cortese S, Faraone SV, Konofal E, Lecendreux M (2009) Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. J Am Acad Child Adolesc Psychiatry 48:894–908

Cortese S, Holtmann M, Banaschewski T et al (2013) Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry 54:227–246

De Crescenzo F, Armando M, Mazzone L et al (2014) The use of actigraphy in the monitoring of methylphenidate versus placebo in ADHD: a meta-analysis. Atten Defic Hyperactivity Disord 6:49–58

Donnelly C, Bangs M, Trzepacz P et al (2009) Safety and tolerability of atomoxetine over 3 to 4 years in children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry 48:176–185

Food and Drug Administration (2013) Methylphenidate ADHD medications: drug safety communication – risk of long-lasting erections. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm378876.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

Dunn DW, Austin JK, Perkins SM (2009) Prevalence of psychopathology in childhood epilepsy: categorical and dimensional measures. Dev Med Child Neurol 51:364–372

Elia J, Ambrosini P, Berrettini W (2008) ADHD characteristics: I. Concurrent co-morbidity patterns in children & adolescents. Child Adolesc Psychiatry Ment Health 2:15

Faraone SV, Biederman J, Morley CP, Spencer TJ (2008) Effect of stimulants on height and weight: a review of the literature. J Am Acad Child Adolesc Psychiatry 47:994–1009

Findling RL, Wigal SB, Bukstein OG et al (2009) Long-term tolerability of the methylphenidate transdermal system in pediatric attention-deficit/hyperactivity disorder: a multicenter, prospective, 12-month, open-label, uncontrolled, phase III extension of four clinical trials. Clin Ther 31:1844–1855

Gillberg C, Gillberg IC, Rasmussen P et al (2004) Co-existing disorders in ADHD – implications for diagnosis and intervention. Eur Child Adolesc Psychiatry 13(Suppl 1):I80–I92

Gould MS, Walsh BT, Munfakh JL et al (2009) Sudden death and use of stimulant medications in youths. Am J Psychiatry 166:992–1001

Graham J, Coghill D (2008) Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. CNS Drugs 22:213–237

Graham J, Banaschewski T, Buitelaar J et al (2011) European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry 20:17–37

Habel LA, Cooper WO, Sox CM et al (2011) ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. JAMA 306:2673–2683

Hammerness PG, Perrin JM, Shelley-Abrahamson R, Wilens TE (2011) Cardiovascular risk of stimulant treatment in pediatric attention-deficit/hyperactivity disorder: update and clinical recommendations. J Am Acad Child Adolesc Psychiatry 50:978–990

Hammerness PG, Karampahtsis C, Babalola R, Alexander ME (2015) Attention-deficit/hyperactivity disorder treatment: what are the long-term cardiovascular risks? Expert Opin Drug Saf 14:543–551

Harfterkamp M, Buitelaar JK, Minderaa RB et al (2013) Long-term treatment with atomoxetine for attention-deficit/hyperactivity disorder symptoms in children and adolescents with autism spectrum disorder: an open-label extension study. J Child Adolesc Psychopharmacol 23:194–199

Harstad EB, Weaver AL, Katusic SK et al (2014) ADHD, stimulant treatment, and growth: a longitudinal study. Pediatrics 134:e935–e944

Hawcutt DB, Mainie P, Riordan A, Smyth RL, Pirmohamed M (2012) Reported paediatric adverse drug reactions in the UK 2000–2009. Br J Clin Pharmacol 73:437–446

Hesdorffer DC, Ludvigsson P, Olafsson E et al (2004) ADHD as a risk factor for incident unprovoked seizures and epilepsy in children. Arch Gen Psychiatry 61:731–736

Hirota T, Schwartz S, Correll CU (2014) Alpha-2 agonists for attention-deficit/hyperactivity disorder in youth: a systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. J Am Acad Child Adolesc Psychiatry 53:153–173

Hoare P, Remschmidt H, Medori R et al (2005) 12-month efficacy and safety of OROS MPH in children and adolescents with attention-deficit/hyperactivity disorder switched from MPH. Eur Child Adolesc Psychiatry 14:305–309

Humphreys KL, Eng T, Lee SS (2013) Stimulant medication and substance use outcomes: a meta-analysis. JAMA Psychiatry 70:740–749
Impey M, Heun R (2012) Completed suicide, ideation and attempt in attention deficit hyperactivity disorder. Acta Psychiatr Scand 125:93–102
Kratochvil CJ, Wilens TE, Greenhill LL et al (2006) Effects of long-term atomoxetine treatment for young children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 45:919–927
Lee WJ, Lee TA, Pickard AS, Caskey RN, Schumock GT (2014) Drugs associated with adverse events in children and adolescents. Pharmacotherapy 34:918–926
McAfee AT, Holdridge KC, Johannes CB, Hornbuckle K, Walker AM (2008) The effect of pharmacotherapy for attention deficit hyperactivity disorder on risk of seizures in pediatric patients as assessed in an insurance claims database. Curr Drug Saf 3:123–131
McGough JJ, Biederman J, Wigal SB et al (2005) Long-term tolerability and effectiveness of once-daily mixed amphetamine salts (Adderall XR) in children with ADHD. J Am Acad Child Adolesc Psychiatry 44:530–538
Mosholder AD, Gelperin K, Hammad TA, Phelan K, Johann-Liang R (2009) Hallucinations and other psychotic symptoms associated with the use of attention-deficit/hyperactivity disorder drugs in children. Pediatrics 123:611–616
National Collaborating Centre For Mental Health (2008) Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults. NICE, London
Ruggiero S, Clavenna A, Reale L et al (2014) Guanfacine for attention deficit and hyperactivity disorder in pediatrics: a systematic review and meta-analysis. Eur Neuropsychopharmacol 24:1578–1590
Schachter HM, Pham B, King J, Langford S, Moher D (2001) How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. CMAJ 165:1475–1488
Schelleman H, Bilker WB, Strom BL et al (2011) Cardiovascular events and death in children exposed and unexposed to ADHD agents. Pediatrics 127:1102–1110
Schwartz S, Correll CU (2014) Efficacy and safety of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: results from a comprehensive meta-analysis and metaregression. J Am Acad Child Adolesc Psychiatry 53:174–187
Schwartz BS, Bailey-Davis L, Bandeen-Roche K et al (2014) Attention deficit disorder, stimulant use, and childhood body mass index trajectory. Pediatrics 133:668–676
Simpson HA, Jung L, Murphy TK (2011) Update on attention-deficit/hyperactivity disorder and tic disorders: a review of the current literature. Curr Psychiatry Rep 13:351–356
Star K, Noren GN, Nordin K, Edwards IR (2011) Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. Drug Saf 34:415–428
Stein MA, Weiss M, Hlavaty L (2012) ADHD treatments, sleep, and sleep problems: complex associations. Neurotherapeutics 9:509–517
Thomas R, Sanders S, Doust J, Beller E, Glasziou P (2015) Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Pediatrics 135(4):e994–e1001
Vaughan B, Kratochvil CJ (2012) Pharmacotherapy of pediatric attention-deficit/hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 21:941–955
Wernicke JF, Faries D, Girod D et al (2003) Cardiovascular effects of atomoxetine in children, adolescents, and adults. Drug Saf 26:729–740
Wilens T, Pelham W, Stein M et al (2003) ADHD treatment with once-daily OROS methylphenidate: interim 12-month results from a long-term open-label study. J Am Acad Child Adolesc Psychiatry 42:424–433
Wilens T, McBurnett K, Stein M et al (2005) ADHD treatment with once-daily OROS methylphenidate: final results from a long-term open-label study. J Am Acad Child Adolesc Psychiatry 44:1015–1023

Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J (2006) Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. J Am Acad Child Adolesc Psychiatry 45:408–414

Willcutt EG (2012) The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics 9:490–499

Zulauf CA, Sprich SE, Safren SA, Wilens TE (2014) The complicated relationship between attention deficit/hyperactivity disorder and substance use disorders. Curr Psychiatry Rep 16:436

Part III
Pharmacovigilance of Psychotropic Drugs in Special Populations

Chapter 13
Safety of Psychotropic Drugs in Children and Adolescents

Florentia Kaguelidou and Eric Acquaviva

Abstract The recent rise in the use of psychotropic drugs to treat mental disease in children and adolescents has not been accompanied by quality research evidence on their efficient and safe use in this population. Currently, 60–70 % of pharmacological prescriptions in pediatric psychiatry are considered "off label," that is, used in age ranges, doses, and indications that are not approved by regulatory authorities. In addition, children and adolescents exposed to psychotropic drugs may be at higher risk than adults for certain adverse events such as metabolic and endocrine abnormalities associated with second-generation antipsychotic treatments. They may also present adverse events not previously assessed in adults such as growth delay with chronic use of methylphenidate. As psychotropic drugs are prescribed to control clinical symptoms in long-lasting psychiatric disorders, specific attention should be paid on the detection of delayed adverse events due to exposure during childhood. Further research should also elucidate the physiopathological mechanisms of psychotropic-induced toxicity and the potential value of personalized approaches based on genetics and neurobiology. In conclusion, additional safety data are urgently needed to clarify the risk-benefit ratio of psychotropic medications in children and adolescents and to adequately guide medical decision-making.

Keywords Psychotropic drugs • Children • Adolescents • Safety • Off-label

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
BMI	Body mass index
EPS	Extrapyramidal symptoms
FGAs	First-generation antipsychotics
MAOIs	Monoamine oxidase inhibitors
NaSSA	Noradrenergic and specific serotoninergic antidepressant
SCD	Sudden cardiac death
SGAs	Second-generation antipsychotics
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
SUD	Substance use disorder
TCAs	Tricyclic antidepressants

13.1 Introduction

Several millions of children and adolescents are being exposed to psychotropic medications worldwide. A five- to ninefold increase on the number of psychotropic prescriptions has been observed in most countries during the past 25 years (Steinhausen 2014; Steinhausen and Bisgaard 2014; Thomas et al. 2006).

There are several explanations to this increase in the use of psychiatric drugs. First, the change in modern psychiatry with the emphasis on a medical model as compared to a psychosocial interpretation of mental illness led to a greater utilization of medical interventions such as pharmacological agents. Moreover, increasing knowledge and awareness about mental disease and its negative social impact motivated early management in children and adolescents. Consequently, psychiatric disorders that have a childhood onset have been increasingly diagnosed and treated. Likewise, there has been a clear trend toward greater acceptability and demand for use of psychotropics in children, especially in those presenting with profound social impairment. Finally, in countries with limited availability of non-pharmacological therapeutic resources and inpatient psychiatric services, the use of these agents is a quick and affordable treatment and the only possibility of shortening hospital stay and favor outpatient care of these vulnerable patients (Harrison et al. 2012).

Despite the rise in the use of psychotropics to treat mental disease in children and adolescents, only a few drugs have a marketing authorization for use in this population. Consequently, psychotropics in children and adolescents are prescribed mainly "off label," i.e., for indications that are not approved by regulatory authorities or in children who are younger than the approved age ranges. Currently, 60–70 % of

prescriptions in pediatric psychiatry are considered "off label" (Koelch et al. 2009; Winterfeld et al. 2009).

Still, the majority of psychotropic medications are associated with significant adverse reactions in adults; thus their use in children is a major public health issue. Children and adolescents may be more susceptible to drug-related adverse events than adults, and this susceptibility may vary with age, growth, and developmental state. Recently, several regulatory warnings have been issued because of specific safety concerns such as the increased risk of suicidal behaviors in depressed children and adolescents treated with antidepressants although the reality of this association is still under debate (Stone 2014). Other recent examples include the rising concerns about the cardiac toxicity of methylphenidate and the potential endocrine adverse events of second-generation antipsychotics in children.

These considerations highlight the need to clarify the safety profile of psychotropic drugs in children and adolescents to promote their efficient and safe use and improve medical decision-making in routine practice.

13.2 Safety of Psychotropic Drugs in Children and Adolescents

13.2.1 Psychostimulants

13.2.1.1 Background

The use of psychostimulants in children with behavioral problems dates back to the 1930s. Currently, methylphenidate is the most frequently prescribed psychostimulant drug worldwide. In most European countries, it is also the only psychostimulant marketed for use in children, whereas in the USA, other molecules such as dextroamphetamine, lisdexamfetamine, dexmethylphenidate, and amphetamine mixed salts are also authorized in children and adolescents with attention deficit hyperactivity disorder (ADHD).

ADHD affects approximately 5 % of school-aged children and about 4 % of adults. The main symptoms are inattention, hyperactivity, and impulsivity. Individuals with ADHD may have difficulties in school, troubled relationships with family and peers, and low self-esteem. Psychostimulants are the most commonly prescribed medications for this indication although other agents such as alpha2-adrenergic (clonidine, guanfacine) or selective norepinephrine reuptake inhibitors (atomoxetine) may also be prescribed. Of course, a multimodal therapeutic approach is often necessary for this condition including pharmacological but also patient and family counseling or behavioral therapies. This chapter will be limited to the description of specific side effects of psychostimulants in children and adolescents with ADHD.

13.2.1.2 Safety of Psychostimulants in Children and Adolescents

The most extensively evaluated agent with regard to safety in the treatment of ADHD is methylphenidate. Nevertheless, all ADHD psychostimulants share similar pharmacological properties, and the described side effects are quite similar for the different molecules.

The main side effects observed are a decrease in appetite, stomachache, nausea, headache, insomnia, and nervousness (Efron et al. 1997; Greenhill et al. 2001). They are typically observed at the initiation of treatment by a psychostimulant agent, and a dose-effect relationship has been demonstrated (Efron et al. 1997; Greenhill et al. 2001). Side effects may lead to treatment discontinuation in less than 5 % of school-aged children treated with methylphenidate. However, this percentage varies widely and is estimated at approximately 9 % of preschoolers and 18 % of children with pervasive developmental disorders (Efron et al. 1997; Greenhill et al. 2001; Wigal et al. 2006).

Three major safety issues associated with the use of psychostimulants in children and adolescents will be discussed in this chapter as they are specific to the pediatric population and have been the subject of safety warnings issued by several regulatory agencies.

Cardiovascular Effects

Effects on Blood Pressure and Heart Rate

ADHD psychostimulants are sympathomimetic agents which increase noradrenergic and dopaminergic transmission. An increase of the heart rate and the blood pressure may be considered as one of their intrinsic pharmacological properties (Volkow et al. 2003). Indeed, clinical examination shortly after administration of methylphenidate has shown a slight, but statistically significant, increase in blood pressure and heart rate (increase of 2–6 bpm for the heart rate, 2–4 mmHg for the systolic blood pressure, and 1–3 mmHg for the diastolic blood pressure) (Cortese et al. 2013; Hammerness et al. 2011; Vitiello 2008).

In the Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study, 579 children aged 7–9 years were randomly assigned to one of the four treatments: medication management, behavioral therapy, combination of medication management and behavioral therapy, or usual community care, for a total of 14 months (Vitiello et al. 2012). No treatment effect on either systolic or diastolic blood pressure could be detected. A moderate increase in the mean heart rate at the end of the trial was observed in children treated with stimulants (84.2 bpm [SD = 12.4] in the medication management group and 84.6 bpm [SD = 12.0] in medication management and behavioral therapy) compared to those treated with behavioral therapy alone or usual community treatment (79.1 [SD = 12.9] and 78.9 bpm [SD = 12.9], respectively). Conversely, a large open-label study including 2,968 children treated for up to 15 weeks with amphetamine salts showed moderate

increases in both heart rate and blood pressure which tended to persist but were considered not clinically relevant (Donner et al. 2007). Furthermore, currently available data do not support the potential association between the use of stimulant medications and risk of electrocardiographic modifications (Awudu and Besag 2014).

Beyond 2 years of treatment, limited evidence on cardiovascular toxicity is available. The MTA study included a naturalistic follow-up of participants at 3, 6, 8 and 10 years and did not show any increased risk of hypertension or tachycardia. Yet, subjects with highest cumulative stimulant exposure during the trial presented higher heart rates 8 years after treatment discontinuation regardless of current medication use (Vitiello et al. 2012). This raises the question of a potential impact of stimulant treatment on long-term blood pressures and heart rates in previously treated patients. Indeed, the risk for cardiovascular disease increases with increasing values of blood pressure even though no specified cutoff has been defined (Vitiello 2008). Currently, there is no evidence supporting the presence of an increased risk for hypertension or cardiovascular disease in adults who were medicated as children. Yet, this issue is still poorly investigated especially with regard to the fact that stimulant treatments are usually prescribed from early childhood to adulthood. It is of note that self-reported cardiac events in adulthood were not associated with past ADHD medications in the 2004–2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Peyre et al. 2014).

Sudden and Severe Cardiovascular Events

In 2006, the FDA has issued several safety warnings after 18 sudden cardiac deaths in children treated with psychostimulant medications between 1992 and 2005. However, six of these patients presented underlying cardiac abnormalities (Bange et al. 2014). Ever since, the potential risk association between stimulant treatment and sudden cardiac events (sudden cardiac death, acute myocardial infarction, and stroke) in children has been a major focus. In a US population-based cohort study of children and young adults, current users of ADHD medications were not found to be at increased risk of severe cardiovascular events when compared to nonusers and former users (Cooper et al. 2011; Gould et al. 2009). Similarly, a review of five population-based studies based on insurance claims data showed a moderate association of ADHD stimulant medications and occurrence of mild cardiovascular events such as tachycardia. However, no association with more serious events such as sudden cardiac death, stroke, or myocardial infarction was found (Winterstein et al. 2012). To date, there is no reliable evidence to support risk association between ADHD stimulant drugs and severe cardiovascular events in children and adolescents.

Thus, the European ADHD Guidelines Group recommends a thorough clinical interview to determine any potential cardiovascular risk factor before starting stimulant medication (Cortese et al. 2013). Baseline heart rate and blood pressure should be recorded and monitored every 3–6 months during therapy. Electrocardiographic and cardiac ultrasound examinations are not to be performed systematically except for individuals with personal or family cardiovascular risk factors.

Growth and Metabolic Effects

The possibility that long-term stimulant treatment of children may impact growth velocity is now well documented. From 6 months to 3.5 years of treatment, an analysis of 18 cohort studies of psychostimulants prescriptions found evidence of significant height and weight deficits in treated populations (Faraone et al. 2008). The effect on weight typically emerges in the first few months of treatment and stabilizes afterward, but the effect on height takes at least 1 year to become clinically detectable. The deficit in height is estimated to be approximately of 1 cm per year during the first 1–3 years of therapy in children treated with methylphenidate daily doses above 20 mg (Cortese et al. 2013; Faraone et al. 2008; Poulton 2005). Nevertheless, weight and height rebounds have been reported after treatment discontinuation, and a full compensation of the initial weight and height drug-induced loss is possible 2 years after the end of stimulant therapy (Cortese et al. 2013; Faraone et al. 2008). No differences on growth suppression were found between users of methylphenidate and those of other psychostimulant agents (Faraone et al. 2008).

The results of the Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study suggest that the effects of stimulants on growth and weight are dose dependent. In the four treatment groups, medication management, behavioral therapy, combination of medication management and behavioral therapy, and routine community care, mean height increase during study period (14 months of treatment and 10 month follow-up) was, respectively, 4.25 cm, 6.19 cm, 4.85 cm, and 5.68 cm. The estimated loss of height was 1.23 cm/year in the medication management group. With regard to weight, the respective gain observed was 1.64 kg, 4.53 kg, 2.52 kg, and 3.13 kg. Again, estimated loss of weight was 2.48 kg/year in the medication management group (MTA Cooperative Group National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24 month outcomes of treatment strategies for attention deficit hyperactivity disorder 2004). During the naturalistic follow-up of the MTA population, growth suppression was especially evident during the first 2 years of stimulant treatment (MTA Cooperative Group National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24 month outcomes of treatment strategies for attention deficit hyperactivity disorder 2004; Biederman et al. 2010).

In a large cohort of adults with ADHD using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), ADHD participants who received stimulants ($n=216$) had a mean height of 68.29 in. (SD = 0.34), those who never received stimulants ($n=591$) had a mean height of 67.90 in. (SD = 0.23), and participants without ADHD ($n=33{,}846$) had a mean height of 66.93 in. (SD = 0.05). Following statistical adjustments, no significant difference in adult height was found between groups (Peyre et al. 2013).

In conclusion, current evidence supports the association between the use of stimulants and height and weight gain delays. Impact on growth seems to be dose dependent and reversible after discontinuation of the stimulant agent. These delays do not seem to affect final height, but further data from children with long-term stimulant

medication and use during puberty are needed to clarify this issue. Also, the underlying physiopathological mechanisms remain to be defined. A first hypothesis is related to the decrease of appetite caused by stimulant medications. According to another hypothesis, hypothalamic dopamine changes induced by stimulants would be associated with modifications of the pituitary function and subsequently growth. This last hypothesis may further be supported by the fact that dopamine antagonists increase weight and appear to accelerate height growth. More recently, a transient decrease in insulin-dependent growth factor after 4 months of stimulant treatment was reported in a small number of children, but no changes were evident after 8 or 14 months of follow-up. Despite these hypotheses, the mechanism implicated in the height growth delay is still unknown (Vitiello 2008).

Giving these elements, the European ADHD Guidelines Group and several national regulatory agencies recommend monitoring of appetite, weight, height, and body mass index every 6 months in children and adolescents under stimulant therapy (Graham et al. 2011). Some clinicians also recommend the administration of medication after meal, use of high-calories snacks or late evening meals, and discontinuation of treatment during weekends or holidays, but evidence on the impact of these measures is extremely limited. Moreover, the reduction of drug dose and switching to alternative drug class or formulation have been proposed. Addressing patients to a pediatric endocrinologist or a growth specialist is advised when height and weight values are below critical thresholds.

Psychiatric and Neurological Effects

The association between the use of stimulant medications and stimulant misuse or substance use disorder has been extensively evaluated. On one hand, most of studies did not find an increased risk in stimulants misuse in treated ADHD children and adolescents. Although the misuse of stimulants is estimated to be between 5 % and 9 % in high school and up to 35 % in college-aged populations (Goldstein 2013; Wilens et al. 2008), ADHD patients were not found to be more at risk of stimulant misuse than non-ADHD subjects. Several factors related to the risk of stimulant misuse have been determined such as the presence of a conduct disorder, use of immediate release psychostimulant agents, and male gender. Therefore, it is advised to closely monitor the use of psychostimulant in patients with current or previous substance abuse history and to preferably use extended release formulations (Cortese et al. 2013; Wilens and Morrison 2011). On the other hand, ADHD children and adolescents are more susceptible to present substance use or substance use disorder (SUD) than non-ADHD individuals (Molina et al. 2013). Several studies have evaluated whether the use of stimulants increases further this existing risk, and results are quite controversial. A meta-analysis of six studies suggests that psychostimulant therapy in childhood might be associated with a reduction in the risk of alcohol or drug use disorders. The ADHD-treated population of children was 1.9 (1.1–3.6) less at risk of abuse compared to nontreated ADHD children (Wilens et al. 2003). A more recent meta-analysis however suggested that the treatment of ADHD with

stimulant medication neither protects nor increases the risk for later substance use disorder (Humphreys et al. 2013). All these results underline the need to carefully monitor children and adolescents with ADHD especially given their increased risk for use and abuse of multiple substances that may not improve with stimulant medication (Molina et al. 2013).

The occurrence of suicidal thoughts and behaviors during stimulant treatment has also been studied. A register-based longitudinal study did not find any evidence of an association between the use of drug treatments for ADHD and the risk of suicidal behavior (Chen et al. 2014). However, it is highly recommended to screen patients for suicidal thoughts and behavior before starting stimulant medication and continue appropriate monitoring during treatment. Due to the high rate of psychiatric comorbidities in ADHD, focus on the management of disorders underlying suicidal thoughts or behaviors is also advised. The European ADHD Guidelines Group does not consider the presence of suicidal thoughts or behaviors as an absolute contraindication for ADHD drugs; however a dose reduction or discontinuation may be warranted (Graham et al. 2011).

Occurrence of other psychiatric symptoms such as psychotic symptoms has been found in approximately 1.5 % of ADHD subjects treated with stimulants in a review of post-marketing surveillance reports and clinical trials (Mosholder et al. 2009). It is recommended to reduce therapeutic doses of ADHD drugs or to consider discontinuation of ADHD treatment in case of occurrence of such symptoms.

Further, in patients with tic disorders, the use of ADHD stimulant agents may worsen clinical symptoms. However, a Cochrane Collaboration meta-analysis concluded that psychostimulants do not overall worsen tics but may do so in individual cases (Pringsheim and Steeves 2011). To date, there is no evidence associating treatment by stimulant to the onset of tic disorders (Roessner et al. 2006).

Finally, there is no evidence of an increased risk of seizure episodes in psychostimulant-treated children with well-controlled epilepsy (Koneski and Casella 2010; Koneski et al. 2011). Nevertheless, the use of methylphenidate is not recommended in case of seizures, and a close collaboration between pediatric neurologists and psychiatrists is recommended in children with epilepsy.

13.2.2 Antidepressants

13.2.2.1 Antidepressant Classes and Indications

The most important classes of antidepressants prescribed in children and adolescents are the following: (1) selective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram), (2) serotonin-norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, milnacipran, duloxetine), (3) tricyclic antidepressants (TCAs) (imipramine, amitriptyline, nortriptyline), (4) noradrenergic and specific serotoninergic antidepressant (NaSSA) (mirtazapine), and (5) monoamine oxidase inhibitors (MAOIs) (phenelzine,

selegiline). Other classes of antidepressants are also marketed for use in adults but marginally used in children such as melatonergic antidepressants (agomelatonin), norepinephrine reuptake inhibitors (reboxetine), or norepinephrine-dopamine reuptake inhibitors (bupropion). In children, SSRIs are the most commonly prescribed agents, representing approximately 70–80 % of total antidepressants' prescriptions (Hoffmann et al. 2014; Ma et al. 2005; Wijlaars et al. 2012).

Antidepressants are prescribed in three main indications in children and adolescents:

1. Depression: In most countries, fluoxetine is the only antidepressant approved by national agencies to treat depression in children over the age of 8 years. In some countries such as the USA, escitalopram is also labeled for use in children aged over 12 years.
2. Obsessive-compulsive disorder: fluvoxamine and sertraline are authorized in several European countries and in the USA. In addition, fluoxetine and clomipramine are also authorized in this indication in the USA.
3. Child enuresis: A tricyclic antidepressant, imipramine, is authorized in many countries for childhood enuresis from the age of 6 years.

The use of antidepressants in children and adolescents has been evaluated in several other indications. The efficacy of SSRIs associated with a cognitive-behavioral therapy (CBT) in anxiety disorders has been extensively studied. SRRIs have also been evaluated in ADHD, but data remain scarce (Mohatt et al. 2014; Park et al. 2014; Piacentini et al. 2014; Strawn et al. 2014). The use of TCAs has been evaluated in depression, ADHD, anxiety disorders, and chronic pain (Ghanizadeh 2013; Hazell and Mirzaie 2013; Kachko et al. 2014; Patten et al. 2012) and specifically that of amitriptyline for the treatment of chronic migraine and functional abdominal pain in children and adolescents (Kaminski et al. 2011; Powers et al. 2013). However, no further regulatory approvals have been issued mainly because of the limited sample size and the low methodological quality of these studies.

13.2.2.2 Safety of Antidepressants in Children and adolescents

Suicidal Behaviors and Use of Antidepressants

Since 2003, concerns have been raised about the possible risk of increased suicidal behaviors in children and adolescents with depression treated with antidepressant agents. In 2004, the FDA and many other national regulatory agencies issued warnings concerning the risk of suicidal behavior associated with the use of antidepressants in children and adolescents. Indeed, a meta-analysis conducted by the FDA showed an increase in the risk of suicidal behaviors and ideations among young patients treated with antidepressants for psychiatric indications as compared with placebo-treated patients (OR = 2.22 [1.40–3.40]) (Friedman and Leon 2007). Another meta-analysis conducted by the Cochrane Collaboration also found an

increased risk of suicide attempts and suicidal ideations of (OR = 1.80 [1.19–2.72]) in depressed children and adolescents treated with SSRIs versus placebo (Hetrick et al. 2007).

Regulatory warnings do not distinguish between the different antidepressant agents. Nevertheless, drug characteristics in terms of receptor selectivity and elimination half-life are different. In this respect, a systematic review of published and unpublished data suggests that fluoxetine presents a favorable risk-benefit profile, paroxetine and sertraline present an equivocal or weak risk-benefit profile, and venlafaxine and citalopram present an unfavorable risk-benefit profile in childhood depression (Whittington et al. 2004).

Furthermore, among 102,647 US depressed children and young adults aged 10–24 years who initiated therapy with antidepressants, similar rates of deliberate self-harm were observed with either SSRI or SNRI agents (Miller et al. 2014a). However, the rate of deliberate self-harm among patients who initiated therapy with antidepressants at high therapeutic doses was approximately twice as high as among matched patients who initiated modal therapeutic doses (hazard ratio (HR) = 2.2 [1.6–3.0]) (Miller et al. 2014b). A 2012 Cochrane meta-analysis found evidence of an increased risk of suicide-related outcome in children and adolescents treated with antidepressants compared to placebo (RR 1.58 [1.02–2.45]). Nevertheless, there was no evidence that the magnitude of the effect (compared with placebo) was modified by individual antidepressant class (Hetrick et al. 2012). It was also found that initiating antidepressants at higher therapeutic doses increased the risk of deliberate self-harm in children and adolescents. Finally, some studies demonstrated a similar risk of suicidal acts for SSRIs and TCAs (RR = 0.92 [0.43–2.00]) (Schneeweiss et al. 2010).

Following regulatory warnings about antidepressants' use, the rate of depression diagnoses and prescription of antidepressant drugs decreased in many countries (Gibbons et al. 2007; Kurdyak et al. 2007; Murray et al. 2005). Thus, the risk of "doing nothing" progressively became a concern and a matter of debate (Friedman 2014; Stone 2014). In fact, some epidemiological studies have shown that the suicide rate in adolescents was inversely associated with the rate of antidepressants' prescriptions (Friedman 2014; Gibbons et al. 2006; Stone 2014).

Other Psychiatric Side Effects

Other psychiatric side effects related to the use of antidepressants in children and adolescents may be grouped into (1) mania spectrum (mania, hypomania, elevated mood), (2) depression spectrum (aggravation of depression, irritability anger, hypersensitivity), (3) agitation spectrum (agitation, akathisia, restlessness, nervousness, hyperactivity), and (4) anxiety symptoms (Emslie et al. 2006; Gordon and Melvin 2013).

The related manic switching in vulnerable adolescents treated with antidepressants is estimated to be 5.4 % (Martin et al. 2004). Randomized trials have suggested that the risk is less than 2 % in the short and medium term after drug initiation

(Cheung et al. 2005). Simple mania spectrum symptoms are globally more prevalent than hypomania. Retrospective studies have found that fluoxetine can cause irritability and hypomania-like symptoms and sertraline "behavioral activation" (Gordon and Melvin 2013). In this context, it is advised to monitor patients closely for emergent suicidality, hostility, agitation, and mania.

Neurological Side Effects

An increased risk of seizure has been reported with the use of clomipramine during premarketing evaluation. This risk was related to either the dose of clomipramine or the duration of the treatment or both. Seizures have also been associated with the use SSRIs in children and adolescents (Cheung et al. 2005). Therefore, caution is advised when clomipramine or SSRIs are prescribed to patients with a history of seizures or other factors that may predispose to seizures.

Metabolic and Endocrine Side Effects

Currently, there are no data on endocrine adverse effects and the use of tricyclic agents. However, concerns have risen about the endocrine side effects of SSRI exposure in children and adolescents although studies remain scarce. Preclinical studies found nonreversible testicular degeneration with histologic abnormalities in young rats exposed to high levels of SSRIs (Monteiro Filho et al. 2014; Schmidt et al. 1988). However, these studies were performed with very high exposures (20-fold higher than clinical pediatric exposure) in animals. No data exist on fertility of adults who had been treated in their childhood with antidepressants (Prozac Product monograph; Schmidt et al. 1988).

Growth delay has also been cited as a potential SSRI side effect. Four cases of children aged from 9 to 13 years treated with SSRIs for obsessive-compulsive disorder and Tourette syndrome had experienced growth delay with decreased growth hormone (GH) levels, without any other anomaly on the gonadotropic axis. Authors suggested that suppression of GH secretion may occur during therapy with SSRIs and emphasize the need for further larger studies (Weintrob et al. 2002). An effect on adult size has not been established.

In a retrospective cohort study including 11,970 children and adolescents under antidepressant therapy, the presence of obesity/weight gain, type 2 diabetes mellitus, and dyslipidemia was more common in those under SSRIs compared to a random sample of 4,500 children nontreated with psychotropic medications (OR = 1.49; 1.37; 1.44) (Jerrell 2010).

Effects of SSRIs on prolactin levels have been reported in animals and adult patients (Muench and Hamer 2010; Peterson 2001), but in children and adolescents, only one study has associated use of SSRIs and hyperprolactinemia in children and adolescents (Jerrell 2010). In this study, reproductive and/or sexual adverse events were not associated with the use of SSRIs.

Thus, despite information included in the summary of product characteristics of SSRIs excluding the possibility of a pubertal delay, it is recommended to monitor growth and pubertal development (size, weight, Tanner level) during and after treatment with an SSRI agent. If a growth or pubertal delay is observed, it is strongly advised to refer to a pediatric endocrinologist.

Serotonin Syndrome

Several case reports describe the occurrence of serotonin syndrome in children and adolescents treated with antidepressant agents. Serotonin syndrome is associated with hyperthermia, hypertension, headache, flushing, shaking, nausea, anxiety, agitation, confusion, hallucination, or insomnia and is probably related to an excess of serotonin. Nevertheless, this adverse event seems to be extremely rare (Ghanizadeh 2013; Boyer and Shannon 2005).

Risk of Cardiac Arrhythmias with Fluoxetine

In 2013, the FDA issued a communication to notify patients and health-care providers about the potential risk of cardiac arrhythmias in patients using fluoxetine. This was related to the reporting of post-marketing cases of QT interval prolongation and ventricular arrhythmias. Therefore, the use of fluoxetine is not recommended in patients with underlying cardiovascular conditions, hypokalemia/hypomagnesemia and those under medications that might predispose to prolongation of the QT interval and occurrence of torsade de pointes. In addition, fluoxetine should be used cautiously in patients with recent myocardial infarction, uncompensated heart failure, congenital QT syndrome, drug overdose risk factors such as hepatic impairment, and those presenting a CYP2D6 poor metabolizer status and/or concurrent use of CYP2D6 inhibitors or other highly bound drugs.

Other Side Effects

The TADS study was conducted by the National Institute of Mental Health (NIMH) to evaluate the efficacy and safety of antidepressants in depressed children and adolescents. Patients were randomized in four treatment groups: fluoxetine, cognitive-behavioral therapy, combination treatment (fluoxetine and cognitive-behavioral therapy), and placebo for 12 weeks (Emslie et al. 2006). Sedation, insomnia, vomiting, and upper abdominal pain were reported in less than 5 % of subjects treated with fluoxetine, and headache was the most frequent side effect appearing in 11.9 % of the patients in this treatment group. Moreover, in a randomized controlled trial (RCT) evaluating the efficacy and safety of sertraline in depressed children and adolescents, the most common side effects were fatigue, insomnia, restlessness,

headache, gastric distress, sore throat, and yawning (Melvin et al. 2006; Walkup et al. 2008). In both trials, the probability of treatment discontinuation due to adverse effects was relatively small (5–10 %) (Cheung et al. 2005) and declined over time (Emslie et al. 2006).

With regard to tricyclic agents, a Cochrane Collaboration meta-analysis found a higher incidence of vertigo (RR = 2.76 [1.73–4.43]), orthostatic hypotension (RR = 4.86 [1.69–13.97]), tremor (RR = 5.43 [1.64–17.98]), and dry mouth (RR = 3.35 [1.98–5.64]) in children and adolescents treated with TCAs compared to those treated with placebo (Hazell and Mirzaie 2013).

13.2.3 Antipsychotics

13.2.3.1 Use of Antipsychotics in Children and Adolescents

Antipsychotic medications are clearly effective in treating several psychiatric conditions in children and adolescents. However, as in adults, prescription of antipsychotics involves a difficult balance between the need to relieve mental disease symptoms and the risk of drug-induced toxicity (Masi and Liboni 2011).

Antipsychotics are classified according to the timeline of their development, their pharmacology, and their safety profiles. First-generation or "typical" antipsychotics (FGAs) act therapeutically by antagonizing dopamine D2 receptors. Their safety profile, in particular neurological toxicity, depends primarily on their relative potency in binding to dopamine D2 receptors. Second-generation or "atypical" antipsychotics (SGAs), launched in the 1990s, bind to other neuroreceptors than only dopamine D2, and a newer antipsychotic, aripiprazole, has been developed which is a partial agonist of dopamine D2 and serotonin 5-HT5 receptors. "Atypical" antipsychotics have been initially perceived as more effective and safer than "typical" antipsychotics.

Hence, over the past three decades, SGAs have dominated prescribing preferences worldwide (Gardner et al. 2005; Muench and Hamer 2010; Verdoux et al. 2010). Indeed, the increase in antipsychotics' use that has been consistently reported in children and adolescents over the years is mainly attributed to an increment in the prescription of SGAs (Cooper et al. 2006; Kalverdijk et al. 2008; Olfson et al. 2006; Rani et al. 2008; Ronsley et al. 2013). Still, a wide variability across countries has been observed with atypical antipsychotic subclass representing 66 % of antipsychotic use in youth in the USA and 48 % in the Netherlands but only 5 % in Germany (data from year 2000) (Zito et al. 2008). The duration of treatment with these agents has also been increasing (Kalverdijk et al. 2008; Rani et al. 2008).

Currently, several FGAs and SGAs have a marketing authorization for use in the pediatric population with certain differences between the USA and Europe (Table 13.1). However, the use of antipsychotics in children and adolescents is principally "off label," that is for indications that are not approved by regulatory

Table 13.1 Approved indications of commonly used antipsychotics for pediatric patients according to regulatory agency

Antipsychotic drug		Indication	FDA approval patient age (years)	EMA approval patient age (years)
FGAs	Haloperidol[a]	Schizophrenia	–	≥3[b]
		Behavioral disorders (hyperactivity, aggression)	–	≥3[b]
		Gilles de la Tourette syndrome	–	≥3[b]
	Chlorpromazine	Childhood schizophrenia	1–12	≥1[b]
		Bipolar disorder (mania)	1–12	–
		Autism	–	≥1[b]
SGAs	Clozapine	Schizophrenia in patients unresponsive or intolerant to other antipsychotics	–	>16
	Risperidone	Schizophrenia	13–17	≥15
		Bipolar I disorder	10–17	≥13
		Irritability associated with autistic disorder	5–16	–
		Persistent aggression in conduct disorder[c]	–	≥5
	Olanzapine	Schizophrenia	13–17	–
		Bipolar I disorder	13–17	–
	Quetiapine	Schizophrenia	13–17	–
		Bipolar I disorder	10–17	–
	Aripiprazole	Schizophrenia	13–17	≥15
		Bipolar I disorder[d]	10–17	≥13
		Irritability associated with autistic disorder	6–17	–

Dashes mean that the product has no pediatric approval in the specific indication. Ziprasidone has no approval for pediatric use in the USA or the EU

[a]Haloperidol solution for injection is the only form available in the USA, but in European countries, both injectable (5 mg/ml) and oral (2 mg/ml) solutions are marketed. Only oral haloperidol is indicated in children.

[b]Approved age ranges provided for haloperidol and chlorpromazine are based on current UK marketing authorizations. There are no centralized EMA authorizations for these molecules in children.

[c]Short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors requires pharmacological treatment

[d]As monotherapy or as an adjunct to lithium or valproate

authorities or used in children who are younger than the approved age ranges. "Off-label" indications include mainly attention deficit hyperactivity disorder (ADHD), conduct and behavioral disturbances (aggression, self-injury, disruptive behavior, etc.), and mood disorders (Penfold et al. 2013; Baribeau and Anagnostou 2014).

13.2.3.2 Safety of Antipsychotics in Children and Adolescents

Because of the paucity of comparative studies in children, there is currently little evidence to support the superiority of SGAs over FGAs or a difference between SGAs for the treatment of children and adolescents with psychosis or behavioral disorders (Kennedy et al. 2007; Kumra et al. 2008; Sikich 2008; Sikich et al. 2008; Loy et al. 2012; Kumar et al. 2013). Conversely, the safety profile of antipsychotics differs substantially. Atypical antipsychotics are associated with a lower risk of neurological adverse reactions than first-generation drugs, but they are clearly associated with a higher risk of weight gain and metabolic abnormalities in both adults and children (Caccia 2013; Maher et al. 2011; Seida et al. 2012). Nevertheless and despite initial expectations, observed variability appears to be greater among specific agents than between the first- and second-generation antipsychotic classes (Masi and Liboni 2011; Muench and Hamer 2010; Vitiello et al. 2009; Fraguas et al. 2011).

Current knowledge on the most prevalent adverse reactions to antipsychotics in children and adolescents is provided in the following sections. Since the use of typical antipsychotics is actually limited in children and adolescents, safety issues are exposed mainly with regard to second-generation compounds. The strength of association between a given agent and a specific adverse event is given as compared to placebo since very few head-to-head comparisons of antipsychotics have been conducted in children and adolescents. Occurrence of neuroleptic malignant syndrome, a rare but potentially life-threatening adverse reaction, is not detailed in this section (*see* Chap. 10).

Neurological Toxicity

Sedation and somnolence are common with all antipsychotic medications, and they are usually dose dependent. Rates tend to be higher with FGAs, clozapine, ziprasidone, olanzapine, and risperidone and lower with aripiprazole and quetiapine (Cohen et al. 2012).

Another major neurological adverse reaction is the occurrence of extrapyramidal symptoms (EPS) which comprises drug-induced parkinsonism, akathisia, acute dystonia, and tardive dyskinesia. Children and adolescents appear to be more sensitive to EPS than adults especially when they present mental retardation or CNS damage or are drug-naïve patients. EPS are more common with typical antipsychotics like haloperidol, but newer antipsychotics are not totally free of such reactions. Treatment with risperidone, olanzapine, and aripiprazole are related to an elevated risk of EPS, especially at high doses. In fact, the incidence of EPS in schizophrenic patients treated with aripiprazole monotherapy compared to placebo treatment is much higher in pediatric patients compared to adults (Correll 2008). The risk of EPS appears to be low with clozapine and quetiapine. Data on ziprasidone are too scarce to draw reliable conclusions. The majority of extrapyramidal symptoms are reversible after discontinuation of the offending agent with the exceptions of tardive

dystonia and tardive dyskinesia that may be difficult to treat and ultimately become permanent in some patients. Moreover, EPS often generate major psychological distress and poor compliance with therapy.

The majority of antipsychotics can lower the seizure threshold and should be used with caution in patients who have a history of seizures and in those with organic brain disorders. Convulsions are more common under treatment by certain FGAs and clozapine, especially at high doses (Masi and Liboni 2011).

Finally, for aripiprazole, a safety warning was issued on the potential risk of increased suicidal ideation and suicide in children, adolescents, and young adults with major depressive disorder. The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Nevertheless, no suicides occurred in any of the pediatric trials.

Metabolic Disorders

All antipsychotics may be associated with weight gain and an increase of body mass index (BMI) though such effects are probably the most significant adverse reactions of atypical agents (Muench and Hamer 2010). Excessive weight gain should not be disregarded in treated children and adolescents because it may contribute to significant morbidity and mortality in adulthood. Being overweight is a major determinant of a general metabolic disorder, the metabolic syndrome (obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol levels, hypertension, and hyperglycemia) associated with atherosclerosis, coronary artery disease, and colorectal cancer in adults (Correll et al. 2006). Also, in long-term use, weight gain has been associated with liver enzyme abnormalities and fatty infiltration (Masi and Liboni 2011). In addition, it contributes to poor medication adherence, social withdrawal, and low self-esteem which may be sources of significant psychological morbidity. Mean weight gain during therapy appears to be important with olanzapine, clozapine, and risperidone; moderate with quetiapine; and low with aripiprazole and ziprasidone. Despite great interindividual variability in weight gain, possibly related to genetic predisposition, dietary recommendations and counseling (lifestyle, exercise) should be provided at the initiation of antipsychotic therapy for all patients. Treatment with metformin to stabilize weight has been proposed, but data are limited in children and adolescents (Klein et al. 2006; Shin et al. 2009).

Increase in the blood levels of glucose, triglycerides, and cholesterol may also be attributable to antipsychotic agents. Glycemic abnormalities may vary from hyperglycemia due to mild insulin resistance to new-onset diabetes and worsening of glycemic control in patients with preexisting diabetes mellitus (Pringsheim et al. 2011a). Incidence is not well established in children and adolescents under treatment, but the risk appears to be high with olanzapine and risperidone, moderate with quetiapine and aripiprazole, and low with ziprasidone and the first-generation agent haloperidol. Moreover, treatment with olanzapine, clozapine, and quetiapine has been associated with increased blood levels of triglycerides and cholesterol, whereas the risk is moderate with aripiprazole and low with risperidone, ziprasidone, and

haloperidol. Adolescents treated with olanzapine have an increased potential for weight gain and hyperlipidemia compared to adult patients. Similar to weight gain, drug-induced metabolic changes may persist over time and become clinically meaningful only after prolonged use of antipsychotic medication. In the absence of long-term follow-up studies, cardiometabolic adverse effects are probably underestimated in children and adolescents.

Endocrine Disorders

Hyperprolactinemia is a direct consequence of the antagonism of dopamine D2 receptors by both first- and second-generation antipsychotic agents. In most cases, hyperprolactinemia is dose dependent, tends to normalize with time, and completely resolves after cessation of antipsychotic treatment. Clinical signs of hyperprolactinemia include amenorrhea and other menstrual cycle disorders, galactorrhea, hirsutism, and sexual disturbances (decreased libido, erectile difficulties, etc.). Nevertheless, hyperprolactinemia may persist throughout treatment and remain totally asymptomatic or cause clinical signs that are difficult to express for a child or an adolescent (e.g., sexual dysfunction). Additional long-term consequences of prolonged hyperprolactinemia and subsequent hypogonadism include pubertal delay, growth arrest, and osteoporosis (Masi and Liboni 2011; Vitiello et al. 2009). Risperidone and olanzapine tend to favor meaningful increase in prolactin secretion, whereas the effect of quetiapine and ziprasidone is moderate and aripiprazole may even lower levels of prolactin.

Hematological Toxicity

Antipsychotic agents may cause neutropenia mainly in patients presenting low baseline blood counts or using cytotoxic concomitant therapy. However, a risk of life-threatening agranulocytosis has been reported in patients treated with clozapine. Neutrophil blood counts generally normalize after discontinuation of clozapine (Masi and Liboni 2011).

Cardiovascular Toxicity

Orthostatic hypotension and tachycardia have been described with the use of antipsychotic medications. These effects are less common in children and adolescents than in elderly patients and in most cases are clinically irrelevant (Masi and Liboni 2011). Cardiovascular effects are more frequent with certain FGAs, such as chlorpromazine and clozapine, though they have also been observed with the use of quetiapine and risperidone especially with rapid uptitration of dose. In fact, quetiapine has been associated with hypertension in children, whereas this event was never observed in treated adults. Moreover, myocarditis occurring at the beginning of treatment has been reported with clozapine (Ronaldson et al. 2010).

A potentially serious adverse event related with antipsychotics' use is prolongation of ventricular repolarization that may lead to ventricular arrhythmia (e.g., torsades de pointes) and ultimately to sudden cardiac death (SCD). The incidence of SCD in adults treated with antipsychotics is twice that of the general population (Muench and Hamer 2010). In children, only one such case has been described in a child treated with ziprasidone. However, subclinical QTc prolongation has been reported in children under ziprasidone (Caccia 2013; Correll 2008). Subsequently, cautious use of all agents is recommended in children especially those with existing cardiac disease or family history of QT prolongation (Germanò et al. 2014).

Overall, children and adolescents tend to be more sensitive to the toxicity of antipsychotics than adult patients, especially when polypharmacotherapy is used. They experience more frequently weight gain, metabolic abnormalities (hyperglycemia, dyslipidemia), hyperprolactinemia, and neurological adverse reactions (sedation/somnolence, extrapyramidal symptoms, seizures). Conversely, they appear to be less susceptible to cardiovascular adverse reactions.

To date, safety data derive almost exclusively from cohort studies and meta-analyses of randomized controlled trials (Caccia 2013; Cohen et al. 2012; Pringsheim et al. 2011a). Yet, these studies were limited in follow-up time and sample size and therefore cannot provide reliable conclusions especially with regard to insulin/glycemic control, metabolic disorders, and occurrence of rare and distant adverse events. Moreover, the impact of antipsychotic medications on the physical, mental, and neurological development of children and adolescents, a safety issue specific to this population, has not been evaluated yet. In recent years, several networks have been created to routinely assess the efficacy and safety of antipsychotics in children: The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) in Canada (http://camesaguideline.org/), the Pediatric Atypical Antipsychotic monitoring Safety (PAMS) Study in the UK (Rani et al. 2009), and the SafEty of NeurolepTics in Infancy and Adolescence (SENTIA) in Spain (http://SENTIA.es). Analyses of large population health databases and patient registries through collaborative projects are actually required to clarify antipsychotics' safety profile and to define their distal risk-benefit ratio in children and adolescents (Rani et al. 2011).

13.2.3.3 Safety Monitoring of Children and Adolescents Treated with Antipsychotics

Antipsychotic medications present highly variable safety profiles. This may complicate prescribing and patient management; however it offers many therapeutic alternatives and, thus, the possibility to match patients with the most appropriate medication. Given the length of use of antipsychotics and the impact of patients' family history or lifestyle on the choice of the antipsychotic agent, thorough evaluation of risks for each distinct patient seems appropriate.

Currently, clozapine and olanzapine are not considered to be first-line antipsychotic treatments in children and adolescents because of their unfavorable safety profile. In particular, clozapine is reserved to patients who are resistant to other agents. Risperidone is actually the most commonly prescribed (Patten et al. 2012) and one of the most extensively evaluated antipsychotic agent in the pediatric population (Pringsheim et al. 2011a). Nevertheless, its safety profile is far from ideal as risperidone is frequently associated with rapid weight gain, metabolic abnormalities, significant somnolence and sedation, and the occurrence of extrapyramidal neurological symptoms. More recently developed agents such as aripiprazole, quetiapine, and ziprasidone offer interesting alternatives; however their efficacy and safety need to be further evaluated in children and adolescents.

Regardless of the drug used, children and adolescents that receive antipsychotic drugs should be proactively monitored for side effects. Physical examination (weight, height, BMI, waist circumference, blood pressure, and neurological examination for EPS) and certain standard laboratory tests (fasting plasma glucose, total cholesterol, LDL and HDL cholesterol, triglycerides, aspartate and alanine aminotransferase, prolactin) should be systematically performed at least in the first month after treatment initiation. More specific laboratory tests should be carried out according to the specific risk of treating agents: insulin levels in olanzapine treatment, thyroid-stimulating hormone (TSH) in quetiapine treatment, and neutrophil counts in clozapine treatment. Guidance on the electrocardiogram monitoring of treated patients has also been developed (Blair et al. 2004).

Evidence-based recommendations for monitoring of children and adolescents under atypical antipsychotics have been developed by the CAMESA guideline group in Canada. These recommendations are extremely useful in practice; however they reflect the paucity of evidence-based knowledge in the area and the need for further targeted research. In addition, they are limited to the first year of treatment because of the absence of long-term prospective studies. Safety of antipsychotics is a major focus especially in the young; however monitoring rates are still very low and studies of pharmacologic and behavioral interventions are extremely limited (Maayan and Correll 2011).

13.2.4 Other Psychotropic Medications

Anxiolytics and sedatives have no marketing authorization for use in child and adolescent psychiatry except for certain drugs (e.g., diazepam, hydroxyzine) in certain countries and under exceptional clinical conditions. Specific safety data on children and adolescents are extremely limited, although the use in children can be very prevalent in some countries (Murray et al. 2004; Pringsheim et al. 2011b; Zito et al. 2008).

Mood regulators such as lithium and anticonvulsants, carbamazepine and valproic acid, are also used beyond their marketing authorizations in pediatric psychiatric indications. The safety of lithium in children and adolescents with bipolar

I disorder has been evaluated in clinical trials of limited sample size (Geller et al. 2012), and adverse events are similar to those observed in adult patients (e.g., thyroid dysfunction). Toxicity of anticonvulsants used mainly for neurological indications has been extensively evaluated and is beyond the scope of this chapter.

13.3 Conclusion

The majority of psychotropic drugs provide only symptomatic management of clinical symptoms in lifelong psychiatric disorders. Children and adolescents are therefore exposed to these agents in a chronic manner or at least for a prolonged period of time. In fact, drug utilization studies have demonstrated not only that the incidence of the use of certain psychotropic drugs such as antipsychotics is increasing in children and adolescents but also that the duration of the therapy (Patten et al. 2012). In addition, young children are more likely to be receiving multiple psychotropic medications to control psychiatric comorbidities and improve social functioning. Currently, 60–70 % of pharmacological prescriptions in pediatric psychiatry are considered "off label" because they concern age ranges, doses, and indications that are not approved by regulatory authorities. For example, antipsychotic use in children and adolescents targets mainly nonpsychotic disorders. All these trends in psychotropic prescribing have significant implications for drug safety and patient monitoring during treatment (Steinhausen 2014). Furthermore, there is a significant rise of prescriptions of psychotropic drugs by family physicians and pediatricians (Ronsley et al. 2013; Meng et al. 2014) that may lack professional experience and resources to monitor children for potential side effects. Physicians who do not have sufficient knowledge and resources to carefully follow patients and assess drug safety should refrain from prescribing these medications and refer the patient to a specialist.

The substantial increase of psychotropic use in children and adolescents has not been accompanied by a similar increase in research-based evidence about the efficacy and safety of these medications. This increase in psychotropic drug use calls for long-term efficacy and, most importantly, safety studies in large samples in order to account for the dynamic processes of growth and brain development in the young patients. Further research should also attempt to elucidate the physiopathological mechanisms of psychotropic-induced toxicity and the potential value of personalized approaches based on genetics and neurobiology. Additional safety data are urgently needed to clarify the risk-benefit ratio of psychotropic medications in children and adolescents and to adequately guide medical decision-making. In the meantime, psychotropic prescribing in children and adolescents should involve a cautious balance between patients' therapeutic needs and a proactive monitoring of clinical efficacy and drug-induced toxicity.

References

Awudu GA, Besag FM (2014) Cardiovascular effects of methylphenidate, amphetamines and atomoxetine in the treatment of attention-deficit hyperactivity disorder: an update. Drug Saf 37(9):661–676. doi:10.1007/s40264-014-0201-8

Bange F, Le Heuzey MF, Acquaviva E, Delorme R, Mouren MC (2014) Cardiovascular risks and management during attention deficit hyperactivity disorder treatment with methylphenidate. Arch Pediatr 21(1):108–112. doi:10.1016/j.arcped.2013.11.001

Baribeau DA, Anagnostou E (2014) An update on medication management of behavioral disorders in autism. Curr Psychiatry Rep 16(3):437. doi:10.1007/s11920-014-0437-0

Biederman J, Spencer TJ, Monuteaux MC, Faraone SV (2010) A naturalistic 10-year prospective study of height and weight in children with attention-deficit hyperactivity disorder grown up: sex and treatment effects. J Pediatr 157(4):635–640, 640 e631. doi:10.1016/j.jpeds.2010.04.025

Blair J, Taggart B, Martin A (2004) Electrocardiographic safety profile and monitoring guidelines in pediatric psychopharmacology. J Neural Transm 111(7):791–815. doi:10.1007/s00702-004-0153-8

Boyer EW, Shannon M (2005) The serotonin syndrome. N Engl J Med 352(11):1112–1120. doi:10.1056/NEJMra041867

Caccia S (2013) Safety and pharmacokinetics of atypical antipsychotics in children and adolescents. Paediatr Drugs 15(3):217–233. doi:10.1007/s40272-013-0024-6

Chen Q, Sjolander A, Runeson B, D'Onofrio BM, Lichtenstein P, Larsson H (2014) Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. BMJ 348:g3769. doi:10.1136/bmj.g3769

Cheung AH, Emslie GJ, Mayes TL (2005) Review of the efficacy and safety of antidepressants in youthdepression.JChildPsycholPsychiatry46(7):735–754.doi:10.1111/j.1469-7610.2005.01467.x

Cohen D, Bonnot O, Bodeau N, Consoli A, Laurent C (2012) Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. J Clin Psychopharmacol 32(3):309–316. doi:10.1097/JCP.0b013e3182549259

Cooper WO, Arbogast PG, Ding H, Hickson GB, Fuchs DC, Ray WA (2006) Trends in prescribing of antipsychotic medications for US children. Ambul Pediatr: Off J Ambul Pediatr Assoc 6(2):79–83. doi:10.1016/j.ambp.2005.11.002

Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, Murray KT, Quinn VP, Stein CM, Callahan ST, Fireman BH, Fish FA, Kirshner HS, O'Duffy A, Connell FA, Ray WA (2011) ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 365(20):1896–1904. doi:10.1056/NEJMoa1110212

Correll CU (2008) Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. J Am Acad Child Adolesc Psychiatry 47(1):9–20. doi:10.1097/chi.0b013e31815b5cb1

Correll CU, Frederickson AM, Kane JM, Manu P (2006) Metabolic syndrome and the risk of coronary heart disease in 367 patients treated with second-generation antipsychotic drugs. J Clin Psychiatry 67(4):575–583

Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, Graham J, Taylor E, Sergeant J (2013) Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry 54(3):227–246. doi:10.1111/jcpp.12036

Donner R, Michaels MA, Ambrosini PJ (2007) Cardiovascular effects of mixed amphetamine salts extended release in the treatment of school-aged children with attention-deficit/hyperactivity disorder. Biol Psychiatry 61(5):706–712. doi:10.1016/j.biopsych.2006.05.002

Efron D, Jarman F, Barker M (1997) Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. Pediatrics 100(4):662–666

Emslie G, Kratochvil C, Vitiello B, Silva S, Mayes T, McNulty S, Weller E, Waslick B, Casat C, Walkup J, Pathak S, Rohde P, Posner K, March J (2006) Treatment for Adolescents with Depression Study (TADS): safety results. J Am Acad Child Adolesc Psychiatry 45(12):1440–1455. doi:10.1097/01.chi.0000240840.63737.1d

Faraone SV, Biederman J, Morley CP, Spencer TJ (2008) Effect of stimulants on height and weight: a review of the literature. J Am Acad Child Adolesc Psychiatry 47(9):994–1009. doi:10.1097/CHI.ObO13e31817eOea7

Fraguas D, Correll CU, Merchan-Naranjo J, Rapado-Castro M, Parellada M, Moreno C, Arango C (2011) Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. Eur Neuropsychopharmacol: J Eur Coll Neuropsychopharmacol 21(8):621–645. doi:10.1016/j.euroneuro.2010.07.002

Friedman RA (2014) Antidepressants' black-box warning – 10 years later. N Engl J Med 371(18):1666–1668. doi:10.1056/NEJMp1408480

Friedman RA, Leon AC (2007) Expanding the black box – depression, antidepressants, and the risk of suicide. N Engl J Med 356(23):2343–2346. doi:10.1056/NEJMp078015

Gardner DM, Baldessarini RJ, Waraich P (2005) Modern antipsychotic drugs: a critical overview. CMAJ: Can Med Assoc J = J Assoc Med Can 172(13):1703–1711. doi:10.1503/cmaj.1041064

Geller B, Luby JL, Joshi P, Wagner KD, Emslie G, Walkup JT, Axelson DA, Bolhofner K, Robb A, Wolf DV, Riddle MA, Birmaher B, Nusrat N, Ryan ND, Vitiello B, Tillman R, Lavori P (2012) A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. Arch Gen Psychiatry 69(5):515–528. doi:10.1001/archgenpsychiatry.2011.1508

Germanò E, Italiano D, Lamberti M, Guerriero L, Privitera C, D'Amico G, Siracusano R, Ingrassia M, Spina E, Calabrò MP, Gagliano A (2014) ECG parameters in children and adolescents treated with aripiprazole and risperidone. Prog Neuropsychopharmacol Biol Psychiatry 51(0):23–27, doi:http://dx.doi.org/10.1016/j.pnpbp.2013.10.020

Ghanizadeh A (2013) A systematic review of the efficacy and safety of desipramine for treating ADHD. Curr Drug Saf 8(3):169–174

Gibbons RD, Hur K, Bhaumik DK, Mann JJ (2006) The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry 163(11):1898–1904. doi:10.1176/ajp.2006.163.11.1898

Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, Herings RM, Mann JJ (2007) Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 164(9):1356–1363. doi:10.1176/appi.ajp.2007.07030454

Goldstein BI (2013) Do stimulants prevent substance use and misuse among youth with attention-deficit/hyperactivity disorder? The answer is still maybe. J Am Acad Child Adolesc Psychiatry 52(3):225–227. doi:10.1016/j.jaac.2012.12.016

Gordon M, Melvin G (2013) Selective serotonin re-uptake inhibitors – a review of the side effects in adolescents. Aust Fam Physician 42(9):620–623

Gould MS, Walsh BT, Munfakh JL, Kleinman M, Duan N, Olfson M, Greenhill L, Cooper T (2009) Sudden death and use of stimulant medications in youths. Am J Psychiatry 166(9):992–1001. doi:10.1176/appi.ajp.2009.09040472

Graham J, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, Dopfner M, Hamilton R, Hollis C, Holtmann M, Hulpke-Wette M, Lecendreux M, Rosenthal E, Rothenberger A, Santosh P, Sergeant J, Simonoff E, Sonuga-Barke E, Wong IC, Zuddas A, Steinhausen HC, Taylor E (2011) European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry 20(1):17–37. doi:10.1007/s00787-010-0140-6

Greenhill LL, Swanson JM, Vitiello B, Davies M, Clevenger W, Wu M, Arnold LE, Abikoff HB, Bukstein OG, Conners CK, Elliott GR, Hechtman L, Hinshaw SP, Hoza B, Jensen PS, Kraemer HC, March JS, Newcorn JH, Severe JB, Wells K, Wigal T (2001) Impairment and deportment responses to different methylphenidate doses in children with ADHD: the MTA titration

trial. J Am Acad Child Adolesc Psychiatry 40(2):180–187. doi:10.1097/00004583-200102000-00012

Hammerness PG, Perrin JM, Shelley-Abrahamson R, Wilens TE (2011) Cardiovascular risk of stimulant treatment in pediatric attention-deficit/hyperactivity disorder: update and clinical recommendations. J Am Acad Child Adolesc Psychiatry 50(10):978–990. doi:10.1016/j.jaac.2011.07.018

Harrison JN, Cluxton-Keller F, Gross D (2012) Antipsychotic medication prescribing trends in children and adolescents. J Pediatr Health Care 26(2):139–145. doi:10.1016/j.pedhc.2011.10.009

Hazell P, Mirzaie M (2013) Tricyclic drugs for depression in children and adolescents. Cochrane Database Syst Rev (6):CD002317. doi:10.1002/14651858.CD002317.pub2

Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M (2007) Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. Cochrane Database Syst Rev (3):CD004851. doi:10.1002/14651858.CD004851.pub2

Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012) Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev (11):CD004851. doi:10.1002/14651858.CD004851.pub3

Hoffmann F, Glaeske G, Bachmann CJ (2014) Trends in antidepressant prescriptions for children and adolescents in Germany from 2005 to 2012. Pharmacoepidemiol Drug Saf 23(12):1268–1272. doi:10.1002/pds.3649

Humphreys KL, Eng T, Lee SS (2013) Stimulant medication and substance use outcomes: a meta-analysis. JAMA Psychiatry 70(7):740–749. doi:10.1001/jamapsychiatry.2013.1273

Jerrell JM (2010) Neuroendocrine-related adverse events associated with antidepressant treatment in children and adolescents. CNS Neurosci Ther 16(2):83–90. doi:10.1111/j.1755-5949.2009.00106.x

Kachko L, Ben Ami S, Lieberman A, Shor R, Tzeitlin E, Efrat R (2014) Neuropathic pain other than CRPS in children and adolescents: incidence, referral, clinical characteristics, management, and clinical outcomes. Paediatr Anaesth 24(6):608–613. doi:10.1111/pan.12375

Kalverdijk LJ, Tobi H, van den Berg PB, Buiskool J, Wagenaar L, Minderaa RB, de Jong-van den Berg LT (2008) Use of antipsychotic drugs among Dutch youths between 1997 and 2005. Psychiatr Serv 59(5):554–560. doi:10.1176/appi.ps.59.5.554

Kaminski A, Kamper A, Thaler K, Chapman A, Gartlehner G (2011) Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents. Cochrane Database Syst Rev (7):CD008013. doi:10.1002/14651858.CD008013.pub2

Kennedy E, Kumar A, Datta SS (2007) Antipsychotic medication for childhood-onset schizophrenia. Cochrane Database Syst Rev (3):CD004027. doi:10.1002/14651858.CD004027.pub2

Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA (2006) A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. Am J Psychiatry 163(12):2072–2079. doi:10.1176/ajp.2006.163.12.2072

Koelch M, Prestel A, Singer H, Keller F, Fegert JM, Schlack R, Hoelling H, Knopf H (2009) Psychotropic medication in children and adolescents in Germany: prevalence, indications, and psychopathological patterns. J Child Adolesc Psychopharmacol 19(6):765–770. doi:10.1089/cap.2009.0018

Koneski JA, Casella EB (2010) Attention deficit and hyperactivity disorder in people with epilepsy: diagnosis and implications to the treatment. Arq Neuropsiquiatr 68(1):107–114, doi:S0004-282X2010000100023 [pii]

Koneski JA, Casella EB, Agertt F, Ferreira MG (2011) Efficacy and safety of methylphenidate in treating ADHD symptoms in children and adolescents with uncontrolled seizures: a Brazilian sample study and literature review. Epilepsy Behav 21(3):228–232. doi:10.1016/j.yebeh.2011.02.029

Kumar A, Datta SS, Wright SD, Furtado VA, Russell PS (2013) Atypical antipsychotics for psychosis in adolescents. Cochrane Database Syst Rev (10):CD009582. doi:10.1002/14651858.CD009582.pub2

Kumra S, Kranzler H, Gerbino-Rosen G, Kester HM, De Thomas C, Kafantaris V, Correll CU, Kane JM (2008) Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. Biol Psychiatry 63(5):524–529. doi:10.1016/j.biopsych.2007.04.043

Kurdyak PA, Juurlink DN, Mamdani MM (2007) The effect of antidepressant warnings on prescribing trends in Ontario, Canada. Am J Public Health 97(4):750–754. doi:10.2105/AJPH.2006.087262

Loy JH, Merry SN, Hetrick SE, Stasiak K (2012) Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Database Syst Rev (9):CD008559. doi:10.1002/14651858.CD008559.pub2

Ma J, Lee KV, Stafford RS (2005) Depression treatment during outpatient visits by U.S. children and adolescents. J Adolesc Health 37(6):434–442. doi:10.1016/j.jadohealth.2005.07.012

Maayan L, Correll CU (2011) Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol 21(6):517–535. doi:10.1089/cap.2011.0015

Maher AR, Maglione M, Bagley S, Suttorp M, Hu JH, Ewing B, Wang Z, Timmer M, Sultzer D, Shekelle PG (2011) Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA 306(12):1359–1369. doi:10.1001/jama.2011.1360

Martin A, Young C, Leckman JF, Mukonoweshuro C, Rosenheck R, Leslie D (2004) Age effects on antidepressant-induced manic conversion. Arch Pediatr Adolesc Med 158(8):773–780. doi:10.1001/archpedi.158.8.773

Masi G, Liboni F (2011) Management of schizophrenia in children and adolescents: focus on pharmacotherapy. Drugs 71(2):179–208. doi:10.2165/11585350-000000000-00000

Melvin GA, Tonge BJ, King NJ, Heyne D, Gordon MS, Klimkeit E (2006) A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. J Am Acad Child Adolesc Psychiatry 45(10):1151–1161. doi:10.1097/01.chi.0000233157.21925.71

Meng X, D'Arcy C, Tempier R (2014) Long-term trend in pediatric antidepressant use, 1983–2007: a population-based study. Can J Psychiatry Rev Can Psychiatr 59(2):89–97

Miller M, Pate V, Swanson SA, Azrael D, White A, Sturmer T (2014a) Antidepressant class, age, and the risk of deliberate self-harm: a propensity score matched cohort study of SSRI and SNRI users in the USA. CNS Drugs 28(1):79–88. doi:10.1007/s40263-013-0120-8

Miller M, Swanson SA, Azrael D, Pate V, Sturmer T (2014b) Antidepressant dose, age, and the risk of deliberate self-harm. JAMA Intern Med 174(6):899–909. doi:10.1001/jamainternmed.2014.1053

Mohatt J, Bennett SM, Walkup JT (2014) Treatment of separation, generalized, and social anxiety disorders in youths. Am J Psychiatry 171(7):741–748. doi:10.1176/appi.ajp.2014.13101337

Molina BS, Hinshaw SP, Eugene Arnold L, Swanson JM, Pelham WE, Hechtman L, Hoza B, Epstein JN, Wigal T, Abikoff HB, Greenhill LL, Jensen PS, Wells KC, Vitiello B, Gibbons RD, Howard A, Houck PR, Hur K, Lu B, Marcus S (2013) Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. J Am Acad Child Adolesc Psychiatry 52(3):250–263. doi:10.1016/j.jaac.2012.12.014

Monteiro Filho WO, de Torres SM, Amorim MJ, Andrade AJ, de Morais RN, Tenorio BM, da Silva Junior VA (2014) Fluoxetine induces changes in the testicle and testosterone in adult male rats exposed via placenta and lactation. Syst Biol Reprod Med 60(5):274–281. doi:10.3109/19396368.2014.933984

Mosholder AD, Gelperin K, Hammad TA, Phelan K, Johann-Liang R (2009) Hallucinations and other psychotic symptoms associated with the use of attention-deficit/hyperactivity disorder drugs in children. Pediatrics 123(2):611–616. doi:10.1542/peds.2008-0185

MTA Cooperative Group (2004) National institute of mental health multimodal treatment study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. Pediatrics 113(4):754–761

Muench J, Hamer AM (2010) Adverse effects of antipsychotic medications. Am Fam Physician 81(5):617–622

Murray ML, de Vries CS, Wong IC (2004) A drug utilisation study of antidepressants in children and adolescents using the General Practice Research Database. Arch Dis Child 89(12): 1098–1102. doi:10.1136/adc.2004.064956

Murray ML, Thompson M, Santosh PJ, Wong IC (2005) Effects of the committee on safety of medicines advice on antidepressant prescribing to children and adolescents in the UK. Drug Saf 28(12):1151–1157, doi:28129 [pii]

Olfson M, Blanco C, Liu L, Moreno C, Laje G (2006) National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. Arch Gen Psychiatry 63(6):679–685. doi:10.1001/archpsyc.63.6.679

Park P, Caballero J, Omidian H (2014) Use of serotonin norepinephrine reuptake inhibitors in the treatment of attention-deficit hyperactivity disorder in pediatrics. Ann Pharmacother 48(1): 86–92. doi:10.1177/1060028013506561

Patten SB, Waheed W, Bresee L (2012) A review of pharmacoepidemiologic studies of antipsychotic use in children and adolescents. Can J Psychiatry Rev Can Psychiatr 57(12):717–721

Penfold RB, Stewart C, Hunkeler EM, Madden JM, Cummings JR, Owen-Smith AA, Rossom RC, Lu CY, Lynch FL, Waitzfelder BE, Coleman KJ, Ahmedani BK, Beck AL, Zeber JE, Simon GE (2013) Use of antipsychotic medications in pediatric populations: what do the data say? Curr Psychiatry Rep 15(12):426. doi:10.1007/s11920-013-0426-8

Peterson MC (2001) Reversible galactorrhea and prolactin elevation related to fluoxetine use. Mayo Clin Proc 76(2):215–216. doi:10.1016/S0025-6196(11)63132-7

Peyre H, Hoertel N, Cortese S, Acquaviva E, Limosin F, Delorme R (2013) Long-term effects of ADHD medication on adult height: results from the NESARC. J Clin Psychiatry 74(11): 1123–1124. doi:10.4088/JCP.13l08580

Peyre H, Hoertel N, Hatteea H, Limosin F, Dubuc C, Delorme R (2014) Adulthood self-reported cardiovascular risk and ADHD medications: results from the 2004–2005 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 75(2):181–182. doi:10.4088/JCP.13l08736

Piacentini J, Bennett S, Compton SN, Kendall PC, Birmaher B, Albano AM, March J, Sherrill J, Sakolsky D, Ginsburg G, Rynn M, Bergman RL, Gosch E, Waslick B, Iyengar S, McCracken J, Walkup J (2014) 24- and 36-week outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS). J Am Acad Child Adolesc Psychiatry 53(3):297–310. doi:10.1016/j.jaac.2013.11.010

Poulton A (2005) Growth on stimulant medication; clarifying the confusion: a review. Arch Dis Child 90(8):801–806. doi:10.1136/adc.2004.056952

Powers SW, Kashikar-Zuck SM, Allen JR, LeCates SL, Slater SK, Zafar M, Kabbouche MA, O'Brien HL, Shenk CE, Rausch JR, Hershey AD (2013) Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. JAMA 310(24):2622–2630. doi:10.1001/jama.2013.282533

Pringsheim T, Steeves T (2011) Pharmacological treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev (4):CD007990. doi:10.1002/14651858.CD007990.pub2

Pringsheim T, Lam D, Ching H, Patten S (2011a) Metabolic and neurological complications of second-generation antipsychotic use in children: a systematic review and meta-analysis of randomized controlled trials. Drug Saf 34(8):651–668. doi:10.2165/11592020-000000000-00000

Pringsheim T, Lam D, Patten SB (2011b) The pharmacoepidemiology of antipsychotic medications for Canadian children and adolescents: 2005–2009. J Child Adolesc Psychopharmacol 21(6):537–543. doi:10.1089/cap.2010.0145

Prozac Product monograph, Lilly research Laboratories, Eli Lily and Compagny; http://www.lilly.ca/en/pdf/product-monograph/27_prozac-pm_20sep2013.pdf

Rani F, Murray ML, Byrne PJ, Wong IC (2008) Epidemiologic features of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. Pediatrics 121(5): 1002–1009. doi:10.1542/peds.2007–2008

Rani FA, Byrne PJ, Murray ML, Carter P, Wong IC (2009) Paediatric atypical antipsychotic monitoring safety (PAMS) study: pilot study in children and adolescents in secondary- and tertiary-care settings. Drug Saf 32(4):325–333. doi:10.2165/00002018-200932040-00006

Rani FA, Byrne P, Cranswick N, Murray ML, Wong IC (2011) Mortality in children and adolescents prescribed antipsychotic medication: a retrospective cohort study using the UK general practice research database. Drug Saf 34(9):773–781. doi:10.2165/11591120-000000000-00000

Roessner V, Robatzek M, Knapp G, Banaschewski T, Rothenberger A (2006) First-onset tics in patients with attention-deficit-hyperactivity disorder: impact of stimulants. Dev Med Child Neurol 48(7):616–621. doi:10.1017/S0012162206001290

Ronaldson KJ, Taylor AJ, Fitzgerald PB, Topliss DJ, Elsik M, McNeil JJ (2010) Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. J Clin Psychiatry 71(8):976–981. doi:10.4088/JCP.09m05024yel

Ronsley R, Scott D, Warburton WP, Hamdi RD, Louie DC, Davidson J, Panagiotopoulos C (2013) A population-based study of antipsychotic prescription trends in children and adolescents in British Columbia, from 1996 to 2011. Can J Psychiatry Rev Can Psychiatr 58(6):361–369

Schmidt MJ, Fuller RW, Wong DT (1988) Fluoxetine, a highly selective serotonin reuptake inhibitor: a review of preclinical studies. Br J Psychiatry Suppl 3:40–46

Schneeweiss S, Patrick AR, Solomon DH, Dormuth CR, Miller M, Mehta J, Lee JC, Wang PS (2010) Comparative safety of antidepressant agents for children and adolescents regarding suicidal acts. Pediatrics 125(5):876–888. doi:10.1542/peds.2009-2317

Seida JC, Schouten JR, Boylan K, Newton AS, Mousavi SS, Beaith A, Vandermeer B, Dryden DM, Carrey N (2012) Antipsychotics for children and young adults: a comparative effectiveness review. Pediatrics 129(3):e771–e784. doi:10.1542/peds.2011-2158

Shin L, Bregman H, Breeze JL, Noyes N, Frazier JA (2009) Metformin for weight control in pediatric patients on atypical antipsychotic medication. J Child Adolesc Psychopharmacol 19(3):275–279. doi:10.1089/cap.2008.094

Sikich L (2008) Efficacy of atypical antipsychotics in early-onset schizophrenia and other psychotic disorders. J Clin Psychiatry 69(Suppl 4):21–25

Sikich L, Frazier JA, McClellan J, Findling RL, Vitiello B, Ritz L, Ambler D, Puglia M, Maloney AE, Michael E, De Jong S, Slifka K, Noyes N, Hlastala S, Pierson L, McNamara NK, Delporto-Bedoya D, Anderson R, Hamer RM, Lieberman JA (2008) Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizoaffective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. Am J Psychiatry 165(11):1420–1431. doi:10.1176/appi.ajp.2008.08050756

Steinhausen HC (2014) Recent international trends in psychotropic medication prescriptions for children and adolescents. Eur Child Adolesc Psychiatry. doi:10.1007/s00787-014-0631-y

Steinhausen HC, Bisgaard C (2014) Nationwide time trends in dispensed prescriptions of psychotropic medication for children and adolescents in Denmark. Acta Psychiatr Scand 129(3): 221–231. doi:10.1111/acps.12155

Stone MB (2014) The FDA warning on antidepressants and suicidality – why the controversy? N Engl J Med 371(18):1668–1671. doi:10.1056/NEJMp1411138

Strawn JR, Welge JA, Wehry AM, Keeshin B, Rynn MA (2014) Efficacy and tolerability of antidepressants in pediatric anxiety disorders: a systematic review and meta-analysis. Depress Anxiety. doi:10.1002/da.22329

Thomas CP, Conrad P, Casler R, Goodman E (2006) Trends in the use of psychotropic medications among adolescents, 1994 to 2001. Psychiatr Serv 57(1):63–69. doi:10.1176/appi.ps.57.1.63

Verdoux H, Tournier M, Begaud B (2010) Antipsychotic prescribing trends: a review of pharmacoepidemiological studies. Acta Psychiatr Scand 121(1):4–10. doi:10.1111/j.1600-0447.2009.01425.x

Vitiello B (2008) Understanding the risk of using medications for attention deficit hyperactivity disorder with respect to physical growth and cardiovascular function. Child Adolesc Psychiatr Clin N Am 17(2):459–474, xi. doi:10.1016/j.chc.2007.11.010

Vitiello B, Correll C, van Zwieten-Boot B, Zuddas A, Parellada M, Arango C (2009) Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. Eur Neuropsychopharmacol: J Eur Coll Neuropsychopharmacol 19(9):629–635. doi:10.1016/j.euroneuro.2009.04.008

Vitiello B, Elliott GR, Swanson JM, Arnold LE, Hechtman L, Abikoff H, Molina BS, Wells K, Wigal T, Jensen PS, Greenhill LL, Kaltman JR, Severe JB, Odbert C, Hur K, Gibbons R (2012) Blood pressure and heart rate over 10 years in the multimodal treatment study of children with ADHD. Am J Psychiatry 169(2):167–177. doi:10.1176/appi.ajp.2011.10111705

Volkow ND, Wang GJ, Fowler JS, Molina PE, Logan J, Gatley SJ, Gifford A, Ding YS, Wong C, Pappas NR, Zhu W, Swanson JM (2003) Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. Psychopharmacology (Berl) 166(3):264–270. doi:10.1007/s00213-002-1340-7

Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, Ginsburg GS, Rynn MA, McCracken J, Waslick B, Iyengar S, March JS, Kendall PC (2008) Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med 359(26):2753–2766. doi:10.1056/NEJMoa0804633

Weintrob N, Cohen D, Klipper-Aurbach Y, Zadik Z, Dickerman Z (2002) Decreased growth during therapy with selective serotonin reuptake inhibitors. Arch Pediatr Adolesc Med 156(7):696–701

Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E (2004) Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 363(9418):1341–1345. doi:10.1016/S0140-6736(04)16043-1

Wigal T, Greenhill L, Chuang S, McGough J, Vitiello B, Skrobala A, Swanson J, Wigal S, Abikoff H, Kollins S, McCracken J, Riddle M, Posner K, Ghuman J, Davies M, Thorp B, Stehli A (2006) Safety and tolerability of methylphenidate in preschool children with ADHD. J Am Acad Child Adolesc Psychiatry 45(11):1294–1303. doi:10.1097/01.chi.0000235082.63156.27

Wijlaars LP, Nazareth I, Petersen I (2012) Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN). PLoS One 7(3):e33181. doi:10.1371/journal.pone.0033181

Wilens TE, Morrison NR (2011) The intersection of attention-deficit/hyperactivity disorder and substance abuse. Curr Opin Psychiatry 24(4):280–285. doi:10.1097/YCO.0b013e328345c956

Wilens TE, Faraone SV, Biederman J, Gunawardene S (2003) Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 111(1):179–185

Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, Sawtelle R, Utzinger L, Fusillo S (2008) Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. J Am Acad Child Adolesc Psychiatry 47(1):21–31. doi:10.1097/chi.0b013e31815a56f1

Winterfeld U, Le Heuzey MF, Acquaviva E, Mouren MC, Brion F, Bourdon O (2009) Off-label use of psychotropic medications in pediatric wards: a prospective study. Arch Pediatr 16(9):1252–1260. doi:10.1016/j.arcped.2009.06.012

Winterstein AG, Gerhard T, Kubilis P, Saidi A, Linden S, Crystal S, Zito J, Shuster JJ, Olfson M (2012) Cardiovascular safety of central nervous system stimulants in children and adolescents: population based cohort study. BMJ 345:e4627. doi:10.1136/bmj.e4627

Zito JM, Safer DJ, de Jong-van den Berg LT, Janhsen K, Fegert JM, Gardner JF, Glaeske G, Valluri SC (2008) A three-country comparison of psychotropic medication prevalence in youth. Child Adolesc Psychiatry Ment Health 2(1):26. doi:10.1186/1753-2000-2-26

Chapter 14
Safety of Psychotropic Drugs in the Elderly

Kate L. Lapane, Anne Hume, Christine Ulbricht, and Giovanni Gambassi

Abstract The past decades have witnessed an unprecedented phenomenon of global aging with a dramatic rise in the number of individuals above the age of 65 years. Drug therapy is the primary approach to managing chronic disease in older adults. It comes as no surprise that increases in drug therapy have accompanied the rise in the older adult population with chronic conditions. The safety profile of drugs in older adults may differ substantially from that in younger individuals. Older adults, especially more frail individuals, may have significantly altered pharmacokinetics such as decreased renal function and pharmacodynamics which increase the likelihood of adverse drug effects. Inappropriate drug selection can lead to complications in drug therapy. Complications in drug therapy may appear as adverse drug events. In this chapter, we review particular safety concerns with major psychiatric medications used in older adults. We specifically focus on antipsychotics, antidepressants, benzodiazepines, and anti-dementia agents.

Keywords Drug safety • Elderly • Antipsychotics • Antidepressants • Benzodiazepines • Anti-dementia agents

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14.1 Introduction

In many countries, the age distribution has slowly changed. In the United States, 13 % of the population is now aged ≥65 years (Census Bureau 2010). This proportion will be 20 % by 2030, and 5 % will be aged 80 years of age or older (OECD 2009). Growth will occur in all racial and ethnic groups (Federal Interagency Forum on Aging-Related Statistics 2004). This will pose challenges as the per capita health-care expenditure is five times higher for those at least 65 years of age compared those younger than 65 years (Lubitz et al. 2001). With increased longevity comes a greater prevalence of multiple chronic diseases including psychiatric conditions (Anderson 2007).

Drug therapy is the primary approach to managing chronic disease in older adults. It comes as no surprise that increases in drug therapy have accompanied the rise in the older adult population with chronic conditions. Over 85 % of adults at least 65 years of age regularly use prescription drugs (Ihara et al. 2002), and 55 % of older adults take three or more drugs on a regular basis (Kaiser Public Opinion Update 2000). Older adults consume 31 % of all prescribed drugs (Baum et al. 1987), the average number being between 2 and 6 (Stewart and Cooper 1994). Polypharmacy may be the new paradigm for quality drug therapy. However, the number of drugs per se is not the primary factor for quality, as appropriateness for the specific individual, life expectancy, burden of concomitant conditions, and personal preferences is most important.

The safety profile of drugs in older adults may differ substantially from that in younger individuals. Older adults, especially more frail individuals, may have significantly altered pharmacokinetics such as decreased renal function and pharmacodynamics which increase the likelihood of adverse drug effects (Sera and McPherson 2012). Inappropriate drug selection (Stuck et al. 1994) can lead to complications in drug therapy. Complications in drug therapy may appear as an adverse drug event. The incidence of adverse drug events has been estimated to be 27.4 % in community-dwelling older adults (Gandhi et al. 2003). The economic costs of preventable adverse drug events are staggering (Field et al. 2005). Gurwitz et al. demonstrated an incidence of adverse drug events of 50.1 per 1,000 person years among a population of elderly Medicare beneficiaries visiting an outpatient physician practice (Gurwitz et al. 2003). Older adults are two to three times more likely to experience an adverse drug event than patients 20–30 years old. Medication-related problems occur in 1.5–44 % of inpatients and over 30 % of outpatients (Monette et al. 1995). Pharmacologic management is the top condition in need of quality of care improvement initiatives in vulnerable older adults (Sloss et al. 2000). The Institute of Medicine (IOM) "To Err is Human" report reinforces the need for improving drug therapy in a population taking multiple medications and having comorbidities (Institute of Medicine 2000).

In this chapter, we review particular safety concerns of major psychiatric medications used in older adults. We specifically focus on antipsychotics, antidepressants, benzodiazepines, and anti-dementia agents.

In older adults, increases in the use of antidepressants have been observed (Newman and Schopflocher 2008; Crystal et al. 2003). Benzodiazepines have either remained stable or declined but are still commonly prescribed to older adults. Although decreases in antipsychotic use in older adults have been noted (Gallini et al. 2014), antipsychotic use among older adults is common.

14.2 Antipsychotics

The off-label use of conventional and atypical antipsychotics to treat the behavioral and psychological symptoms in dementia remains common despite their limited efficacy. Despite their perceived better safety, some atypical antipsychotics may still possess anticholinergic and hypotensive effects, as well as extrapyramidal effects including tardive dyskinesias, although at a lower rate than conventional antipsychotics.

In April 2005, the US Food and Drug Administration (FDA) issued a public health advisory that the use of atypical antipsychotics such as risperidone, olanzapine, quetiapine, and aripiprazole to treat older adults with dementia was associated with an increased risk for death compared with placebo. In a pooled analysis of trials involving atypical antipsychotics, the mortality rate was 60–70 % higher than with placebo in 15 of the 17 trials. Evidence providing support for these warnings has also raised further safety concerns about conventional antipsychotics (Scneider et al. 2005; Wang et al. 2005; Kryzhanovskaya et al. 2006). In June 2008, the FDA stated that the conventional antipsychotics share a similar or even higher risk of increased mortality with the atypical antipsychotics. The FDA concluded that antipsychotics should not be used for the treatment of dementia-related psychosis. Despite these warnings, a recent review suggested that antipsychotics should be "used with caution only when non-pharmacologic approaches have failed to adequately control behavioral and psychological symptoms in dementia" (Trifirò et al. 2009).

Antipsychotics appear to confer a greater mortality risk in older adults than any other psychotropic medication. A retrospective case-control study of 90,786 dementia patients within the Veterans Health Administration from 1998 to 2009 found that newly prescribed antipsychotic users had an increased mortality risk when compared to both matched nonusers and antidepressant users (Maust et al. 2015). This risk ranged from 2.0 % for those receiving quetiapine to 3.8 % for those receiving haloperidol when comparing antipsychotic users to nonusers. When comparing antipsychotic users to antidepressant users, the mortality risk ranged from 3.2 % for those receiving quetiapine to 12.3 % for those receiving haloperidol. Additionally, a dose-response increase in mortality risk was observed for atypical antipsychotics (olanzapine, quetiapine, and risperidone).

The potential causes of death associated with antipsychotic use merit consideration of the potential for drug-drug and drug-disease interactions. Several plausible

mechanisms can be proposed, including cerebrovascular events, arrhythmias and sudden cardiac death, venous thromboembolism and pulmonary embolism, and aspiration pneumonia. Metabolic effects of antipsychotics may be a longer-term safety concern. Antipsychotics may contribute to events that are not initially recognized as the first step in a sequence that promotes premature death, such as falls leading to hip fractures. Apart from mortality, other serious safety issues have been raised regarding the use of antipsychotics including cerebrovascular events, cardiac events, peripheral vascular disease, metabolic disease, infections, and falls/fractures. Hip fracture, stroke, myocardial infarction, and ventricular arrhythmias partially explain the mortality difference between first- and second-generation antipsychotics (Jackson et al. 2014).

A pooled analysis documented a threefold increased risk of stroke and transient ischemic attacks for risperidone and olanzapine compared with placebo (De Deyn et al. 2005). Following the warning on stroke and antipsychotic use, observational studies compared the risk of stroke between atypical and conventional antipsychotics, most in the general elderly population and in patients with dementia. The studies suggest no increased risk of stroke with atypical compared to conventional antipsychotics but could not explore the dose and duration effect and risks of individual compounds or rule out confounding by indication because of the strong interrelationship between ischemia, dementia, and subsequent strokes. Stroke may be related to the first weeks of treatment (Sacchetti et al. 2010).

With respect to cardiac events, since the 1960s, sudden cardiac death has been reported with conventional antipsychotic use (Straus et al. 2004) because of their ability to prolong the QTc interval which may result in torsade de pointes and other ventricular arrhythmias (Reilly et al. 2000). Observational studies have confirmed the signals from spontaneous reports, and suggested conventional antipsychotics are associated with an increased risk of sudden cardiac death. A recent systematic review of the association between antipsychotics and myocardial infarction was inconclusive owing to the heterogeneity of the studies, but the largest study revealed no association (Brauer et al. 2011).

A relationship between antipsychotics and venous thromboembolism (VTE) was first suggested five decades ago. Reviews of the available data for aripiprazole, clozapine, and olanzapine have led to warnings about VTE being added to their Summaries of Product Characteristics (MPA Report 2009). The studies on VTE and antipsychotics mostly focus on schizophrenia or young patients and have methodological issues such as small sample sizes and inadequate control of confounding. Inconsistencies in findings have been noted, but an increased risk of VTE is likely (Zhang et al. 2011). Little data are available on the peripheral vascular effects of antipsychotics in dementia, which is highly relevant given the large potential for interacting comedication on serotonin receptors and platelet function.

In patients with either schizophrenia or bipolar disorder, atypical antipsychotics such as olanzapine, quetiapine, and clozapine are associated with metabolic abnormalities including weight gain, lipid disturbances, and altered glucose homeostasis,

known risk factors for cardiovascular events (Newcomer 2005). Whether older adults with behavioral and psychological symptoms in dementia receiving antipsychotics develop similar disturbances is controversial as food intake is reduced in these patients. Only a few small studies have been published so far on this association. A study of 36 residents showed treatment with low-dose atypical antipsychotics did not lead to weight gain or increased risk of developing type 2 diabetes or lipid metabolism abnormalities (Rondanelli et al. 2006). In contrast, CATIE-AD reported weight gain but no effect on glucose, total cholesterol, or triglyceride levels during the use of olanzapine, quetiapine, and risperidone, and the risk increased over time. Post-hoc analyses of other studies with olanzapine and risperidone were consistent with the CATIE-AD results. A recently published Canadian study found that among older patients with diabetes, the initiation of treatment with antipsychotic drugs was associated with an increased risk of hospitalization for hyperglycemia (Lipscombe et al. 2009). The risk was high during the initial course of treatment and was increased with the use of all antipsychotic agents. Among nursing home residents with dementia, conventional antipsychotics particularly short-term therapy, but not atypical antipsychotic use, increased risk of diabetes onset (Jalbert et al. 2011).

Infections, primarily pneumonia, have been listed as one of the most prevalent causes of death among demented older adults using antipsychotics both in clinical trials and observational studies. Although one study reported a threefold increased risk with atypical antipsychotics and a 1.6-fold increase with conventional antipsychotics compared with nonuse (Knol et al. 2008), others found a slightly higher rate of fatal pneumonia during conventional antipsychotic use relative to atypical antipsychotic use. The overall risk of antipsychotic use was not increased compared to nonuse in a cohort of elderly persons (Setoguchi et al. 2008). Trifirò showed that the use of either atypical or typical antipsychotics in older patients is associated in a dose-dependent fashion with the development of community-acquired pneumonia (Trifirò et al. 2010). More work is needed to understand this effect (Trifirò 2011).

Information regarding adverse effects of antipsychotic treatment in older adults with schizophrenia is scant. While older adults with schizophrenia are thought to have a greater sensitivity to treatment-related adverse effects (Masand 2000), the overall incidence of adverse events was low (Lasser et al. 2004).

14.3 Antidepressants

In general, antidepressants are equally effective in the treatment of depression (Mottram et al. 2006). The major categories of antidepressants and individual drugs differ in their side effect and drug interaction profiles. Although for younger patients evidence exists that suggests the use of antidepressants may increase the risk of suicidality and suicidal ideation, among older adults with depression, the risk is reduced. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly

prescribed antidepressant class including in frail older adults. Their widespread use has been based primarily on their lack of traditional tricyclic antidepressant (TCA) side effects, although SSRIs commonly produce adverse gastrointestinal and sexual symptoms and less frequently central nervous system effects including insomnia, anxiety, and tremors (Grimsley and Jann 1992).

Both tertiary and secondary amine TCAs have been used in older adults for many years. TCA side effects commonly include dry mouth, blurred vision, urinary retention, and constipation due to their anticholinergic and antihistaminic activity. Amoxapine has been associated with a higher risk of extrapyramidal side effects including akathisia and tardive dyskinesia due to its metabolism to loxapine, a neuroleptic, and maprotiline with seizures (Rosenstein 1993). Frail older adults remain at the greatest risk of anticholinergic effects, cardiovascular effects, and effects on appetite. The anticholinergic effects of older TCAs have included the loss of accommodation with blurring of vision, dry mouth, constipation, urinary retention, tachycardia, confusion, and delirium (Cole and Bodkin 1990). These effects range from what might be considered minor in nature (i.e., blurring of vision and dry mouth), to moderate (i.e., urinary retention), to potentially very serious reactions (i.e., delirium). Anticholinergic side effects minor in nature might potentially have important effects on the older adult's quality of life. As an example, while tolerance to some anticholinergic effects is known to occur, the loss of accommodation generally does not improve over time and would limit the individual's ability to perform the simple pleasurable act of reading a book. The presence of concomitant diseases such as prostatic hypertrophy or diabetes mellitus, for example, in older adults may increase the risk that clinically important urinary retention will occur resulting in detrimental effects on the individual's continence and overall functional status. Most importantly, confusion and delirium may develop from the use of strongly anticholinergic drugs such as amitriptyline in individuals with preexisting cognitive impairment. Potentially, the resulting problems with memory, concentration, and behavioral disturbances may be overlooked as part of the patient's primary illness or inappropriately treated with a neuroleptic such as haloperidol or with physical restraints. Trazodone has sedating properties (Nierenberg 1994).

Cardiovascular side effects of TCAs must also be considered. Orthostatic hypotension and cardiac conduction defects are the most common TCA cardiovascular side effects. Orthostatic hypotension is due to the blockade of alpha-1 adrenergic receptors. When orthostatic hypotension is symptomatic and results in syncope, older adults are at increased risk of falls and fractures. Although symptomatic orthostatic hypotension can be minimized by the use of small doses of secondary amines and adequate ambulation and hydration, the risk of this side effect remains. TCAs may induce heart block in individuals with preexisting conduction delays.

TCAs may increase appetite and weight, potentially due to their effects on histaminergic systems. Although viewed as a negative outcome in younger populations, weight gain may have beneficial effects in older adults if their nutritional status is poor or marginal due to decreased appetite.

SSRIs other than paroxetine generally lack the anticholinergic properties associated with TCAs. With respect to effects on appetite and weight, SSRIs have been associated with either no change or a decrease in weight at least in the short term (Kinney-Parker 1988). The effects of SSRIs on the cardiovascular system are controversial with citalopram associated with QT prolongation. In one clinical trial for treating agitation in patients with probable Alzheimer's disease, citalopram titrated from 10 to 30 mg daily was associated with significant improvements in agitation but also with an increase in QTc interval when compared to placebo (Porsteinsson et al. 2014). Worsened cognition was also seen in this trial. Current recommendations are to limit the dosage of citalopram to no more than 20 mg daily in people over 60 years of age. In older adults, multiple risk factors for torsade de pointes are frequently present including hypokalemia, hypomagnesemia, and bradyarrhythmias. SSRIs have been associated with an increased risk of bleeding episodes especially among older adults. Concomitant use of antiplatelet or anticoagulant drugs for atrial fibrillation or myocardial infarction in older adults likely increases the underlying risk (Jiang et al. 2015). Although hyponatremia has been reported to occur in an estimated 10 % of older adults treated with antidepressants (Mannesse 2013), the risk may be greater than SSRIs even considering their widespread usage. In addition, serotonin syndrome presenting as restlessness, anxiety, agitation, and confusion in older adults has been associated with the use of SSRIs and SNRIs. This side effect has been reported to occur primarily when the antidepressant was used in combination with other drugs which have an effect on serotonin such as buspirone, tramadol, and dextromethorphan.

Venlafaxine and bupropion generally have fewer anticholinergic effects, while duloxetine possesses this property and may result in urinary retention. Increases in blood pressure have been associated with these antidepressants (Augustin et al. 1997).

In addition to differences in side effects among major antidepressant classes, the presence or absence of drug-drug interactions has become an increasingly important issue in selecting among the available drugs. Traditionally TCAs have had relatively few drug-drug interactions of clinical significance. Newer drugs such as the SSRI, however, have been implicated in many potentially serious interactions which may be important in older populations due to the number of prescribed medications and the variety of interactions which have been reported. Monoamine oxidase (MAO) inhibitor use has been limited for several reasons, most important of which is the presence of many potentially serious drug-drug and drug-food interactions which potentially can result in palpitations, severe headache, and hypertensive crisis.

Depression increases the risk of falls (Quach et al. 2013). Antidepressants have the potential to impair gait, balance, and blood pressure regulation, although an inconsistent association between antidepressants and falls has been noted (Hartikainen et al. 2007). Serotonin norepinephrine reuptake inhibitors (SNRIs) may also increase the risk of falls on the same order that SSRIs and TCAs do (Gribbini et al. 2011). A recent finding that antidepressants increase the risk of outdoor falls, but not indoor falls (Quach et al. 2013), seems counter to studies documenting the link between antidepressants and falls in nursing homes (Thapa et al. 1998). Excess fractures associated with both SSRIs and TCAs have been confirmed

(Rosenstein 1993; Rabenda et al. 2013). The estimated contribution of antidepressant use to the population rate of hip fractures varies between 3 and 7 % (Prieto-Alhambra et al. 2014).

Falls and fractures have been associated with the use of many antidepressants. People who have a history of falls or fractures should avoid SSRIs and SNRIs unless safer alternatives are not available due to SSRIs' ability to produce ataxia and syncope and impair psychomotor functioning (American Geriatrics Society 2012). TCAs should also be avoided for people with a history of falls or fractures because of the same reasons as SSRIs.

14.4 Benzodiazepines and BZDP Receptor Agonists

Benzodiazepines continue to be overprescribed in older adults, with recent data showing that 8.7 % of community-dwelling Americans between 65 and 80 years of age have been prescribed the drugs despite their known risks (Olfson et al. 2015). A quarter of the drugs were long acting and almost one-third of benzodiazepine use in this age group was for more than 4 months (Olfson et al. 2015). Sedation and impaired driving from the use of benzodiazepines are familiar to clinicians as well as withdrawal seizures from acutely stopping short-acting benzodiazepines. Hip fractures continue to be associated with the use of benzodiazepines including the short-acting drugs when used in higher dosages, concomitantly with other drugs, and shortly after initiating therapy (Zint et al. 2010). Although cognitive impairment has also been associated with these drugs, a recent case-control study from the Quebec Health Insurance Program database evaluated the association between past benzodiazepine use in independently living older adults and the subsequent risk of developing Alzheimer's disease (Billioti de Gage et al. 2014). A dose-effect relationship was demonstrated with higher dosages associated with a greater risk of Alzheimer's disease, as well as with longer-acting benzodiazepines relative to shorter-acting agents (Billioti deGage et al. 2014).

In addition, benzodiazepine receptor agonists such as zolpidem, zopiclone, and zaleplon are commonly prescribed for acute and chronic insomnia in older adults. Initially these drugs were perceived to lack many of the adverse effects attributed to benzodiazepines. Since their initial introduction, however, multiple observational studies have reported adverse effects such as falls and hip fractures in older adults similar to those as associated with benzodiazepines (Diem et al. 2014; Bakken et al. 2014). More recently, these drugs particularly zolpidem have been associated with anterograde amnesia the day after administration, although this is likely less common than with the short-acting benzodiazepine triazolam. Similar to benzodiazepines, reports of impaired driving have been reported especially with the use of zolpidem by women (Farkas et al. 2013). In a small crossover study of 16 healthy adults with a mean age of 59.4 years, the use of zolpidem resulted in poorer psychomotor and driving performance as well as memory recall compared with sustained-release melatonin (Otmani et al. 2008).

14.5 Anti-dementia Medications

Two broad categories of drugs, the cholinesterase inhibitors and memantine, are commonly used to treat cognitive impairment, Alzheimer's disease, and other dementias. For the cholinesterase inhibitors including donepezil, rivastigmine, and galantamine, the primary safety concern has been on their potential gastrointestinal effects, especially anorexia, nausea, vomiting, and diarrhea. In a meta-analysis of clinical trials of cholinesterase inhibitors, the excess rates of dropouts due to adverse events were low (donepezil 2 %, rivastigmine 9 %, galantamine 14 %) and gastrointestinal in nature (Lanctôt et al. 2003). The recent introduction of donepezil 23 mg tablet has an increased risk of gastrointestinal symptoms including weight loss and vomiting over the 10 mg tablet yet only modest additional benefits on rating scales (Farlow et al. 2010). For the frail patient with Alzheimer's disease, this may result in additional challenges to maintain an adequate weight. In addition, cholinesterase inhibitors may make worsen urinary incontinence in older adults, resulting in the subsequent prescribing of urinary antimuscarinic drugs such as tolterodine and oxybutynin which in turn may further increase confusion. More recently, in a Canadian population-based cohort, the use of cholinesterase inhibitors has been linked to an increased risk of bradycardia and syncope with subsequent falling and fractures in community-dwelling older adults (Gill et al. 2009). Although the precise mechanism for developing bradycardia is unclear, the drugs may enhance vagal tone (Gill et al. 2009).

Memantine is well tolerated with few adverse events (Lanctôt et al. 2003; Farlow et al. 2010). In a recent multicountry study including 46,737 Medicare beneficiaries and 29,496 Danish participants, cholinesterase inhibitor users had similar risks of heart failure and myocardial infarction, but memantine was associated with increased risks of cardiac events in the Danish sample. In both countries, memantine users had greater mortality rates most likely due to channeling of the sickest patients to memantine therapy (Gill et al. 2009).

14.6 Conclusions

The safe use of psychiatric drugs presents special concerns in older adults. Interactions due to comorbid conditions and concomitant drugs, as well as pharmacokinetic and pharmacodynamics changes, increase the risk of adverse effects with psychiatric drugs. Seemingly simple side effects such as blurred vision may have significant negative effects on quality of life in the older adult. More importantly, despite limited efficacy, the use of antipsychotics in older adults is associated with increased risks of death, adverse cardiac outcomes, and pneumonia. Falls and fractures are commonly linked to many psychiatric medications. The risks of treatment must be considered carefully in older adults.

References

American Geriatrics Society (2012) Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 60(4):616–631

Anderson G (2007) Chronic conditions: making the case for ongoing care. Johns Hopkins University, Baltimore. http://www.fightchronicdisease.com/news/pfcd/documents/ChronicCareChartbook_FINAL.pdf

Augustin BG, Cold JA, Jann MW (1997) Venlafaxine and nefazodone, two pharmacologically distinct antidepressants. Pharmacotherapy 17:511–530

Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S (2014) Risk of hip fracture among older people using anxiolytic and hypnotic drugs: a nationwide prospective cohort study. Eur J Clin Pharmacol 70:873–880

Baum C, Kennedy DL, Knapp DE et al (1987) Drug utilization in the US – 1986. Department of Health and Human Services, Food and Drug Administration, Rockville

Billioti deGage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M et al (2014) Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ 349:g5205

Brauer R, Douglas I, Smeeth (2011) The association between antipsychotic agents and the risk of myocardial infarction: a systematic review. Br J Clin Pharmacol 72:871–878

Census Bureau (2010) Census. http://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf

Cole JO, Bodkin JA (1990) Antidepressant side effects. J Clin Psychiatry 51:21–26

Crystal S, Sambamoorthi U, Walkup JT, Akincigil A (2003) Diagnosis and treatment of depression in the elderly medicare population: predictors, disparities, and trends. J Am Geriatr Soc 51:1718–1728

De Deyn P, Katz I, Brodaty H, Lyons B, Greenspan A, Burns A (2005) Management of agitation, aggression, and psychosis associated with dementia: a pooled analysis including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. Clin Neurol Neurosurg 107:497–508

Diem SJ, Ewing SK, Stone KL, Ancoli-Israel S, Redline S, Ensrud KE (2014) The Osteoporotic Fractures in Men (MrOS) Study Group. Use of non-benzodiazepine sedative hypnotics and risk of falls in older men. J Gerontol Geriatr Res 3:158

Farkas RH, Unger EF, Temple R (2013) Zolpidem and driving impairment – identifying persons at risk. N Engl J Med 369:689–691

Farlow MR, Salloway S, Tariot PN, Yardley J, Moline ML, Wang Q et al (2010) Effectiveness and tolerability of high dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: a 24-week, randomized double-blind study. Clin Ther 32:1234–1251

Federal Interagency Forum on Aging-Related Statistics (2004) Older Americans 2004: key indicators of well-being. Federal interagency forum on aging-related statistics. US Government Printing Office, Washington, DC. Available at: http://www.agingstats.gov/chartbook2004/OA_2004.pdf

Field TS, Gilman BH, Subramanian S, Fuller JC, Bates DW, Gurwitz JH (2005) The costs associated with adverse drug events among older adults in the ambulatory setting. Med Care 43:1171–1176

Gallini A, Andrieu S, Donohue JM, Oumouhou N, Lapeyre-Mestre M, Gardette V (2014) Trends in use of antipsychotics in elderly patients with dementia: impact of national safety warnings. Eur Neuropsychopharmacol 24:95–104

Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E et al (2003) Adverse drug events in ambulatory care. N Eng J Med 348:1556–1564

Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand SL, Rochon PA (2009) Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. Arch Intern Med 169:867–873

Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S (2011) Serotonin-norepinephrine reuptake inhibitor antidepressants and the risk of falls in older people: case-control and case-series analysis of a large UK primary care database. Drugs Aging 28:895–902

Grimsley SR, Jann MW (1992) Paroxetine, sertraline and fluvoxamine: new selective serotonin reuptake inhibitors. Clin Pharmacol 11:930–957

Gurwitz JH, Field TS, Harrold LR, Rothschild J, Debellis K, Seger AC et al (2003) Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 289:1107–1116

Hartikainen S, Lönnroos E, Louhivuori K (2007) Medication as a risk factor for falls: critical systematic review. J Gerontol A Biol Sci Med Sci 62:1172–1181

Ihara E, Summer L, Shirey L (2002) Prescription drugs: a vital component of health care. In: Challenges for the 21st century: chronic and disabling conditions. Center on an Aging Society, Georgetown University, Washington, DC, pp 1–5. Available at: http://ihcrp.georgetown.edu/agingsociety/pdfs/rxdrugs.pdf

Institute of Medicine (2000) In: Kohn L, Corrigan J, Donaldson M (eds) To err is human: building a safer health care system. National Academy Press, Washington, DC

Jackson JW, Schneeweiss S, VanderWeele TJ, Blacker D (2014) Quantifying the role of adverse events in the mortality difference between first and second-generation antipsychotics in older adults: systematic review and meta-synthesis. PLoS ONE 9:e105376

Jalbert JJ, Daiello LA, Eaton CB, Miller SC, Lapane KL (2011) Antipsychotic use and the risk of diabetes in nursing home residents with dementia. Am J Geriatr Pharmacother 9:153–163

Jiang HY, Chen HZ, Hu XJ, Yu ZH, Yang W, Deng M, Zhang YH, Ruan B (2015) Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 13:42–50.e3

Kaiser Public Opinion Update (2000) The public and prescription drugs. The Kaiser Family Foundation, Washington, DC. Available at: http://www.kff.org/rxdrugs/loader.cfm?url/commonspot/security/getfile.cfm&PageID=13541

Kinney-Parker JL (1988) Fluoxetine and weight: something lost and something gained? Clin Pharmacol 8:727–733

Knol W, van Marum R, Jansen P, Souverein P, Schobben A, Egberts A (2008) Antipsychotic drug use and risk of pneumonia in elderly people. J Am Geriatr Soc Sci Med 56:661–666

Kryzhanovskaya LA, Jeste DV, Young CA, Polzer JP, Roddy TE, Jansen JF et al (2006) A review of treatment emergent adverse events during olanzapine clinical trials in elderly patients with dementia. J Clin Psychiatry 67:933–945

Lanctôt KL, Herrmann N, Yau KK et al (2003) Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ: Can Med Assoc J 169:557–564

Lasser R, Bossie CA, Zhu Y et al (2004) Efficacy and safety of long-acting risperidone in elderly patients with schizophrenia and schizoaffective disorder. Int J Geriatr Psychiatry 19: 898–905

Lipscombe L, Lévesque L, Gruneir A, Fischer H, Juurlink D, Gill S et al (2009) Antipsychotic drugs and hyperglycemia in older patients with diabetes. Arch Intern Med 169:1282–1289

Lubitz J, Greenberg LG, Gorina Y, Wartzman L, Gibosn D (2001) Three decades of health care use by the elderly 1965–1998. Health Aff 20:19–32

Mannesse CK (2013) Characteristics, prevalence, risk factors, and underlying mechanism of hyponatremia in elderly patients treated with antidepressants: a cross-sectional study. Maturitas 76:357–363

Masand PS (2000) Side effects of antipsychotics in the elderly. J Clin Psychiatry 61(S 8):43–49; discussion 50–51

Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, Kales HC (2015) Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry 2015;72(5):438–445

Monette J, Gurwitz JH, Avorn J (1995) Epidemiology of adverse drug events in the nursing home setting. Drugs Aging 7:203–211

Mottram PG, Wilson K, Strobl JJ (2006) Antidepressants for depressed elderly. Cochrane Database Syst Rev (1):CD003491

Newcomer J (2005) Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 19(S 1):1–93

Newman SC, Schopflocher D (2008) Trends in antidepressant prescriptions among the elderly in Alberta during 1997 to 2004. Can J Psychiatry 53:704–707

Nierenberg AA (1994) Trazodone for antidepressant-associated insomnia. Am J Psychiatry 151:1069–1072

OECD Fact Book (2009) OECD Paris. http://oberon.sourceoecd.org/vl=865128/cl=23/nw=1/rpsv/factbook2009/index.htm

Olfson M, King M, Schoenbaum M (2015) Benzodiazepine use in the United States. JAMA Psychiatry 72:136–142

Otmani S, Demazieres A, Staner C, Jacob N, Nir T, Zisapel N, Staner L (2008) Effects of prolonged-release melatonin, zolpidem, and their combination on psychomotor functions, memory recall, and driving skills in healthy meddle aged and elderly volunteers. Hum Psychopharmacol 23:693–705

Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG, CitAD Research Group (2014) Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA 311(7):682–691

Prieto-Alhambra D, Petri H, Goldenberg JS, Khong TP, Klungel OH, Robinson NJ, de Vries F (2014) Excess risk of hip fractures attributable to the use of antidepressants in five European countries and the USA. Osteoporos Int 25:847–855

Quach L, Yang FM, Berry SD, Newton E, Jones RN, Burr JA, Lipsitz LA (2013) Depression, antidepressants, and falls among community-dwelling elderly people: the MOBILIZE Boston study. J Gerontol A Biol Sci Med Sci 68:1575–1581

Rabenda V, Nicolet D, Beaudart C, Bruyère O, Reginster JY (2013) Relationship between use of antidepressants and risk of fractures: a meta-analysis. Osteoporos Int 24:121–137

Reilly J, Ayis S, Ferrier I, Jones S, Thomas S (2000) QTc interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 355:1048–1052

REPORT MPA (2009) The risk of venous thromboembolism associated with antipsychotics. http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Productspecificinformationandadvice/Antipsychoticdrugs/index.htm

Rondanelli M, Sarra S, Antoniello N, Mansi S, Govoni S, Falfo F et al (2006) No effect of atypical antipsychotic drugs on weight gain and risk of developing type II diabetes or lipid abnormalities among nursing home elderly patients with Alzheimer's disease. Minerva Med 97:147–151

Rosenstein DL (1993) Seizures associated with antidepressants: a review. J Clin Psychiatry 54:289–299

Sacchetti E, Turrina C, Valsecchi P (2010) Cerebrovascular accidents in elderly people treated with antipsychotic drugs: a systematic review. Drug Saf 33:273–288

Schneider LS, Dagerman KS, Insel P (2005) Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 294:1934–1943

Sera LC, McPherson ML (2012) Pharmacokinetics and pharmacodynamics changes associated with aging and implications for drug therapy. Clin Geriatr Med 28:273–286

Setoguchi S, Wang PS, Alan Brookhart M, Canning CF, Kaci L, Schneeweiss S (2008) Potential causes of higher mortality in elderly users of conventional and atypical antipsychotic medications. J Am Geriatr Soc 56:1644–1650

Sloss EM, Solomon DH, Shekelle PG et al (2000) Selecting target conditions for quality of care improvement in vulnerable older adults. J Am Geriatr Soc 48:363–369

Stewart RB, Cooper JW (1994) Polypharmacy in the aged. Practical solutions. Drugs Aging 4:449–461

Straus S, Bleumink G, Dieleman J, van der Lei J, 't Jong G, Kingma J et al (2004) Antipsychotics and the risk of sudden cardiac death. Arch Int Med 164:1293–1297

Stuck A, Beers MH, Steiner A, Aronow HU, Rubenstein LZ, Beck JC (1994) Inappropriate medication use in community-residing older persons. Arch Intern Med 154:2195–2200

Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA (1998) Antidepressants and the risk of falls among nursing home residents. N Engl J Med 339:875–882

Trifirò G (2011) Antipsychotic drug use and community-acquired pneumonia. Curr Infect Dis Rep 13:262–268

Trifirò G, Spina E, Gambassi G (2009) Use of antipsychotics in elderly patients with dementia: do atypical and conventional agents have a similar safety profile? Pharmacol Res 59:1–12

Trifirò G, Gambassi G, Sen EF, Caputi AP, Bagnardi V, Brea J, Sturkenboom MC (2010) Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. Ann Intern Med 152:418–425

Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH et al (2005) Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 353:2335–2341

Zhang R, Dong L, Shao F, Tan X, Ying K (2011) Antipsychotics and venous thromboembolism risk: a meta-analysis. Pharmacopsychiatry 44:183–188

Zint K, Haefeli WE, Glynn RJ, Mogun H, Avorn J, Sturmer T (2010) Impact of drug interactions, dosage, and duration of therapy on the risk of hip fracture associated with benzodiazepine use in older adults. Pharmacoepidemiol Drug Saf 19:1248–1255

Chapter 15
Safety of Psychotropic Drugs in Pregnancy and Breastfeeding

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Abstract Pharmacovigilance studies are vital to our understanding of the safety of medications in pregnancy, but great care must be taken in the analysis and interpretation of observational data to avoid problems with confounding and bias. Data on drug excretion in breast milk and possible effects of the breastfed infant often stem from case reports or small case series, making the generalization of the results a challenge. This chapter reviews the safety of psychotropic drugs in pregnant and breastfeeding women and discusses methodological issues that have to be dealt with in the interpretation of published data.

Keywords Pregnancy • Teratology • Fetal safety • Postpartum depression • Breastfeeding • Breast milk

15.1 Introduction

The most common mental disorders during pregnancy and in the postpartum period are depression, bipolar disorder, and anxiety disorders. For women with mild symptoms, non-pharmacological treatment is often sufficient, but in patients with moderate to severe symptoms, drug treatment is frequently used.

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15.2 Drug Safety in Pregnancy

In the general population, knowledge of medication efficacy and safety is primarily based on prospective and randomized clinical trials. Pregnant women, however, are routinely excluded from these studies due to uncertainties about the effects on fetal development. Available information on medication safety in human pregnancies is therefore most commonly based on case reports or case series initially and then, several years after the drug has reached the market, on pharmacoepidemiological studies. Case reports are most commonly limited by retrospective reporting ("reporting bias") and lack of information about important potential confounding factors, making causality difficult or impossible to determine. However, history has shown that many known teratogens have been identified through case reports (e.g., thalidomide, isotretinoin, mycophenolate) and that such reports therefore may be valuable, especially when the particular outcome is infrequent in the unexposed population and the risk is clearly increased.

Pharmacoepidemiological studies in pregnancy typically have case-control or cohort design and are based on data from adverse drug reaction surveillance systems, pregnancy registries, clinical networks (e.g., teratology information services), or large health-care databases (e.g., a prescription registry linked to a medical birth registry). Such studies are vital to our understanding of the safety of medications in pregnancy, but as they are based on observational data, great care must be taken in the analysis and interpretation of their results. Major methodological challenges are related to sample size/power, errors in measurement of medication use, bias in the form of, e.g., selection bias and information bias (misclassification of exposure or outcome), and confounding. Potential sources of confounding in studies with psychotropic drugs are sociodemographic status, alcohol intake, smoking, nutritional status including vitamin intake, and concomitant drug therapy.

A major challenge in pregnancy studies is confounding by indication, i.e., to distinguish between a fetal effect caused by the drug under study and by the maternal disorder being treated. In fact, in many cases the underlying (and untreated) illness might pose a greater risk to the unborn child than the medication. Including a disease comparison group (women with the same disease and ideally also the same disease severity, but not treated with the drug), or comparing drug use across different indications, offers advantages over studies comparing exposed cases to healthy controls only.

In all pharmacoepidemiological studies, sources of errors or bias should be acknowledged and discussed and preferably quantified by performing sensitivity analysis of estimates under an array of assumptions about possible bias directions and magnitudes.

Many fetal adverse events (e.g., malformations, neonatal persistent pulmonary hypertension) occur spontaneously at low rates, and most human teratogens increase such risk modestly. For example, 800 exposed cases and 800 unexposed controls are required to detect a twofold increased risk for malformations with 80 % statistical power and an alpha value of 0.05, assuming a baseline prevalence rate of 3 % (Strom 2012). When studying specific malformations, the absolute risk is

Table 15.1 Overview of the most commonly used medications for treatment of mental disorders according to their safety during pregnancy

	First trimester exposure	Second trimester exposure	Third trimester exposure
Antidepressants[a]	May be used. Avoid paroxetine due to a possible increased risk of cardiac defects	May be used	May be used. Transient perinatal complications may occur in infants exposed up to delivery
Antipsychotics	May be used	May be used	May be used. Transient dyskinesias may occur in neonates exposed up to delivery, particularly for first generation drugs
Lithium	Avoid if possible. Small increased risk of cardiac defects (in particular Ebstein's anomaly)	Avoid if possible	May be used
Carbamazepine	Should be avoided. Increased risk of malformations	Avoid if possible	Avoid if possible
Valproic acid	Contraindicated. Considerably increased risk of malformations	Contraindicated. Risk of long-term cognitive impairment	Contraindicated. Risk of long-term cognitive impairment
Lamotrigine	May be used	May be used	May be used
Anxiolytics and hypnotics	May be used sporadically	May be used sporadically	May be used sporadically. Respiratory distress may occur in infants exposed up to delivery

Light gray: Generally considered safe, but uncertainties may exist, e.g., for some of the drugs within a group or related to the total amount of data available
Medium gray: Increased risk of harmful effects cannot be excluded
Dark gray: The fetal risk exceeds the therapeutic advantage for the mother in the treatment of mental disorders in pregnancy
[a]For other antidepressants than selective serotonin reuptake inhibitors, see text

considerably lower (i.e., the background risk of any cardiac defects is about 1 %; of a neural tube defect about 1:1000), and several thousand exposed cases are often needed to detect a true increase in fetal risk.

15.2.1 Antidepressants

Antidepressants, and in particular selective serotonin reuptake inhibitors (SSRIs), are probably the most studied and debated drug group with respect to safety in pregnancy. There has been a marked increase in the use of antidepressants in pregnancy

over the last 10 years, with the most recent prevalence data ranging from 3 % to 4 % in Europe and in Australia to more than 8 % in North America (Nordeng 2016).

The majority of studies that have evaluated the safety of antidepressants in early pregnancy do not indicate an enhanced risk of major congenital malformations after exposure to SSRIs in general (Koren and Nordeng 2012). A meta-analysis including studies published on SSRIs up to 2010, however, suggested an increased risk of cardiac defects (especially septal defects) with first-trimester exposure to paroxetine. For cardiac defects, the odds ratio (OR) was 1.46, with a 95 % confidence interval (CI) of 1.17–1.82 (Wurst et al. 2010).

In one of our studies based on data from more than 60,000 pregnant women and their children in the Norwegian Mother and Child Cohort Study, we found that exposure to SSRIs during the first trimester was not associated with an increased risk of overall congenital malformations (adjusted OR 1.22; 95 % CI 0.81–1.84) or cardiovascular malformations (adjusted OR 1.51; 95 % CI 0.67–3.43) (Nordeng et al. 2012). Exposure to antidepressants in general was not associated with low birth weight (adjusted OR 0.62; 95 % CI 0.33–1.16). In the crude analysis, exposure to antidepressants was associated with preterm birth (OR 1.46; 95 % CI 1.04–2.04); however, after adjustment for depression and sociodemographic characteristics, this increased risk disappeared (adjusted OR 1.21; 95 % CI 0.87–1.69). Moreover, having symptoms of depression in pregnancy was in itself associated with preterm birth (adjusted OR 1.13; 95 % CI 1.03–1.25). These findings are reassuring and illustrate the importance of adjustment for the underlying illness in pharmacoepidemiological studies. Without adjustment, antidepressant use would wrongly have been accused for being associated with preterm birth (Nordeng et al. 2012).

Studies have shown conflicting results as to whether SSRIs increase the risk of other outcomes in the newborn, such as low birth weight and perinatal complications; however most of these studies have not been able to distinguish whether this is due to antidepressant treatment or is caused by the underlying mental disorder. A systematic review of the literature showed that depression in itself increased the risks for low birth weight by 49 %, for intrauterine growth restriction by 45 %, and for preterm delivery by 39 % (Grote et al. 2010).

In a literature review on third trimester safety of antidepressants, we found that neonatal adverse findings were quite common among infants exposed to SSRIs close to delivery (2–3 out of 10 exposed infants) (Nordeng and Spigset 2005). Respiratory distress, irritability, and suckling difficulties were most frequent and resolved spontaneously in most cases within 2 weeks postpartum (Nordeng and Spigset 2005; Moses-Kolko et al. 2005). However, such findings are relatively common also among unexposed newborns. Although several studies have found a statistical significant association between prenatal exposure to SSRIs and persistent pulmonary hypertension of the newborn (OR: 2.5; 95 % CI 1.3–4.7), the absolute risk of this serious complication remains low (3–12 of 1000 exposed infants) (Grigoriadis et al. 2013).

As serotonin plays a critical role in hemostasis, concern has been raised with respect to perinatal bleeding complications. We identified no overall increased risk

of vaginal bleeding during pregnancy or after delivery among women exposed to antidepressants. Interestingly, women not medicated with antidepressants but with depressive symptoms had a moderately increased risk of vaginal bleeding in early and mid pregnancy (Lupattelli et al. 2014).

Recently, concerns about long-term neurodevelopmental outcomes after prenatal antidepressant exposure have been raised. Animal studies have found exposure to elevated serotonin levels to be associated with abnormal development of the central nervous system (Schaefer et al. 2015). Results from human neurodevelopmental studies, however, have been inconsistent: some link antidepressants to adverse neurodevelopmental outcomes like ADHD, autism spectrum disorders, and motor and cognitive dysfunction, whereas others do not (Gentile and Galbally 2011). A recent review of the literature found no clear evidence of negative effects by SSRIs on early neurodevelopment, but studies on later neurodevelopment showed conflicting results with respect to untoward effects on psychomotor, cognitive and language development, temperament, and behavioral problems (Hermansen and Melinder 2015). General recommendations for SSRI use in pregnancy are summarized in (Table 15.1).

Tricyclic antidepressants (TCA) and serotonin/noradrenaline reuptake inhibitors (SNRIs) are less well studied than SSRIs, but may be used in women who do not respond to SSRIs. Most data exists for amitriptyline, clomipramine, imipramine, nortriptyline, and venlafaxine (Schaefer et al. 2015). Data do not indicate any increased risk of major malformations, but most studies have been too small or have other methodological limitations to draw definite conclusions. An increased risk of poor neonatal adaptation has been reported after use of venlafaxine during pregnancy, as for other serotonergic antidepressants.

15.2.2 Antipsychotics

Antipsychotics are prescribed to 0.2–0.3 % of all pregnant women (Petersen et al. 2014), mainly for bipolar disorder and schizophrenia. First-generation antipsychotics are known to affect the menstrual cycle and may also reduce fertility secondary to the group's prolactin-increasing effects. Second-generation antipsychotics, on the other hand, have metabolic side effects that may increase the risk of excessive maternal weight gain during pregnancy, gestational diabetes, and preeclampsia. None of the published studies indicate an increased risk of teratogenic effects, though less data are available for the newest second-generation antipsychotics (Galbally et al. 2014).

Concern has been regarding the use of antipsychotics in the third trimester and transient dyskinesias in the newborn. These findings, however, have been mostly related to the use of first-generation antipsychotics. Most guidelines nevertheless recommend continuing antipsychotic treatment until delivery to avoid the risk of relapse and to monitor the newborn for possible neuromuscular adverse effects and

feeding problems. General recommendations for the use of antipsychotics in pregnancy are summarized in (Table 15.1).

15.2.3 Mood Stabilizers

Lithium has traditionally been considered a teratogenic drug due to an association with cardiac malformations, in particular Ebstein's anomaly. This risk, however, may have been overestimated, and today it is generally considered that the absolute risk of Ebstein's anomaly after first-trimester exposure to lithium is low (0.5–1:1000, as compared to 1: 20,000 in the general population). Lithium should be reserved for cases where drugs with a more favorable fetal risk profile are unsuitable. Women using lithium in pregnancy could be offered an early ultrasound examination to exclude possible fetal cardiac defects (Schaefer et al. 2015). The newborn should be monitored for signs of neuromuscular toxicity first week postpartum.

Carbamazepine, valproic acid, and lamotrigine are antiepileptic drugs frequently used in patients with bipolar disorders. Carbamazepine and valproic acid should be avoided in pregnant women with psychiatric illness due to an increased risk of malformations and adverse neurodevelopmental effect in the offspring. Both carbamazepine and valproic acid interfere with folate metabolism, which may be one of the mechanisms involved. First-trimester exposure to carbamazepine has been associated with a twofold to fivefold increased risk of neural tube defects. An increased risk of other malformations, e.g., cleft palate, cardiac malformations, and hypospadias, has also been reported. A meta-analysis including more than 60,000 women with epilepsy using carbamazepine as monotherapy reported an overall malformation rate of 5.7 % (95 % CI 3.7–7.7 %) (Meador et al. 2008), which is significantly higher than the expected baseline rate of 3–4 %. There is plausible evidence of a dose-response effect with increased risk with doses above 1000 mg/day (Tomson et al. 2011).

Valproic acid is one of the most teratogenic antiepileptic drugs and should not be prescribed to women in reproductive age. The meta-analysis mentioned above found a malformation rate of 17.6 % (95 % CI 5.3–30.0 %) among women on valproic acid monotherapy (Meador et al. 2008). The most common malformations include neural tube defects, cardiac defects, and defects of the extremities and urogenital tract, with a dose-dependent increased risk at least for spina bifida and hypospadia (Vajda and Eadie 2005). It has also been suggested that a fetal valproic acid syndrome, including specific anomalies of the face and fingers, may exist (Kozma 2001). Finally, exposure to valproic acid is linked to impaired cognitive function with lower IQ scores, especially after exposure to doses above 800–1000 mg/day (Bromley et al. 2014).

A principal limitation of the literature on the safety of carbamazepine and valproic acid in pregnancy is that most studies have been conducted among women with epilepsy where the underlying disease in itself is associated with an increased fetal risk. Moreover, the doses are generally higher than those used in psychiatric

disorders. However, as the risks related to use of these drugs are clearly significant, it is not justifiable to be less restrictive in the recommendations in bipolar disorder than in epilepsy, although the risk possibly is lower.

Knowledge on the safety of lamotrigine in pregnancy stems from thousands of pregnancies showing no increased risk of malformations or long-term adverse effects in prenatally exposed children. Lamotrigine could therefore be considered the antiepileptic drug of choice for pregnant women with bipolar disorders (Schaefer et al. 2015). General recommendations for the use of mood stabilizers in pregnancy are summarized in (Table 15.1).

15.2.4 Anxiolytics and Hypnotics

Among benzodiazepines and benzodiazepine-like hypnotics (zopiclone, zolpidem, and zaleplon), most data on safety during pregnancy exists for diazepam and zolpidem. One meta-analysis and a recent literature review concluded that there is little evidence for major malformations after use of benzodiazepines during pregnancy (Dolovich et al. 1998; Bellantuono et al. 2013). A study including more than 500 early pregnancy exposures to zolpidem found no overall increased risk of major malformations (Wikner and Källen 2011). There were four cases of non-atresial intestinal malformations (0.8 cases expected), but the authors suggest that this finding could be spurious due to multiple testing (Wikner and Källen 2011).

Prolonged use of benzodiazepines, particularly in high doses and close to delivery, has been associated with neonatal pharmacological effects and withdrawal symptoms, including poor suckling, floppy infant syndrome, and respiratory distress. Moreover, after prolonged use of benzodiazepines throughout pregnancy, concern has been raised about unfavorable long-term neurodevelopmental effects. However, although some data indicate that a small number of children may have a delayed development during the first year or so, they have generally developed normally by 4 years of age (McElhatton 1994).

Several important limitations exist for studies on the safety of benzodiazepines in pregnancy. Most studies did not have information about duration of therapy or indication for use, they did not differentiate between the various benzodiazepines, and in most studies there was a high degree of co-medication with other psychotropic drugs. Moreover, recall bias has been a major problem in the studies employing a case-control design (Dolovich et al. 1998). Women using benzodiazepines also drink more alcohol, are more often smokers, and have lower socioeconomic status than women not using benzodiazepines in pregnancy, factors that clearly could confound the results.

According to current knowledge, benzodiazepines and benzodiazepine-like hypnotics could be prescribed for short-term use in the lowest possible doses during pregnancy. Special precautions should be taken close to delivery. General recommendations for the use of anxiolytics and hypnotics in pregnancy are summarized in (Table 15.1).

15.3 Drug Safety During Breastfeeding

Human milk represents the ideal source of nutrients for small infants and provides superior immunological and antioxidant protection to milk substitutes (Newton 2004). As the infant should not unnecessarily be denied the benefits of breast milk, women are strongly encouraged to breastfeed whenever possible (World Health Organization 2003; American Academy of Pediatrics 2012). The obvious dilemma when treating a breastfeeding mother with a psychotropic drug is weighing the potential risk to the infant due to drug exposure through the milk against the disadvantage of not receiving breast milk. Another alternative, stopping or not commencing maternal drug treatment, might be even more harmful, taking into account the risk for the mother and thereby indirectly also for the infant if the mother is not receiving adequate treatment for her mental disorder (Cornisha et al. 2005).

Specific questions to be answered when deciding how to handle drug treatment in a woman with a mental disorder postpartum include: What are the risks for the mother and the infant if the maternal disease is not adequately treated? How strong is the mother's desire to breastfeed? What are the disadvantages for the infant of not receiving breast milk? What are the risks for the infant of being exposed to the medication through breast milk? Is there any evidence to suggest that some specific drugs within a therapeutic group are more favorable than others to use related to infant risk? If necessary, could any practical strategies be used to reduce drug exposure to the infant? And finally, if there is a (often small or even just theoretical) risk of adverse effects in the infant due to drug exposure and breastfeeding nevertheless is allowed, should the infant be monitored in any way?

In order to provide precise answers to these questions, knowledge about to which extent the various psychotropic drugs are excreted into breast milk and about the infant's age-related capacity to metabolize these drugs is a prerequisite. Moreover, knowledge about the theoretical infant dose and plasma concentrations of the drugs that could be expected in the infant and whether any adverse effects have been reported is also required. Unfortunately, available information about milk or infant plasma concentrations and effects of psychotropic drugs in breastfed infants is almost exclusively based upon case reports and small case series rather than upon prospective studies with unexposed control groups. For many drugs, information is extremely sparse.

15.3.1 Pharmacokinetic Considerations

Passage of psychotropic drugs between maternal plasma and breast milk is based upon principles of passive diffusion and will therefore follow a gradient from high to low concentration of free (unbound) drug. The timing of breastfeeding in relation to the time of maternal ingestion of the drug will thus be an important determinant for the concentration of the drug in the milk. When the concentration reaches its peak level in the maternal plasma, usually within a couple of hours after intake, it will, after a short delay, also reach its highest level in breast milk. Thereafter, as the

maternal plasma drug concentration gradually declines, the concentration in breast milk will decrease until the mother ingests the next dose. For drugs with a short elimination half-life, such as zolpidem ($t_{1/2}$ = 2–3 h), the risk of adverse effects in the infant can thus be reduced by breastfeeding at times when the drug concentration in breast milk is at its lowest level. This can be achieved – as obvious for zolpidem but also valid for non-hypnotic drugs with short elimination half-lives – by taking the daily dose in the evening and avoiding breastfeeding during the night. However, the vast majority of psychotropic drugs have long or very long elimination half-lives with quite stable concentrations in breast milk. For such drugs, avoiding breastfeeding during the peak concentration period will only reduce the infant's drug intake to a small extent. Simulation of data from a study from our group of the excretion of paroxetine (Öhman et al. 1999) showed that total infant exposure would be reduced only by about 20–30 % by avoiding the peak phase in milk.

As psychotropic drugs are lipophilic, concentrations in breast milk increase and decrease in parallel with the milk triglyceride content. In two previous studies from our group, we have shown that the concentrations of paroxetine and aripiprazole were considerably higher in hindmilk than in foremilk, related to the higher triglyceride content in hindmilk (Öhman et al. 1999; Nordeng et al. 2014a). However, as also the nutritional value of milk is linked to its triglyceride levels, efforts to avoid additional drug exposure by discarding milk with high triglyceride levels, such as hindmilk, cannot be recommended.

Because newborns, and in particular premature infants, have an immature liver and kidney function, they eliminate drugs at a lower rate than older children and adults (for an overview related to psychotropic drugs, see Spigset and Hägg 1998). This applies both to enzymes belonging to the cytochrome P-450 (CYP) system (by which most psychotropic drugs are metabolized) and to the family of glucuronidating (UGT) enzymes (by which, e.g., oxazepam and lamotrigine are metabolized). For example, the elimination half-life of diazepam (which is mostly metabolized by CYP2C19) is approximately 80 h in premature infants, about 30 h in full-term newborns, and 10–20 h in infants after the newborn period. During the first months of life, hepatic function gradually matures, and after about 3–4 months of age, the metabolic capacity reaches adult levels. In contrast, renal function is not fully developed until the infant is at least 6 months old. Therefore, drugs with a high degree of renal elimination, such as lithium, are of particular concern related to accumulation in young infants.

In addition to the pharmacokinetic aspects discussed above, premature or seriously ill infants will often have a lower tolerance to the pharmacological action of drugs than healthy children, including possible unfavorable effects.

15.3.2 Calculation of Infant Dose

If the drug concentration in breast milk is known, the infant's theoretical dose can be estimated by multiplying this value with the volume of milk that the infant ingests. In such calculations, milk intake in an infant who is fully breastfed is standardized to 150 ml/kg body weight per day. To assess the risk of adverse effects, the

estimated dose can then be related, e.g., to the recommended pediatric dosage for that drug for individuals of the same age. For example, for lamotrigine a fully breastfed infant is exposed to amounts corresponding to between 25 % and 50 % of the therapeutic pediatric dosage for infants, indicating that there might be a risk of pharmacological effects in the infant (Nordmo et al. 2009; Hale 2014).

It is even more common to calculate the infant's weight-adjusted relative dose, i.e., the dose the infant ingests per kilogram bodyweight in relation to the maternal dose per kilogram bodyweight. Infant exposure is regarded as minimal when the relative dose is below 2 %, small when the relative dose is 2–5 %, moderate when the relative dose is 5–10 %, and high when the relative dose is above 10 %. With relative doses above 10 %, it is generally considered that a risk of pharmacological effects in the infant does exist (Hale 2014; Ito 2000). With lower relative doses than 10 %, breastfeeding is in principle assumed to be safe, although infrequent cases of possible untoward infant affection have been reported also for drugs with relative doses below (but close to) 10 %, such as citalopram and aripiprazole (Hale 2014; Berle and Spigset 2011). On the other hand, breastfeeding is not necessarily always contraindicated during maternal treatment with drugs for which the relative doses are above 10 %, such as lithium and lamotrigine (see later).

15.3.3 Evidence of Adverse Effects

Most data on adverse effects in breastfed infants are derived from case reports (Rubin et al. 2004). Such reports are clearly of interest for drugs for which no or very little previous data exist, but it is often complicated or even impossible to determine whether there is a causal connection between reported infant symptoms and drug exposure.

A literature review of 183 reports on the use of psychotropic drugs during breastfeeding (Fortinguerra et al. 2009) found that infant adverse effects had been published for all groups of psychotropic drugs (but not for all individual drugs!). Notably, another review found that in about 80 % of the cases with adverse effects after maternal drug use in general, the infant was younger than 2 months of age (Anderson et al. 2003). This is accordance with the expected gradual maturation of hepatic and renal function during the first months of life and clearly illustrates that infant age is a critical factor to take into account when assessing the individual infant risk.

Very few prospective and systematic studies have compared the occurrence of symptoms possibly related to psychotropic drug exposure in breastfed infants of mothers taking and not taking the medication under study. One of a few such studies has been performed by our group (Berle et al. 2004). In that study, excretion of selective serotonin reuptake inhibitors (SSRIs) or venlafaxine to breast milk was investigated in 25 mothers with 26 exposed infants. Ten common symptoms of SSRI exposure (regurgitation/vomiting, irritability, tremor, suckling or feeding problems, decreased or increased sleep, yawning, etc.) were rated by the mothers and compared

to a control group of 68 breastfed infants of the same age where the mother did not use any medication. There were no differences between the groups neither regarding any of the specific symptoms nor regarding the total symptom score (5.9 in the antidepressant group vs. 7.6 in the control group on a scale ranging from 0 to 30).

15.3.3.1 Antidepressants

Depression is a common illness among women in the postpartum period with an incidence of 10–15 % (O'Hara and Schwain 1996). In addition to the potentially harmful effects the depression may have on the mother, challenges exist related to caretaking of the newborn infant. Chronic maternal depression in the first year

Table 15.2 Infant doses and plasma concentrations of newer antidepressants after exposure via breast milk

Drug	Relative infant dose[a]	Absolute infant plasma concentration	Relative infant plasma concentration[b]
Selective serotonin reuptake inhibitors			
Citalopram	3–10 %	Negligible[c]	Up to 10 %[d]
Escitalopram	3–6 %	<5 ng/ml	<4 %
Fluoxetine[e]	<12 %	Up to 100 ng/ml[f]	Up to 80 %[f]
Fluvoxamine	<2 %	<LOD[g]	–
Paroxetine	0.5–3 %	<LOD[g]	–
Sertraline	0.5–3 %	<LOD[g]	–
Other newer antidepressants			
Venlafaxine[h]	6–9 %	Up to 40 ng/ml	Up to 30 %
Duloxetine	<1 %	<LOD[g]	–
Reboxetine	1–3 %	<5 ng/ml	<2 %
Bupropion[i]	2 %	<LOD[g]	–
Mirtazapine	0.5–3 %	0.2 ng/ml	<1 %

[a]Infant daily dose per kg body weight expressed as a percentage of maternal daily dose per kg body weight. A value below 10 % is generally considered negligible

[b]Infant plasma concentration expressed either as a percentage of the measured maternal plasma concentration or as a percentage of what could be considered a low therapeutic concentration in adults

[c]In most cases below the lower limits of detection for the analytical methods employed, which were mostly in the range of 2–5 ng/ml. However, in a few cases, which also have been associated with suspected adverse effects, concentrations up to 15 ng/ml have been found

[d]In a few cases, which also have been associated with suspected adverse effects, concentrations up to about 50 % of the therapeutic concentration range have been found

[e]Sum of fluoxetine and the active metabolite norfluoxetine

[f]In some cases, which also have been associated with suspected adverse effects, concentrations as high as about 500 ng/ml, i.e., clearly within the therapeutic concentration range, have been found

[g]Below the lower limits of detection for the analytical methods, which were mostly in the range of 1–5 ng/ml

[h]Sum of venlafaxine and the active metabolite O-desmethylvenlafaxine

[i]Including one or several of the active metabolites of bupropion

postpartum is associated with delayed psychomotor development in the child at 15 months and may also affect the cognitive and emotional development (Cornisha et al. 2005; Poobalan et al. 2007).

Key data on infant exposure for antidepressants are presented in Table 15.2. Regarding the choice of specific drug, it is sometimes recommended that sertraline should be preferred over other SSRIs due to the low infant exposure to that drug (Gentile 2007). It has also been recommended that when possible, fluoxetine and citalopram should be avoided or used with caution due to the higher infant plasma levels (Table 15.2) and the possible risk of adverse effects such as irritability, sleep disturbances, colic, and poor suckling.

Nevertheless, irrespective of which SSRI if the mother has been treated with during pregnancy, we suggest that the same drug could also be used in the postpartum period (Berle and Spigset 2011; Berle et al. 2004). Based upon the current literature including a prospective study from our group (Berle et al. 2004), we recommend that when antidepressant treatment is indicated in the postpartum period, the woman should generally not be advised to discontinue breastfeeding. Some reviews and guidelines recommend infant monitoring, particularly if the infant is sick, is premature, or has a low body weight (Weissman et al. 2004; Lanza di Scalea and Wisner 2009). However, given the very low risk of any untoward effects, we consider there is no general need for routine follow-up examinations.

The numbers of exposed infants vary significantly between drugs, with about 100 cases for fluoxetine, paroxetine, sertraline, and citalopram, but less than 25 for the other newer antidepressants. Some degree of uncertainty inevitably exists for the drugs with the lowest numbers of exposed infants, even when no adverse effects have been reported. On this basis, drugs for which little data exist, such as fluvoxamine, venlafaxine, duloxetine, reboxetine, bupropion, and mirtazapine, should not be viewed as first-line therapies, but could be considered in special cases.

15.3.3.2 Antipsychotics

The risk of a psychotic reaction is higher in the postpartum period than anytime during a woman's life. In a study of female patients with bipolar disorder, 36 % had had their first psychotic episode in the postpartum period (Hunt and Silverstone 1995). In another study of women who previously had been hospitalized with psychiatric symptoms, the risk of postpartum psychosis was increased about 100-fold (Nager et al. 2008). Thus, treatment with antipsychotics related to breastfeeding is not an uncommon issue.

In general, sparse data exist for the excretion of second-generation antipsychotics in breast milk, and even less data is available regarding possible effects in the breastfed infants. In total, about 60 cases for olanzapine, 20–30 cases for quetiapine, about 10 cases for risperidone and clozapine, 4 cases for aripiprazole, and 2 cases for ziprasidone have been published to date (Nordeng et al. 2014a; Hale 2014; Klinger et al. 2013). Key data on infant exposure for these drugs are presented in Table 15.3.

Table 15.3 Infant doses and plasma concentrations of second-generation antipsychotics and mood stabilizers after exposure via breast milk

Drug	Relative infant dose[a]	Absolute infant plasma concentration	Relative infant plasma concentration[b]
Second-generation antipsychotics			
Aripiprazole	Up to 8.3 %[c]	NA[d]	NA[d]
Clozapine	1.2 %	NA[d]	NA[d]
Olanzapine	1–4 %	<LOD[e,f]	–[f]
Quetiapine	0.1–0.4 %	1.4 ng/ml	6 %
Risperidone	2–5 %[g]	<LOD[e]	–
Ziprasidone	1.2 %	<LOD[e]	–
Mood stabilizers			
Lithium	Up to 40–80 %	Up to 0.7 mmol/l	Up to ~100 %
Carbamazepine	1–8 %	0.5–1.0 μg/ml[h]	10–40 %
Lamotrigine	Up to 20 %	0.8–1.6 μg/ml	20–50 %
Valproic acid	0.5–4 %[i]	0.5–2.0 μg/ml	4 %

[a]Infant daily dose per kg body weight expressed as a percentage of maternal daily dose per kg body weight. A value below 10 % is generally considered negligible
[b]Infant plasma concentration expressed either as a percentage of the measured maternal plasma concentration or as a percentage of what could be considered a low therapeutic concentration in adults
[c]Sum of aripiprazole and the active metabolite dehydroaripiprazole
[d]No data available
[e]Below the lower limit of detection for the analytical methods employed, which were mostly in the range of 1–5 ng/ml
[f]In one infant at one specific point of time the concentration was 40 % of the maternal concentration
[g]Sum of risperidone and the active metabolite 9-hydroxyrisperidone
[h]A concentration of 4.5 μg/mL, which is within the therapeutic range, has been reported in a single case
[i]Maximum 7 % in a single case

In a case series of four breastfed infants exposed to clozapine, agranulocytosis was reported in one and drowsiness in another of the infants (Dev and Krupp 1995). Although the relative infant dose is low, these adverse effects could be readily explained from the drug's adverse effect profile. Due to the severity of these reactions, it is generally recommended that women treated with clozapine should avoid breastfeeding.

For olanzapine and quetiapine, some prospective data are available, although only five and six subjects have been included, respectively (Gardiner et al. 2003; Misri et al. 2006). Whether the infant dose seems to be even lower for quetiapine than for olanzapine, it is remarkable that two of the six infants exposed to quetiapine (Misri et al. 2006) scored slightly below the normal range for mental and psychomotor development (82/82 and 84/91, respectively; normal range 85–115 for both subscales). However, as no quetiapine was found in breast milk in any of these cases, the low scores may well have been unrelated to the drug exposure. No untoward effects have been suspected for olanzapine. For risperidone, infant exposure is

in the same range as for olanzapine and quetiapine, and no untoward effects have been reported. In a recent case study, we found that infant exposure to aripiprazole was higher than previously reported and also higher than for olanzapine, quetiapine, and risperidone (Nordeng et al. 2014a). Although no adverse effects were observed in our case, others have reported that somnolence could occur (Hale 2014). Thus, we recommend that infants exposed to aripiprazole should be monitored for potential adverse effects including drowsiness, poor feeding, and sleeping pattern changes. For ziprasidone very little information exists; thus any specific advice cannot be given.

In the counseling of mothers treated with second-generation antipsychotics in the postpartum period, an individualized risk/benefit approach should be applied regardless of which drug is preferred. As stated above, most evidence of non-risk exists for olanzapine. However, with the exception of clozapine, no clear-cut evidence of harmful effects exists for the other drugs either.

15.3.3.3 Mood Stabilizers

For lithium, there have been two reports of toxicity in breastfed infants exposed via breast milk (for a review, see Spigset and Hägg 1998). In these infants, the plasma levels of lithium were 0.6 and 0.7 mmol/l, respectively. The infants presented with symptoms such as tremor and involuntary movements, and the high lithium concentrations were thought to be caused by decreased renal clearance due to dehydration during a common cold. Based upon these reports, lithium is often considered not compatible with breastfeeding. However, there are also studies suggesting that lithium administration is not an absolute contraindication to breastfeeding: Although the infant plasma levels regularly amount to 20–40 % of the maternal plasma concentration (Spigset and Hägg 1998; Viguera et al. 2007), most often no untoward effects have been observed. Therefore, if the mother has a strong desire to breastfeed and the infant is healthy, breastfeeding could be allowed. In these cases, however, the mother should be instructed to watch for symptoms of lithium toxicity in the infant, e.g., neuromuscular affection and feeding difficulties, and be particularly observant during situations where the infant could become dehydrated (infections, vomiting, etc.). It might also be helpful to monitor infant plasma concentrations of lithium, creatinine, and possibly also thyroxin and thyroid-stimulating hormone.

For valproic acid and carbamazepine, infant exposure is generally low (Table 15.3). For carbamazepine there are a few reports on possible adverse effects in breastfed infants, including sedation and poor suckling. However, these reports are not clear-cut and cannot be viewed as conclusive evidence for a relationship (for a review, see Fortinguerra et al. 2009; Hägg and Spigset 2000). Carbamazepine is generally considered compatible with breastfeeding, but as the infant plasma concentrations of carbamazepine in some cases have been relatively high, it could be pertinent to observe the infant for drowsiness and poor suckling, particularly if the infant is premature or the mother is using combination therapy (Hale 2014;

Fortinguerra et al. 2009). For valproic acid, infant plasma levels after exposure via breast milk are considerably lower than the therapeutic plasma concentrations obtained in the treatment of seizures in infants and children (for a review, see Fortinguerra et al. 2009; Hägg and Spigset 2000). Thus, valproic acid is considered fully compatible with breastfeeding (Hale 2014; Fortinguerra et al. 2009). However, due to its teratogenic potential if the breastfeeding mother should become pregnant once again, it has been argued that valproic acid nevertheless is best avoided also in the postpartum period. Notably, recent recommendations from the European Medicines Agency (EMA) state that valproic acid should only be prescribed to women of fertile age if other treatments are ineffective or not tolerated and if so that the women should be advised to use effective contraception (EMA 2014).

Lamotrigine is excreted in breast milk to a relatively high extent, and there is a consistent finding across studies in mothers with epilepsy that the infant plasma concentrations amount to about 20 % of the maternal drug levels but in some cases up to 50 % (Hale 2014; Newport et al. 2008), i.e., levels where pharmacological effects cannot be excluded. Although more than 50 cases of exposed infants have been reported in the literature, infant adverse reactions have been reported in a single case only. In this case, severe apnea was seen in a 16-day-old infant (Nordmo et al. 2009). Based upon these data, an individualized risk/benefit approach should be applied, and, if breastfeeding is allowed, it would be advisable to monitor the infant for adverse effects such as sedation and poor suckling. Moreover, if adverse reactions are suspected, the infant plasma concentration of lamotrigine should be measured.

15.3.3.4 Anxiolytics and Hypnotics

In general, benzodiazepines have long elimination half-lives, which are even longer in neonates than in adults. For diazepam (plus the active metabolite desmethyldiazepam), the relative infant dose ranges from 3 % to 14 %. Infant plasma concentrations above 10 % of the maternal levels are regularly seen, and a certain percentage of exposed infants have been reported to have signs of central nervous system (CNS) affection such as sedation, lethargy, and lack of response to stimuli (Spigset and Hägg 1998; Hale 2014; Rubin et al. 2004; Kelly et al. 2012). Thus, diazepam in more than single doses is not considered compatible with breastfeeding. Oxazepam is excreted to a lower extent and is, although less studied, probably preferable to diazepam. However, also oxazepam has been associated with infant CNS affection and should, if allowed during breastfeeding, be used in the lowest possible dose and for the shortest possible time. Moreover, the infant should in such cases be observed for signs of CNS depression. If high doses and/or long-term treatment are required in young infants, breastfeeding should preferably be stopped.

When treatment with hypnotics is indicated during breastfeeding, we suggest that benzodiazepines with relatively long elimination half-lives, such as flunitrazepam and nitrazepam, should be avoided due to the risk of accumulation in the infant.

In contrast, zopiclone and zolpidem are more swiftly eliminated. Of these, zolpidem is, in contrast to zolpidem, completely cleared from the milk after 10 h, and as the mother should be asleep and not breastfeed during the first hours after intake, infant exposure for zolpidem will be close to zero (Spigset and Hägg 1998). Although both zopiclone and zolpidem are often considered compatible with breastfeeding, we recommend zolpidem as the preferred choice.

15.4 General Clinical Recommendations

A maternal mental disorder should be appropriately treated during pregnancy and in the postpartum period because untreated or inadequately treated disease will result in maternal suffering and could lead to poor compliance with prenatal and postnatal care, missed maternity checkups, and poor lifestyle (i.e., inappropriate nutrition, smoking, use of alcohol and illicit drugs), being potentially harmful both to the mother and the child.

The risk of relapse in pregnancy after discontinuation of psychotropic medication is high, ranging from 52 % among women with bipolar disorder (Viguera et al. 2000) to 68 % in women with major depression (Cohen et al. 2006). Psychotherapy is recommended as the treatment for mild to moderate mental disorders during pregnancy and should also be used complementary to pharmacotherapy.

Many women with moderate to severe mental illness will have to continue treatment with psychotropic drugs during pregnancy. The selection of a psychotropic drug should be guided by the women's prior treatment response bearing in mind the individual drug's possible adverse effects on her pregnancy. Informing about the pros and cons of pharmacological treatment requires focus on risk communication and documentation of decision processes. Doctors should be aware that women tend to overestimate the risks associated with the use of psychotropic drugs during pregnancy (Nordeng et al. 2010; Petersen et al. 2015) and that adherence to prescribed psychotropic drugs often is low (Lupattelli et al. 2015). In a study among women in 18 countries, we found that low adherence in pregnancy was reported by 51 % of women using drugs for anxiety disorders during pregnancy, 47 % using drugs for depression, and 43 % using drugs for other mental disorders. The belief that the benefit of pharmacotherapy outweighed the risks was positively correlated with higher medication adherence ($r = 0.282$; $p < 0.001$) (Lupattelli et al. 2015).

The metabolism of many psychotropic drugs increases during pregnancy. This effect is best documented and possibly also most pronounced for lamotrigine but is apparent also for antidepressants and antipsychotics. Also the renal clearance of lithium is increased in pregnancy, causing lower plasma concentrations than in non-pregnant women. Thus, for psychotropic drugs in general, therapeutic drug monitoring is advised and it should be expected that the dosage has to be gradually increased during pregnancy. Monitoring should preferably start prior to pregnancy and be performed regularly throughout pregnancy. For lamotrigine a frequency of

every to every other month has been recommended (Pennel et al. 2008); for other drugs a frequency of at least every 2–3 months has been suggested, depending on the individual drug concentration measured. At delivery, the dosage should be lowered to that given before pregnancy.

Some psychotropic drugs can be safely given to breastfeeding mothers, but for other drugs, an individual risk-benefit assessment has to be performed. Such an assessment should be based upon factors including infant age, the importance of breastfeeding for the mother, and the availability of alternative drugs with a more favorable risk profile. When breastfeeding needs to be individually adapted, extra efforts from the doctor in terms of providing information to the mother and performing follow-ups of the mother and infant are often required. Such a solution also presupposes that the mother is able to comply with the advices given.

15.5 Future Directions for Research

15.5.1 Pregnancy

Future research on the safety of psychotropic drugs in pregnancy should focus on prospective, longitudinal studies with sufficient information on key confounding factors including maternal mental health and psychiatric diagnosis, as well as adequate follow-up times to assess long-term outcomes in children.

The possibility of record linkage between large health databases and birth cohorts in Europe and North America has opened up for fast-track high-quality epidemiological studies and will be important data sources for studies on drug safety in pregnancy in the future. International collaboration is also advancing and will not only allow replication of previous findings but also pooling of data to investigate less frequently used medications and rare pregnancy outcomes that none of the individual research institutions would have adequate study power to examine alone. This possibility has already been explored among the five Nordic countries linking national prescription databases and medical birth registries to study the risk of stillbirth and infant mortality after prenatal exposure to SSRIs among more than 1.6 million singleton pregnancies (Stephansson et al. 2013).

As the size of the data sources increases, alternative study designs, like the sibling-control design, can be applied to study medication safety in pregnancy (Brandlistuen et al. 2013). The sibling-control design offers important advantages over studies comparing unrelated individuals because siblings share familial environment (e.g., maternal chronic disease) as well as on average 50 % of their genetic setup, but they may differ in medication exposure during pregnancy. In fact, it has been suggested that the sibling-control design may provide one of the most effective approaches to control for family factors when large cohorts with a sufficient number of discordant siblings are available (Susser et al. 2010). In addition, use of advanced techniques in biostatistics, including directed acyclic graphs (DAGs), propensity score matching, and marginal structural models, will enable

us to control complex, time-varying exposures and confounding factors in drug safety studies in pregnancy to obtain estimates of effects that are less biased than traditional statistical methods, thereby giving us greater confidence in the validity of the findings.

At the same time, it is becoming increasingly clear to scientists, clinicians, and the public alike that the reproductive safety of medications cannot be assured without studying long-term consequences for the child. In the near future, large birth cohorts being followed into adolescence and even longer will enable such studies, thereby filling an important knowledge gap on medication safety (Nordeng et al. 2014b).

Several birth cohorts are now also collecting biological samples of the mother and/or child (e.g., blood, urine, hair). Enabling linkage between epidemiological and biological data. Such data sources will be an extremely valuable data source in the future. It opens up for pharmacogenetic analyses, biomarker analyses, and toxicology analyses and even for new research fields like human pharmacoepigenetics. Human studies have just started to emerge showing alterations in DNA methylation patterns after in utero exposure to medications and linking these alterations to neurobehavioral disorders (Soubry et al. 2011; Non et al. 2014; van Mil et al. 2014). These sparse human findings must be replicated, but if proven correct, they will have profound consequences since it would imply that our current understanding of pharmacology is an oversimplification.

15.5.2 Lactation

Obviously, a single published case report has a limited value in the guidance of whether a woman treated with a drug could be allowed to breastfeed or not. However, also single case reports can be valuable if performed and reported properly. Preferably, repeated drug concentration measurements in milk during a full-dose interval should be carried out, and also maternal and infant plasma drug concentrations are of interest. Moreover, thorough and repeated clinical examinations of the infant should be performed. Infant age is crucial and should be reported. If relevant, also active drug metabolites and the maternal and infant CYP genotypes should be included.

Far too often, published reports of possible untoward reactions in breastfed infants have severe methodological limitations. Most importantly, there is often not possible to separate potential drug effects from the infant's normal state or from concurrent disease. In order to assess causality when an adverse effect is suspected in an exposed infant, analysis of the infant plasma concentration of the drug is central. Moreover, a period without breastfeeding, i.e., when the mother pumps and discards milk, should be scheduled to observe whether the symptoms disappear. If breastfeeding later is resumed and the symptoms return, this would provide an even stronger indication of causality.

In order to further clarify the possible risks associated with drug exposure through breast milk, prospective studies with age-matched control groups and with systematic adverse effect ratings are clearly warranted. To date, only very few such studies have been performed for psychotropic drugs. Although it is a challenge to

collect such large clinical materials, it is feasible if sufficient time, effort, and patience are put into the task.

References

Anderson PO, Pochop SL, Manoguerra AS (2003) Adverse drug reactions in breastfed infants: less than imagined. Clin Pediatr (Phila) 42(4):325–340

American Academy of Pediatrics (2012) Policy statement: breastfeeding and the use of human milk. Pediatrics 129(3):e827–e841

Bellantuono C, Tofani S, Di Sciascio G, Santone G (2013) Benzodiazepine exposure in pregnancy and risk of major malformations: a critical overview. Gen Hosp Psychiatry 35(1):3–8

Berle JO, Spigset O (2011) Antidepressant use during breastfeeding. Curr Womens Health Rev 7(1):28–34

Berle JO, Steen VM, Aamo TO, Breilid H, Zahlsen K, Spigset O (2004) Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome p450 genotypes. J Clin Psychiatry 65(9):1228–1234

Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H (2013) Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol 42(6):1702–1713

Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ et al (2014) Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev 10:CD010236

Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC et al (2006) Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 295(5):499–507

Cornisha AM, McMahona CA, Ungerera JA, Barnettb B, Kowalenkoc N, Tennant C (2005) Postnatal depression and infant cognitive and motor development in the second postnatal year: the impact of depression chronicity and infant gender. Infant Behav Dev 28:407–417

Dev VJ, Krupp P (1995) Adverse event profile and safety of clozapine. Rev Contemp Pharmacother 6:197–208

Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR (1998) Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ 317(7162):839–843

EMA (2014) CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/11/WC500177638.pdf Cited 20.05.2015

Fortinguerra F, Clavenna A, Bonati M (2009) Psychotropic drug use during breastfeeding: a review of the evidence. Pediatrics 124(4):e547–e556

Galbally M, Snellen M, Power J (2014) Antipsychotic drugs in pregnancy: a review of their maternal and fetal effects. Ther Adv Drug Saf 5(2):100–109

Gardiner SJ, Kristensen JH, Begg EJ, Hackett LP, Wilson DA, Ilett KF et al (2003) Transfer of olanzapine into breast milk, calculation of infant drug dose, and effect on breast-fed infants. Am J Psychiatry 160(8):1428–1431

Gentile S (2007) Use of contemporary antidepressants during breastfeeding: a proposal for a specific safety index. Drug Saf 30(2):107–121

Gentile S, Galbally M (2011) Prenatal exposure to antidepressant medications and neurodevelopmental outcomes: a systematic review. J Affect Disord 128(1-2):1–9

Grigoriadis S, VonderPorten EH, Mamisashvili L, Eady A, Tomlinson G, Dennis CL et al (2013) The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. J Clin Psychiatry 74(4):e309–e320

Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ (2010) A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry 67(10):1012–1024

Hägg S, Spigset O (2000) Anticonvulsant use during lactation. Drug Saf 22(6):425–440
Hale TW (2014) Medications and mothers' milk, 16th edn. Hale Publishing, Plano
Hermansen TK, Melinder A (2015) Prenatal SSRI exposure: effects on later child development. Child Neuropsychol 21(5):543–569
Hunt N, Silverstone T (1995) Does puerperal illness distinguish a subgroup of bipolar patients? J Affect Disord 34(2):101–107
Ito S (2000) Drug therapy for breast-feeding women. N Engl J Med 343(2):118–126
Kelly LE, Poon S, Madadi P, Koren G (2012) Neonatal benzodiazepines exposure during breast-feeding. J Pediatr 161(3):448–451
Klinger G, Stahl B, Fusar-Poli P, Merlob P (2013) Antipsychotic drugs and breastfeeding. Pediatr Endocrinol Rev 10(3):308–317
Koren G, Nordeng H (2012) Antidepressant use during pregnancy: the benefit-risk ratio. Am J Obstet Gynecol 207(3):157–163
Kozma C (2001) Valproic acid embryopathy: report of two siblings with further expansion of the phenotypic abnormalities and a review of the literature. Am J Med Genet 98(2):168–175
Lanza di Scalea T, Wisner KL (2009) Antidepressant medication use during breastfeeding. Clin Obstet Gynecol 52(3):483–497
Lupattelli A, Spigset O, Koren G, Nordeng H (2014) Risk of vaginal bleeding and postpartum hemorrhage after use of antidepressants in pregnancy: a study from the Norwegian Mother and Child Cohort Study. J Clin Psychopharmacol 34(1):143–148
Lupattelli A, Spigset O, Björnsdóttir I, Hameen-Anttila K, Mårdby AC, Panchaud A et al (2015) Patterns and determinants of low adherence to psychotropic medications during pregnancy – a multinational study. Depress Anxiety 32(6):426–436
McElhatton PR (1994) The effects of benzodiazepine use during pregnancy and lactation. Reprod Toxicol 8(6):461–475
Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C (2008) Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 81(1):1–13
Misri S, Corral M, Wardrop AA, Kendrick K (2006) Quetiapine augmentation in lactation: a series of case reports. J Clin Psychopharmacol 26(5):508–511
Moses-Kolko EL, Bogen D, Perel J, Bregar A, Uhl K, Levin B et al (2005) Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. JAMA 293(19):2372–2383
Nager A, Sundquist K, Ramirez-Leon V, Johansson LM (2008) Obstetric complications and postpartum psychosis: a follow-up study of 1.1 million first-time mothers between 1975 and 2003 in Sweden. Acta Psychiatr Scand 117(1):12–19
Newport DJ, Pennell PB, Calamaras MR, Ritchie JC, Newman M, Knight B et al (2008) Lamotrigine in breast milk and nursing infants: determination of exposure. Pediatrics 122(1):e223–e231
Newton ER (2004) Breastmilk: the gold standard. Clin Obstet Gynecol 47(3):632–642
Non AL, Binder AM, Kubzansky LD, Michels KB (2014) Genome-wide DNA methylation in neonates exposed to maternal depression, anxiety, or SSRI medication during pregnancy. Epigenetics 9(7):964–972
Nordeng H (2016) Drug utilisation studies in pregnancy. In: Elseviers M, Andersen M, Benko R (eds.). Drug utilization research: methods and application. Wiley-Blackwell, Hoboken, NJ, USA
Nordeng H, Spigset O (2005) Treatment with selective serotonin reuptake inhibitors in the third trimester of pregnancy: effects on the infant. Drug Saf 28(7):565–581
Nordeng H, Ystrom E, Einarson A (2010) Perception of risk regarding the use of medications and other exposures during pregnancy. Eur J Clin Pharmacol 66(2):207–214
Nordeng H, van Gelder MM, Spigset O, Koren G, Einarson A, Eberhard-Gran M (2012) Pregnancy outcome after exposure to antidepressants and the role of maternal depression: results from the Norwegian Mother and Child Cohort Study. J Clin Psychopharmacol 32(2):186–194
Nordeng H, Gjerdalen G, Brede WR, Michelsen LS, Spigset O (2014a) Transfer of aripiprazole to breast milk: a case report. J Clin Psychopharmacol 34(2):272–275
Nordeng H, Ystrøm E, Eberhard-Gran M (2014b) Medication safety in pregnancy – results from the MoBa-study. Nor J Epidemiol 24(1-2):161–168

Nordmo E, Aronsen L, Wasland K, Smabrekke L, Vorren S (2009) Severe apnea in an infant exposed to lamotrigine in breast milk. Ann Pharmacother 43(11):1893–1897
O'Hara MW, Schwain AM (1996) Rates and risk of postpartum depression – a meta-analysis. Rev Psychiatry 8:37–54
Öhman R, Hagg S, Carleborg L, Spigset O (1999) Excretion of paroxetine into breast milk. J Clin Psychiatry 60(8):519–523
Pennell PB, Peng L, Newport DJ, Ritchie JC, Koganti A, Holley DK et al (2008) Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology 70(22 Pt 2): 2130–2136
Petersen I, McCrea RL, Osborn DJ, Evans S, Pinfold V, Cowen PJ et al (2014) Discontinuation of antipsychotic medication in pregnancy: a cohort study. Schizophr Res 159(1):218–225
Petersen I, McCrea R, Lupattelli A, Nordeng H (2015) Women's perception of risks in pregnancy: multinational population based internet survey. BMJ Open 5(6):e007390
Poobalan AS, Aucott LS, Ross L, Smith WC, Helms PJ, Williams JH (2007) Effects of treating postnatal depression on mother-infant interaction and child development: systematic review. Br J Psychiatry 191:378–386
Rubin ET, Lee A, Ito S (2004) When breastfeeding mothers need CNS-acting drugs. Can J Clin Pharmacol 11:e257–e266
Schaefer C, Peters PWJ, Miller RK (2015) Drugs during pregnancy and lactation: treatment options and risk assessment, 3rd edn. Elsevier, Amsterdam
Soubry A, Murphy S, Huang Z, Murtha A, Schildkraut J, Jirtle R et al (2011) The effects of depression and use of antidepressive medicines during pregnancy on the methylation status of the IGF2 imprinted control regions in the offspring. Clin Epigenetics 3:2
Spigset O, Hägg S (1998) Excretion of psychotropic drugs into breast milk. CNS Drugs 9:111–134
Stephansson O, Kieler H, Haglund B, Artama M, Engeland A, Furu K et al (2013) Selective serotonin reuptake inhibitors during pregnancy and risk of stillbirth and infant mortality. JAMA 309(1):48–54
Strom BL, Kimmel SE, Hennessy S (eds.) (2012) Pharmacoepidemiology, 5th edn. Wiley-Blackwell, Hoboken, NJ, USA
Susser E, Eide MG, Begg M (2010) Invited commentary: the use of sibship studies to detect familial confounding. Am J Epidemiol 172(5):537–539
Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A et al (2011) Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 10(7):609–617
Vajda FJ, Eadie MJ (2005) Maternal valproate dosage and foetal malformations. Acta Neurol Scand 112(3):137–143
van Mil NH, Steegers-Theunissen RP, Bouwland-Both MI, Verbiest MM, Rijlaarsdam J, Hofman A et al (2014) DNA methylation profiles at birth and child ADHD symptoms. J Psychiatr Res 49:51–59
Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ (2000) Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry 157(2):179–184
Viguera AC, Newport DJ, Ritchie J, Stowe Z, Whitfield T, Mogielnicki J et al (2007) Lithium in breast milk and nursing infants: clinical implications. Am J Psychiatry 164(2):342–345
Weissman AM, Levy BT, Hartz AJ, Bentler S, Donohue M, Ellingrod VL et al (2004) Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. Am J Psychiatry 161(6):1066–1078
Wikner BN, Källen B (2011) Are hypnotic benzodiazepine receptor agonists teratogenic in humans? J Clin Psychopharmacol 31(3):356–359
World Health Organization (WHO) (2003) Infant and young child feeding. World Health Organization, Geneva
Wurst KE, Poole C, Ephross SA, Olshan AF (2010) First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. Birth Defects Res A Clin Mol Teratol 88(3):159–170