Chapter 14
Pharmacometrics in Psychiatric Diseases

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14.1 Introduction

Psychiatric disorders include a very long list of mental illnesses that have a huge impact on someone's daily behavior and functioning as well as interaction with others. Major psychiatric diseases include attention deficit hyperactivity disorder (ADHD), addiction, anxiety, bipolar disorder, depression, and schizophrenia. According to the World Health Organization (WHO), over a third of people in most countries report problems at some time in their life that meet the criteria for diagnosis of one or more of the common types of mental disorder (WHO 2000). Thereby, these diseases have a huge impact on society and health care costs. Psychiatric diseases are very complex, which makes diagnosis very difficult. In treatment, psychoactive drugs are helpful, but it is tough to measure the "true effects" at the mental and behavior level. With psychiatric diseases and drug effects both displaying high variability, there is much room for improvement of drug treatment and modalities.

For the development of better drugs and treatments there is a need for more insight into the disease processes as well as the fate of psychoactive drugs in the body, particularly the brain, and their associated effects. Also, more insight is needed into the sources of intra- and interindividual differences in the pharmacodynamic (PD) responses of psychoactive drugs. Thus, quantitative research approaches are needed on the factors that play a role in the relationship between disease conditions as well as drug dosing and ultimate effects, both at the population and individual level. To that end, pharmacometrics is needed, being the science that develops and applies mathematical and statistical methods to quantitatively characterize, understand, and predict drug's pharmacokinetic (PK), PD, and biomarker outcomes (Williams 2007). Therewith the pharmacometric approach is anticipated to contribute to improved treatment modalities, paving the way to individualized medicine in psychiatric diseases.

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In this chapter, first, the major psychiatric diseases anxiety, depression, and psychosis will be briefly introduced. Then, current available anxiolytic, antidepressants, and antipsychotic drugs used to treat such conditions will be presented. Finally, pharmacometric investigations on these drugs will be presented, with special focus on antipsychotics. It will be shown that the application of pharmacometrics in psychiatric diseases so far is scarce, but is a prerequisite to aid in further understanding of the complexity of psychiatric diseases and their drug treatments. Improvements of the quality the pharmacometric models, in the first place, lies in improvement of the quality of the data. This can be brought about by inclusion of multiple quantitative and objective measures as a composite biomarker for disease condition and treatment effects. The emphasis should lie on measures that can be obtained both preclinically and clinically, to enhance translational insights and therewith predictive power in an early stage of drug development. Then, in clinical trials, a lot can be gained by improvement of the quality of the design and explicit consideration of placebo effects and dropouts.

14.2 Psychiatric Diseases

Mental illness is a term used to describe a broad range of mental and emotional conditions. It is different from mental retardation, organic brain damage, and learning disabilities. The term "psychiatric disease" is used when mental illness significantly interferes with the performance of major life activities, such as learning, working, and communicating. Psychiatric conditions may come and go and do not always follow a regular pattern. Moreover, the type, intensity, and duration of symptoms vary from person to person. This makes it very difficult to predict when psychiatric symptoms will bristle and proper functioning will decline. Medication and psychotherapy often are helpful in the control of the symptoms. In part of the patients, the mental illness may even go into remission, while in others the illness pursues. The most common forms of psychiatric disorders are anxiety disorders, depression, and psychosis.

14.2.1 Anxiety

Anxiety (fear) is a psychological and physiological state characterized by (non)specific worries or fear(s) and avoidance behavior. Examples include panic disorder, social phobia, specific phobia, obsessive–compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, and substance-induced anxiety disorder. Anxious individuals show increased attentional capture by potential signs of danger, and interpret expressions, comments, and events in a negative manner (Bishop 2007).

14.2.2 Major Depressive Disorder

Major depressive disorder (also known as recurrent depressive disorder, clinical depression, major depression, unipolar depression, or unipolar disorder) is a mental disorder characterized by episodes of all-encompassing low mood accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities (Weihs and Wert 2011).

14.2.3 Psychosis

Psychosis is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality." It is typically characterized by radical changes in personality, impaired functioning, and a distorted or nonexistent sense of objective reality. Patients experience hallucinations and/or delusions that they believe are real, and may behave and communicate in an inappropriate and incoherent fashion. Psychosis may appear as a symptom of a number of mental disorders, including mood and personality disorders. It is also the defining feature of schizophrenia. People diagnosed with schizophrenia usually experience a combination of symptoms, including positive (i.e., hallucinations, delusions, racing thoughts), negative (i.e., apathy, lack of emotion, poor, or nonexistent social functioning), and cognitive symptoms (disorganized thoughts, difficulty concentrating and/or following instructions, difficulty completing tasks, memory problems; Andreasen and Olsen 1982).

14.2.4 Current Problems in Psychiatric Diseases

Today's lack of quantitative objective measures of psychiatric diseases is one reason that the causative factors of psychiatric diseases remain obscure (Agarwal et al. 2010; Van et al. 2008). To measure the severity of psychiatric conditions in humans, clinicians are using subjective rating scales. There are many rating scales available that provide an indication of the disease condition and guide the evaluation of recovery. For anxiety, an example of a rating scale is the Hamilton Anxiety Rating Scale (HAM-A), in the form of a psychological questionnaire (Hamilton 1959; Maier et al. 1988). For depression, the Hamilton Rating Scale for Depression (HRSD) is often used, being a multiple item questionnaire (Hamilton 1960; Hedlund and Viewig 1979). For measuring symptom severity of patients with schizophrenia, the Positive and Negative Syndrome Scale (PANSS) is widely used in the study of antipsychotic therapy (PANSS, Table 14.1; Kay et al. 1987; Marder et al. 1997). However, such scales are not truly objective because it is based on observations of a psychiatrist, primary care staff, and family members (Kay et al. 1987). The PANSS and other scoring tools can be useful in the guidance of schizophrenia treatment,

Table 14.1 The positive and negative syndrome scale (PANSS). To assess a patient using PANSS, an approximately 45-min clinical interview is conducted. The patient is rated from 1 to 7 on 30 different symptoms based on the interview as well as reports of family members or primary care hospital workers. PANSS Total score minimum = 30, maximum = 210

Positive scale: 7 items (minimum score = 7, maximum score = 49)
Delusions
Conceptual disorganization
Hallucinations
Hyperactivity
Grandiosity
Suspiciousness/persecution
Hostility
Negative scale: 7 items (minimum score = 7, maximum score = 49)
Blunted affect
Emotional withdrawal
Poor rapport
Passive/apathetic social withdrawal
Difficulty in abstract thinking
Lack of spontaneity and flow of conversation
Stereotyped thinking
General psychopathology scale: 16 items (minimum score = 16, maximum score = 112)
Somatic concern
Anxiety
Guilt feelings
Tension
Mannerisms and posturing
Depression
Motor retardation
Uncooperativeness
Unusual thought content
Disorientation
Poor attention
Lack of judgment and insight
Disturbance of volition
Poor impulse control
Preoccupation
Active social avoidance

but patient-specific factors cannot be taken into account. A more quantitative approach to determine the clinical outcome of antipsychotics is the use of biomarkers (Danhof et al. 2005). Biomarkers can also be investigated in animal models (like rats) and used to provide more mechanistic insights into the pathophysiology of the disease and prediction of treatment response in humans (Stevens et al. 2012).

Identification of the neurochemical processes in the central nervous system (CNS) associated with psychiatric disorders has led to the development of many psychoactive drugs. Psychoactive drugs can be categorized into the main categories of antidepressants, anxiolytics, mood stabilizers, antipsychotics, and stimulants. Many of these drugs are helpful to patients, but there is much room for improvement (Lader 2008).

For development of better drugs and treatments there is a need for more insight into the disease processes as well as the fate of psychoactive drugs in the body and particularly the brain and their effects measured by different biomarkers, both at the population and individual level. To that end, it is helpful to identify sources of the disease and (associated) sources of variability.

The prominent role of genetics in psychiatric diseases has been established in various family-, twin-, and adoption studies, but the identification of concrete contributing genes is difficult. This may in part be due to inconsistencies in psychiatric classification systems, complexity and heterogeneity of psychiatric disorders, genetic expression modification effects, and intervening environmental factors. Over the past years, many reliable genetic associations with complex diseases have been reported, including some associations with complex neurological and psychiatric diseases. Many of these disease associations are believed to lead to genetic variability in gene expression and splicing. The genetic epidemiology of complex psychiatric diseases has been extensively studied and it is widely believed that many genetic factors contribute to the various phenotypes and diseases, with overall contributions of a single factor being comparatively minor. More recently, the focus has shifted towards establishing endophenotypes for psychiatric diseases, including electrophysiological abnormalities and alterations in structural and functional brain imaging.

In search for contributing genetic factors, animal models with (single) gene mutation are used. However, the fact that human behavior is complex and that it cannot be easily tested in laboratories or reproduced in animal models further complicates our understanding of psychiatric diseases. Still, valuable information on mechanisms of brain dysfunction can be learned via experimental animals, like the potential impact of the P-glycoprotein (P-gp) efflux transporter at the blood–brain barrier that might influence brain distribution of part of the psychiatric drugs. That is why polymorphisms in the drug transporter gene ABCB1 encoding for P-gp is thought to account for differences in the clinical efficacy of the most drugs, most likely by influencing their access to the brain.

With overwhelming complexity of psychiatric diseases and treatment with psychoactive drugs, there is a need for quantitative description of these diseases, drug effects and variability. As a follow up of model-based drug development (Lalonde et al. 2007), pharmacometrics is the multidisciplinary science that makes use of advanced mathematical models that integrate pharmacology, physiology, and disease for quantitative analysis of interactions between drugs and biological systems, with special emphasis on sources of variability, to aid efficient drug development, regulatory decisions, and rational drug treatment in (individual) patients.

14.3 Psychoactive Drugs

14.3.1 Anxiolytics

Anxiolytics and hypnotics act on the CNS to alleviate the symptoms of anxiety and nervousness, mood stabilizing and improving sleep. Long-term use may develop psychological and physiological dependence. Fear and anxiety research to understand how to treat the potentially devastating effects of anxiety disorders in humans has utilized classical fear conditioning, a simple paradigm that has been extensively investigated in animals, helping outline a brain circuitry thought to be responsible for the acquisition, expression, and extinction of fear (Delgado et al. 2006). Categories of antianxiety drugs include benzodiazepine tranquilizers, the "new" antidepressants, and β-blockers (Kodish et al. 2011; Farach et al. 2012; Huh et al. 2011).

14.3.1.1 Benzodiazepines

Benzodiazepine tranquillizers, such as alprazolam (Xanax®), diazepam (Valium®) and lorazepam (Ativan®) fluorozapam (Dalmane®), oxazepam (Serax®), and clozapam (Klonopin®), are used to relieve the symptoms of anxiety. They also have calming and sleep-promoting effects. The actions of benzodiazepines are due to the potentiation of the neural inhibition that is mediated by gamma-aminobutyric acid (GABA). Practically, all effects of the benzodiazepines result from their actions on the ionotropic GABA(A) receptors in the CNS. Benzodiazepines do not activate GABA(A) receptors directly but they require GABA (Olkkola and Ahonen 2008).

Main effects of benzodiazepines are sedation, hypnosis, decreased anxiety, anterograde amnesia, centrally mediated muscle relaxation, and anticonvulsant activity. In addition to their action on the CNS, benzodiazepines have a dose-dependent ventilatory depressant effect and they also cause a modest reduction in arterial blood pressure and an increase in heart rate as a result of a decrease of systemic vascular resistance (Olkkola and Ahonen 2008; Vinkers et al. 2012). Side effects include dizziness, drowsiness, somnolence, fatigue, body imbalance, loss of memory, difficulty in carrying out voluntary movements, dry mouth, impaired coordination, drugs dependence and withdrawal symptoms, etc. (Vgontzas et al. 1995).

14.3.1.2 Antidepressants

The "new" antidepressants, i.e., the serotonin and noradrenaline reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) include fluvoxamine (Luvox®), venlafaxine (Effexor®), desvenlafaxine (Pristiq®), duloxetine (Cymbalta®, Yentreve®), and milnacipran (Dalcipran®, Ixel®, Savella®). These are used for the treatment of depression and other mood disorders, but also anxiety, by balancing the disorder of neurotransmitters, serotonin, and noradrenaline in the

brain to provide clinical effects. Side effects include dry mouth, gastrointestinal upsets, nausea, fatigue, and sweating. Pharmacotherapy for anxiety disorders by these drugs is effective in improving clinical symptoms, particularly in combination with psychotherapy. SSRIs are thought to be relatively safe and effective for acute treatment of several classes of anxiety disorders (Kodish et al. 2011).

14.3.1.3 Beta-blockers

The benzodiazepines have been most extensively prescribed and are still often used by many clinicians, despite the fact that it has become clear that SSRIs are better as first-choice drugs for treating anxiety disorders, alongside newer agents, such as pregabalin or SNRIs, and combined with cognitive-behavioral therapy (Lader 2008; Cloos and Ferreira 2009; Figgitt and McClellan 2000). Flumazenil is very useful in antagonizing benzodiazepine-induced sedation as well as to diagnose or treat benzodiazepine overdose (Olkkola and Ahonen 2008).

Apart from rating scales that are prone to subjectiveness, effort have been put into finding more objective measures for effectiveness of psychoactive drugs. For measurement of the effects of benzodiazepines, in healthy volunteers, measures of alertness were most sensitive to benzodiazepines. The most consistent effects were observed on saccadic peak velocity (SPV) and visual analog scores (VAS) of alertness (De Visser et al. 2003).

But, significant challenges in the field include barriers to appropriate diagnosis and treatment of anxiety disorders, failure of a significant proportion of patients to respond to first-line pharmacotherapy agents, and a limited database of efficacy or effectiveness studies to guide treatment in such cases (Koen and Stein 2011). Thus, improved treatment guidelines and algorithms are needed. More recently developed computational supports and biological markers serve as decision supports (Himmerich and Wranik 2012).

Many sources of variability in PK–PD relationships for anxiolytics are known. The SSRIs differ in their PK properties (Hiemke and Härtter 2000) and widely in their qualitative and quantitative interaction with cytochrome P450 (CYP) isozymes in the liver. CYP2D6 is inhibited by SSRIs, in order of decreasing potency paroxetine, norfluoxetine, fluoxetine, sertraline, citalopram, and fluvoxamine (Baumann 1996). Drug–drug interaction may, therefore, occur at the level of metabolism (Olkkola and Ahonen 2008; Muscatello et al. 2012; Mahmood and Sahajwalla 1999; Yuan et al. 1999; Fahey et al. 1998; Lin 2007). In addition to PK interactions, benzodiazepines have synergistic interactions with other hypnotics and opioids. Then, age is a factor in variability, and can affect PK as well as PD. In general, however, it seems that the elderly people are more sensitive to drug action, while PK remains relatively unchanged (Strawn et al. 2012; Lenze and Wetherell 2011; Klotz 1998). Genetic polymorphism also contributes to variability (Sakai and Ishizuka 2009). Furthermore, also circadian rhythm (Nagayama 1993), and pathological conditions of the liver (Mahmood and Sahajwalla 1999) and the kidneys (Baghdady et al. 2009) may affect the PK–PD relationship of anxiolytics.

14.3.2 Antidepressants

Antidepressants are the most widely prescribed therapy for depression. The exact mechanism of action of antidepressants is unknown. The prevailing theory is that antidepressants increase the concentration of one or more neurotransmitters, such as norepinephrine, serotonin, or dopamine. The different classes of antidepressants differ in the neurotransmitters they affect (Cusack et al. 1994). This determines some of their side effects and potential drug interactions. Antidepressants include:

14.3.2.1 Tricyclics

These drugs are called "tricyclics" because the drug molecules contain three rings. This class of medication is used to treat depression, and also some types of anxiety, fibromyalgia, and to control chronic pain (von Wolff et al. 2013). Tricyclics may have the following side effects: seizures, insomnia, anxiety, arrhythmia, hypertension, rash, nausea, vomiting, abdominal cramps, weight loss, constipation, urinary retention, increased pressure on the eye, and sexual dysfunction. Examples of tricyclic antidepressants are amitriptyline (Elavil®), clomipramine (Anafranil®), desipramine (Norpramin®), doxepin (Sinequan®), imipramine (Tofranil®), nortriptyline (Pamelor®), protriptyline (Vivactil®), and trimipramine (Surmontil®).

14.3.2.2 Noradrenaline and Specific Serotoninergic Antidepressants

These are a class of compounds that are used in the treatment of anxiety disorders, some personality disorders, and depression. Noradrenaline and specific serotoninergic antidepressants (NASSAs) have the following possible side effects: constipation, dry mouth, weight gain, drowsiness, sedation, blurred vision, and dizziness. More serious adverse reactions include: seizures, white blood cell reduction, fainting, and allergic reactions. Examples of NASSs include mianserin (Tolvon®) and mirtazapine (Remeron®, Avanza®, Zispin®).

14.3.2.3 SNRIs and SSRIs

SNRIs are a class of drugs used to treat major depression, mood disorders, and possibly but less commonly ADHD, obsessive compulsive disorder, anxiety disorders, menopausal symptoms, fibromyalgia, and chronic neuropathic pain. Examples of SNRIs are duloxetine (Cymbalta®), venlafaxine (Effexor®), and desvenlafaxine (Pristiq®). SNRIs raise levels of serotonin and norepinephrine that both play a key role in stabilizing mood.

Examples of SSRI antidepressants are: citalopram (Celexa®), escitalopram (Lexapro®), fluoxetine (Prozac®, Sarafem®), fluvoxamine (Luvox®), paroxetine (Paxil®), and sertraline (Zoloft®). These drugs are used to treat depression, but

some are used for anxiety, as earlier indicated (Hiemke and Härtter 2000). SSRIs will often take a month to have a noticeable effect. This is because first the brain needs to adapt to the "overflow" of serotonin by downregulating the sensitivity of the autoreceptor, which needs time (Mandrioli et al. 2012; von Wolff et al. 2013).

SSRIs and SNRIs may have the following side effects: hypoglycemia, low sodium, nausea, rashes, dry mouth, constipation, diarrhea, weight loss, sweating, tremor, sedation, sexual dysfunction, insomnia, headache, dizziness, anxiety, agitation, and abnormal thinking. Currently, the SSRIs are the most commonly prescribed antidepressants (von Wolff et al. 2013) as SSRIs are not only very effective in treating depression but are also believed that they have fewer side effects than the other types.

14.3.2.4 Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) are drugs that inhibit brain metabolism and thereby increase brain levels of monoamines, such as serotonin and norepinephrine. Examples are phenelzine (Nardil®), tranylcypromine (Parnate®), isocarboxazid (Marplan®), and selegiline (EMSAM®, Eldepryl®). MAOIs are typically only used when tricyclic antidepressants or SSRIs exacerbate or fail to prevent depression. MAOIs have the following possible side effects: blurred vision, rash, seizures, edema, weight loss, weight gain, sexual dysfunction, diarrhea, nausea, constipation, anxiety, insomnia, drowsiness, headache, dizziness, arrhythmia, fainting, feeling faint when standing up (postural hypotension), and hypertension.

Antidepressants are not all the same in how they affect neurotransmitters, how they are used, and what adverse effects or drug interactions are associated with them differ (Baumann 1996). One patient may not respond to one type of antidepressant and do better with another, while another person with a similar condition might respond the other way round.

Variation in the effects of antidepressants is a problem and the relation between severity of depression and outcome is complex (Van et al. 2008). Only a small part can be related to factors know to contribute to variability. CYP450 genes play a major role in the metabolism of a substantial part of psychotropics, including antidepressants, and the first estimates of dosage adjustments for antidepressants have been provided based on metabolizer status (Spina et al. 2008; Schosser and Kasper 2009).

Two functional polymorphisms of the serotonin transporter gene, 5-HTTLPR and STin2, have been investigated in a large number of pharmacogenetic studies of depression; other candidate genes include serotonin receptor genes, brain-derived neurotrophic factor (BDNF), P-gp located in the BBB, G-proteins, TPH1 and TPH2, MAOA, the noradrenaline transporter gene, FKBP5, or cytochrome P450 (CYP450) genes (Schosser and Kasper 2009). Based on an extensive literature search, PK of antidepressants can be substantially different between women and men. Likewise, the response to antidepressants can be quite variable, including sex differences in adverse effects and time to response. Despite the many sex differences reported, there is still little published work systematically evaluating potential sex differences in antidepressant PK and PD (Bigos et al. 2009).

De Klerk et al. (2012) concluded that adverse drug effects with SSRI treatment, in particular serotonergic effects, are predicted by two common polymorphisms of the ABCB1 gene encoding for P-gp. Since P-gp is present at the BBB and (some) SSRIs display affinity as substrate for P-gp, this may affect brain distribution of SSRIs. De Klerk and colleagues found a significant association between the number of SSRI-related adverse drug effects and ABCB1 gene variants. Moreover, serotonergic effects (sleeplessness, gastrointestinal complaints, and sexual effects) were significantly predicted by these variants and haplotype.

There is an on going debate on whether or not antidepressant effects are true or the result of placebo effects. Kirsch evaluated by meta-analysis new-generation antidepressants in relation to the placebo response (Kirsch 2009). They concluded that most trials failed to show a significant advantage of SSRIs over inert placebo, and the differences between drug and placebo are not clinically significant for most depressed patients. Fountoulakis and Möller (2011) recalculated and reinterpreted the data of the Kirsch (2008) study. Their conclusion was that Kirsch et al.'s meta-analysis suffered from important flaws in the calculations; reporting of the results was selective and conclusions unjustified and overemphasized. Overall, Fountoulakis and Möller (2011) suggested that although a large percentage of the placebo response is due to expectancy, this is not true for the active drug, and effects are not additive. The drug effect is always present and is unrelated to depression severity, while this is not true for placebo.

14.3.3 Antipsychotics

Antipsychotics are drugs used to treat various symptoms of psychosis, such as those caused by psychotic disorders or schizophrenia. Antipsychotic medication is usually prescribed to bring psychotic symptoms under control and into remission. Possible side effects of antipsychotics include dry mouth, drowsiness, and Parkinson's disease like muscle stiffness and involuntary movements of the body (tardive dyskinesia) or the so-called extrapiramidal side effects (EPS; Mauri et al. 2007). The most severe side effect of antipsychotics is agranulocytosis, the destruction of white blood cells with unknown cause. It is a potentially serious but reversible health condition, and blood cell counts need to be monitored. There are two categories of antipsychotics: typical and atypical.

14.3.3.1 Typical Antipsychotics

These drugs are also called first-generation antipsychotics (FGAs) that can be categorized by inducing EPS. Most conventional antipsychotics work by blocking the D2 dopamine receptors. Side effects include muscle stiffness and shakiness, like Parkinson's disease, sluggish feeling, slow thinking, uncomfortable restlessness (akathisia), and problems with sex life. Examples of these drugs include chlorpromazine (Largactil®), haloperidol (Haldol®), pimozide (Orap®), trifluoperazine (Stelazine®), and sulpiride (Dolmatil®).

14.3.3.2 Atypical Antipsychotics

Atypical or second-generation antipsychotics (SGAs) induce significantly less EPS (Mauri et al. 2007). Atypical antipsychotics block both the D2 dopamine receptors as well as 5HT2A serotonin receptors. Compared to the older drugs they seem less likely to cause Parkinsonian side effects and tardive dyskinesia (at not too high doses), but they are more likely to produce weight gain, to produce diabetes, to give sexual problems, and to induce sleepiness and slowness. Examples of the atypical antipsychotics include amisulpride (Solian®), aripiprazole (Abilify®), chlorpromazine (Thorazine®), clozapine (Clozaril®), olanzapine (Zyprexa®), quetiapine (Seroquel®), risperidone (Risperdal®), sertindole (Serdolect®), zotepine (Zoleptil®), and paliperidone (Invega®). The atypical antipsychotics are rather expensive, but may be more effective than older medications for (negative) symptoms of schizophrenia.

Risperidone is one of the most commonly used atypical antipsychotics that can improve both the positive and the negative symptoms of schizophrenia with a low report of EPS. The pharmacological response of risperidone depends on the concentration of risperidone and its active metabolite 9-hydroxy-risperidone (9-OH-RSP), also known as paliperidone. Paliperidon was recently marketed as an independent antipsychotic drug (Invega®).

Mauri et al. (2007) provided a literature review on the relationships between plasma concentrations of SGAs and clinical responses by dividing the studies on the basis of the length of their observation periods (therapeutic ranges). The usefulness of therapeutic drug monitoring is well established. Plasma clozapine concentrations seem to be influenced by many factors, such as altered CYP450 1A4 activity, age, sex, and smoking. High plasma concentrations of clozapine can increase the risk of epileptic seizures. In use of risperidone, the metabolite 9-OH-risperidone (paliperidon) is formed, and both should be measured ("active moiety") to prevent erroneous interpretations on the pharmacological effects of risperidone. For olanzapine, the literature strongly indicates a relationship between clinical outcomes and plasma concentrations. There is little evidence in favor of the existence of a relationship between plasma quetiapine concentrations and clinical responses. Positron emission tomography (PET) studies of receptor blockade indicated a discrepancy between the time course of receptor occupancy and plasma quetiapine concentrations. There is no direct evidence concerning optimal plasma concentration ranges of ziprasidone, aripiprazole, or sertindole.

Risperidone is metabolized by CYP2D6 and CYP3A to paliperidone, indicating variability will be observed by differences in metabolism (fast and slow metabolizers). The receptor-binding affinity for the dopamine receptor and the 5HT2A receptor of paliperidone are reported to be equal to risperidone (Mauri et al. 2007). Brain distribution is another aspect that may influence PK–PD relationships of antipsychotics (and CNS drugs in general). Drugs with a poor brain distribution (risperidone) will require higher doses to be administrated to obtain similar receptor occupancy when compared to compounds with a relatively good transport (olanzap-

ine, quetiapine; Fitzgerald and Dinan 2008). Both risperidon and paliperidone are substrates for Pgp in vitro and in vivo.

Possible biomarkers for antipsychotic drugs are certain hormones, in particular prolactin (PRL). PRL is mainly associated with reproductive and metabolic functions, and is synthesized and stored in lactotrophs located in the anterior lobe of the pituitary. The release of PRL is predominantly under hypothalamic inhibitory control of dopaminergic neurons. Dopaminergic neurons project dopamine into the anterior lobe of the pituitary via several pathways. Activation of dopamine D2 receptors on the cell surface of lactotrophs inhibits the release of PRL into plasma. Likewise, blockade of D2 receptors leads to release ofPRL. Besides the dopaminergic control on PRL release, PRL concentrations in plasma are also influenced by changes in synthesis rate, lactotroph storage capacity, homeostatic feedback mechanisms and rate of plasma elimination (Freeman et al. 2000; Ben Jonathan and Hnasko 2001; Fitzgerald and Dinan 2008). Interestingly, PRL synthesis, pathways of release and homeostatic feedback and elimination half-life are similar in rats when compared to man. This makes PRL concentrations in plasma an interesting candidate for evaluation as a translational biomarker for D2 receptor activity (Ben Jonathan et al. 2008), in particular for dopamine receptor antagonists and possibly also partial agonists. Since the synthesis, pathways for release, and elimination of prolactine in humans are comparable to rats, prolactine is a good translational biomarker for the effect of dopamine receptor antagonists (Stevens et al. 2012), as will be shown in the pharmacometric section for antipsychotic drugs below.

14.4 Pharmacometric Approaches

14.4.1 Anxiolytics

Although the definition of “pharmacometrics” (quantitative pharmacology) as research field is young, approaches to that end have initiated long time ago. Especially for the group of benzodiazepines, this was possible as their effects could be well characterized from a quantitative analysis of the electroencephalogram (EEG) as a biomarker (Krijzer and Van der Molen 1987). When observed in conjunction with blood sampling, the plasma PK–PD relationships of benzodiazepines could be characterized in individual animals and humans. The EEG appeared to be an ideal biomarker of changes in CNS functionality in the sense that it can be obtained in a strict objective, continuous, sensitive, and reproducible manner in individual animals.

In the early 1990s, the first quantitative investigations on PK–PD modeling of benzodiazepines in the rat were performed in freely moving rats, using the EEG effects (Mandema and Danhof 1992). By this approach, quantitative information on the potency and intrinsic efficacy of CNS drugs could be obtained. As a measure of pharmacological effect intensity of benzodiazepines the amplitudes in the beta

frequency band of EEG signals are relevant, which reflects their affinity and intrinsic efficacy at the central GABA–benzodiazepine receptor complex.

Détári et al. (1999) studied the influence of serotonergic- and benzodiazepine-type anxiolytic drugs on the cortical activation and sleep–wakefulness cycle. The EEG signals were obtained in freely moving rats, and other measures of sleep in mice. Based on sleep quality by increasing sleep episode length and time spent in deep sleep the authors concluded that the serotonergic anxiolytic drugs seem to be superior compared to the benzodiazepine–type anxiolytic drug studied. Lau et al. (1998) published a rat study in which the possibility of both stimulation and sedation effects of midazolam were investigated by EEG effects. A stimulation–sedation model was developed suggesting that midazolam possesses both stimulatory and sedative effects in a continuous but sequential fashion, and hypothesizes the coexistence of stimulation and sedation components for midazolam. Cleton et al. (1999) showed that the rate of change in plasma concentrations is an important determinant of the EEG effects of midazolam in rats. In two groups of male volunteers with different ages (the younger ~25 years, the elderly ~75 years), Albrecht et al. (1999) investigated the pharmacologic properties of midazolam with special regard to age using EEG as a measure of the hypnotic-sedative effect. PK parameters were similar in both groups, while the PD data showed substantial hysteresis and a large difference in half-maximum concentration (EC50), being ~factor-2 lower in the elderly. So, in the elderly lower doses are needed due to increased sensitivity to midazolam action.

Acute dosing and chronic dosing might have different PK–PD relationships due to possible tolerance or other homeostatic feedback mechanisms. Laurrijssens and Greenblatt (2002) studied the influence of chronic midazolam exposure on its PK–PD relationship by EEG recordings and parallel serial blood sampling. The concentration–EEG effect relationships were consistent with a sigmoidal E_{max} (maximal effect) model. No differences in PK or PD parameters were found between day 1 and 7. However, by repeated exposure, a modest degree of tolerance to midazolam was found, the effect only being evident after correction for the fraction unbound of midazolam.

With time, the experimental approaches were refined and more statistical issues were addressed Quantitative EEG analysis and statistical procedures were applied under specific design conditions to objectively evaluate the functional bioavailability of psychotropic drugs in the human brain (Barbanoj et al. 2002a)**.** Methodological aspects were discussed (different treatments, doses, time points, states, target variables, electrodes, and even different groups). Statistical PK–PD modeling was introduced as a tool to enlarge the scope of inferences that can be derived when using "pharmaco-EEG." Statistical comparisons were discussed for making conclusions about acute, repetitive, or superimposed effects, and in relation to human psychotropic interactions (such as mechanistic drug–drug interaction descriptions, drug metabolites and enantiomers as well as the importance of acquiring drug plasma concentrations, elapse of time, and topographic distributions) to accurately identify its occurrence. Examples were presented on some anxiolytic drugs, including benzodiazepines.

Oral midazolam is widely used for preoperative sedation in children, and the contribution of the formed active 1-hydroxy metabolite 1-hydroxymidazolam (1-OHMDZ) to the EEG effects was studied (Johnson et al. 2002). Age, weight, sex, concomitant drugs, and the metabolic ratio, 1-OHMDZ/midazolam were investigated as covariates of the PK of midazolam and 1-OHMDZ. The metabolite 1-OHMDZ had approximately half the activity of the parent drug and can compensate for at least part of the decreased effect due to increased midazolam metabolism. This indicated that studies of midazolam should evaluate the contribution of 1-OHMDZ to the overall PD effect.

To place pharmaco-EEG within the clinical context, the distinction between biomarkers, surrogate end points, clinical end points, and clinical outcomes was introduced by Barbanoj et al. (2002b). State-of-the-art applications of pharmaco-EEG were discussed, together with PK–PD modeling in everyday clinical practice. For psychiatry, the applications can be used to discriminate between responders and nonresponders to pharmacological treatment using the test dose. The combination of pharmaco-EEG and PK–PD modeling, although successfully used during some drug development programs (e.g., benzodiazepines), is not widely applied in the clinical scenario where the CNS is concerned. The authors concluded that to develop fully the potentials of pharmaco-EEG together with PK–PD modeling in neuroscience therapeutics much work still needs to be done.

Using EEG, Visser et al. (2003) developed a mechanism-based PK–PD model for neuroactive steroids, comprising a separate characterization of the receptor activation process and the stimulus–response relationship was applied to various nonsteroidal GABAA receptor modulators. The model yielded estimates of both the apparent in vivo receptor affinity (KPD) and the in vivo intrinsic efficacy ePD. Significant linear correlations were observed between KPD for unbound concentrations and the affinity in an in vitro receptor bioassay and between ePD and the GABA-shift in vitro. This study showed that the in vivo effects of nonsteroidal GABAA receptor modulators and (synthetic) neuroactive steroids can be described on the basis of a single unique transducer function. Furthermore, it was found that the nonsteroidal GABAA receptor modulators behave as partial agonists relative to neuroactive steroids.

Jonker et al. (2003) investigated the PD interaction between midazolam, an allosteric modulator of the GABAA receptor, and tiagabine, an inhibitor of synaptic GABA uptake, by EEG recording and parallel plasma concentrations in the rat. They found that the in vivo PD interaction between midazolam and tiagabine is additive rather than synergistic.

14.4.2 Antidepressants

Using the rat as experimental animal, Geldof et al. (2007, 2008a, b, c) performed a series of studies that investigated different mechanisms between SSRI dosing and CNS effect in a strict quantitative manner using (semi-)mechanistic PK–PD modeling. Fluxoxamine was used as a paradigm SSRI compound. Plasma PK was

investigated by a population approach by nonlinear mixed-effects modeling (Geldof et al. 2008a). In six studies with a different experimental setup, study site and/or sampling design, rats received an intravenous infusion of a low, medium, and high dose of fluvoxamine. A population three-compartment PK model adequately described the fluvoxamine plasma concentrations. Body weight was identified as a significant covariate of the intercompartmental clearance. The PK was independent of factors, such as dose, surgery, and study site. The utility of the model in animal behavioral studies was demonstrated in a PK–PD analysis of the effects on rapid-eye-movement (REM) sleep in which a sparse PK sampling design was used. This indicates that limitations of blood sampling in particular study designs can be overcome by a mixed-effects-modeling approach.

The next study was on the kinetics of brain distribution of fluvoxamine, estimated by simultaneous analysis of plasma, free brain extracellular fluid (ECF), and total brain tissue concentrations. The PK model consisted of three compartments for fluvoxamine concentrations in plasma in combination with a catenary two compartmental model for distribution into the brain. In this catenary model, the mass exchange between a shallow perfusion-limited and a deep brain compartment was described by a passive diffusion term and a saturable active efflux term. With increasing dose, a disproportional increase in brain concentrations was observed (Geldof et al. 2008a).

The next question was how brain distribution kinetics of fluvoxamine would relate to 5-HT transporter (SERT) occupancy. SERT occupancy of fluvoxamine was determined in rat frontal cortex ex vivo. Highest SERT occupancy was at early time-points after acute administration. Duration of SERT occupancy was longer for the higher dose. The maximal SERT occupancy (B_{max}) was 95 %. SERT occupancy could be directly related to plasma, brain ECF, and brain tissue concentrations by a hyperbolic function (B_{max} model; Geldof et al. 2008c).

In the final study of this series, a mechanistic model was developed to predict the time course of the concentrations of 5-HT and its metabolite 5-hydroxyindolacetic acid (5-HIAA) in rat frontal cortex following acute administration of fluvoxamine. In the model, fluvoxamine increase synaptic 5-HT concentrations by reversible blockade of the SERT in a direct concentration-dependent manner, while the 5-HT response is attenuated by negative feedback via 5-HT autoreceptors. In principle, the model allows for the description of oscillatory patterns in the time course of 5-HT and 5-HIAA concentrations in brain ECF. The PK–PD analysis revealed that inhibition of 5-HT reuptake was directly related to the fluvoxamine concentration in plasma. The proposed mechanistic model was the first step in modeling of complex neurotransmission processes. The model constitutes a useful basis for the prediction of the time course of median 5-HT and 5-HIAA concentrations in the frontal cortex in behavioral pharmacology studies in vivo (Geldof et al. 2008b).

With a proper study design and modeling, sparse sampling may provide useful data. Feng et al. (2006) used sparse sampling to develop a population PK model to described paroxetine data in an elderly (>70 years) depressed population, with data obtained in a 5-year clinical trial investigating “maintenance therapies in late-life depression” (MTLD-2). The data indicate that female and male subjects with different CYP2D6 polymorphisms have different elimination rates and therefore may need to be dosed differently based on metabolizer genotype.

As mentioned in the introduction, disease severity measures, such as the Hamilton depression rating scale (HAM-D), are used as end points in the assessment of treatment results as well as response to newly developed drugs. Della Pasqua et al. (2010) discussed the implications of the limited sensitivity of global scales and their individual items in discriminating response, and that increasing evidence reveals that individual HAM-D items are insensitive to the mechanism of action of existing antidepressant drugs. Moreover, little distinction can be made between active treatment and placebo. They concluded that differentiation of novel compounds based on such clinical scales is unlikely and that a mechanism-based approach accounting for the multidimensional nature of symptoms and signs is required.

For improved insight into drug action in diseases as complex as psychiatric diseases, there is a need for more "composite" end points that reflect the underlying mechanisms of action need to be developed. Such was done by Zuideveld et al. (2007), who investigated hypothermia and corticosterone increase of the 5-HT(1A)-receptor agonists flesinoxan and buspiridone in the rat and mechanism-based PK–PD models were developed and characterized. Flesinoxan is a potent and selective 5-HT1A receptor partial/near-full agonist that possesses antidepressant and anxiolytic effects in animals (van Hest et al. 1992; Rodgers et al. 1994). In human clinical trials it was found to have robust efficacy with very high tolerability (but for unclear reasons development was halted and it was never marketed). In patients it enhances REM sleep latency, decreases body temperature, and increases adrenocoticotropin (ACTH), cortisol, PRL, and growth hormone secretion (Grof et al. 1993; Pitchot et al. 2004). Zuideveld et al. (2007) applied allometric scaling to predict drug effects in the human situation, on the basis of simulation, taking into account the interindividual variability and clinical study design. The model-predicted effects of both flesinoxan and buspirone were compared to those published in the literature. The main finding of this analysis was that for both hypothermia and the increase in cortisol levels, the model could predict the extent of the pharmacological response in man adequately. For the hypothermic response, the time course of the response was also predicted with a high degree of accuracy. In contrast, in the case of the cortisol response, the observed time lag was not predicted, despite the fact that it fell within the model uncertainty. All together, these results indicated that allometrically scaled mechanism-based PK–PD models are promising as a means of predicting the PD responses in man.

14.4.3 Antipsychotics

14.4.3.1 Human Studies

Human Plasma PK

Due to high interindividual variability in peripheral PK parameters, dosing of antipsychotics relies on clinical trial and error. This blind process of upward or downward clinical dose titration carries a risk of relapse and adverse effects in the

treatment of schizophrenia. Using population PK methods, insight into sources of variability has been sought for.

Mannaert et al. (2005) investigated the single-dose PK profiles of long-acting injectable risperidone and oral risperidone. Plasma concentrations of the unchanged risperidone and its metabolite 9-OH-risperidone (together referred to as the active moiety) were measured in plasma after a single oral dose of risperidone in healthy volunteers, and up to 84 days after a single intramuscular injection of long-acting injectable risperidone in schizophrenic patients. These data were projected to multiple dose regimens and average steady-state PK profiles were predicted. The most interesting results, obtained at steady state, were a lower predicted peak plasma level and a lower predicted degree of fluctuation between steady-state maximal and minimal concentrations with long-acting injectable compared to oral administration, which indicates that this long-acting injectable formulation is to be preferred.

Vermeulen et al. (2007) developed a population model to simultaneously describe risperidone and 9-hydroxyrisperidone PK, to assess information on inter- and intra-individual variability of risperidone and 9-OH-risperidone, and to evaluate the influence of patient demographic characteristics and other factors on risperidone, 9-OH-risperidone, and active moiety PK. Phase 1 (serial blood sampling) and phase 3 data (sparse sampling) were included. The PK model contained two-compartment submodels for risperidone and 9-hydroxyrisperidone disposition and a sequential zero- and first-order absorption pathway (selected based on prior knowledge). To address CYP2D6 polymorphism of risperidone conversion to 9-hydroxyrisperidone, a mixture model was incorporated. The PK model described the plasma PK for risperidone and 9-OH-risperidone reasonably well and was able to determine each patient's phenotype. Potential covariates were tested: age, sex, race, body weight, lean body mass, body mass index, creatinine clearance, liver function laboratory parameters, study, and carbamazepine comedication. Of these, carbamazepine comedication and study were significantly affecting the PK. Carbamazepine also decreased active moiety concentrations.

Using sparse sampling, Feng et al. (2008) assessed covariate effects of age (18–93 years), weight, sex, smoking status, race, and concomitant medications, on risperidone and 9-OH risperidone PK parameters. A nonlinear mixed-effects model (NONMEM) was developed to describe simultaneously the risperidone and 9-OH risperidone PK. A one-compartment mixture model with first-order absorption adequately described the risperidone and 9-OH risperidone concentrations. Age was identified as a significant covariate on 9-OH risperidone clearance in this study. Thyssen et al. (2010) studied the PK of oral risperidone in children and adolescents. The PK of oral risperidone was investigated through noncompartmental analysis and population PK analysis on a pooled database including both pediatric and adult data. Monte Carlo simulations were performed to evaluate the relevance of the effects of covariates on the plasma exposure of the active antipsychotic fraction. The PK analysis showed that, after correcting doses for bodyweight, plasma exposure was comparable between children and adolescents. None of the tested demographic or biochemical characteristics were found to have a relevant effect on any of the PK parameters of risperidone and the active antipsychotic fraction. Also, Sherwin et al.

(2012) investigated risperidone and 9-OH-risperidone PK in children and adolescents, searching for covariate effects on PK parameters. A NONMEM modeled the PKs of risperidone and 9-OH-hydroxy-risperidone; covariates included age (in contrast to Thyssen et al. 2010), weight, sex, and CYP2D6 phenotype (by metabolizer subpopulations: extensive, intermediate, and poor).

Ismail et al. (2012) studied the magnitude and variability of plasma concentrations of clozapine and norclozapine across the lifespan in a real-world clinical setting in a population PK study. “Inpatients” and “outpatients” of the Centre for Addiction and Mental Health in Toronto with schizophrenia spectrum disorders (age between 11 and 79) with clozapine (Clozaril®) treatment were included. A one-compartment model with first-order absorption and elimination best described the data. The only covariates with a significant effect on clearance were age and sex: clearance for both parent and metabolite decreased exponentially with age at least 39 years. Decreased clearance of clozapine and norclozapine with age results in increased blood concentrations and, hence, the potential for adverse drug reactions. These findings have particular clinical relevance for the dosing and safety monitoring of clozapine in older adults, highlighting a need for increased vigilance.

The PK of paliperidone was determined following intramuscular administration of its supposedly long-acting palmitate ester at various doses and at two different injection sites (deltoid and gluteal muscle) by Samtani et al. (2009). Polled patient data were used from phase 1, 2, and 3 trials. The plasma PK for paliperidone following intramuscular administration of its palmitate ester was best fitted to a one-compartment model with first-order elimination. The absorption component of the model allowed a fraction of the dose to enter relatively quickly into the central compartment via a zero-order process. After a lag time the remaining fraction entered the systemic circulation, via a first-order process (dual absorption PK). Inter individual variability was found for clearance, central volume of distribution, and the absorption rate constant. An additive-error model with log-transformed data was used to describe the residual variability. Sex, age, injection volume, injection site, body mass index, needle length, and injection volume were all influencing the PK of paliperidone after intramuscular administration, resulting in a complex dose–PK relationship.

For perphenazine, Jin et al. (2010) characterized the population PK in patients with schizophrenia from the clinical antipsychotic trials of intervention effectiveness (CATIE). Perphenazine was given daily for 14–600 days. A 1-compartment linear population PK model best described the data and race and smoking status were found to have significant impacts on perphenazine clearance estimates.

The contribution of genetic polymorphisms in the metabolizing enzyme (CYP2D6) and in the transporter (ABCB1) genes in healthy subjects was found in a population PK analysis of risperidone and 9-OH-risperidone (Yoo et al. 2012). A two-compartment model with a first-order absorption and lag time fitted well to serum concentration-time curve for risperidone. 9-OH-risperidone was well described by a one-compartment model as an extension of the parent drug (risperidone) model with first-order elimination and absorption partially from the depot. The results suggest the interplay of CYP2D6 and ABCB1 on the PK of risperidone and 9-OH-risperidone according to genetic polymorphisms.

Population PK of oral risperidone from (male) patients with schizophrenia or schizoaffective disorder maintained on risperidone was investigated by, using the mixed-effects model that was derived from the data of the clinical antipsychotic trials in intervention effectiveness study, to predict antipsychotic plasma concentrations before risperidone dose adjustment. In light of the known relationship between plasma drug concentration, dopamine D2 receptor occupancy, and clinical effects (see below), the authors concluded that individualized dosing with the measurement of antipsychotic plasma concentrations has the potential for bedside clinical application.

Human D2 Receptor Occupancy

Among various adverse reactions of atypical antipsychotics, weight gain and impaired glucose tolerance are clinically significant. Matsui-Sakata et al. (2005) analyzed the quantitative contributions of various receptors to these antipsychotics-induced adverse reactions in humans using receptor occupancy, assuming cerebrospinal fluid (CSF) concentrations to be representative for target site concentrations, which may to a certain extent be true (De Lange 2013b). Mean receptor occupancies of alpha 1 adrenergic, alpha 2 adrenergic, dopamine D2, histamine H1, muscarinic acetylcholine (mACh), serotonin 5-HT1A, 5-HT2A, and 5-HT2C receptors by antipsychotics were estimated by using the PK parameters and receptor dissociation constants. These receptor occupancy values were correlated to the extent of adverse reactions reported in literature, being two indices of antipsychotics-induced weight gain and the morbidity rate of type 2 diabetes mellitus during treatment with antipsychotics. For weight gain, the correlation between H1 and mACh receptors occupancies was significant. The morbidity rate of type 2 diabetes mellitus was highly correlated with H1, mACh, and 5-HT2C receptor occupancies. However, H1 receptor occupancy was also highly correlated with mACh receptor occupancy among antipsychotics, so that only one of them may be critically associated with the adverse reactions. As these adverse reactions have not been reported for drugs with mACh receptor antagonistic action, other than antipsychotics, the authors argued that the H1 receptor may contribute predominantly to the antipsychotics-induced weight gain and diabetes mellitus. It was concluded that model analysis based on receptor occupancy indicates that H1 receptor blockade is the primary cause of antipsychotics-induced weight gain and diabetes mellitus.

Also, using the same approach, Matsui-Sakata et al. (2005) investigated literature data on the relation between receptor occupancy and EPS induced by typical (haloperidol) and atypical (risperidone, olanzapine, and quetiapine) antipsychotics in patients. Matsui-Sakata and colleagues took five indices of EPS: (1) The ratio of patients obliged to take anticholinergic medication; (2) the occurrence rates of plural extrapyramidal symptoms (more than one of tremor, dystonia, hypokinesia, akathisia, extrapyramidal syndrome, etc.); (3) parkinsonism; (4) akathisia (inability to remain motionless); and (5) extrapyramidal syndrome (involuntary muscle spasms in the face and neck). Two models were tested. The first was a model that

incorporated endogenous dopamine release owing to 5-HT2A receptor inhibition, and the second was a model that did not consider this endogenous dopamine release. The models were used to examine the relationship between the D2 receptor occupancy of endogenous dopamine and the extent of drug-induced EPS. The model that incorporated the endogenous dopamine release better described the relationship between the mean D2 receptor occupancy of endogenous dopamine and the extent of EPS than the other model. Furthermore, the model incorporating endogenous dopamine release could appropriately predict the risks of EPS induced by two other atypical antipsychotics, clozapine, and ziprasidone, as external data that were not incorporated into the model development. It was concluded that the developed model incorporating endogenous dopamine release owing to 5-HT2A receptor inhibition may be useful for the prediction of antipsychotics-induced EPS.

Human PRL in Plasma

PRL is secreted by the anterior pituitary gland into the blood stream. It influences gonadal function in both sexes, initiates and sustains lactation in females, and controls libido in males. Secretion of PRL by the pituitary is under inhibitory control via dopamine from the hypothalamus. Dopamine acts on the pituitary as an inhibitor of PRL secretion. Blockade of dopamine D2 receptors by typical antipsychotics and risperidone can cause hyperprolactinemia in males and females, and may lead to amenorrhea, galactorrhea, infertility, loss of libido and erectile dysfunction. Increase of PRL concentrations in plasma is an unwanted effect, but can be used to have indirect information on functionality of the dopaminergic system. Movin-Osswald and Hammarlund-Udenaes (1995) were the first to develop a mechanism-based PK–PD model for the effects of remoxipride on human plasma concentrations of the biomarker PRL. The effect of remoxipride on plasma PRL levels is exterted via remoxipride preventing the inhibitory effect of dopamine D2 receptors in the anterior pituitary lactotrophs. The model described the time course of PRL plasma levels after administration of two consecutive doses of remoxipride at different time intervals, given to eight healthy non-obese volunteers in a randomized cross-over study. This design allowed the estimation of the rate of PRL synthesis in the lactotrophs. The model consists of three parts: (1) The pharmacokinetics of remoxipride, (2) a physiological substance model for PRL, incorporating the synthesis of PRL and its release into and elimination from plasma, and (3) a PD model describing the influence of remoxipride on the PRL release from the pool as an indirect response. A linear PD model gave the best description of the time course of PRL. It was shown that the limitation in the PRL release is the amount available in the pool, which takes 1–2 days to fully restore, rather than a maximal effect of remoxipride. The intra- and interindividual variability of remoxipride as well as of the PRL response was low (Fig. 14.1; Movin-Oswald and Hammarlund-Udenaes 1995).

Friberg et al. (2009b) developed a quantitative mechanism-based model to describe PRL release in patients for paliperidone and risperidone. They used data for

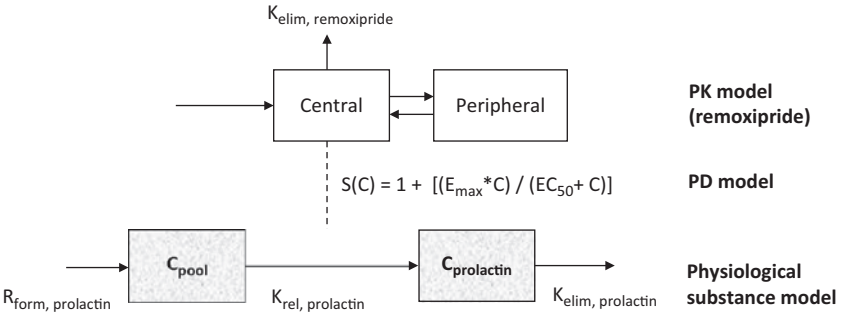

Fig. 14.1 The integrated model of neuroleptic influence on prolactin (PRL) release. (From Movin-Oswald and Hammarlund-Udenaes 1995)

the time course of PRL in healthy as well as schizophrenic subjects, following the administration of various doses and formulations of these antipsychotic drugs. A competitive agonist–antagonist interaction (AAI) model described the competition between these drugs and dopamine for the D2 receptors that regulate the PRL release. Tolerance development was explained by a feedback loop with PRL stimulating dopamine release. This feedback loop better explained the data compared with a model that included tolerance described in terms of depletion of a PRL pool. Further, the diurnal PRL rhythm was described by a two-period cosine function. Baseline PRL was health status dependent and higher in women than in men, although the drug-induced release was less than proportional to baseline. Also, the model confirmed that paliperidone and risperidone have similar potencies for PRL release.

Ma et al. (2010) evaluated tolerance to the PRL response following administration of antipsychotic drugs for the two-abovementioned models using the remoxipride data. The first was the PRL pool model (Movin-Oswald and Hammarlund-Udenaes 1995) and the second the AAI model (Friberg et al. 2009b). The remoxipride data were collected from healthy male subjects who received two remoxipride infusions on five occasions. The pool model with a circadian rhythm function fitted the data slightly better, while the AAI model was better in describing the circadian rhythm of PRL. Visual predictive checks revealed that the models predicted the PRL profiles equally well.

Clinical Trials Using Human PANSS Scores: Effects, Placebo Effects, and Dropouts

The PANSS is one of the most important rating instruments for patients with schizophrenia. All 30 items range from 1 to 7 leading to a minimum total score of 30, implying that the PANSS is an interval scale. For such interval scales, calculation of relative changes needs to be performed (which is not straightforward), and these relative (percent) changes are the widely accepted response criterion (Obermeier et al. 2011). PANSS has been used in many clinical trials to evaluate the effects of newly developed compounds.

Clinical trials aiming to prove the efficacy of newly developed molecule typically compare the effects with those observed following placebo treatment in placebo-controlled trials. However, high failure rates are encountered that are thought to be caused by considerable magnitude and variability in placebo response, high dropout rates and low sensitivity of the subjective rating scales used for assessing treatment effects. So far, non-model-based approaches make the general assumption that both placebo effect and disease progression are constant over time, which actually is not the case. This may lead to biased clinical trial outcomes. With advanced modeling and simulation approaches, one can discriminate among disease progression, placebo effects and drug effects. The use of an appropriate modeling strategy that is capable of identifying the potential sources of variable placebo responses and dropout rates is recommended for improving the sensitivity in discriminating between the effects of active treatment and placebo (Pilla Reddy et al. 2011).

The effectiveness of paliperidone extended-release (ER) tablets and olanzapine was quantified on the basis of PANSS scores in adult schizophrenia patients was modeled by Ortega et al. (2010). Patients received daily doses of paliperidone ER, olanzapine, or matched placebo for a number of weeks. An indirect response model described the time course of the PANSS. Deterioration rate was modeled as a function of baseline PANSS score, placebo, and drug effects, and the dropout effect. An exponential decrease of the placebo response was also implemented. Paliperidone ER and olanzapine treatment were characterized by a long-lasting drug effect, with a larger but short-lasting placebo effect and a notable dropout rate. The covariate exploration failed to identify any clinically relevant factors. The visual predictive check supported the model's adequacy to reproduce observed PANSS time courses. It was concluded that the population model would be useful in clinical trial simulation activities for the time course of PANSS scores in schizophrenia patients.

Large variation in placebo response within and among clinical trials can substantially affect conclusions about the efficacy of new medications in psychiatry. Developing a robust placebo model to describe the placebo response is important to facilitate quantification of drug effects, and eventually to guide the design of clinical trials for psychiatric treatment via a model-based simulation approach. In addition, high dropout rates are very common in the placebo arm of psychiatric clinical trials. While developing models to evaluate the effect of placebo response, the data from patients who drop out of the trial should be considered for accurate interpretation of the results. Better understanding of the patterns of dropout and the factors leading to dropouts are crucial in identifying the true placebo response. By modeling and simulation Friberg et al. (2009a) characterized the PK–PD relationship of sublingual asenapine in patients with schizophrenia, including placebo response and dropouts. The time course of total PANSS scores was characterized for placebo and asenapine treatments in a PK–PD model in which the asenapine effect was described by an E(max) model, increasing linearly over the study period. A logistic regression model described the time course of dropouts, with previous PANSS value being the most important predictor. The last observation carried forward (LOCF) time courses were well described in simulations from the combined

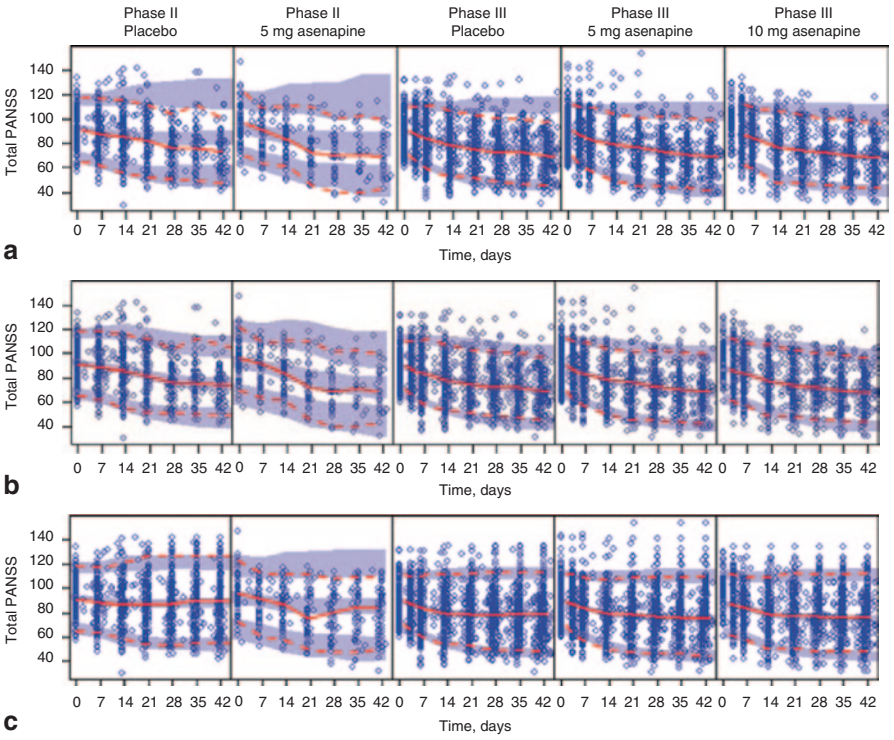

Fig. 14.2 Visual predictive checks of the final PANSS model on the PK–PD relationship of sublingual asenapine in patients with schizophrenia, including placebo response and dropouts. **a** Simulations from the realized design, **b** simulations from the combined PANSS + dropout model and all the planned visits, with PANSS score following a simulated dropout event discarded, and **c** simulations from the combined PANSS + dropout model and all planned visits, with PANSS score following a simulated dropout treated as last observation carried forward (LOCF) data. The *red lines* indicate the 5th, 50th, and 95th percentiles of the observed data or LOCF data (*blue circles*). The *shaded areas* are the 95 % confidence intervals of the corresponding percentiles of the simulated data. (From Friberg et al. 2009a)

PANSS + dropout model. The observed trial outcomes were successfully predicted for all the placebo arms and the majority of the treatment arms (Fig. 14.2).

Pilla Reddy et al. (2012) analyzed how to (1) develop a longitudinal placebo model that accounts for dropouts and predictors of the placebo effect, using the PANSS score, (2) compare the performance of empirical and semi-mechanistic placebo models, and (3) compare different time-to-event (TTE) dropout modeling approaches used to account for dropouts. Among the different tested placebo models, the Weibull model and the indirect response model adequately described the PANSS data. Covariate analysis showed that the disease condition, study duration, study year, geographic region where the trial was conducted, and route of administration were important predictors for the placebo effect. All three parametric TTE dropout models, namely the exponential, Weibull and Gompertz models, described

the probability of patients dropping out from a clinical trial equally well. The study duration and trial phase were found to be predictors for high dropout rates. Results of joint modeling of the placebo effect and dropouts indicated that the probability of patients dropping out is associated with an observed high PANSS score. Data analyses suggest that the Weibull and indirect response models are more robust than other placebo models to describe the nonlinear trends in the PANSS score. The developed placebo models accounts for dropouts and predictors of the placebo effect. This can be a useful tool in the evaluation of new trial designs and for better quantification of antipsychotic drug effects.

While the use advanced modeling the design of the trial and impact of dropouts and predictors of the placebo effects can be accounted for. However, the quality of the model also relies on the quality of the data used to develop the model. (Obermeier et al. 2011) performed a systematic review of publications in which the PANSS was used. They found that the majority of publications (62 %) actually appear to use incorrect PANSS calculations, i.e., ignoring the scale level (interval vs. ratio scale), while, moreover, in most instances the method of calculation was not even described in the manuscript. This might have led to erroneous results concerning the efficacy of the treatment. These alarming results underline the need for standardized procedures for PANSS calculations.

Apart from that, the use of rating scales such as PANSS inherently include subjectivity. It would therefore be of value to have more objective measures of mechanisms in psychosis. In that respect, preclinical research may be of added value, although it is clear that the human disease conditions cannot be reflected.

14.4.3.2 Preclinical Studies and Translational Approaches

While human studies are needed for ultimate investigation of the treatment value of antipsychotic drugs, animal studies may provide useful information as obtained under well-controlled conditions, and under well-controlled challenges, to be compared to those obtained in humans. Also, animal studies may provide mechanistic information that cannot be obtained from humans, such as drug distribution into and within the brain. The more knowledge is available on processes on the causal chain between drug dosing and effect, the better insight we will have in impact of these processes on the ultimate effect in different conditions.

Rat D2 Receptor Occupancy

In the rat, selective suppression of conditioned avoidance response has been widely reported as a test with high predictive validity for antipsychotic efficacy. Furthermore, it has been shown that the relationship between dopamine D2 receptor occupancy and the suppression of conditioned avoidance response behavior correlates well with the relationship between human dopamine D2 receptor occupancy and clinical effect. Evaluated PK–PD predictions of therapeutic effective steady-

state plasma levels by means of conditioned avoidance response behavior in rodents. Also, how this would correlate with clinically relevant plasma exposure for the classical antipsychotic drug haloperidol and four SGAs: sertindole, clozapine, risperidone, and olanzapine, including selected metabolites, like 9-OH-risperidone (paliperidone). First, the validity of the conditioned avoidance response and in vivo striatal dopamine D2 receptor occupancy was determined in parallel, using 3H-raclopride as the radioligand. The PK–PD relationship was established by modeling the time-response and time-plasma concentration data. The order of dopamine D2 receptor occupancy required to suppress conditioned avoidance response behavior according to EC50 measurements to be sertindole (+ dehydrosertindole) = dehydrosertindole = paliperidone = haloperidol = olanzapine > risperidone >> clozapine. Overall, a good agreement was observed between the rat dopamine D2 receptor occupancy levels providing 50 % response in the conditioned avoidance response test and the dopamine D2 receptor occupancy levels reported from responding schizophrenic patients treated with antipsychotics. Predictions of therapeutically effective steady-state levels for sertindole (+ dehydrosertindole) and olanzapine were three- to fourfold too high whereas for haloperidol, clozapine, and risperidone the predicted steady-state EC_{50} in conditioned avoidance responding rats correlated well with the therapeutically effective plasma levels observed in patients. This indicates that the proposed PK–PD model may serve as a guide for determining effective plasma concentrations of potential antipsychotics in the clinical setting and thereby accelerating the overall drug development process.

For rats, a mechanism-based PK–PD population model was developed to predict the time course of dopamine D2 receptor occupancy in striatum as PD biomarker following administration of olanzapine in rats by different routes (Johnson et al. 2011). A two-compartment PK model was used to describe the plasma PK. A hybrid physiology- and mechanism-based model was developed to characterize the D2 receptor occupancy in the striatum. Plasma, brain concentration profiles, and time course of D2 receptor occupancy were well described by the model. The validity of the proposed model is supported by good agreement between estimated association and dissociation rate constants and in vitro values from literature. This model includes both receptor–binding kinetics and PK as the basis for the prediction of the D2 receptor occupancy in rats. Moreover, this modeling framework can be applied to scale the in vitro and preclinical information to clinical receptor occupancy. For risperidone and paliperidone, the same approach in rats was used by Kozielska et al. (2012), now taking both dopamine D2 and serotonin 5-HT(2A) receptor occupancy as biomarkers of the PD of these drugs. The model of Johnson et al. (2011) was expanded to include metabolite kinetics, active efflux from brain, and binding to 5-HT(2A) receptors in the frontal cortex. A two-compartment model best described the plasma PK profile of risperidone and paliperidone. The expanded model described brain concentrations and D2 and 5-HT(2A) receptor occupancy well. Inclusion of binding to 5-HT(2A) receptors was necessary to describe observed brain-to-plasma ratios accurately. Interestingly, simulations showed that receptor affinity strongly influences brain-to-plasma ratio pattern. It was found that binding to both D2 and 5-HT(2A) receptors influences brain distribution of risperidone and

paliperidone. This may stem from their high affinity for D2 and 5-HT(2A) receptors. It was concluded that receptor affinities and brain-to-plasma ratios need to be considered before choosing the best PK–PD model for centrally active drugs.

To elucidate the effects of D2 receptor blockade on neurocognitive function Sakurai et al. (2013) evaluated the impact of estimated dopamine D2 receptor occupancy with antipsychotic drugs on several domains of neurocognitive function in patients with schizophrenia in the CATIE trial. Subjects treated with risperidone, olanzapine, or ziprasidone, received assessments for neurocognitive functions (verbal memory, vigilance, processing speed, reasoning, and working memory) and psychopathology. D2 receptor occupancy levels on the day of neurocognitive assessment were estimated from plasma antipsychotic concentrations, using population PK analysis and their recently developed model (Uchida et al. 2011). A multivariate general linear model was used to examine effects of clinical and demographic characteristics, including estimated D2 receptor occupancy levels, on neurocognitive functions. D2 receptor occupancy levels showed significant associations with the vigilance and the summary scores. Neurocognitive functions, including vigilance, were especially impaired in subjects who showed D2 receptor occupancy level of >77%. These findings suggest a nonlinear relationship between prescribed antipsychotic doses and overall neurocognitive function and vigilance. This study shows that D2 receptor occupancy above approximately 80% not only increases the risk for extrapyramidal side effects as consistently reported in the literature but also increases the risk for cognitive impairment. While 65–80% occupancy of dopamine D2 receptors optimizes therapeutic efficacy while minimizing risks of extrapyramidal symptoms in treating schizophrenia, it is unclear as to whether it is necessary to keep D2 receptor occupancy within this therapeutic window to maintain response. Mizuno et al. (2012) studied daily peak and trough D2 receptor occupancy levels in clinically stable patients with schizophrenia who were receiving risperidone or olanzapine. Plasma antipsychotic concentrations at peak and trough were estimated with population PK techniques. Corresponding dopamine D2 receptor occupancy levels were then estimated, using their recently developed model (Uchida et al. 2011). Of the male subjects with stable schizophrenia (Asians and Caucasians, of middle age), around 50% did not achieve a continuous blockade of ≥65%. Moreover, around 12% of the subjects did not achieve the 65% threshold at estimated peak concentrations. The results suggest that sustained D2 receptor occupancy levels of ≥65% may not always be necessary for the maintenance treatment of schizophrenia.

Translational Approach to Predict Human Effects of Antipsychotics

Stevens et al. (2012) developed a mechanism-based PK–PD model for the biological system PRL response following a dopamine inhibition challenge using remoxipride in the rat. Remoxipride concentrations were determined in plasma and in brain caudate putamen extracellular fluid (brain ECF), following a single intravenous administration of a low, medium and high dose. In these studies, PRL response was measured in plasma as well as following double dosing of the low dose with

different time intervals. Baseline variation in PRL concentrations was also assessed. The mechanistic PK–PD model consisted of: (1) a PK model for remoxipride concentrations in brain ECF; (2) a pool model incorporating PRL synthesis, storage in lactotrophs, release into- and elimination from plasma; (3) a positive feedback component interconnecting PRL plasma concentrations and PRL synthesis; and (4) a dopamine antagonism component interconnecting remoxipride brain ECF concentrations and stimulation of PRL release. The most important findings were that the brain ECF concentrations of remoxipride drive the PRL release into plasma, and the positive feedback of plasma PRL concentrations on the PRL synthesis in the lactotrophs. The latter is in contrast to the negative feedback found in the previous human models on the PK–PD correlation of remoxipride, paliperidone, and risperidone (Friberg et al. 2009b; Ma et al. 2010). An external validation of the model was performed using a dataset obtained in rats following intranasal administration of low, medium, and high doses of remoxipride. Following simulation of human remoxipride brain ECF concentrations, PD extrapolation from rat to humans was performed, using allometric scaling in combination with independent information on the values of biological system specific parameters as prior knowledge. The PK–PD model successfully predicted the system PRL response in humans as obtained by indicating that positive feedback on PRL synthesis and allometric scaling thereof could be a new feature in describing complex homeostatic mechanisms.

14.4.3.3 Summary

Psychiatric diseases are extremely complex with regard to diagnosis and treatment. This is due to the heterogeneity in the expression of the disease features and the current subjective scales used for diagnosis, the difficulties in assessment of drug treatment outcomes, and the problems in distinguishing between the "true effects from the placebo effects." The current knowledge on psychiatric diseases is largely based on empirical approaches, but it is clear that pharmacometrics in psychiatric diseases is upcoming, with the number of publications that has increased especially in the past 5 years. These publications have already aided in better understanding drug versus placebo and effects, impact of dropouts on assessment of such effects, and sources of variability. The pharmacometric models on antipsychotics so far have identified interindividual variability at the level of human plasma PK such as age (Ismail et al. 2012; Sherwin et al. 2012), sex (Ismail et al. 2012; Sherwin et al. 2012), body mass index (Sherwin et al. 2012), genetic polymorphism in CYP2D6 and ABC1 (Yoo et al. 2012), and modes of drug administration. Then, the models have improved knowledge on the relation between plasma drug concentration, human brain receptor occupancy and its, and clinical effect. H1 receptor occupancy was mostly related to anti-psychotics-induced weight gain and diabetes mellitus (Matsui-Sakata et al. 2005), and D2 receptor occupancy by endogenous dopamine released via 5-HT2A receptor inhibition mainly related to the extent of drug-induced EPS. Also, it has been concluded that sustained receptor occupancy of the D2 receptor to an extent larger than 65 % is not always necessary to maintain anti-

psychotic effects (Mizuno et al. 2012). For the effect of a number of antipsychotic drugs it should be realized that dopaminergic functionality can be reflected by PRL concentrations in plasma, but with that the rate of synthesis of PRL in the lactotroph for repetitive dosing needs to be taken into account, as has been shown for remoxipride (Movin-Osswald and Hammarlund-Udenaes 1995). Then, a very important contribution of modeling and simulation is the potential of a better distinction between drug effect and placebo effect, by inclusion of placebo and dropout models.

14.5 Discussion and Conclusions

14.5.1 Current Problems in Diagnosing and Treatment of Psychiatric Diseases

The first problem in finding good treatment for psychiatric diseases is the highly heterogeneous nature of these diseases and (therewith) the treatment outcomes (Leucht et al. 2012). The "one drug fits all" approach obviously does not work and indicates the need for personalized medicine. Second, these diseases are displayed at a behavioral and psychological level. What makes how we feel, think, and behave like we do? Human behavior and psychology is extremely complex and involve the contribution and complex interaction of a plethora of underlying mechanisms for which lots of knowledge still needs to be gained. The fact that human behavior cannot be easily tested in laboratories or reproduced in animal models further complicates our understanding of psychiatric symptoms or even diseases (Agarwal et al. 2010). Third, classification of type and severity of the diseases as well as treatment outcomes are currently still based on subjective rating scales. Fourth, in testing new treatments for psychiatric diseases, clinical trials have dealt with problems of placebo effects and dropouts during the trials that need to be taken into consideration, as otherwise in essence biased and not valid conclusions may be drawn.

14.5.2 Towards Better Treatment of Psychiatric Disorders

Nothing can be done about the heterogeneity of the psychiatric diseases, and improvements in drug treatment of psychiatric diseases must come from better diagnosis of the disease and from (more) objective assessment of drug treatment effects, as well as knowledge on sources of variability in drug treatment outcomes. Also, we need to (further) improve clinical trial design for distinction between drug effects versus placebo effects, and need to include the impact of dropouts during the trial. With such knowledge, combined with pharmacometric modeling approaches, we will be able to improve our knowledge on processes that govern our behavior and psychology, in terms of "normal" and "deviations" thereof, as well as sources of variability between "subjects" in terms of disease expression and treatment variation.

14.5.2.1 Increased Insight into Sources of Variability

Due to high interindividual variability in peripheral PK parameters, current dosing of antipsychotics relies on clinical trial and error. This "blind" process of upward or downward clinical dose titration carries a risk of relapse and adverse effects in the treatment of schizophrenia (Leucht et al. 2012). Using population PK methods, insight into sources of variability has been sought for. Pharmacometric models that have been discussed before have shown interindividual variability at the level of human plasma PK of antipsychotics include age, sex, body mass index, smoking, genetic polymorphism, and modes of drug administration, as covariates in the models.

14.5.2.2 Use of Quantitative, Objective, and Combined (Composite) Biomarkers

A pharmacometric model can never be better than the data that have been used for development of such a model. So, for that reason, here the use of different quantitative and objective types of data is recommended. A first improvement in the quality of data is to use objective biomarkers. The scores that have been used till now in essence rely on more or less extensive questionnaires (such as the PANSS score). These are highly subjective as it is about the opinion of the patient, the clinician, and possibly close relatives or friends. This is far from ideal and the search should therefore be on finding objective measures that can serve as quantitative and objective biomarkers for individual diagnosis of the disease and for individual therapeutic effects. Given the multiple processes involved in the disease, it can be seen that a single biomarker will never provide enough insights, and there is a need for a composite biomarker (combination of biomarkers) obtained at different levels of biological system functionality (for categorization see Danhof et al. 2005). Given the fact that the human brain is not really accessible for invasive measurements, information should come from accessible body compartments like blood sampling, and, if from brain, by using noninvasive techniques. These techniques can all be used in animals as well as in humans and are of high value as therefore they may be included in translational approaches, and will aid in better prediction (Stevens et al. 2012; De Lange 2013a).

Imaging Techniques

With imaging methods, brain disorders and the related occupancy of specific receptors (PET), and function of neurotransmitter pathways (magnetic resonance (MR)-based tools) can be investigated in a noninvasive way. Being noninvasive, it provides the ideal tool for translation from preclinical to clinical investigations (Klomp et al. 2012). PET studies have already been included in pharmacometric models on schizophrenia including receptor occupancy (as discussed in Sect. 14.3). Other imaging techniques can be very informative as well. During the past three decades, several MR-based tools such as MR morphometry, diffusion-tensor imaging, functional MR

imaging (fMRI) connectivity and MR spectroscopy have yielded findings that provide tangible evidence of the neurobiologic manifestations of psychiatric diseases (Agarwal et al. 2010). This holds promise to reveal more of the neurobiological underpinnings of psychiatric disorders but also enhancing our understanding of healthy (human) behavior. Structural MRI studies have indicated that patients with schizophrenia, and to some extent their unaffected relatives, have subtle deficits in several brain regions, including prefrontal and temporal lobes. Whalley et al. (2004) were curious how this inherited vulnerability leads to psychosis. They used a covert verbal initiation fMRI task that elicits frontal and temporal activity (the Hayling sentence completion task) to examine this issue. It was found that vulnerability to schizophrenia may be inherited as a disruption in a fronto-thalamic-cerebellar network, and the earliest changes specific to the psychotic state may be related to hyperactivation in the parietal lobe. Whalley et al. (2005) discussed schizophrenia from the perspective of cognitive function, along with structural and functional brain abnormalities, most notably in pre-frontal and temporal lobes. An important risk factor for developing the disorder is in the first place the inherited vulnerability. Similar deficits are apparent in relatives but less marked than those seen in patients with schizophrenia. With a hypothalamic MRI study Goldstein et al. (2007) investigated potential changes in schizophrenia with respect to supposed abnormal volumetric increases. These were indeed found, with greater severity in multiplex families (more than one ill member) compared with simplex families (one ill member). Their findings demonstrated significantly increased hypothalamic volume in psychotic cases and nonpsychotic relatives. This increase was linear from simplex to multiplex cases and positively correlated with anxiety, with a greater propensity in women. These findings suggest important implications for understanding genetic vulnerability of schizophrenia and the high rate of endocrine abnormalities. Brain MR morphometry studies on heterogeneity within the diagnostic category of schizophrenia have shown that brain structure per se is not a uniform endophenotype, but rather a combination of regional deficits highly heterogeneous in both meeting endophenotype criteria as well as in their distribution within the disease category. As fMRI brain connectivity is able to study impaired brain connectivity in schizophrenia, it also provides a tool to investigate the effect of drug treatment and challenges on the disconnectivity of functional networks in schizophrenia (Nejad et al. 2012). It can be concluded that the use of imaging methods is of great value in further investigation on schizophrenia and treatment.

Quantitative EEG, Pharmaco-EEG

Another interesting but apparently controversial technique is the quantitative electroencephalogram (QEEG; or termed pharmaco-EEG when drug treatment is evaluated). An early QEEG study was performed by Kuperman et al. (1996), who identified electrophysiological differences between children with distinct disorders of attention and/or hyperactivity and indicated that QEEG techniques may prove useful in differentiating specific subtypes of ADHD. But the introduction of pharmaco-EEG approaches into clinical practice appears problematic (Mucci et al.

2006). Prichep (2005) argued that the clinical utility of the EEG, especially in psychiatric, learning, and cognitive disorders, has been greatly enhanced by the use of quantitative analysis (QEEG), but emphasized that adequate sampling across a broad age range, inclusion/exclusion criteria, adequate sample of artifact-free data to demonstrate reliability and reproducibility of norms and specificity and sensitivity should be carefully considered. With that a normative database could be developed that allows the multivariate description of patterns of QEEG abnormalities in patients as compared to age appropriate normative values, and the exploration of neurophysiological heterogeneity within populations. They further showed the existence of the clinical significance of this approach in the scientific literature that demonstrated that QEEG provides high sensitivity and specificity to abnormalities in brain function seen in psychiatric populations. The latest publication on QEEG is a plea for this technique. According to Alhaj et al. (2011), the use of EEG offers two potential major means of addressing assessment of neurological information in psychiatric diseases. First, QEEG is able to provide direct data relating to neural activity that may be abnormal in certain disorders. With that as a given, there are opportunities for utilizing the QEEG in a variety of ways as an objective outcome measure. Second, there is growing evidence that in certain circumstances the QEEG can be used to predict which patients are likely to respond to treatment, thus potentially increasing the power of studies by decreasing non-response rates and increasing mean changes in outcome measure. It therefore seems that the QEEG approach hold promise in objective assessment of deviations in neural activity that underlies normal as well as changes in our brain functioning.

Blood Hormone Levels

Another, less expensive and more readily useful approach is (serial) blood sampling. As the brain is in constant endocrinal communication with the rest of the body, plasma may provide very useful information on brain functioning. The hypothalamus' most important function is to link the nervous system to the endocrine system, via the pituitary gland (hypophysis). Interestingly, plasma hormone levels may be assessed as well in response to administration of endogenous compounds. A very old but highly relevant study has been performed by Ferrier et al. (1983). Comparing blood sample concentrations obtained from chronic schizophrenics and controls before and after the intravenous administration of protirelin and from controls, they found reductions in basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the schizophrenic group. The FSH and PRL responses to the administration of protirelin and gonadorelin gonadorelin or gonadotropin releasing hormone (GnRH) were reduced in the schizophrenic group. This pattern of hypothalamic-pituitary dysfunction, which is distinct from that seen in other psychiatric and endocrinological conditions, suggests a reduction in spontaneous GnRH release from the hypothalamus in schizophrenia and may be of potential pathophysiological significance. Then, in this chapter it has already been shown that for antipsychotic drugs, PRLconcentrations in plasma may change upon administration

of antipsychotics (Movin-Osswald and Hammarlund-Udeneas 1995; Stevens et al. 2012). This is by induced changes in the hypothalamus that is taken further effect on the pituitary release, reflecting changes in dopaminergic functionality of (specific parts of) the brain. Bernstein et al. (2010) wrote a review on the hypothalamus being involved in many pathways that have been found to be disturbed in schizophrenia (hypothalamus–pituitary axis, hypothalamus–pituitary–thyroid axis, hypothalamus–pituitary–gonadal axis, metabolic syndrome, sleep–wakefulness cycle, and neuroimmune dysfunction). While it was earlier assumed that the hypothalamus plays only a subordinate role in schizophrenia, but on the basis of Bernsteins's review (Bernstein et al. 2010) the place of the hypothalamus should be reconsidered in the puzzle of schizophrenia. So, via blood sampling there is a lot to be gained in understanding the disease and effects of drugs on the disease phenotype.

14.5.2.3 Improvement in Clinical Trial Design

For the design of clinical trials also a number of issues need to be taken into consideration, which being inclusion/exclusion criteria, randomization, ethical issues, placebo effects, and dropouts.

Inclusion/Exclusion Criteria

Another consideration in clinical trial design is on selection of a representative selection of the target population as potential differences between the "ideal" and "average" patient may bias the outcomes. This is related to restrictive inclusion/exclusion criteria, ethical considerations, differences in the severity of psychopathology between clinical and trial patients, or safety issues. This was investigated by Riedel et al. (2005) using retrospective analysis of particular clinical trials. It was found that the patients included in their clinical trials were representative of the patient encountered in routine clinical practice. Their recommendations were to adhere to inclusion and exclusion criteria to prevent inclusion of severely ill (e.g. suicidal) patients requiring a more intensive treatment setting, inclusion of the more chronic, rather treatment refractory patients as this population may arguably not represent the average clinical patient either.

Randomization

Another key feature of the quality of a clinical trial is the level of randomization. Study subjects should be randomly allocated to receive one or other of the alternative treatments under study, after assessment of eligibility and recruitment but before the intervention to be studied begins (en.wikipedia.org/wiki/Randomized_controlled_trial). Random implies that each individual or unit being entered into a trial has the same chance of receiving each of the possible interventions. It also implies that the probability that an individual will receive a particular inter-

vention is independent of the probability that any other individual will receive the same intervention. After randomization, the two (or more) groups of subjects are followed in exactly the same way, and the only differences between the treatment (in terms of procedures, tests, outpatient visits, follow-up calls, etc.) should be only associated with the treatments being compared. The most important advantage of proper randomization is that it minimizes allocation bias, balancing both known and unknown prognostic factors, in the assignment of treatments. From most to least common in the medical literature, the major categories of randomized clinical study designs are: (1) Parallel-group—each participant is randomly assigned to a group, and all the participants in the group receive (or do not receive) an intervention; (2) crossover—over time, each participant receives (or does not receive) an intervention in a random sequence; (3) cluster—pre-existing groups of participants are randomly selected to receive (or not receive) an intervention; and (4) factorial—each participant is randomly assigned to a group that receives a particular combination of interventions or non-interventions (e.g. group 1 receives compound X and compound Y, group 2 receives compound X and placebo Y, group 3 receives placebo X and compound Y, and group 4 receives placebo X and placebo Y; Hopewell et al. 2010).

Ethical Issues

In addition, in clinical trials, ethical issues need to be taken into consideration. Silverman (2007) emphasized that the ethical conduct of a clinical trial does not end with the formulation of study design or the obtainment of a signature on the informed consent form. An important question is whether it is a right of investigators to have patients omitted from treatment if there is a chance that they will suffer from that. Then it is necessary to monitor responsibilities to ensure the adequate protection of the rights and welfare of human subjects and the four parties who share such responsibilities: the institutional review board, the data monitoring committee (or the data safety and monitoring board), the sponsor, and the investigator. There are numerous challenges, being associated with monitoring—such as overlapping responsibilities, communication gaps, and lack of standards—and attempts to provide recommendations to address some of these issues.

Placebo Effects

The design and conduct of clinical trials present a complex array of challenging problems, one of which is that of the placebo effect. The effect of placebo observed in schizophrenia clinical trials represents a growing problem that interferes with signal detection for treatments, increases costs of development, discourages investment in schizophrenia research, and delays the introduction of new treatments (Alphs et al. 2012). The first step in addressing the issue of placebo effect is acknowledgment of its existence. The focus should then be on its potential causes

in order to adjust clinical trial design elements. Clearly, the sources of placebo response are diverse. Understanding placebo response as a neurobiological effect is different from the sources of "placebo response" in a population that includes a much broader range of issues that relate to trial design, conduct, and factors such as ascertainment bias and regression to the mean. The latter may be associated with strong regional differences. All of these factors should be taken into consideration when interpreting results from clinical trials. Increasing placebo response is frequently associated with increased variance around study end point measurement, leading to poor signal detection. This, in turn, has led to increasing sample sizes, increasing numbers of failed studies and much higher treatment development costs. Therefore, failure to address these issues threatens the support for investments in and the success of CNS drug development.

Dropouts

Typically, high dropout rates characterize clinical trials of antipsychotic treatment and can be even higher than 50% and dropout leads to missing data that can vary so much that it affects modeling and analysis (Rabinowitz and Davido 2008a, b). Accordingly, questions have been raised about the most appropriate method for analyzing efficacy data in clinical trials of antipsychotic treatment in general, and specifically the validity of the commonly used LOCF method, mixed-effects models, and of other methods used in these trials. Three types of dropouts can be distinguished. First is the "missing completely at random" (MCAR). MCAR refers to a situation where the lack does not depend on either observed or unobserved data. MCAR can readily be handled in the analysis. Nevertheless, MCAR leads to loss of power due to diminished sample size. Second is the "missing at random" (MAR). MAR occurs if the missing data depend on variables that are observed during the trial but not on unobserved data (e.g., the increased dropout in the placebo arm of a study or high dropout rates in a particular study center). In such cases, dropout is explained by the observed data and can be accounted for in the data analysis. Third is the "missing not at random" (MNAR). MNAR occurs if the lack depends on unobserved data. For example, if a patient who was doing well but got lost to follow up because he/she had relapsed after the last observed visit and was admitted to a different hospital. Then, the observed data could not predict the missing data. The unobserved data contained information not foreseen by the observed data. MNAR cannot be corrected for without explicitly specifying a model for the missing data mechanism, which by definition cannot be observed or tested. A standard approach used in clinical trials is LOCF. LOCF uses the last completed observation while on treatment to estimate a (hypothetical) last study visit value. This is problematic because it assumes that the data are MCAR and that symptoms would remain absolutely unchanged from the last visit before dropout to the end of the study. Thereby, this approach is underestimating variability in the data. Mixed-effects models and imputation methods work if data are MCAR or MAR; however, if the data are

MNAR then inferences based on these methods will not be valid. Key to choosing an appropriate method for analyzing data in clinical trials is the extent to which dropout and outcomes are related. Rabinowitz and Davido (2008a, b) examined whether dropout is related to outcome in clinical trials of antipsychotic treatment and concluded that dropout in such clinical trials corresponds with efficacy outcomes, the dynamics of symptom change and baseline symptom severity. Therefore, methods for statistical analysis should examine both efficacy and dropout and cannot assume that missing data due to dropout are completely at random. In real life, dropout is probably often related to symptomatology and it is also an important outcome. In these situations, MNAR cannot be ruled out. Therefore, methods that can handle MNAR are needed. One such method that is not dependent on the mechanism of missing data is the composite approach that does not impute data but simultaneously tests the combined outcome of completing the trial and improvement. Because dropout corresponds with symptom severity, attention to missing data due to dropout in analyzing efficacy data in trials of antipsychotic medication is important. By meta-analysis of randomized controlled trials of antipsychotic treatment using meta-analytic random effects models Rabinowitz et al. (2009) shown that dropout was higher for first- than second-generation drugs. Mixed-effects models for meta-analysis were used to identify design features that effected dropout and to develop equations to derive expected dropout rates based on trial design features. All together, this study indicated that dropout rates are lower for second- than first-generation antipsychotic drugs and appear to be partly explained by trial design features thus providing direction for future trial design.

14.5.3 Towards a Multidisciplinary Approach

It can be seen that progress in the quality of treatment of psychiatric diseases will come from a multidisciplinary approach including (neuro)biology, (neuro)pharmacology, psychiatrists, drug companies, family and friends, regulatory agencies, and last but not least pharmacometrics. Quantitative and combined (composite) biomarkers of which most can be obtained in animals as well as humans will allow the development of translational models (Stevens et al. 2012; De Lange 2013a) and help to provide insight in the disease-related changes in schizophrenic conditions and the effects of drug treatment.

14.5.4 Conclusion

As the highest possible quality of a model is determined by the quality of the data used to develop the model (Obermeier et al. 2011; De Lange 2013a), individual diagnosis of psychiatric diseases and therapeutic effects of drugs today can, and therefore should, include quantitative and objective biomarkers at different physi-

ological levels, which can even be combined with/ compared to the PANSS score. Furthermore, pharmacometrics modeling and simulation has an important role in better selection of the right population, treatment duration, and disease conditions in clinical trials, as well as in much improved design of clinical trials, to better discriminate between drug and placebo effects. Model-based clinical trial simulation will allow reliable prediction of the outcomes of future trials, if various predictors of the placebo response and dropout are taken into consideration. Therefore, it needs to completely integrate disease-progression models, placebo models, drug-response models, covariate models, and dropout models (Pilla Reddy et al. 2011). Moreover, important additional insights can come from preclinical studies if designed according to the mastermind to allow for development of predictive translational models approach (De Lange 2013a).

Finally, it is important to realize that people suffering from psychiatric diseases need to be helped by appropriate drug treatment but also by attention and care of their surroundings.

Bullet Point Summary

- Psychiatric diseases are difficult to treat. This is due to the following issues:
  - Psychiatric diseases are highly heterogeneous and complex.
  - These diseases are displayed at a behavioral and psychological level that we do not really understand.
  - A number of drugs are available for treatment of these diseases, but there is much room for improvement.
  - Classification of type and severity of the disease and treatment outcomes are currently still based on subjective rating scales.
  - Clinical trials on testing the effects of new treatments for psychiatric diseases have dealt with problems of placebo effects and dropouts during the trial.
- Improvements in drug treatment of psychiatric diseases must come from:
  - The use of (more) objective measures and especially their combination (composite biomarkers) for better diagnosis of the disease and of drug treatment effects.
  - Inclusion of objective (composite) biomarkers that can be obtained both preclinically and clinically, to enhance translational insights.
  - More knowledge on sources of variability in disease.
  - More knowledge on sources of variability in drug treatment outcomes.
  - (Further) improvement of clinical trial design for valid distinction between drug effects versus placebo effects, the impact of dropouts during the trial on the outcome.
  - Inclusion of pharmacometric approaches, to develop and apply mathematical and statistical methods for quantitative characterization, understanding, and predicting the PK and (biomarkers of) PD of a drug, and covariates for sources of variability.

14.6 Recommendations

For improved treatment of psychiatric diseases, a highly important role has to be played by pharmacometric modeling approaches. In order to tackle practical questions in drug development in the area psychiatric disorders the following is recommended:

- The use of objective and composite biomarkers to inform on the functioning of the biological system at and treatment perturbation thereof at distinct levels/biomarker types, in a mechanistic manner.
- The use of animal studies for development of preclinical translational models, as animal research allows for obtaining more information than can be obtained from humans (although it is clear that the human disease conditions cannot be reflected).
- Inclusion of pharmacometric simulation in the design preclinical studies.
- Inclusion of model-based clinical trial simulation for reliable prediction of the outcomes of future trials (i.e., with complete integration of placebo-, dropout-, disease progression-, and drug effect models).

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