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Preface

Six decades after the serendipitous discovery of chlorpromazine as an antipsychotic and four decades after the launch of clozapine, the first atypical or second-generation antipsychotic, psychopharmacology has arrived at an important crossroad. Revealing the different modes of action of available antipsychotics on biochemical, electrophysiologic, neuroanatomic, and behavioral grounds has not only helped to develop new medications with improved tolerability but also contributed to our understanding of mechanisms relevant for psychosis in general and schizophrenia and bipolar disorder in particular. It is remarkable in this context the extent to which such research has moved towards using imaging techniques and more empirical clinical assessments. Although research targeted at specific receptors and pathways of antipsychotic drug action has extended our knowledge considerably, it remains true that all currently approved antipsychotic drugs share one common mechanism, i.e., dopamine D_2 receptor antagonism. There is still uncertainty as to whether first- and second-generation antipsychotics can really be separated and if the assumed progress exemplified by newer compounds is sufficient to survive the challenges of evidence-based medicine. Although the use of antipsychotics has become safer, adverse metabolic and cardiac effects remain as major issues in the clinic and in the development of new agents. It became clear that all clinically used antipsychotic medications are effective in treating positive symptoms, but certainly not for negative symptoms and also not for the core cognitive deficits that have been widely neglected in research in the time between Kraepelin and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative.

The efforts to develop antipsychotics based on D_2 receptor antagonism in combination with effects on other receptors (with or without intention) have remained the focus of the last two decades. It is clear that pharmacological research and pharmaceutical development must now focus on complementary or even alternative mechanisms of action to address unmet medical needs, i.e., poorly treated domains of schizophrenia, improved acceptance by patients, better adherence to medication, safety in psychoses in demented patients, and avoiding cardiac and metabolic adverse effects. The first completely novel mechanisms evolving from our insights into the pathophysiology of psychotic disorders, especially the

role of glutamatergic mechanisms in schizophrenia, are now under development, and further principles are on the horizon. This situation, in many respects similar to that when the initial second-generation antipsychotics became available, can be rewarding for all. Preclinical and clinical researchers now have the opportunity to confirm their hypotheses, and the pharmaceutical industry may be able to develop really novel classes of therapeutics.

When we were approached by the publishers of the Handbook of Experimental Pharmacology to prepare a new volume on antipsychotics, our intention was to capture both the accumulated preclinical and clinical knowledge about current antipsychotics as well as prospects for new and potentially more specific antischizophrenia principles. These efforts should be based on the pathophysiology of the diseases and the affected neurotransmitter systems. Since preclinical research on antipsychotic compounds is only reliable when intimately linked through translational aspects to clinical results, we decided to include clinical science as well. It turned out that this endeavor could not be covered by a single volume. We thank the editorial board and the publishers for supporting our decision to prepare two volumes: Current Antipsychotics and Novel Antischizophrenia Treatments. These topics cannot really be separated from one another and should be seen as a composite entity despite the somewhat arbitrary separation of contributions into two volumes. The continuing challenges of developing improved and safer antipsychotic medications remain of concern and are discussed in the first volume. The new opportunities for the field to develop and license adjunctive treatments for the negative symptoms and cognitive deficits that are treated inadequately by existing compounds have been incentivized recently and provide the focus for the second volume. We hope these collective contributions will facilitate the development of improved treatments for the full range of symptomatology seen in the group of schizophrenias and other major psychotic disorders.

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The Dopamine Dysfunction in Schizophrenia Revisited: New Insights into Topography and Course

Rebecca Kuepper, Mette Skinbjerg, and Anissa Abi-Dargham

Contents

Abstract Schizophrenia has long been associated with an imbalance in dopamine (DA) neurotransmission, and brain imaging has played an important role in advancing our knowledge and providing evidence for the dopaminergic abnormalities. This chapter reviews the evidence for DA dysfunction in different brain regions in schizophrenia, in particular striatal, extrastriatal, and prefrontal regions, with emphasis on recently published findings. As opposed to the traditional view that most striatal dopaminergic excess, associated with the positive symptoms of

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schizophrenia, involves the dopaminergic mesolimbic pathway, recent evidence points to the nigrostriatal pathway as the area of highest dysregulation. Furthermore, evidence from translational research suggests that dopaminergic excess may be present in the prodromal phase, and may by itself, as suggested by the phenotype observed in transgenic mice with developmental overexpression of dorso-striatal D_2 receptors, be an early pathogenic condition, leading to irreversible cortical dysfunction.

Keywords Schizophrenia • Psychosis • Dopamine dysfunction • Neurochemical imaging

1 Introduction

The psychotomimetic effects of stimulant drugs, in combination with the observed antipsychotic effects of D_2-blocking drugs, gave rise to the initial dopamine (DA) hypothesis of schizophrenia (Carlsson 1977, 1978; van Rossum 1966). Refined and modified in the intervening years, this theory to date remains central to the pathophysiology of schizophrenia (Howes and Kapur 2009; Laruelle et al. 2003; Lieberman et al. 1997).

Based on the observation that DA-enhancing drugs such as amphetamine show psychotomimetic properties while the effectiveness of classic antipsychotic medication, blocking DA D_2 receptors, had been shown to directly correlate with its affinity for the D_2 receptor (Creese et al. 1976), the dopamine hypothesis initially assumed a general dopaminergic hyperfunction (Carlsson 1977, 1978). However, subsequent findings, including reduced cerebral blood flow in the prefrontal cortex (PFC) of patients with schizophrenia and the observation that negative symptoms such as flattened affect, anhedonia, and compromised cognitive function did not respond to classic antipsychotic treatment targeting D_2 receptors, were incompatible with a generally overactive DA system. Accordingly, the dopamine hypothesis was reformulated as an imbalance in DA neurotransmission in different regions of the brain, characterized in particular by hyperactivity in the subcortical DA pathway and hypoactivity in the cortical DA system (Davis et al. 1991; Knable and Weinberger 1997; Weinberger 1987). It was also suggested that DA hyperactivity in subcortical brain regions, in particular striatal areas, accounted primarily for the positive symptoms of schizophrenia, while the negative symptoms were mostly associated with DA hypoactivity in cortical areas, particularly PFC (Abi-Dargham 2004).

In this chapter, we present the history as well as the latest research findings relating to dopamine dysfunction in schizophrenia. The two main new findings that will be emphasized here are the following: Unlike the traditional thinking that most dopaminergic excess causing positive symptoms involves the dopaminergic mesolimbic pathway, recent evidence points to the nigrostriatal pathway, projecting to the anterior caudate, part of the associative striatum, as the area of highest dysregulation. Furthermore, as opposed to the thinking that dopamine is a final

common pathway, recent evidence from studies in mice with a developmental overexpression of D_2 receptors (Kellendonk et al. 2006) and in patients at high risk for developing schizophrenia (Howes et al. 2009) suggests that dopamine dysregulation may be an early pathogenic mechanism that may lead to further dysregulation of brain function. We will review the evidence and outline future research needed to understand the molecular mechanisms and develop better therapeutic interventions.

2 Evidence for Dopamine (DA) Dysfunction in Schizophrenia

Direct empirical evidence for DA alterations in schizophrenia was initially elusive. Postmortem studies were difficult to interpret due to the possible confounding by prior antipsychotic exposure and the first imaging studies using Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT) produced inconsistent findings. Advances in PET and SPECT imaging techniques, such as the development of new, high-affinity radiotracers, made it possible to study DA neurotransmission in several regions of the brain, including striatal, extrastriatal, and prefrontal cortical regions with more anatomical detail than previously possible.

2.1 Striatal DA Alterations

Using PET and SPECT imaging techniques, different paradigms have been employed in order to study aspects of presynaptic and postsynaptic striatal DA alterations in schizophrenia. These approaches include markers of DA synthesis, release and reuptake, as well as DA receptor availability and differences in receptor affinity states (Erritzoe et al. 2003; Laruelle 1998; Seeman et al. 2006).

2.1.1 Presynaptic DAergic Parameters

Dopamine Synthesis

DA is synthesized by hydroxylation of the precursor tyrosine to L-DOPA, which then is decarboxylated to DA by aromatic acid decarboxylase (AADC). Radioactive analogues of L-DOPA, such as [^{11}C]L-DOPA and [^{18}F]DOPA, have been used to estimate enzymatic activity of AADC, as an indicator of DA synthesis capacity (Brown et al. 1999; Cumming and Gjedde 1998; Garnett et al. 1978, 1983). However, this is overly simplified and other factors may affect the overall signal measured with [^{11}C]L-DOPA and [^{18}F]DOPA, including delivery of [^{11}C]L-DOPA and [^{18}F]DOPA to the brain, crossing the plasma membrane, storage in

presynaptic vesicles as a result of vesicular monoamine transporter (VMAT) activity, release of [^{11}C]L-DOPA and [^{18}F]DOPA, and degradation, all may play a role in addition to the activity of DOPA decarboxylase. Better knowledge of these mechanisms is needed to better understand the exact molecular processes underlying [^{11}C]L-DOPA and [^{18}F]DOPA uptake and their disturbance in schizophrenia.

Nevertheless, a number of studies have used radiolabeled L-DOPA, such as [^{11}C]L-DOPA or [^{18}F]DOPA, in schizophrenia. The first study, by Reith et al. (1994), revealed significantly elevated [^{18}F]DOPA uptake in drug-naïve patients compared to healthy controls. While the majority of the following studies using the same technique replicated this finding (Hietala et al. 1995, 1999; Howes et al. 2009; Lindstrom et al. 1999; McGowan et al. 2004; Meyer-Lindenberg et al. 2002; Nozaki et al. 2009), two studies failed to find markers of elevated DA synthesis capacity: One study reported a small but not significant increase in [^{18}F]DOPA uptake (Dao-Castellana et al. 1997), while another found decreased levels of [^{18}F]DOPA uptake (Elkashef et al. 2000). This discrepancy might be explained by differences in study population: Studies reporting positive findings were all conducted in acutely psychotic, mostly drug-naïve, patients (with the exception of McGowan and colleagues), while the two studies reporting negative or inverse findings were done in chronic, previously medicated, patients. Recently, DA synthesis capacity was investigated in twins discordant for schizophrenia. No elevation in striatal DA synthesis was observed in the unaffected twin, nor in the low-symptomatic medicated twin with chronic schizophrenia when compared to controls, suggesting that increased DA synthesis is not a genetic marker for schizophrenia (Shotbolt et al. 2011). Most recently, Howes et al. (2009) showed increases in [^{18}F]DOPA uptake in associative striatum in patients prodromal for schizophrenia, predicting conversion (Howes et al. 2011b) and progressing further on follow-up after 2 years to involve the sensorimotor striatal subregion (Howes et al. 2011a).

Dopamine Release

The next step in DA transmission is the release of DA from the presynaptic terminal. An estimation of DA release from striatal DA neuron terminals can be obtained by measuring changes in D_2 binding potential after pharmacologically induced DA release with SPECT and PET imaging techniques (Kegeles et al. 1999; Laruelle 2000; Laruelle et al. 1995). One of the first studies to investigate amphetamine-induced DA release in schizophrenia was conducted by Laruelle et al. (1996), using SPECT and the radiotracer [^{123}I]IBZM, an antagonist at $D_{2/3}$ receptors. Changes in $D_{2/3}$ binding potential as an estimation of amphetamine-induced DA release were measured in 15 medication-free patients with schizophrenia and 15 healthy control participants at the level of the striatum as a whole. The decrease in binding potential induced by amphetamine was significantly greater in patients with schizophrenia compared to controls. Furthermore, the amphetamine-induced decrease in $D_{2/3}$ binding potential was associated with the

transient increase in positive symptoms induced by amphetamine in the schizophrenia group (Laruelle et al. 1996). The results of a subsequent PET study using [^{11}C]raclopride as radiotracer were in line with these observations (Breier et al. 1997): The schizophrenia group showed greater amphetamine-induced decreases in [^{11}C]raclopride binding compared to controls, indicative of greater amphetamine-induced release of endogenous DA. Furthermore, the study did not find differences in amphetamine effects on [^{11}C]raclopride binding between medication-free ($N = 5$) and medication-naïve ($N = 6$) patients with schizophrenia, indicating that the effect occurs independent of earlier treatment with antipsychotics. Abi-Dargham et al. (1998) have since then replicated these findings. Furthermore, it was shown that changes in amphetamine-induced dopamine release in schizophrenia might be associated with illness phase, as amphetamine-induced transient worsening of psychotic symptoms correlated with changes in [^{11}C]raclopride binding in patients with schizophrenia and no difference in [^{11}C]raclopride binding was seen in patients in remission compared to controls (Laruelle et al. 1999).

The amphetamine paradigm shows stimulated release, as amphetamine increases dopamine levels by reversing DA transport. Another aspect of DA transmission is uncovered with depletion paradigms: The administration of alpha-methyl-para-tyrosine (αMPT), a reversible competitive inhibitor of tyrosine hydroxylase, causes acute depletion of endogenous DA and can be used as a method to assess the degree of baseline (nonstimulated) intrasynaptic DA concentration indirectly measured through $D_{2/3}$ occupancy (Laruelle et al. 1997), most likely reflecting basal release as a result of neuronal firing. Abi-Dargham et al. (2000) used this technique in combination with SPECT and [^{123}I]IBZM in 18 untreated patients with schizophrenia and 18 matched control participants before and after αMPT-induced DA depletion. Exposure to αMPT led to increased D_2 receptor availability in both patients with schizophrenia and healthy controls; however, the effect was larger in schizophrenia patients, indicative of higher baseline DA activity in this group. The magnitude of the effect did not differ between medication-naïve patients with schizophrenia and those previously treated with antipsychotics (Abi-Dargham et al. 2000). Similar results were recently obtained by Kegeles et al. (2010a), who employed the same depletion paradigm in combination with PET and [^{11}C]raclopride. Kegeles and colleagues furthermore showed that the largest effect of acute DA depletion on D_2 receptor binding was observed in the associative striatum and not in limbic striatum as was long hypothesized. Recently, it was shown that amphetamine-stimulated DA release and baseline DA activity are related in patients with schizophrenia but not in controls (Abi-Dargham et al. 2009). Pilot data from Canada furthermore suggest that DA release in patients with schizophrenia and individuals at high risk compared to healthy controls is also increased in response to psychosocial stress (Mizrahi 2010). Altogether, studies have consistently demonstrated increased amphetamine-stimulated DA release in schizophrenia. Depletion studies further suggest that schizophrenia is characterized by increased baseline DA activity.

Dopamine Reuptake

DA transmission in the striatum is regulated by DA transporters (DAT), which are located on the presynaptic membrane of DA terminals and rapidly remove DA from the synaptic cleft (Goto et al. 2007). Several studies have investigated DAT density in schizophrenia, using PET or SPECT, to obtain an index of density of DA terminals and striatal innervation (Hsiao et al. 2003; Laakso et al. 2000, 2001; Laruelle et al. 2000; Lavalaye et al. 2001; Mateos et al. 2005, 2007; Schmitt et al. 2005, 2006, 2008; Yang et al. 2004; Yoder et al. 2004). The majority of studies did not observe differences in DAT availability between antipsychotic-naïve patients with schizophrenia and controls (Hsiao et al. 2003; Laakso et al. 2000; Laruelle et al. 2000; Lavalaye et al. 2001; Schmitt et al. 2005, 2006; Yoder et al. 2004). Two studies reported reduced DAT binding in patients with schizophrenia compared to controls (Laakso et al. 2001; Mateos et al. 2005). However, since the patients were not medication-naïve, the researchers concluded that the observed reduction in DAT binding was secondary to prior treatment with antipsychotics. In order to clarify this issue, Mateos et al. (2007) repeated the experiment in a cohort of antipsychotic-naïve patients with schizophrenia and also found lower DAT density (Mateos et al. 2007). Still, this remains the only study, which reported decreased DAT binding in schizophrenia. So, taken together the evidence suggests that schizophrenia is not associated with changes in DAT density.

Recently, two dual-isotope SPECT studies used [^{99}mTc]TRODAT and [^{123}I]IBZM to simultaneously measure DAT and D_2 receptor availability in drug-naïve patients with schizophrenia and controls (Schmitt et al. 2008; Yang et al. 2004). In line with most of the previous findings, no overall differences in DAT or D_2 receptor availability were observed. However, in patients but not controls, DAT density correlated positively with D_2 receptor availability (Yang et al. 2004), which was most pronounced in patients presenting with predominantly positive symptoms (Schmitt et al. 2008).

2.1.2 Postsynaptic DAergic Parameters

DA Receptor Availability

The most extensively studied receptor in schizophrenia is the D_2 receptor, which is abundantly present in the human striatum. Numerous studies have measured the density of striatal D_2 receptors in schizophrenia, both in vivo and postmortem, and three meta-analyses have reviewed the strength and consistency of the reported findings (Kestler et al. 2001; Laruelle 1998; Zakzanis and Hansen 1998). We should note here that most of these studies refer to both D_2 and D_3 receptors, as the ligands are not specific to one subtype. Unless otherwise specified, when we mention the D_2 receptor in this review, we also refer to both subtypes. The first of these meta-analyses was conducted by Zakzanis and Hansen (1998) and included 17 studies of which 7 were postmortem. The results from 511 patients with schizophrenia and

534 controls suggested that, although D_2 receptor availability was elevated in approximately 70 % of the patients, increased receptor density failed to discriminate patients from controls and is therefore unlikely to represent a general marker of schizophrenia (Zakzanis and Hansen 1998). In line with this are the findings of the second meta-analysis, which included 15 in vivo studies on D_2 receptor density in schizophrenia, and concluded that there was small but significant elevation of receptor availability along with greater variability in schizophrenia patients compared to controls (Laruelle 1998). The more recent, comprehensive meta-analysis by Kestler et al. (2001) included 20 postmortem studies and 17 in vivo studies on D_2 receptor availability in schizophrenia and took into account differences in methodology such as in vivo versus postmortem measures as well as the possible influence of sample characteristics such as age, gender, or medication status. The authors concluded that the data were compatible with the idea of a subgroup of patients with schizophrenia being characterized by elevated D_2 density (Kestler et al. 2001). The results of a recent study using the high-affinity $D_{2/3}$ ligand [^{18}F]fallypride were also in line with this, showing selective alterations in D_2 density in schizophrenia patients (5 drug naïve, 16 drug free) (Kegeles et al. 2010b). Meta-analysis of D_2 receptor studies in schizophrenia has shown a modest increase in D_2 receptor density; however, the findings are likely to be confounded by prior treatment with antipsychotics. Chronic administration of antipsychotic medication has been shown to upregulate D_2 receptor density both in preclinical animal models and humans (Burt et al. 1977; Kashihara et al. 1986; Silvestri et al. 2000). A recent PET study in cats suggested that the magnitude of D_2 receptor upregulation depends on the percentage occupancy of D_2 receptor and the temporal pattern of the antipsychotic administration. A high dose (80 % occupancy of D_2 receptor) of haloperidol administered continuously by osmotic mini-pumps over 4 weeks produced a robust upregulation of D_2 receptor, still detectable 2 weeks after withdrawal. On the other hand, a lower dose (60 % occupancy D_2 receptor) or s.c administration once a day (transient 80 % occupancy for few hours) of haloperidol did not change D_2 receptor availability (Ginovart et al. 2009). For patients with schizophrenia, antipsychotics are prescribed both as oral and as depot medication and require occupancy between 60 and 80 % for therapeutic effect, beyond which the risk of side effects increases notably (Farde et al. 1992; Fitzgerald et al. 2000). The majority of studies of D_2 receptor availability in schizophrenia used mixed drug-free and drug-naïve patient groups; thus it is likely that increased D_2 receptor density may be, at least in part, related to prior exposure to antipsychotic rather than to the disease process per se.

Several lines of research indicate that, in addition to the D_2 receptor, the D_3 receptor might play an important role in the pathophysiology of schizophrenia (Griffon et al. 1995; Gurevich et al. 1997; Sokoloff et al. 2006). However, until recently it was not feasible to selectively target D_3 receptors with neurochemical imaging to obtain a direct measure of D_3 in schizophrenia, since the available radiotracers exhibited similar affinities for the D_2 and D_3 receptors and therefore could not distinguish between them. Using the $D_{2/3}$ agonist radiotracer [^{11}C]PHNO, which has higher affinity for D_3 than for D_2, a recent study did not reveal differences in receptor levels between patients with schizophrenia compared to

controls (Graff-Guerrero et al. 2009), although a more selective tracer would be needed to replicate this initial finding.

Several postmortem studies have used ligand subtraction methods to measure the distribution of striatal D_4 receptors in schizophrenia. However, these studies produced inconsistent results, some reporting increased availability of D_4 (Marzella et al. 1997; Murray et al. 1995; Seeman et al. 1993; Sumiyoshi et al. 1995), while others did not find differences in D_4 receptors between schizophrenia patients and controls (Lahti et al. 1996, 1998; Reynolds and Mason 1994). More selective tracers are needed to better characterize these receptors.

Most (postmortem) studies did not find altered levels of D_1 receptors in the striatum (Cross et al. 1981; Joyce et al. 1988; Knable et al. 1994; Pimoule et al. 1985; Reynolds and Czudek 1988; Seeman et al. 1987); one reported a slight decrease in D_1 density (Hess et al. 1987). The results of two in vivo studies of striatal D_1 density in schizophrenia are in line with the majority of postmortem findings and do not suggest alterations in striatal D_1 receptor levels in schizophrenia (Abi-Dargham et al. 2002; Okubo et al. 1997).

Taken together, it seems that a subgroup of schizophrenia patients is characterized by increased density of D_2-like (i.e., $D_{2/3}$) receptors, independent of age, gender, and prior antipsychotic exposure. The density of striatal D_1 receptors on the other hand seems to be unaltered. No conclusive data are available for D_4.

Balance in D_2 Receptor Affinity States

Being the primary target of antipsychotic medication, the D_2 receptor plays a major role in schizophrenia and psychosis (Kapur and Mamo 2003; Kapur and Remington 2001), although, as discussed earlier, its involvement in the pathophysiology of psychotic disorders remains unclear (Kestler et al. 2001; Laruelle 1998; Zakzanis and Hansen 1998). The D_2 receptor has been shown to exist in two different affinity states: a high-affinity, active state (D_2^{high}) and a low-affinity, inert state (D_2^{low}) (Sibley et al. 1982; Willeit et al. 2006). Preclinical work has shown that radiolabeled DA agonists such as (+)-PHNO, which selectively binds to $D_{2/3}$ receptors in the high-affinity state, in combination with PET can be used to study the distribution of D_2^{high} both in vitro (Nobrega and Seeman 1994) and in vivo (Galineau et al. 2006; Ginovart et al. 2006). The distribution of D_2^{high} using PET and [^{11}C](+)-PHNO was recently demonstrated also in human volunteers (Graff-Guerrero et al. 2008; Willeit et al. 2006).

For schizophrenia, it has been suggested that the observed supersensitivity to DA-enhancing drugs such as amphetamine is the result of an imbalance in D_2 affinity states, in particular elevated availability of D_2^{high} receptors (Seeman 2010; Seeman et al. 2005). However, evidence for this conclusions stems primarily from animal models of schizophrenia (for a review see Seeman 2010). Recently, the distribution of D_2^{high} was for the first time studied in patients with schizophrenia, and contrary to what could be expected from preclinical work, no elevation in D_2^{high} was observed in medication-free patients with schizophrenia compared to

controls (Graff-Guerrero et al. 2009). Although the authors acknowledge that differences in D_2^{high} between schizophrenia patients and controls could have been masked by endogenous DA, to date, there is no evidence for D_2^{high} dysregulation in schizophrenia.

2.2 Extrastriatal DA Alterations

Several studies have now used high-affinity radiotracers such as [^{18}F]fallypride, [^{11}C]FLB 457, and [^{123}I]epidepride to measure the distribution of D_2-type receptors in low-density brain regions such as the thalamus, anterior cingulate cortex, temporal cortex, or substantia nigra in unmedicated and medication-naïve patients with schizophrenia. Some studies found decreased D_2 receptor availability in the thalamus (Buchsbaum et al. 2006; Kessler et al. 2009; Talvik et al. 2003, 2006; Yasuno et al. 2004), anterior cingulate cortex (Buchsbaum et al. 2006; Suhara et al. 2002), temporal cortex (Buchsbaum et al. 2006; Tuppurainen et al. 2003), and midbrain (Tuppurainen et al. 2006), while some found no differences in the thalamus (Tuppurainen et al. 2006), anterior cingulate, and temporal cortex (Glenthoj et al. 2006; Kessler et al. 2009; Talvik et al. 2003), and one study found an increase in D_2 receptor availability in schizophrenia in the substantia nigra (Kessler et al. 2009). A large recent study did not confirm any of the above reported extrastriatal D_2 receptor alterations in schizophrenia (Kegeles et al. 2010b).

Another recent study has used the radiotracer [^{11}C]PE21 in combination with PET to visualize thalamic DAT in patients with schizophrenia, who were either medication-naïve or off medication for at least 6 months (Arakawa et al. 2009). In contrast to striatal brain regions, where DAT seems to be unaffected in schizophrenia, this study reported increased DAT binding in the thalamus of patients with schizophrenia compared to controls. Another study measured extrastriatal DA synthesis capacity using PET and [^{11}C]L-DOPA and found no differences between medication-naïve patients with schizophrenia and controls with regard to DA synthesis capacity in the thalamus or anterior cingulate and temporal cortex (Nozaki et al. 2009), although the ability of this tracer to measure extrastriatal dopamine synthesis is questionable (Cropley et al. 2008).

2.3 Prefrontal Cortical DA Alterations

While D_2 receptors are abundantly present in striatal regions of the brain, the predominant DA receptors in prefrontal cortical regions are of the D_1 type (Hall et al. 1994). The distribution of D_1 receptors in schizophrenia has been studied using the PET radiotracers [^{11}C]NNC 112 or [^{11}C]SCH 23390. However, the few studies that have been conducted produced conflicting results. While Okubo et al. (1997), using [^{11}C]SCH 23390, found a decrease in receptor binding in patients with schizophrenia compared to controls, the study by Karlsson et al. (2002), using the

same radiotracer, did not reveal any differences between groups (Karlsson et al. 2002; Okubo et al. 1997). However, patients in this latter study were all drug-naïve, while the former study also included drug-free patients. The more recent study by Hirvonen et al. (2006) reported decreased [^{11}C]SCH 23390 binding in fronto-temporal brain regions of previously medicated patients with schizophrenia compared to their unaffected co-twins and healthy comparison twins and higher doses of antipsychotics were associated with greater decreases in D_1 receptor binding. Interestingly, unaffected monozygotic co-twins displayed increased receptor binding compared to healthy comparison twins, and unaffected dizygotic co-twins showed intermediate levels. Two other studies used the radiotracer [^{11}C]NNC 112: One reported increased D_1 receptor binding in the schizophrenia group, which correlated with deficits in working memory performance (Abi-Dargham et al. 2002), and the second study found increases limited to the drug-naïve patients but not the previously treated ones (Abi-Dargham et al. in press). Studies of D_1 receptor availability in schizophrenia are summarized in Table 1.

While it is possible that the discrepancy in findings is due to the influence of antipsychotic medication, it might also be that differences in radioligand properties contributed to the diverging results, as shown by Guo et al. (2003): Using a DA depletion paradigm the researchers could demonstrate that the in vivo binding of the two radiotracers [^{11}C]SCH 23390 and [^{11}C]NNC 112 was affected differentially by changes in endogenous DA, indicating that the increased D_1 receptor availability observed in the studies by Abi-Dargham et al. (2002) using [^{11}C]NNC 112 might reflect an upregulation of D_1 receptors, secondary to chronically low DA levels. This interpretation would also be consistent with the observed correlation between increased D_1 receptor binding and deficits in working memory. However, since both radioligands also bind to the serotonergic 5-HT_{2A} receptor (Ekelund et al. 2007; Slifstein et al. 2007), selective tracers are needed to pursue these investigations of the role of cortical D_1 receptors in schizophrenia.

2.4 Dopamine in At-Risk and Prodromal States

The studies described earlier have revealed several aspects of DA dysfunction in patients with established schizophrenia. In order to extend these findings and shed light on the timing of DA dysfunction in schizophrenia, researchers have started recently to examine different aspects of DA transmission in individuals with prodromal signs of schizophrenia and individuals at genetic or psychometric risk for psychosis.

Three studies have investigated striatal DA synthesis capacity with PET and [^{18}F]DOPA. While Huttunen et al. (2008) observed increased [^{18}F]DOPA uptake in the caudate-putamen in low-symptomatic first-degree relatives of patients with schizophrenia compared to controls, the study by Shotbolt et al. (2011) did not reveal any changes in radiotracer uptake in unaffected and completely asymptomatic co-twins of schizophrenia patients compared to controls. Howes et al. (2009) found increased [^{18}F]-DOPA uptake in individuals with prodromal signs of

Table 1 PET studies on D_1 receptor availability in PFC in schizophrenia

Study	Ligand	*N*		Results
		Patients (drug-naïve/drug-free)	Controls	
Okubo et al. (1997)	[^{11}C]SCH23390	17 (10/7)	18	Decreased receptor binding in patients versus controls
Karlsson et al. (2002)	[^{11}C]SCH23390	10 (10/0)	10	No difference between patients and controls
Hirvonen et al. (2006)	[^{11}C]SCH23390	9 (0/9)	24	Decreased receptor binding in patients versus controls (i.e., their unaffected co-twins and healthy comparison twins), but increased receptor binding in unaffected co-twins versus healthy comparison twins
Abi-Dargham et al. (2002)	[^{11}C]NNC112	16 (9/7)	16	Increased receptor binding in patients versus controls
Abi-Dargham et al. (2011)	[^{11}C]NNC112	25 (12/13)	40	Increased receptor binding only in drug-naïve patients versus controls; no change in drug-free patients

schizophrenia compared to controls. Interestingly, this effect was most pronounced in the associative striatum and correlated positively with severity of prodromal symptoms. Moreover, in a subsequent study the authors could indicate that the increase in DA synthesis capacity observed in individuals in the prodromal phase of the illness progressed over time only in those individuals who later developed schizophrenia, but not in those who did not develop the disease (Howes et al. 2011a). However, in contrast to the findings in prodromal individuals, where the effect was most pronounced in associative striatum, the progression in DA synthesis alteration in those who developed the disease was only seen in sensorimotor striatum (Howes et al. 2011a).

Three other studies have examined stimulated DA release in individuals psychometrically at risk for schizophrenia (i.e., individuals with schizoptypal traits). Soliman et al. (2007) employed a psychosocial stress paradigm in combination with PET and [^{11}C]raclopride to study stress-induced DA release in psychometric

schizotypes compared to controls. No changes in DA release in response to stress were observed in normal controls, nor in the "positive" schizotypes (i.e., individuals with perceptual aberrations). Only the "negative" schizotypes (i.e., individuals with physical anhedonia) showed an increase in DA release in response to stress compared to baseline (Soliman et al. 2007). Abi-Dargham et al. (2004) as well as Woodward et al. (2010) studied amphetamine-induced DA release in individuals with schizotypal personality disorder (SPD) and individuals with schizotypal traits, respectively. In the SPD subjects of the first study, amphetamine caused a larger decrease in [^{123}I]IBZM binding compared to controls (Abi-Dargham et al. 2004). Similarly, amphetamine-induced DA release measured indirectly through D_2 occupancy with PET and [^{18}F]fallypride correlated positively with schizotypal traits in the second study (Woodward et al. 2010). In accordance with previous findings showing that DA dysregulation might be most pronounced in associative striatum as opposed to limbic or sensorimotor regions (Howes et al. 2009; Kegeles et al. 2010a), the correlation between stimulated DA release and schizotypal traits was strongest in associative striatum.

Finally, one study has investigated striatal D_2 receptor availability in six monozygotic and five dizygotic unaffected co-twins of patients with schizophrenia and compared them to control twins without a family history of psychosis. Elevated caudate D_2 receptor availability was observed only in the monozygotic co-twins of schizophrenia patients, compared to dizygotic co-twins and controls. No changes, however, were revealed in the dizygotic co-twins compared to controls (Hirvonen et al. 2005).

In summary, studies suggest an increase in DA in schizotypal states and in relation to schizotypal and prodromal symptoms, linking DA dysfunction to the expression of the schizophrenia phenotype. Combined with the findings of Shotbolt et al. (2011) who did not observe any changes in DA synthesis capacity in unaffected co-twins of patients with schizophrenia, this finding suggests that DA dysfunction does not relate to a general genetic vulnerability in the absence of behavioral manifestations but rather represents a biological marker for the very early expression of schizophrenia symptomatology.

2.5 Summary

The most consistently found dopaminergic alteration in schizophrenia is elevated presynaptic DA function in striatal brain regions (see Figs. 1 and 2 for an illustration), in particular associative striatum, as demonstrated by imaging studies showing (1) increased L-DOPA uptake as an index of increased DA synthesis capacity, (2) elevated amphetamine-induced DA release, and (3) elevated D_2 receptor occupancy by DA as revealed by the acute DA depletion. DAT seems to be unaffected in schizophrenia, and increased D_2 receptor availability was only found in a subgroup of patients. Although preclinical work suggests an imbalance in D_2 receptor affinity states being associated with psychosis, the only study in patients with schizophrenia did not find elevated D_2^{high}. The evidence concerning DA alterations in extrastriatal

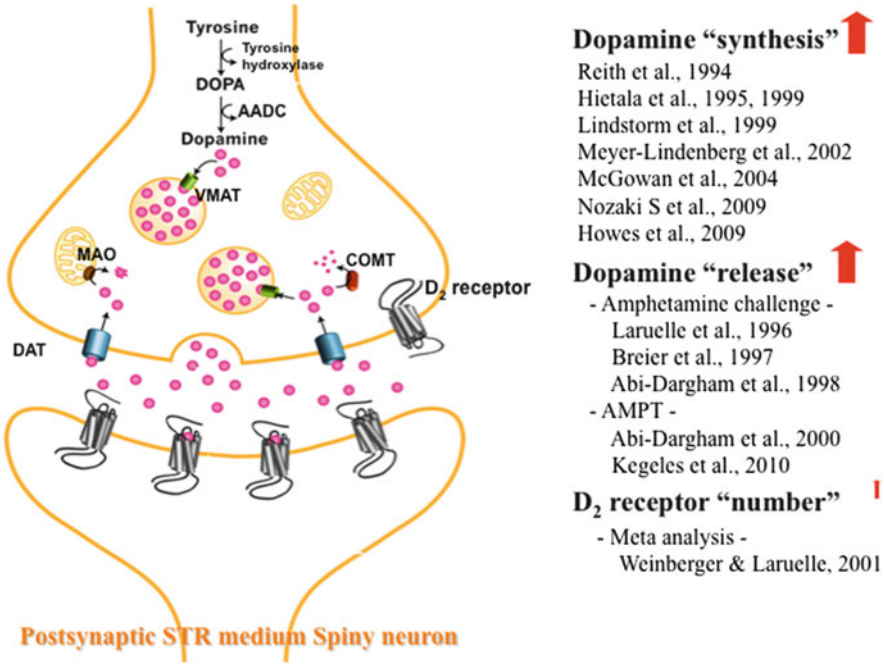

Fig. 1 *Dopaminergic* transmission at striatal (STR) medium spiny neurons. The most consistently found dysregulation in schizophrenia points to increased DA synthesis, increased stimulated DA release, and increased D_2 receptor binding after acute DA depletion

and prefrontal cortical brain areas in schizophrenia seems less consistent. While some studies found elevated levels of D_2 receptors in areas such as the thalamus, anterior cingulate, and temporal cortex or the midbrain and substantia nigra, others did not. The results of the few studies on D_1 receptor availability in prefrontal cortex in schizophrenia are also conflicting. Findings concerning the distribution of D_3 and D_4 remain understudied. To date, only one study used PET and the radiotracer [^{11}C] PHNO to investigate D_3 receptor in a small sample of patients with schizophrenia compared to controls and found no differences (Graff-Guerrero et al. 2009). Thus, while a lot of effort has been put into the investigation of striatal DA alterations in schizophrenia, research has been less successful with regard to extrastriatal and prefrontal cortical regions. More research is needed to resolve the inconsistencies in findings research has provided so far.

3 Functional and Clinical Implications

As defined in the current, fourth version of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2000), schizophrenia is a highly heterogeneous disease, presenting with positive, negative, and cognitive

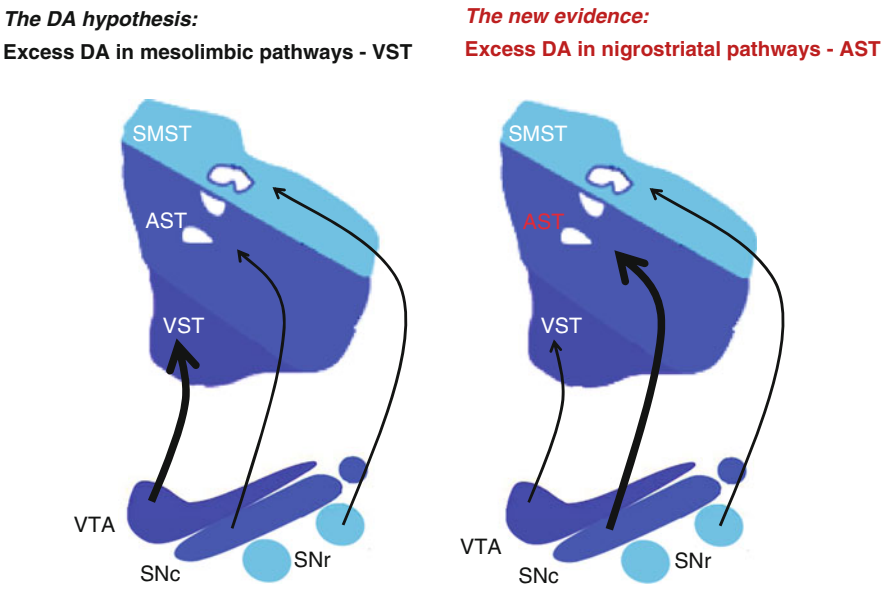

Fig. 2 New data bringing new evidence: The DA dysfunction in schizophrenia seems to be most pronounced in AST as opposed to VST as previously assumed. Adapted with permission from Simpson et al. (2010). SMST (sensorimotor striatum), AST (associative striatum), VST (ventral striatum), VTA (ventral tegmental area), SNc (substantia nigra pars compacta), SNr (substantia nigra pars reticulate)

symptoms. Positive symptoms include hallucinations and delusions, while negative symptoms refer to flattened affect, anhedonia, and loss of motivation. Cognitive disturbances are mostly seen in domains such as working memory, executive function, and aspects of social cognition. DA dysregulation plays a role within each of these dimensions. While positive symptoms seem to most directly relate to excessive striatal DA transmission, negative and cognitive symptoms have been associated with decreased DA function in PFC. The latter assumption was primarily based on the known and crucial involvement of the PFC in cognitive and emotional processes (Arnsten 2007, 2011; Goldman-Rakic and Selemon 1997). Still, after decades of research into DA and schizophrenia, it remains elusive how DA dysregulation actually translates into the complex and multifactorial symptoms that characterize the clinical picture of schizophrenia.

3.1 Relating DA Dysfunction to Positive Symptoms

Several of the imaging studies discussed in this chapter have reported associations between alterations in striatal DA function and symptomatology in patients with schizophrenia. Regarding DA synthesis, Hietala et al. (1999) found a negative correlation between striatal F-DOPA uptake and depressive symptoms and a

positive correlation with paranoid symptoms, although this was significant at trend level only. Howes et al. (2009) reported a positive correlation between severity of positive prodromal symptoms as well as neuropsychological impairment and increased DA synthesis capacity in associative striatum. However, this was not true for depressive symptoms. With regard to DA release, Laruelle et al. (1996) found that amphetamine-induced decrease in D_2 binding potential was associated with positive symptoms. In a subsequent study the authors could furthermore establish a relation between amphetamine-stimulated DA release and illness phase, as amphetamine-stimulated DA release was only increased in patients presenting with acute schizophrenia but not in patients in remission (Laruelle et al. 1999). Recently, Woodward et al. (2010) revealed a positive correlation between stimulated DA release and schizotypal personality traits in healthy individuals.

Assuming that striatal hyperdopaminergia plays a role in the emergence and experience of positive psychotic symptoms, the question arises as to how dopaminergic alterations in striatal brain regions ultimately give rise to the experience of hallucinations and delusions. Altered salience attribution has been suggested as a possible mechanism (Kapur et al. 2005). Burst firing of dopamine neurons in the ventral tegmental area markedly increases dopamine release in the striatum (Floresco et al. 2003) and is believed to mediate the perception of salience or reward associated with stimuli (Berridge and Robinson 1998; Schultz 1998; Stuber et al. 2008). The phasic bursts of dopamine release, which are highly dependent on glutamatergic excitatory afferents, have been shown to be regulated by constant low-frequency tonic firing of dopamine neurons (Goto et al. 2007). Tonic dopamine tone in turn is under control of GABAergic inhibition. Increased levels of tonic dopamine firing may result in decreased amplitude of phasic dopamine burst firing, thus dampening responsivity of this system. Decreased tonic dopamine levels, on the other hand, may result in a heightened responsivity of the phasic dopamine component (Bilder et al. 2004; Goto et al. 2007). Kapur has suggested that, in schizophrenia, dopamine dysregulation results in a psychological state of aberrant salience, in which mundane events and ideas may be attributed with undue significance (Kapur et al. 2005). Thus, a hyperdopaminergic state in striatal brain regions, which most likely reflects dysregulation of the phasic component of DA release (Grace 1991, 1995), is believed to create a condition in which logically unconnected ideas and associations are weaved together and elaborated upon, eventually leading to the emergence of a delusional system. The process of salience attribution has been related to associative and reinforcement learning, in which what is called "reward prediction error" plays a key role (Smith et al. 2006). It is hypothesized that previous reward outcomes are used to form a reward prediction, which is then compared to the actual current reward. The difference between reward prediction and actual outcome is referred to as the reward prediction error (Smith et al. 2006) and has been shown to be mediated, in animals as well as in humans, by dopamine activity in ventral midbrain and striatum (Abler et al. 2006; Bayer and Glimcher 2005; D'Ardenne et al. 2008; Pessiglione et al. 2006). Compared to healthy controls, patients with psychosis seem to exhibit aberrant reward prediction and reward-related learning, both at the behavioral and the neural level (Jensen et al. 2008; Juckel et al. 2006).

However, the relationship between dopamine dysfunction in these brain regions, alterations in reward processing, and symptomatology in schizophrenia has not directly been studied and remains speculative.

3.2 Relating DA Dysfunction to Negative and Cognitive Symptoms

As intact dopaminergic neurotransmission is critical for PFC functioning and cognition (Arnsten 2007; Goldman-Rakic 1999), the negative and cognitive symptoms of schizophrenia have been particularly associated with cortical hypodopaminergia (Abi-Dargham et al. 2002; Goldman-Rakic et al. 2004; Lynch 1992), although direct evidence for this association in schizophrenia is missing. The nature of dopamine dysfunction in the cortex remains unclear, although one study showing decreased tyrosine hydroxylase immunolabeling suggests decreased innervation (Akil et al. 2000). Recently, the group of Simpson et al. (2010) suggested a role for the striatum in the etiology of negative and cognitive symptoms of schizophrenia. Based on their preclinical work in D_2 overexpressing mice, the researchers demonstrated that striatal DA alterations in form of overexpression of D_2 receptors lead to changes in DA turnover and prefrontal D_1 receptor stimulation (Kellendonk et al. 2006). Behaviorally, this alteration was accompanied by deficits in working memory (Kellendonk et al. 2006) and operant performance, expressed in both reduced motivation and deficits in timing of the rewards (Drew et al. 2007). It was moreover shown that the deficits in cognitive performance were secondary to the motivational deficit directly resulting from the D_2 overexpression (Ward et al. 2009), and remained even after the D_2 receptor overexpression had been reversed (Drew et al. 2007). In line with these preclinical findings, studies in individuals with prodromal symptoms of schizophrenia have revealed an association between increased striatal DA synthesis capacity and altered activation in prefrontal cortical brain regions during cognitive engagement (Fusar-Poli et al. 2010, 2011). These studies highlight the concept of dopamine dysregulation occurring early on in the disease process and having pathogenic effects on the rest of the circuitry. It is likely that dopamine dysregulation early on may influence the development and function of other systems, as well as reciprocally, dopamine dysregulation itself may be a consequence of dysregulation in glutamatergic and GABAergic systems. We will discuss the interdependence of these alterations below.

3.3 Neural Circuitry; the Interdependence of Dopaminergic, Glutamatergic, and GABAergic Processes

We have outlined the dopaminergic alterations in schizophrenia in this chapter. There is also clear evidence for GABAergic abnormalities (Lewis and Gonzalez-Burgos

2000) and glutamatergic abnormalities. The hypothesis of a glutamatergic NMDA hypofunction initially derived from the observation that NMDA antagonists induce all three classes of symptoms (negative, cognitive, and positive) observed in schizophrenia and has received additional support from genetic, postmortem, and preclinical studies; for a review, see Moghaddam (2003). These alterations in GABA, dopamine, and glutamate can be interdependent. With imaging, we have observed that acute or chronic NMDA dysfunction can lead to striatal dopamine dysregulation (Kegeles et al. 2002) or to an increase in cortical D_1 receptors (Narendran et al. 2005), respectively. It is also believed that alterations in GABAergic interneurons in hippocampus (Zhang and Reynolds 2002) can lead to excess glutamate drive which in turn may lead to a dysregulation of midbrain dopamine activity. Preclinical studies have shown that the hippocampus is involved in the regulation of striatal dopamine by affecting firing patterns of midbrain dopamine cells (Grace 2012; Lodge and Grace 2008) and thus suggested that disinhibition due to NMDA receptor hypofunction on GABAergic interneurons in hippocampus may contribute to the hyperdopaminergic state in striatum (Lisman 2012). Recent work by Schobel and colleagues showed a significant increase in cerebral blood volume (CBV) in the hippocampus CA1 field in the prodromal stage predicting conversion to psychosis. CBV alterations were similar, although smaller in magnitude to those observed in patients with schizophrenia by Schobel et al. (2009), Harrison (2004), and Meyer-Lindenberg et al. (2005). Notably, the CA1 field is densely packed with pyramidal neurons and serves as the primary output area to the hippocampal-VTA loop. In the cortex, hypofunction of NMDA receptors on fast-spiking GABAergic interneurons leads to disinhibition of cortical excitatory neurons and impairment of synchronized oscillatory activity; for a review, see Lisman et al. (2008), which may relate to the cognitive deficits in schizophrenia as well as at least some of the negative symptoms that are less responsive to antipsychotics. In summary, the dopaminergic alterations have to be considered within the overall context of disordered circuitry and transmission in schizophrenia affecting multiple systems. Presynaptic dopamine alterations may be secondary to abnormal regulation by these systems. However, this suggestion does not necessarily mean that dopamine alterations cannot be in turn pathogenic, as observed in the D_2 overexpressing mouse model (Kellendonk et al. 2006). More work is needed to understand the sequence of alterations within patients' brains, but so far it is clear that both the hippocampal excess activity and the subcortical dopaminergic overactivity occur early on, could be related, and precede full onset of the disease.

4 Conclusions

This chapter reviewed evidence for DA dysfunction in schizophrenia. Most of this evidence stems from imaging studies applying PET and SPECT techniques. Due to advances in these imaging techniques it has become possible to study neurochemical alterations in the DA system in several regions of the brain. Accordingly, recent studies were able to examine DA neurotransmission in the different substructures of

the striatum and revealed that, in contrast to the prevailing idea of DA hyperactivity in the mesolimbic DA pathway, it is rather hyperactivity in associative striatum that is implicated in schizophrenia pathology, as illustrated in Fig. 2. It further seems that the dysfunction is predominantly presynaptic but also postsynaptic, characterized by increased DA synthesis capacity and increased phasic release to pharmacological and possibly also psychosocial challenges (see Fig. 1). Furthermore, this dysfunction occurs early in the disease and may represent an early pathogenic process leading to further dysregulation.

Despite recent advances in the study of DA dysregulation in schizophrenia, the etiology of DA imbalance remains unknown. It has been assumed that striatal DA hyperactivity results from decreased activity in PFC, due to its functional role in inhibiting subcortical DA transmission (Deutch 1992; Meyer-Lindenberg et al. 2002). Conversely, preclinical work has recently shown that striatal DA abnormalities result in altered PFC DA activity (Kellendonk et al. 2006). The striatum is a complex integrative structure, receiving among others input from the hippocampus, an area of pathology in schizophrenia (Harrison 2004; Meyer-Lindenberg et al. 2005), and in animal models changes in hippocampal activity lead to dysregulation of DA neuronal activity (Lodge and Grace 2008). Future research should combine imaging with translational models of the disease to understand the cellular mechanisms involved in the striatal and cortical dopamine dysfunction in schizophrenia.

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Role of Dopamine D_2 Receptors for Antipsychotic Activity

Nathalie Ginovart and Shitij Kapur

Contents

Abstract This review summarizes the current state of knowledge regarding the proposed mechanisms by which antipsychotic agents reduce the symptoms of schizophrenia while giving rise to adverse side effects. The first part summarizes the contribution of neuroimaging studies to our understanding of the neurochemical substrates of schizophrenia, putting emphasis on direct evidence suggestive of a presynaptic rather than a postsynaptic dysregulation of dopaminergic neurotransmission in this disorder. The second part addresses the role of D_2 and non-D_2 receptor blockade in the treatment of schizophrenia and highlights a preponderant role of D_2 receptors in the mechanism of antipsychotic action. Neuroimaging studies have defined a narrow, but optimal, therapeutic window of 65–78 %

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D_2 receptor blockade within which most antipsychotics achieve optimal clinical efficacy with minimal side effects. Some antipsychotics though do not conform to that therapeutic window, notably clozapine. The reasons for its unexcelled clinical efficacy despite subthreshold levels of D_2 blockade are unclear and current theories on clozapine's mechanisms of action are discussed, including transiency of its D_2 receptor blocking effects or preferential blockade of limbic D_2 receptors. Evidence is also highlighted to consider the use of extended antipsychotic dosing to achieve transiency of D_2 blockade as a way to optimize functional outcomes in patients. We also present some critical clinical considerations regarding the mechanisms linking dopamine disturbance to the expression of psychosis and its blockade to the progressive resolution of psychosis, keeping in perspective the speed and onset of antipsychotic action. Finally, we discuss potential novel therapeutic strategies for schizophrenia.

Keywords Schizophrenia • Antipsychotic drugs • Dopamine receptor • D_2 blockade • PET imaging

1 Introduction

Schizophrenia is a chronic and disabling disease afflicting nearly 1 % of the general population (Perala et al. 2007). Clinically, the disorder manifests with a large variety of symptoms that fall into three categories: positive, negative, and cognitive (Kapur and Mamo 2003; Lieberman et al. 2005). Positive symptoms typically reflect a distortion of normal functions that are regarded as manifestations of psychosis and include hallucinations, delusions, and disorganized thoughts. Negative symptoms are associated with a diminution or loss of normal emotions and behaviors and manifest as affective blunting, social isolation, poverty of speech, anhedonia, and avolition. Cognitive symptoms relate to abnormal thought processes and manifest as deficits in attention, working memory, and executive functioning. Schizophrenia appears to be a polygenic disorder in which genetic factors combined with abnormalities in early brain development (including apoptosis, synaptic pruning, and disruption of neuronal migration) may confer a constitutional vulnerability to the disease (Walker et al. 2004). Subsequent environmental insults (including exposure to infectious, toxic, or traumatic insults and stress in utero or during childhood) may unmask this vulnerability and trigger overt manifestation of schizophrenia (Tsuang 2000). Within this framework, dysregulations of the dopamine (DA) neurotransmitter system have been most intimately associated with the pathophysiology of schizophrenia. Moreover, all antipsychotics act by blocking DA receptors, indicating that opposing DA signaling is central for alleviating psychotic symptoms. It is this aspect of the illness that is the focus of this review, with special attention given to the DA D_2 receptors.

1.1 Role of Dopamine in the Pathophysiology of Schizophrenia

For almost 50 years, schizophrenia research has focused on dopaminergic signaling as a key feature in the treatment and etiology of the disease. In particular, the original "DA hypothesis" posits a hyperdopaminergic function in brain as a possible cause of the illness (van Rossum 1966). This hypothesis was initially based on several lines of indirect evidence. First, exposure to psychostimulants such as amphetamine, which increase brain DA activity, can induce psychotic symptoms in normal individuals and worsen psychotic symptoms in schizophrenia patients (Connell 1958), whereas drugs known as DA depleters, such as reserpine, alleviate them (Carlsson et al. 1957). Further evidence for a DA hyperfunction in schizophrenia came from research on the mechanism of antipsychotic action. Notably, early work from Carlsson and Lindqvist (1963) indicated that central DA receptor blockade by chlorpromazine and haloperidol was the mechanism of their antipsychotic action. Actually, all antipsychotics act by blocking DA D_2 receptors and there is a tight correlation between the clinical potency of these drugs and their pharmacological potency at blocking D_2 receptors (Seeman and Lee 1975). This observation leads to the dominant theory that the positive symptoms of the illness are directly related to a subcortical dopaminergic overactivity, which may be due to an excess of DA itself or to hypersensitive D_2 receptors.

1.1.1 Dopamine Receptor Studies in Schizophrenia

Since all current antipsychotics block D_2 receptors, there has been tremendous interest in whether the expression of those receptors is altered in schizophrenia. While early postmortem studies showed a D_2 elevation in schizophrenia (Lee et al. 1978; Seeman et al. 1984), the finding that antipsychotic treatment per se increased striatal D_2 receptor density in experimental animals (Burt et al. 1977; Owen et al. 1980) raised the concern that the D_2 receptor elevation observed in schizophrenia was the consequence of prior drug treatment (Seeman 1987). With the advent of positron emission tomography (PET) and single positron emission computed tomography (SPECT) imaging technologies came the opportunity to investigate D_2 receptor availability in drug-naive patients in vivo. Initial imaging studies in drug-naïve or drug-free patients remained inconclusive, with some studies reporting higher than normal striatal D_2 receptor density and others showing no difference from controls (Farde et al. 1987; Hietala et al. 1994; Pilowsky et al. 1994; Tune et al. 1993; Wong et al. 1986). Since these initial reports, other studies have followed and failed to detect significant alteration in striatal D_2 receptors in drug-naïve schizophrenic patients (Buchsbaum et al. 2006; Glenthoj et al. 2006; Lomena et al. 2004; Nordstrom et al. 1995; Talvik et al. 2006; Yang et al. 2004). More recently, meta-analyses examining the aggregate results of previous D_2 receptor imaging studies revealed that there is an increase in striatal D_2 receptor density in schizophrenia, although modest (around 13–14 %), that is independent of

the effects of antipsychotic treatment (Kestler et al. 2001; Laruelle 1998; Zakzanis and Hansen 1998). Striatal D_1 receptor density appears unaffected (Abi-Dargham et al. 2002; Karlsson et al. 2002). With the recent availability of high-affinity PET radiotracers, there has been a tremendous interest in investigating extrastriatal dopamine D_2 receptors in schizophrenia. Several PET imaging studies with high-affinity ligands have found consistently lower D_2 receptor densities (in the 20 % range) in the thalamus, as well as in the amygdala, cingulate gyrus, and temporal cortices (Buchsbaum et al. 2006; Kessler et al. 2009; Suhara et al. 2002; Talvik et al. 2003), thus providing no support for a D_2 receptor supersensitivity in schizophrenia. It has been proposed that while there may not be an absolute change in the overall number of D_2 receptors, a higher proportion of D_2 receptors with functional high affinity for DA may explain hyperdopaminergia (Seeman et al. 2005). However, a recent clinical study to investigate levels of those high-affinity state D_2 receptors found no difference between schizophrenia patients and controls (Graff-Guerrero et al. 2009b). Thus, despite extensive efforts over the past 40 years, no convincing evidence has emerged yet that unequivocally points to a D_2 receptor abnormality in schizophrenia.

Dopamine Presynaptic Dysregulation in Schizophrenia

Contrasting with studies looking at postsynaptic D_2 receptors, PET imaging of the presynaptic aspect of DA neurotransmission has provided converging evidence for the existence of presynaptic dopamine overactivity in schizophrenia. In vivo presynaptic DA activity has been investigated using several methods carried out to study particular elements of DA function. The first method involved the use of the DA precursor analog radioligand [^{18}F]DOPA, whose accumulation in brain represents the activity of the aromatic acid decarboxylase enzyme and the storage capacity of presynaptic DA (Brown et al. 1999) and is generally considered as an index of DA synthesis. The other methods take advantage of the well-described in vivo competing effect exerted by endogenous DA on the binding of some D_2 radiotracers to index evoked DA release or baseline levels of extracellular DA (Ginovart 2005; Laruelle 2000). Without a few exceptions (Dao-Castellana et al. 1997; Elkashef et al. 2000), all studies investigating presynaptic dopamine metabolism indicate a heightened presynaptic capacity of DA synthesis in schizophrenia (Hietala et al. 1995, 1999; Kumakura et al. 2007; Lindstrom et al. 1999; McGowan et al. 2004; Meyer-Lindenberg et al. 2002; Nozaki et al. 2009; Reith et al. 1994) that might be used as an index to discriminate patients from controls (Bose et al. 2008). Interestingly, it has recently been demonstrated that patients with prodromal symptoms of schizophrenia also show elevated striatal DA synthesis (Howes et al. 2009), indicating that presynaptic DA abnormalities predate the onset of illness and are thus likely related to the cause rather than being a consequence of the disorder. Further evidence for an elevated DA availability in schizophrenia comes from studies showing an exaggerated release of DA in the striatum of schizophrenic patients both at basal conditions (Abi-Dargham et al.

2000) and in response to amphetamine (Abi-Dargham et al. 1998; Bertolino et al. 2000; Breier et al. 1997; Laruelle et al. 1996). Taken together, these data suggest that an increased presynaptic capacity of DA synthesis and release may constitute part of the dysfunctional neural connectivity underlying schizophrenia and may be the concurring proximate causes of psychoses. In contrast, a DA hypofunction may prevail in the neocortex (Grace 1991). A reconceptualization of the original DA hypothesis of schizophrenia followed that refined the notion of a global hyperdopaminergia to a cortical/subcortical imbalance of DA tone in brain (Davis et al. 1991; Howes and Kapur 2009). According to this new hypothesis, positive symptoms of the disorder would result from a subcortical hyperdopaminergia, whereas negative symptoms and cognitive deficits would result from a concomitant hypodopaminergia in frontal cortex.

2 Mechanism of Antipsychotic Action

2.1 Antipsychotic Treatment

Antipsychotics fall into two classes, typical and atypical, which differ in their side-effect and receptor binding profiles. Typical antipsychotics such as haloperidol and chlorpromazine have been available since the 1950s and belong to the first generation of antipsychotics drugs. Typical antipsychotics are effective in treating both the positive and negative symptoms of schizophrenia, although the degree of improvement of negative symptoms is usually less than that of positive symptoms (Goldberg 1985). Besides their therapeutic efficacy, first-generation agents cause a variety of undesirable adverse events, including acute (parkinsonism, akathisia, dystonia) and later-onset (tardive dyskinesia; TD) extrapyramidal side effects (EPS) and a propensity to cause prolactin elevation. In addition to EPS, typical antipsychotics also cause subjective side effects that are characterized by symptoms of dysphoria/anhedonia, depressed mood, and a slowed mentation (Marder 2005; Voruganti and Awad 2004). These subjective effects can manifest within the first few days of treatment (see reviews in Awad and Voruganti 2005; Lambert et al. 2003) and distinguishing them from the primary negative symptoms of schizophrenia can be difficult (Lewander 1994; Schooler 1994). Subjective distress associated with motor and subjective side effects of typical antipsychotics has a negative impact on patient's quality of life and well-being and can lead to noncompliance (Naber et al. 2005; Robinson et al. 2002), and subsequent relapse (Morken et al. 2008; Robinson et al. 1999). Moreover, the lack of response in 20–40 % of patients with schizophrenia represents another limitation of typical antipsychotic for adequate treatment of the disease (Hellewell 1999).

Atypical (or second-generation) antipsychotics are comparable to typical agents with respect to efficacy in reducing positive symptoms but have been associated with a lower risk to cause EPS (Correll and Schenk 2008; Haro and Salvador-Carulla 2006). However, there are considerable variations in the

propensity of individual atypical agents to cause EPS, with some atypical drugs, such as clozapine and quetiapine, showing no greater EPS than placebo across their full dosage range (Arvanitis and Miller 1997; Goldstein 2000) and some others, such as risperidone and olanzapine, showing increased risk with increased dosage (Lemmens et al. 1999). Studies comparing atypical versus typical agents with respect to EPS risk have commonly used haloperidol, a highly potent typical agent comparator that carries a high liability for EPS, particularly at the relatively high doses used—and not surprisingly in these studies atypicals showed a substantial advantage in terms of EPS. However, large efficacy studies such as CATIE (Rosenheck et al. 2006) and CUtLASS (Jones et al. 2006), which have used moderate doses of midpotency typical antipsychotics such as perphenazine and sulpiride, show that it is possible to get equivalent clinical efficacy with typical antipsychotics at doses that do not confer higher risk for EPS. Thus, while it is generally agreed that atypical antipsychotics have, overall, a more favorable side-effect profile than typical agents, it is uncertain whether this superiority can be sustained when controlling for antipsychotic potency and dose inequities. Similarly, and contrary to common thinking that atypicals have improved efficacy against negative symptoms, meta-analyses revealed rather moderate advantage, if any, of atypical versus typical drugs in the treatment of negative symptoms (Carman et al. 1995; Davis et al. 2003; Leucht et al. 1999, 2009). Several studies even indicate that typical and atypical drugs can be equally effective in this domain (Arvanitis and Miller 1997; Buchanan et al. 1998; Copolov et al. 2000; Leucht et al. 1999; Möller et al. 2008). It has been suggested that the apparent superior efficacy of atypical versus typical drugs may only relate to the relative absence of confounding, secondary negative symptoms with atypical drugs due to use of a high-dose comparator, haloperidol (Kapur and Remington 2001a). Interestingly, the meta-analysis by Leucht et al. (2009) demonstrated that when compared with midpotency typical antipsychotics or moderate doses of haloperidol (7.5 or 12 mg per day), some atypical antipsychotics such as aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine are as effective as typical drugs for treatment of negative symptoms, whereas others such as amisulpride, clozapine, olanzapine, and risperidone are superior. Thus, atypical antipsychotics are a heterogeneous group of drugs with regard to efficacy against negative symptoms, and it remains unclear whether this only reflects a different propensity to induce EPS and dysphoria or a primary efficacy against negative symptoms. Atypical antipsychotics may thus offer only modest efficacy advantages over typical drugs. However, because they are less prone to induce secondary negative symptoms, in terms of EPS and dysphoria, than typical antipsychotics, they are associated with improved subjective experience (Lambert et al. 2011) and compliance to treatment (Haro et al. 2009; Möller et al. 2008) and may thus achieve a better overall prognosis. This advantage must be balanced though with the occurrence of other, nonmotor adverse effects, since some atypicals are associated with a higher risk of prolactin elevation and others with metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain (Luft and Taylor 2006; Newcomer 2005).

2.2 *Role of D_2 Receptor Blockade*

Besides exhibiting a different side-effect profile, typical and atypical antipsychotics also differ in their receptor binding profiles, with atypical agents acting through a larger spectrum of receptor types, including DA but also serotonergic, cholinergic, and adrenergic receptors. Nevertheless, all antipsychotics share the common ability to antagonize DA D_2 receptors, albeit with different affinities. Early pharmacological studies have established the existence of a close relationship between the clinical potency of antipsychotic drugs and their affinity for D_2 receptors (Creese et al. 1976; Seeman and Lee 1975), pointing to a role of this DA receptor subtype in antipsychotic action. The lack of such correlation for any other DA receptor subtypes (Seeman 1987) further substantiates the view that antipsychotic effects occur primarily through antagonism at D_2 receptors.

Further evidence for this comes from neuroimaging studies in schizophrenia patients that investigated the relationship between antipsychotic-induced D_2 receptor blockade, clinical efficacy, and occurrence of side effects. With a few exceptions, most antipsychotics are effective when 65 % or more of D_2 receptors are blocked in the striatum, indicating that antipsychotic effect is driven primarily by D_2 antagonism (Farde et al. 1992; Kapur et al. 2000a). Increasing striatal D_2 blockade by increasing antipsychotic dosage does not provide additional antipsychotic efficacy but is associated with an increased risk of adverse side effects. Indeed, D_2 blockade exceeding 72 % and 78 % leads to the emergence of hyperprolactinemia and extrapyramidal motor symptoms (EPS), respectively, underscoring the need to carefully control antipsychotic dosage during treatment to avoid adverse effects. These neuroimaging findings have permitted the definition of an optimal therapeutic window of 65–78 % D_2 receptor blockade within which most antipsychotics achieve optimal efficacy with minimal side effects. Although originally demonstrated with the prototypical typical antipsychotic haloperidol, a similar relationship between D_2 receptor blockade and clinical effects was subsequently confirmed for atypical drugs having low EPS liability. Drugs such as remoxipride, olanzapine, and risperidone induce dose-dependent levels of striatal D_2 receptor blockade but achieve therapeutic efficacy only at doses that cross the 65 % threshold level (Kapur et al. 1998, 1999; Nordstrom et al. 1998). However, these drugs dose-dependently lose their low EPS profile because D_2 blockade crossing the 72–75 % level is associated with the emergence of EPS and sustained hyperprolactinemia (Jauss et al. 1998; Knable et al. 1997). Although both the EPS and prolactin elevation are associated with D_2 receptor blockade, different neuroanatomical pathways mediate these effects. Whereas EPS are mediated through excessive blockade of D_2 receptor in striatum, hyperprolactinemia relates to excessive blockade of D_2 receptors in the anterior pituitary, a structure located outside the blood–brain barrier and accessible to drugs that do not penetrate the brain. Atypical antipsychotics vary considerably with regard to their ability to increase prolactin levels (Kapur and Remington 2001a). Drugs such as amisulpride and sulpiride, which display a limited brain penetration, cause few EPS but have a profound effect

on plasma prolactin concentrations when compared to other atypicals such as quetiapine and olanzapine (O'Connor and Brown 1982; Stanniland and Taylor 2000). This dissociation between the occurrence of EPS and prolactin-elevating effect reflects a differential disposition of the drugs across the blood–brain barrier, resulting in higher levels of D_2 receptor blockade in the pituitary than in the striatum (Kapur et al. 2002). Thus, the different propensity of atypical drugs to induce prolactin elevation at therapeutic doses is critically dependent on their ability to cross the brain–blood barrier and the degree to which they induce differential D_2 receptor blockade in the pituitary versus the striatum. Antagonism at the D_2 receptors thus appears central to both the therapeutic and adverse side effects of antipsychotics. Reducing exaggerated DA function through D_2 receptor blockade in the mesolimbic pathway would underlie the progressive resolution of psychosis, whereas excessive reduction of DA function in the nigrostriatal and tuberoinfundibular pathways would lead to EPS and prolactin elevation, respectively. On the other hand, concurrent blockade of D_2 receptors in the mesocortical pathway, where DA function is already deficient in schizophrenia, may even worsen the negative symptoms and cognitive impairment of the disease.

A second approach in the treatment of schizophrenia is to prevent excessive D_2 receptor activation by the use of D_2 partial agonists. Unlike antagonists, which block D_2 activation by endogenous DA, partial agonists activate D_2 receptors but to a lower degree than endogenous DA. The consequence of D_2 partial activation is thus dependent on the local concentration of endogenous DA. When the receptor is hyperactivated by high levels of DA, competitive partial agonist binding to the receptor will have the effect of reducing that activation whereas the opposite effect ensued when the receptor is hypoactivated because of low levels of endogenous DA (Tamminga 2002). Partial DA agonists are therefore believed to restore the cortical/subcortical imbalance of DA tone in schizophrenia by dampening excessive mesolimbic D_2 stimulation and by restoring deficient mesocortical D_2 stimulation (Tamminga 2002). Moreover, by avoiding excessive nigrostriatal D_2 inactivation, a partial D_2 agonist would have a low propensity to cause EPS and prolactin elevation. Aripiprazole, the first successful D_2 partial agonist to come into practice, is effective against both the positive and negative symptoms of schizophrenia (Burris et al. 2002; Kane et al. 2002). At therapeutic doses, aripiprazole occupies 85–95 % of the striatal D_2 receptors without causing the EPS and prolactin elevation commonly associated with such high degrees of D_2 occupancy with antagonists (Gründer et al. 2008; Mamo et al. 2007). With an intrinsic activity of circa 25 %, aripiprazole thus produces levels of D_2 receptor inactivation (i.e., blockade) that ideally fall within the optimal 65–78 % therapeutic window when about 90 % of D_2 receptors are occupied (Mamo et al. 2007). Taken together, studies on the pharmacological action of D_2 antagonists and D_2 partial agonists concur to underline the importance of a fine-tuning of D_2 receptor blockade for achieving optimal antipsychotic benefit and thus further emphasize the central role of this receptor subtype in antipsychotic action.

A few atypical antipsychotics though, namely clozapine and quetiapine, do not fit the conventional window of D_2 receptor blockade suggested for optimal therapeutic response. Clozapine, the prototype of atypical antipsychotic drugs, is

effective in treating patients with refractory schizophrenia (Kane et al. 1988) and, like quetiapine, produces fewer and milder EPS compared to typical antipsychotics and does not induce hyperprolactinemia (Goldstein 1999; Lieberman et al. 1989). Both drugs produce robust antipsychotic effect at less than the conventional 65 % threshold of striatal D_2 receptor blockade (Farde et al. 1989, 1992; Kapur et al. 2000b), suggesting that beyond D_2 receptor blockade in striatum, other receptors or mechanisms also contribute to the therapeutic effect of these drugs. On the other hand, since both clozapine and quetiapine never exceed the 75 % threshold of D2 blockade, they do not give rise to EPS.

2.2.1 Role of Non-D_2 Receptor Blockade

In the search for the involvement of non-DA D_2 receptor mechanisms in antipsychotic action, the D_3 receptor, which has a high homology with the D_2 receptor but displays a preferential distribution in limbic versus motor regions of the dopaminergic systems, has received special attention. In vitro studies have shown that many antipsychotics display comparable affinity for the D_2 and D_3 receptors (Levant 1997; Schotte et al. 1996). However, the relative contribution of D_3 versus D_2 blockade to antipsychotic efficacy has been difficult to establish due to the lack of selective D_3 receptor radioligands and to the partially overlapping distribution of D_2 and D_3 receptors in brain. The development of [^{11}C](+)-PHNO, a preferring-D_3 receptor agonist, has recently permitted to investigate the impact of stable treatment with antipsychotics on D_3 receptors (Graff-Guerrero et al. 2009a). This neuroimaging study, performed in patients with schizophrenia on long-term treatment (>4 weeks) with olanzapine, clozapine, and risperidone, revealed that while antipsychotics induce high levels of D_2 receptor blockade, they do not block D_3 receptors (Graff-Guerrero et al. 2009a). Thus despite displaying D_3 receptor affinity in vitro, these data suggest either that antipsychotics do not bind D_3 receptor in vivo or that they induce a D_3 receptor upregulation on long-term treatment. Subsequent studies performed in rats and comparing D_2 versus D_3 receptor blockade obtained in vitro and ex vivo indicate that, in contrast to what is obtained in vitro, olanzapine, clozapine, risperidone, and haloperidol selectively block D_2 receptors and have only a marginal effect on D_3 receptors ex vivo (McCormick et al. 2011). Altogether, these studies suggest that at clinically relevant doses, the therapeutic effects of antipsychotic are likely not attributable to D_3 receptor blockade. For additional information and discussion, the reader is referred to Gross and Drescher (2012) in the accompanying volume of the Handbook.

The higher affinity of clozapine for D_4 than for D_2 receptors led to the speculation that the superior clinical profile of this drug was due to D_4 receptor blockade (Van Tol et al. 1991). However, several typical antipsychotic drugs, including haloperidol, have similar affinity for D_2 and D_4 receptors (Roth et al. 1995), whereas several atypical drugs, including quetiapine and amisulpride, have very low D_4 affinity, suggesting that D_4 affinity per se does not confer therapeutic efficacy or low EPS liability. Moreover, several clinical trials with D_4 selective

antagonists failed to show antipsychotic efficacy (Bristow et al. 1997; Corrigan et al. 2004; Kramer et al. 1997).

In addition to having D_2-blocking properties, many atypical antipsychotics are also antagonists at the serotonin 5-HT_{2A} receptor and it has been determined that a high 5-HT_{2A}/D_2 affinity ratio is actually the pharmacological feature that best distinguishes atypical from typical antipsychotics (Meltzer et al. 1989). Antagonism at the serotonin 5-HT_{2A} receptor per se does not mediate antipsychotic activity since subtherapeutic doses of atypical drugs such as risperidone and olanzapine induce nearly complete blockade of 5-HT_{2A} receptor in brain, and become therapeutically effective only at doses that cross the conventional 65 % levels of D_2 receptor blockade (Kapur et al. 1999). A balanced inhibition at the D_2 and 5-HT_{2A} receptors is however thought to be important for the reduced side-effect liability and greater ability of atypical versus typical drugs to improve the negative and cognitive symptoms of schizophrenia (Meltzer 2004; Meltzer et al. 2003). This view is however partly challenged by the high incidence of EPS observed with drugs such as chlorpromazine and loxapine despite high levels of 5-HT_{2A} receptor blockade (Kapur et al. 1997; Trichard et al. 1998) and by the lack of EPS observed with amisulpride despite any action on 5-HT_{2A} receptors (Schoemaker et al. 1997; Trichard et al. 1998). Thus, although 5-HT_{2A} may offer advantages against the negative and cognitive symptoms of schizophrenia, low EPS liability is likely unrelated to 5-HT_{2A} receptor blockade.

Preferential Limbic D_2 Receptor Blockade

The underlying mechanism for clozapine's favorable clinical profile, especially with regard to its low EPS liability, has been the focus of intense research. Apart from being attributed to its multireceptor binding profile, especially its binding at the 5-HT_{2A} receptor, it has been suggested that the reduced EPS liability of clozapine, as well as other atypical antipsychotics, is due to a preferential action in limbic and cortical regions (Strange 2001). Indeed, converging evidence from behavioral (Gardner and Seeger 1983; Ljungberg and Ungerstedt 1985; Oakley et al. 1991), electrophysiological (Chiodo and Bunney 1983; White and Wang 1983), and neurochemical (Lane et al. 1988) studies indicate that, in contrast to classical antipsychotic drugs such as haloperidol, clozapine selectively targets the mesolimbic DA system, while leaving the nigrostriatal system relatively unaffected. For instance, while the acute administration of atypical drugs such as clozapine, quetiapine, sertindole, and olanzapine increases the activity of DA neurons in the VTA but not in the SN, haloperidol activates both subpopulations of DA neurons (Goldstein et al. 1993; Hand et al. 1987; Skarsfeldt and Perregaard 1990; Stockton and Rasmussen 1996). As a consequence, atypical antipsychotics preferentially increase DA output in the nucleus accumbens and prefrontal cortex as compared to the striatum whereas the opposite is observed with haloperidol (Hertel 2006; Moghaddam and Bunney 1990; Youngren et al. 1999). Such a preferential modulation of VTA DA neuronal activity likely contributes to the selective development of

depolarization blockade of VTA DA neurons and consequent selective decrease in mesolimbic DA output seen after chronic clozapine treatment, while both the mesolimbic and nigrostriatal DA systems are equipotently affected by chronic haloperidol (Chiodo and Bunney 1983; Goldstein et al. 1993; Lane et al. 1988; Skarsfeldt 1988; White and Wang 1983). Atypical drug's selectivity for limbic, as opposed to striatal, regions is thought to contribute to the lower incidence of EPS as compared to typical drugs. Accordingly, the "limbic selectivity" hypothesis postulates that atypical antipsychotics induce a preferential blockade of limbic and cortical D_2 receptors, which is associated with clinical efficacy, and a relatively lower striatal D_2 receptor blockade, which is associated with a lower incidence of EPS. However, although some imaging studies indicate that atypical drugs such as clozapine, quetiapine, olanzapine, and risperidone block a higher proportion of temporolimbic than striatal D_2 receptors (Bigliani et al. 2000; Bressan et al. 2003; Kessler et al. 2006; Pilowsky et al. 1997; Stephenson et al. 2000; Vernaleken et al. 2011; Xiberas et al. 2001), other studies fail to do so (Agid et al. 2007; Ito et al. 2009; Kessler et al. 2005; Nyberg et al. 2002; Talvik et al. 2001). Atypical drugs have also been shown to produce equipotent D_2 receptor blockade in the ventral striatum (herein the nucleus accumbens is located) and in the dorsal part of the structure (Kessler et al. 2005, 2006), further calling into question the limbic selectivity theory. Moreover, positive symptom reduction in patients treated with risperidone, olanzapine, or aripiprazole appears to be correlated with striatal rather than cortical or other extrastriatal D_2 receptor blockade (Agid et al. 2007; Kegeles et al. 2008), suggesting that the antipsychotic response may be directly mediated through modulation of striatal rather than cortico–limbic DA activity. Clearly, more clinical investigations are needed to determine the exact role of limbic D_2 receptors in the treatment of schizophrenia.

Transient Versus Continuous D_2 Receptor Blockade

Another aspect of D_2 blockade that has been proposed to be central to atypical antipsychotic action is the between-dose kinetic pattern of receptor blockade achieved during clinical dosing (Kapur and Remington 2001b). In vitro work has demonstrated that while drugs such as haloperidol bind with high affinity and display slow dissociation from D_2 receptors, atypical drugs as a group display faster dissociation rates and are only loosely bound to the receptor (Seeman 2002). Such a rapid dissociation is believed to allow D_2 receptors to be released from the drug and to regain responsiveness relatively quickly during the between-dose interval as surges of dopamine can reaccess the receptors. As opposed to typical drugs with slow receptor dissociation, which produce enduring receptor inactivation, atypical antipsychotics would thus only briefly silence D_2 neurotransmission, thereby allowing antipsychotic action with a lower propensity to induce EPS and sustained hyperprolactinemia. As a consequence, and taking into account plasma half-life of the drug and its active metabolites (Tauscher et al. 2002; Tort et al. 2005), drugs with different receptor dissociation properties may produce different kinetics of D_2 blockade. A number of vivo neuroimaging studies concur

to demonstrate that while clinical dosing with haloperidol gives rise to sustained high levels of D_2 receptor blockade (Baron et al. 1989; Nordstrom et al. 1992), D_2 blockade achieved by clinical dosing with quetiapine is only transiently high and declines rapidly after dose intake to reach undetectable levels at 12–14 h postdosing (Catafau et al. 2008; Gefvert et al. 1998; Kapur et al. 2000b; Tauscher-Wisniewski et al. 2002). The demonstration that transiently high D_2 receptor blockade is sufficient for obtaining and maintaining antipsychotic effect, even in drug-naïve schizophrenic patients, thus called into question the presumed necessity of continuous D_2 receptor blockade to control schizophrenia symptoms (Kapur et al. 2000b). In keeping with a precedent pilot study (Remington et al. 2005), a recent double blind study comparing daily with alternate day (also called "extended") antipsychotic dosing in stabilized patients over a 6-month trial period supports this idea (Remington et al. 2011). Patients on extended dosing with risperidone or olanzapine did not show any greater risk of relapse or worsening of positive symptoms as compared to those receiving daily dosing, challenging the common presumption that patients need to receive daily dosing to remain stabilized. It is thus possible that transient D_2 blockade is all that is needed to achieve and/or maintain clinical response and that continuous blockade is unnecessary and may even be detrimental to some aspects of patient outcome. Recent preclinical studies provide further support for this view by documenting the effects of transient versus continuous D_2 receptor blockade in animal models predictive of antipsychotic-like efficacy and side-effect liability. Within-day transient D_2 blockade achieved by transient antipsychotic delivery was found to be more effective than continuous D_2 blockade (Samaha et al. 2007, 2008). Moreover, while continuous D_2 blockade resulted in D_2 receptor upregulation and behavioral tolerance (Ginovart et al. 2009; Samaha et al. 2008) and to an increased risk for the development of vacuous chewing movements (i.e., an animal model for tardive dyskinesia) (Turrone et al. 2003), transient D_2 receptor blockade did not. This finding suggests that between-dose transient D_2 blockade may be sufficient to induce antipsychotic response and may even improve therapeutic efficacy by avoiding the development of compensatory and likely counterproductive D_2 supersensitivity that is obtained under conditions of sustained D_2 blockade. Moreover, as the development of behavioral tolerance and D_2 receptor upregulation is thought to correspond, at least partially, to the emergence of tardive dyskinesia (TD) in patients on long-term antipsychotic treatment (Tarsy and Baldessarini 1977), a transient pattern of D_2 blockade might also have a lower incidence of TD. On the other hand, since D_2 blockade falls quickly after dosing, transiency of D_2 blockade may lead to more rapid relapse on sudden discontinuation or missed doses, especially when using drugs with fastest dissociation kinetics such as clozapine and quetiapine. A central question thus remains that is to determine the optimal between-dose interval producing appropriate D_2 blockade transiency to achieve and/or maintain symptom remission with low risk of relapse. This balance may be a challenge because this between-dose interval is likely to be quite variable amongst patients (given the wide interpatient variability in metabolism), but also amongst antipsychotic drugs (given their variable D_2 dissociation properties and half-life of time residency in plasma).

Pharmacokinetic analysis of D_2 blockade however has good heuristic value for exposing processes underlying the various degrees of atypicality seen among antipsychotics and is thus worth further investigation.

3 Mechanisms Underlying Speed and Onset of Antipsychotic Response

One important measure of antipsychotic effectiveness is the time lag between the initiation of antipsychotic treatment and the onset of therapeutic response. It has long been held that time to onset of clinical response is delayed by 2–3 weeks after initiation of treatment. This delayed onset of antipsychotic response is thought to reflect the induction of late-onset phenomena, such as the cessation of midbrain DA neurons firing, also known as depolarization blockade. Indeed, while acute D_2 receptor blockade increases the firing of mesolimbic DA neurons, this initial activation gradually subsides with successive antipsychotic administration and ultimately leads, after 2–3 weeks of chronic treatment, to a reversible cessation of midbrain DA neuron firing. The delayed onset of antipsychotic response is thus thought to correlate with the delayed inactivation of midbrain DA neurons (Grace et al. 1997). Another hypothesis postulates that long-term drug-induced changes in gene expression, protein synthesis, and synaptic remodeling could also mediate the delayed onset of antipsychotic action (Kuhar and Joyce 2001). Given that steady-state levels of D_2 receptor blockade are achieved within 1–2 days of antipsychotic treatment (Nordstrom et al. 1992; Tauscher et al. 2002), the dissociation between rapid effect of antipsychotics on D_2 receptor blockade and their delayed therapeutic efficacy is thus difficult to reconcile with a central role of D_2 blockade in the mechanism of antipsychotic action. However, recent research does not lend support to the "delayed-onset" hypothesis and growing evidence indicates that response to antipsychotic treatment occurs much earlier than originally thought. In a large and pioneering meta-analysis involving nearly 7,500 patients with schizophrenia treated with typical (haloperidol, chlorpromazine) and atypical (risperidone and olanzapine) antipsychotics, Agid et al. (2003, 2006) found that antipsychotics produce discernible clinical improvement within the very first week of treatment and that improvement in psychosis is actually greater in the first week than in each subsequent 3 weeks of treatment. Such an early onset of symptom response has been found to be true for other antipsychotic drugs, including quetiapine (Pae et al. 2007; Small et al. 2004) and amisulpride (Leucht et al. 2005), and to be a reliable marker of subsequent clinical outcome as early nonresponse to antipsychotics strongly predicts subsequent lack of response to continued treatment with the same medication (Correll et al. 2003; Kinon et al. 2008, 2011; Leucht et al. 2005). Further, it has now been demonstrated that robust clinical improvement of psychosis occurs as early as the first 24 h of treatment (Agid et al. 2008; Kapur et al. 2005) and that early improvement is strongly predictive of eventual improvement (Agid et al. 2008; Kinon et al. 2008). In addition to a consistent finding of early

onset of therapeutic benefit, the degree of D_2 receptor blockade measured as early as 48 h after treatment initiation correlates positively with clinical improvement after 2 weeks of treatment (Catafau et al. 2006), thus suggesting that early response is likely to be directly linked to D_2 blockade. Contrary to the common belief that there is delayed onset of antipsychotic benefit, compelling evidence indicates that effective doses of antipsychotics have nearly immediate effects with symptom improvement occurring within the first week of treatment. The fact that discernible clinical effects occur close in time to the almost immediate neuropharmacological action of antipsychotics suggests that antipsychotic efficacy likely results from direct blockade of the D_2 receptors, rather than a purported indirect and delayed downstream effect on DA neuronal pathways.

4 Linking Dopaminergic Disturbances, Psychology and Pharmacology in Schizophrenia

If we accept a causal relationship between dopaminergic disturbances and psychosis, how can we understand the link between such a biological disturbance and the psychological expression of the disease? In other words, how can an excessive DA function in schizophrenia lead to hallucinations and delusions and not to some other manifestations? Moreover, why do full benefits of antipsychotic treatment take several weeks to months whilst steady levels of D_2 receptor blockade and first effects of treatment can be seen as early as after one day of treatment? A model has been proposed (Kapur 2003; Kapur et al. 2005) that links DA to symptom expression, and its blockade to symptom resolution. Inherent to this model is the central role of mesolimbic DA in the neural processing of motivation and reward-based associative learning (Day et al. 2007). Indeed, DA neurons in the mesolimbic system are activated by reward-predicting stimuli, leading to the release of DA in the terminal fields that regulate behavior. Rather than encoding the hedonic value of reward, activation of DA mesolimbic neurons predicts the likelihood of a reward to occur when a reward-related cue is presented (Schultz 2006). In this context, DA released in response to the reward-predicting cue determines its incentive salience and establishes reward-associated memories such that subsequent exposure to the cue can trigger reward-directed behaviors (Berridge 2007). In the case of schizophrenia, it is hypothesized that excessive mesolimbic DA transmission occurs irrespective of the contextual experience and therefore exaggerated salience is attributed to impertinent stimuli and to internal representations (Kapur 2003; Kapur et al. 2005). In support of this hypothesis, increasing evidence obtained in schizophrenia patients indicates an abnormally high physiological response of the ventral striatum to non-reinforced stimuli during reward conditioning, suggesting an abnormal ability to differentiate neutral from motivationally salient stimuli (Diaconescu et al. 2011; Jensen et al. 2008; Murray et al. 2008). Misattribution of motivational salience to irrelevant events translates into distorted thoughts and false perceptions of events that contribute to the formation of delusion as a way for the

patient to provide a rational explanation to abnormal internal and external events and give sense to his/her surrounding world. By blocking mesolimbic DA transmission, antipsychotics would not resolve delusional beliefs per se but would rather dampen aberrant salience such that new experiencing can progressively change the patient's cognitive and emotional experience. Resolution of delusions thus follows a slower course than the immediate antipsychotic-induced dampening of salience because it requires cognitive and psychological work from the patient to overcome the false beliefs. Moreover, since antipsychotics also dampen normal incentive salience, they may contribute to the depressed mood, increased anhedonia, and amotivation associated with treatment, thus explaining some of the undesirable effects of antipsychotics.

5 Conclusion and Future Directions

The last 50 years of research have provided unquestionable evidence for a central role of D_2 receptor blockade in the mechanism of antipsychotic action. The demonstration that therapeutic response is a function of the degree of D_2 blockade and that adequately high levels of D_2 blockade are needed to achieve therapeutic efficacy has constituted key discoveries for our understanding of how antipsychotics work. The complex pharmacology, the different DAergic properties, and differential clinical profiles of atypical versus typical antipsychotic agents have moreover provided useful clues with regard to uncovering the potential mechanisms underlying lower EPS liability. While action at the D_2 receptor remains indispensable for controlling the positive symptoms, sustained D_2 blockade may not be necessary for maintaining antipsychotic response and extended antipsychotic dosing leading to transiently high D_2 blockade may represent an effective strategy to circumvent undesirable side effects associated with continuous dosing. Other key modulators of antipsychotic activity include activity at other receptors, especially at the 5-HT_2 receptor, and are probably required for ameliorating the negative and cognitive symptom domains for which D_2 blockade appears ineffective. Yet, and despite continuous research in the field, the fundamental principle has remained unchanged—D_2 blockade remains necessary and sufficient for the antipsychotic response.

Nevertheless, currently available antipsychotics are not ideal since even atypical drugs, which show benefits in terms of EPS, have an increased risk of weight gain and metabolic disturbances. Additional progress is thus still needed and the search for other pharmacological strategies to treat schizophrenia continues. New treatment approaches to tackle schizophrenia could aim at more directly interrupting the pathophysiological mechanism leading to psychosis rather than just blocking its downstream effect. Indeed, whilst most current antipsychotics are D_2 blockers, no conclusive D_2 abnormalities have yet been identified in schizophrenia and converging evidence indicates that the definitive abnormality contributing to abnormally high DA functioning largely resides presynaptically. Rather than just blocking the downstream effects of inappropriately released DA, new therapeutic strategies

could be directed on upstream factors that control the presynaptic release of DA. One such strategy is currently focused on the use of a glutamate receptor agonist and has provided promising results in patients (Patil et al. 2007), and may thus offer a future alternative to complement or replace the use of D_2 blockers. The pathophysiological mechanisms underpinning a presynaptic DAergic hyperfunction in schizophrenia are however still poorly understood, which limits the rational development of new therapeutics. A better elucidation of those mechanisms will be the challenge of future research on schizophrenia and may provide a rational basis for new pharmacotherapies. The next decade of research will tell whether the DA system has delivered all it can for the treatment of schizophrenia—or whether there are further opportunities to harness it for the benefit of our patients.

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Dopamine Receptor Signaling and Current and Future Antipsychotic Drugs

Kevin N. Boyd and Richard B. Mailman

Contents

Abstract All currently efficacious antipsychotic drugs have as part of their mechanism the ability to attenuate some or all of the signaling through the dopamine D_2 receptor. More recently, the dopamine D_1 receptor has been hypothesized to be a promising target for the treatment of negative and/or cognitive aspects of schizophrenia that are not improved by current antipsychotics. Although cAMP has been presumed to be the primary messenger for signaling through the dopamine receptors, the last decade has unveiled a complexity that has provided exciting avenues for the future discovery of antipsychotic drugs (APDs). We review the signaling mechanisms of currently approved APDs at dopamine D_2 receptors, and note that aripiprazole is a

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compound that is clearly differentiated from other approved drugs. Although aripiprazole has been postulated to cause dopamine stabilization due to its partial D_2 agonist properties, a body of literature suggests that an alternative mechanism, functional selectivity, is of primary importance. Finally, we review the signaling at dopamine D_1 receptors, and the idea that drugs that activate D_1 receptors may have use as APDs for improving negative and cognitive symptoms. We address the current state of drug discovery in the D_1 area and its relationship to novel signaling mechanisms. Our conclusion is that although the first APD targeting dopamine receptors was discovered more than a half-century ago, recent research advances offer the possibility that novel and/or improved drugs will emerge in the next decade.

Keywords Dopamine • Schizophrenia • Antipsychotic drug • Functional selectivity • Drug discovery

1 Introduction

Dopamine plays a role in numerous biological processes, making it unsurprising that many drugs target dopamine receptors. Although dopamine neurons are relatively scarce in the brain, their importance is highlighted by the number of normal brain processes (e.g., memory, motor behavior, and reward) and diseases that are modulated by dopamine receptor signaling. For example, the loss of dopamine neurons in the substantia nigra results in Parkinson's disease, whereas hyperactive dopaminergic signaling is believed to be a major factor in the positive symptoms of schizophrenia. Since the serendipitous discovery of the antipsychotic drug (APD) chlorpromazine over 50 years ago, many advances have been made in the understanding of dopamine structure and signaling. After 50 years of schizophrenia drug development, however, the efficacy of APDs has not significantly improved, although therapeutic indices are somewhat better because of a reduction in many side effects. Although positive symptoms of schizophrenia can be treated effectively by current drugs, negative symptoms and cognitive defects are much less responsive to current drugs. Thus, there is clearly a need for novel therapies. Drugs that activate D_1-mediated signaling pathways may alleviate the negative symptoms and cognitive deficits and decrease some of the side effects of current APDs. Because the mechanisms of many APDs are not completely understood, understanding how different dopamine signaling pathways play a role in the actions of APDs will be one critical direction for the design of novel treatments. This review will provide an overview of the current state of research in these areas.

1.1 Background on Dopamine Receptors

Dopamine receptors are members of the G protein-coupled receptor (GPCR) superfamily. There are five dopamine receptor genes that produce six distinct

dopamine receptors in humans. Dopamine receptors were initially divided into two pharmacological families based on their ligand recognition properties and their effects on cAMP production: the D_1-like receptors and the D_2-like receptors (Garau et al. 1978; Kebabian and Calne 1979). The D_1-like receptors consist of the D_1 and D_5 dopamine subtypes, whereas the D_2-like receptors include two major splice variants of the D_2 receptor [D_{2L} (long), and D_{2S} (short)] plus the D_3 and D_4 receptors. There are also splice variants for the D_3 (Giros et al. 1989; Sokoloff et al. 1990) and D_4 (O'Malley et al. 1992; van Tol et al. 1991) receptors, but the effects of these variants on behavioral phenotypes have been controversial (Jönsson et al. 2001, 2002; Kotler et al. 2000; Mill et al. 2001; Schmidt et al. 2001; Swanson et al. 1998). No splice variants exist for the D_1-like receptors because their genes are intron-less. The D_1-like receptors activate $G\alpha_{s/olf}$ and stimulate cAMP production, whereas the D_2-like receptors activate $G\alpha_{i/o}$ to inhibit adenylate cyclase activity and cAMP production. There are also differences in the localization of the dopamine receptors. The D_1-like receptors are predominately found postsynaptically (Levey et al. 1993), whereas the D_2-like receptors are found postsynaptically on dopaminergic target neurons (Levey et al. 1993; Sesack et al. 1994) and as presynaptic and autoreceptors on dopamine neurons (L'hirondel et al. 1998; Mercuri et al. 1997). Although several subtypes of dopamine receptors may co-localize on some cells (Surmeier et al. 1996), the receptors are often largely segregated (Gerfen et al. 1990; Le Moine and Bloch 1995).

There are three major brain dopamine pathways that are involved in brain actions: the nigrostriatal (from cells in the A9 region), the mesolimbic–cortical (from cells in the A10 or ventral tegmentum), and the tuberoinfundibular (hypothalamic) system (Ungerstedt 1971). In addition, peripheral dopamine neurons are involved in important physiological functions, such as renal and cardiovascular functions and immune regulation. Given that dopamine is involved in both central nervous system (CNS) and peripheral functions, it is not surprising that alterations in dopaminergic signaling are related to numerous diseases and disorders, such as Parkinson's disease, schizophrenia, depression, dyskinesias, and hypertension.

1.2 Dopamine Receptors and Antipsychotic Drug Action

Dopaminergic signaling is critical for a variety of functions, and abnormal dopaminergic signaling is involved in a variety of CNS disorders. Early studies demonstrated that dopamine and its receptors play a role in the therapy or etiology of psychiatric and neurological disorders (Carlsson 1964; Carlsson and Lindqvist 1963; Carlsson et al. 1957; Creese et al. 1976; Ehringer and Hornykiewicz 1960). For motor function, the localization of dopamine receptors in the two principal striatal outflow pathways was shown to affect their role in neurological diseases (Albin et al. 1989; DeLong 1990; Gerfen 2000a, b; Graybiel 1990; Robertson et al. 1992; Starr 1995). D_1 receptors are expressed on striatal GABAergic medium spiny neurons (MSNs) that project to the medial globus pallidus and the substantia nigra pars reticulata (i.e., the direct nigrostriatal pathway), whereas D_2 receptors are expressed on MSNs that project to the lateral globus pallidus (i.e., the indirect pathway).

In schizophrenia, antidopaminergic drugs have been used clinically for more than 50 years, yet many mechanisms of dopaminergic drug actions remain unknown. The classical dopamine hypothesis postulated that the positive symptoms of schizophrenia were a response to hyperactive dopaminergic signaling, a hypothesis that was supported by the ability of APDs to block D_2 receptors and the psychotic effects induced by dopaminergic drugs (Carlsson and Lindqvist 1963; Creese et al. 1976; Seeman et al. 1975; Seeman and Lee 1975). Based on these early data, much of the effort in APD development has been focused on antagonizing D_2 receptors. Although D_1 and D_2 receptors are generally not found on the same neurons, the activation of D_1 receptors can enhance the stereotyped and motor D_2-mediated behavioral responses (LaHoste et al. 2000; Mailman et al. 1984; Martin-Iverson and Yamada 1992; White et al. 1988). In addition, both D_1 and D_2 receptors are involved in learning and memory (Goldman-Rakic et al. 2004). Dopamine D_1 and D_2 receptors signal through $G\alpha$ subunits with opposing effects; however, they often signal through the same $\beta\gamma$ subunits, suggesting that $\beta\gamma$ signaling may mediate some of the interactions between these receptors. The interactions between D_1 and D_2 receptors may play an important role in schizophrenia and the design of novel APDs to treat all of the symptoms of schizophrenia. Selective D_1 receptor antagonists have not shown efficacy in treating schizophrenia and may actually exacerbate extrapyramidal side effects and tardive dyskinesia (Den Boer et al. 1995; Karle et al. 1995; Karlsson et al. 1995). Conversely, all currently approved antipsychotics have actions at dopamine D_2 receptors, suggesting that this action is an important, if not obligatory, aspect of efficacy against positive symptoms (Miyamoto 2000). As discussed below, the combination of a D_1 agonist and D_2 antagonist/functionally selective drug may be one route to next generation therapy.

1.3 Dopamine Receptors and Functional Selectivity

The first evidence for a biochemical mechanism of dopamine systems was the observation that dopamine could dose-dependently stimulate the synthesis of the second messenger cAMP (Kebabian et al. 1972), and this activation of cAMP was antagonized by APDs (Clement-Cormier et al. 1974) in proportion to the clinical potency of the drugs (Clement-Cormier et al. 1974; Iversen 1975). For many years, the primary focus of drug discovery efforts was on the regional and cellular localization of different dopamine receptors and how subtype-selective drugs might be useful in schizophrenia and other CNS disorders. The common assumption was that drug effects on dopamine receptor-mediated cAMP signaling would be predictive of clinical action (see reviews, e.g., Beaulieu and Gainetdinov 2011; Huang et al. 2001; Mailman 2007). Thus, the development of novel APDs focused on several areas: (1) non-dopamine receptor targets; (2) dopamine isoform-selective antagonists; (3) multitargeted ligands (“magic shotguns”); and/or

(4) selective presynaptic dopamine agonists (Roth et al. 2004). A drug that worked via any of these mechanisms usually would be assessed preclinically by its biochemical actions on receptor-mediated cAMP synthesis. The accepted concept in all such discovery research was that a drug would have a property called "intrinsic efficacy" that could be assessed by its action at *any* signaling pathway of the targeted receptor. Thus, classical pharmacology posited that a ligand either acts as an agonist, partial agonist, antagonist, or inverse agonist (i.e., its intrinsic efficacy); and a drug would always cause the same type of functional change, although this change could be affected quantitatively by factors such as receptor reserve and strength of signaling.

Although dopamine receptors were originally classified based on their effects on cAMP synthesis, it became clear that signaling through modulation of adenylate cyclases is only a fraction of how dopamine receptors modulate cellular function. Many recent reviews have covered the signaling mechanisms of dopamine receptors (Beaulieu and Gainetdinov 2011; Mailman and Huang 2007; Neve et al. 2004). Dopamine receptor signaling is now widely appreciated to be more complex than simply changes in cAMP levels. Recent studies have shown that dopamine receptors may even signal through G protein-independent pathways such as those involving β-arrestin (Beaulieu et al. 2007a). With this awareness of the complexity of mechanisms of signaling, there is also mounting evidence that some drugs can cause markedly different responses at the signaling cascades mediated by a single receptor isoform. This remarkable departure from classical pharmacological dogma has been referred to by many names, but the most commonly used term is "functional selectivity" (Urban et al. 2007a).

The term "functional selectivity" was used first to describe findings with the APD aripiprazole (Lawler et al. 1994) and with experimental dopamine agonists (Mailman et al. 1998). Essentially, functional selectivity means that a drug may have different actions at different signaling pathways mediated by the same receptor (e.g., a ligand could be an agonist at one pathway and an antagonist at another), and these differences are not explicable by classical concepts, such as receptor reserve or strength of signaling. A consequence of this idea is that assigning a specific type of intrinsic efficacy (*vide supra*, a constant inherent property of a drug) to a drug may not be valid. Thus, drugs that are functionally selective will have different *intrinsic activity* (agonist, partial agonist, antagonist, or inverse agonist) in two or more different assay systems after accounting for factors such as receptor reserve. This fact places particular importance on the milieu in which a drug is characterized (e.g., the cell or tissue being studied, the signaling pathway being assessed, and/or the degree of receptor expression). We recently provided an overview of the molecular mechanisms that may influence the functional selectivity of a variety of GPCRs (Urban et al. 2007a); many of the mechanisms are relevant to dopamine receptors.

Upon reflection, it should not be surprising that functional selectivity exists. GPCRs can couple with multiple G proteins and signal through G protein-independent mechanisms, such as β-arrestins. Moreover, the presence of various kinases, phosphatases, and other signaling molecules [e.g., G protein-coupled receptor

kinases (GRKs) and regulators of G protein signaling (RGS) proteins] is dependent on cellular localization and can influence dopamine signaling. For example, RGS proteins can affect ligand actions and signaling by negatively modulating G protein signaling, and RGS proteins may be particularly important for D_2 signaling because they enhance GTP hydrolysis through $G\alpha_{i/o}$ but not $G\alpha_s$. As if the signaling mechanisms are not already complicated enough, dopamine receptors and other GPCRs can form homodimers as well as heterodimers with receptors from other superfamilies, and these receptor complexes may result in significant pharmacological changes. For functional considerations, we must consider the interaction of drugs with receptor-based signaling complexes, sometimes called the "signalsome" (Mercurio et al. 1997; Wang and Malbon 2011), rather than the receptor alone (Urban et al. 2007a) because different ligands induce or stabilize different receptor conformational states that influence which signaling pathways are activated by the receptor. Understanding the signaling molecules that are important for specific functions will be critical for the development of functionally selective drugs.

Rather than simply targeting specific receptor isoforms, taking advantage of the functionally selective nature of novel ligands could, in theory, allow for greater control over the effects of drugs. For example, drugs could be designed that selectively activate the signaling pathways that are responsible for the therapeutic effects of a drug without stimulating pathways that are involved in side effects. With the exciting possibilities of functionally selective ligands, however, comes a greater importance for understanding receptor structure, dynamics, and signal transduction. Using APDs as an example, understanding all of the signaling mechanisms of clinically used APDs and the signaling pathways responsible for drug effects and disease manifestation will provide invaluable knowledge for the development of novel therapeutics.

1.4 Allosteric Targeting of Dopamine Receptors

Recently, the idea of allosteric ligands for GPCRs has been an important arena of investigation because of the potential of allosteric ligands to have actions (Conn et al. 2009; Jakubik et al. 1996). Although no allosteric ligands have been conclusively demonstrated for dopamine receptors, this is likely to become important in the future. The conservation in the ligand-binding domains of the dopamine receptor family sometimes has created difficulties in discovering ligands with adequate pharmacological selectivity (e.g., D_1 vs. D_5). This problem could be overcome if less conserved aspects of the receptor could be targeted. Second, allosteric ligands can theoretically have actions far more diverse than orthosteric ligands. Indeed, allosteric ligands could cause conformational changes that directly activate the receptor (allosteric agonist) or conformational changes that block the actions of orthosteric ligands (allosteric antagonist). In addition to these direct actions on receptor function, allosteric ligands could have modulatory functions via interactions with orthosteric ligands, either synergizing (positive allosteric modulation) or attenuating (negative allosteric modulation) the actions of the endogenous

ligand. In theory, allosteric ligands offer the potential for fine-tuning cellular signaling, especially in situations where the discovery of orthosteric ligands has been unsuccessful, and there are now examples that allosteric targeting can lead to an approved drug for a GPCR (e.g., cinacalcet; Block et al. 2004). These possibilities may be useful for both D_1 and D_2 receptors as it relates to aspects of the treatment of schizophrenia. As noted earlier, no allosteric ligand has yet been identified for any of the dopamine receptors that is a clear allosteric ligand, but there has been some suggestion that this may be possible (Agnati et al. 2006; Huber et al. 2012).

2 D_2-Like Signaling

A major mediator of D_2-like signaling (i.e., D_2, D_3, and D_4 receptors) is the $G\alpha_{i/o}$ class of G proteins, which are inactivated by pertussis toxin-catalyzed ADP-ribosylation (Bokoch et al. 1983; Kurose et al. 1983). The $G\alpha_{i/o}$ class of G proteins inhibits adenylate cyclase and cAMP accumulation (De Camilli et al. 1979; Stoof and Kebabian 1981). Interestingly, studies have shown that D_2-like inhibition of adenylate cyclase can lead to presynaptic/autoreceptor decreases in tyrosine hydroxylase activity and decreased firing of nigrostriatal dopamine neurons. The two isoforms of D_2 receptors [i.e., D_{2Long} (D_{2L}) and D_{2Short} (D_{2S})] appear to activate multiple $G\alpha_{i/o}$ subtypes, but the $G\alpha_o$ subtype is the subtype that is most robustly activated by both D_{2L} and D_{2S} (Jiang et al. 2001). Both D_2 and D_4 receptors inhibit adenylate cyclase in most clonal and in situ cells (Huff 1997; Oak et al. 2000); however, inhibition of adenylate cyclase by D_3 receptors is usually undetectable without molecular manipulation. Interestingly, D_3 dopamine receptors tend to bind agonists with higher affinity than the other D_2-like receptors. In addition, D_3 dopamine receptors bind agonists in a GTP-insensitive manner (Sokoloff et al. 1992), which has been hypothesized to be because of a receptor conformation with high affinity for agonists regardless of interactions with G proteins (Vanhauwe et al. 2000).

Although D_2 receptors are a target of all APDs, differences in the therapeutic profiles of APDs are influenced by interactions with other receptors and differential activation of D_2-mediated signaling pathways. In addition to D_2-like receptor signaling through adenylate cyclase, D_2-like receptors modulate many other signaling pathways, including phospholipases, ion channels, mitogen activated protein (MAP) kinases, and the Na^+/H^+ exchanger (Huff et al. 1998). Moreover, the dissociation of $G\beta\gamma$ subunits following D_2 receptor activation has significant effects on K^+ currents, and D_2 receptor-mediated increases in K^+ currents decrease cell excitability. D_2-like receptors activate a G protein-regulated inwardly rectifying potassium channel (GIRK or Kir3), which modulates several potassium currents in various tissues (Greif et al. 1995; Lacey et al. 1987; Liu et al. 1994; Oxford and Wagoner 1989). In addition, dopamine release-regulating autoreceptors are coupled to potassium channels (Cass and Zahniser 1991) rather than inhibition of adenylate

cyclase (Memo et al. 1986), and there is robust regulation of GIRK currents by D_2 receptors in substantia nigra dopamine neurons (Davila et al. 2003).

D_2-like receptors can also regulate Na^+ channels and L, N, and P/Q-type Ca^{2+} channels, and the regulation of these ion channels may involve Gβγ actions (Kuzhikandathil and Oxford 1999; Lledo et al. 1992; Okada et al. 2003; Seabrook et al. 1994a, b; Surmeier and Kitai 1993; Yan et al. 1997; Zamponi and Snutch 1998). Interestingly, D_2-like receptor stimulation can either increase or decrease Na^+ currents depending on the subtype of D_2-like receptors that are expressed by a given cell (Surmeier et al. 1992; Surmeier and Kitai 1993). In most D_2 agonist-responsive neurons, however, D_2-like receptor stimulation decreases Na^+ currents. In addition, D_2-like receptor signaling tends to inhibit Ca^{2+} channel activity. Moreover, D_2-like receptor signaling can regulate neurotransmitter release via N-type Ca^{2+} channels (Dunlap et al. 1995; Koga and Momiyama 2000; Svensson et al. 2003). Agonist effects at heterologously expressed D_2, D_3, or D_4 receptors can also activate the widely expressed Na^+/H^+ exchanger NHE1 (Neve et al. 2004).

D_2 receptor activation has also been shown to stimulate MAP kinases, including the two isozymes of extracellular signal-regulated kinase (ERK) (Choi et al. 1999; Ghahremani et al. 2000; Huff 1996; Kim et al. 2004; Luo et al. 1998; Oak et al. 2001; Voyno-Yasenetskaya et al. 1994; Welsh et al. 1998) and stress-activated protein kinase/Jun amino terminal kinase (SAPK/JNK) (Luo et al. 1998). In addition, D_2 and D_4 receptors can potentiate arachidonic acid release induced by calcium-mobilizing receptors both directly and through cytosolic phospholipase A2 (Chio et al. 1994; Kanterman et al. 1991; Piomelli et al. 1991; Vial and Piomelli 1995). Arachidonic acid and its lipoxygenase and cyclooxygenase metabolites have numerous effects on cellular function, including feedback regulation of D_2-like signaling and dopamine transport (DiMarzo and Piomelli 1992; L'hirondel et al. 1995; Piomelli and Greengard 1990; Zhang and Reith 1996). Interestingly, D_2 receptors can also stimulate phospholipase D, which catalyzes the hydrolysis of phosphatidylcholine to form choline and phosphatidic acid (Mitchell et al. 1998; Senogles 2000).

Dopamine D_2 receptor activation can also result in G protein-independent signaling, such as direct interactions with ion channels (e.g., NMDA) and signaling through GRKs and arrestins. Importantly, the GRK/arrestin pathway can both suppress G protein signaling and promote G protein-independent signaling. Although differential effects can occur based on the cellular expression of GRKs and arrestins, most evidence of G protein-independent signaling relates to the role of β-arrestin 2. β-Arrestin 2 is a key member of the GPCR desensitization machinery that is involved in dopamine signaling through protein kinase B (Akt) and glycogen synthase kinase 3 (GSK3) (Beaulieu et al. 2008, 2007b). Indeed, GRK phosphorylation of dopamine receptors leads to the recruitment and binding of β-arrestins, which prevents G protein-dependent signaling even if an agonist is still present. The majority of the evidence is based on studies using a variety of genetically altered mice that were deficient in major constituents of GPCR signaling, including GRKs, β-arrestins, dopamine transporter (DAT), and Akt.

Mechanistically, the time course of β-arrestin/Akt signaling at the D_2 receptor takes much longer to develop (hours vs. minutes) compared with the G protein-mediated cAMP/PKA response (Beaulieu et al. 2004, 2005, 2007b). Thus, drugs that alter D_2 receptor signaling (e.g., APDs) may result in opposing responses following drug administration. For example, the initial response would be a rapid G protein (i.e., cAMP)-mediated response that could be desensitized, whereas delayed responses (e.g., β-arrestin mediated) might last for a longer period of time and may not be able to be desensitized. The slow response of the β-arrestin/Akt pathway may be indicative of its downstream effects on gene transcription, which can alter target protein transcriptional profiles and chromatin remodeling (Alimohamad et al. 2005; Beaulieu and Caron 2005; Kang et al. 2005; Li et al. 2007). Although it is tempting to speculate that the β-arrestin/Akt pathway is the one primarily involved in clinical response to APDs, it is unlikely that the answer will be so simple.

2.1 Evidence for Functional Selectivity at D_2-Like Receptors

2.1.1 Hypothesized Presynaptic/Autoreceptor Selective Ligands and Functional Selectivity

Dopamine D_2 receptors have been studied as a drug target for more than 50 years, and D_2 ligands have been used for schizophrenia, Parkinson's disease, and a variety of other psychiatric and neurological conditions. One of the major driving forces for the search for D_2 drugs was the "dopamine hypothesis of schizophrenia," which posits that excess dopamine release and/or excess sensitivity of dopamine-receptive neurons was the cause of what are now called positive symptoms. Interestingly, this hypothesis is highly relevant to the discovery and validation of the functional selectivity of dopamine receptor ligands. The classical APDs were D_2 antagonists, and antagonism of D_2 receptors has been accepted as a way of controlling the positive symptoms of schizophrenia (Creese et al. 1976). Interestingly, activation of dopamine autoreceptors, which are primarily D_2 receptors and some D_3 receptors, causes a decrease in both the synthesis and the release of dopamine and a decrease in the firing of dopamine neurons. Interestingly, both dopamine and D_2 agonists tend to have higher potency at the effects mediated by the autoreceptors compared with the postsynaptic D_2 functions (Feenstra et al. 1983). These important findings explain why the behavioral response to a full D_2 agonist is typically biphasic with respect to dose: the inhibition seen at low doses is the result of autoreceptor stimulation, and the stimulation at higher doses is the result of direct postsynaptic activation. One of the major mechanisms explaining this biphasic effect is greater presynaptic D_2-like receptor reserve (Meller et al. 1987).

Pharmacological theory suggests that high receptor reserve in the D_2 presynaptic receptors would make partial agonists much more efficacious (Kenakin 1997); thus, researchers suggested the use of D_2 partial agonists as APDs. Data from in vitro and

animal studies suggested that the partial agonist (−)3-PPP (preclamol) might be an excellent candidate. Because studies had shown that low doses of agonists selectively activate D_2 autoreceptors and activation of D_2 autoreceptors inhibits dopamine release and postsynaptic activation, another treatment strategy was to use a low dose of a full agonist. Although both mechanisms have a good theoretical basis, the early clinical data were disappointing (Corsini et al. 1981; Lahti et al. 1998; Smith et al. 1977; Tamminga et al. 1978, 1986, 1992). In retrospect, this disappointment was probably not unexpected because of issues in achieving the "right" presynaptic relative receptor occupancy without temporal fluctuations or finding a partial agonist with just the "right" intrinsic activity. Nevertheless, the "partial agonist hypothesis" was revived when aripiprazole was shown to have clinical efficacy. The difference between aripiprazole and several earlier drugs, however, is that aripiprazole is a functionally selective drug.

2.1.2 Early Evidence for the Functional Selectivity of Dopaminergic Compounds

To the best of our knowledge, the first clear example of dopamine receptor functional selectivity resulted from serendipitous findings with dihydrexidine (DHX). Dihydrexidine was designed to be a selective D_1 agonist, but studies showed that it also had D_2 affinity (Brewster et al. 1990; Mottola et al. 1992). An examination of the functional characteristics of DHX and a more D_2-selective analog (*N*-*n*-propyldihydrexidine; PrDHX) showed that both compounds competed for D_2 receptors in heterologous systems and in brain tissue with shallow, guanine-nucleotide-sensitive curves that were similar to typical agonists (Kilts et al. 2002; Mottola et al. 1992, 2002). We also examined the functional effects of these compounds in many in vitro systems, and both compounds had full intrinsic activity at inhibiting adenylate cyclase activity, which could be blocked by D_2 antagonists (Kilts et al. 2002; Mottola et al. 2002). The compounds also inhibited prolactin secretion in vivo. Although the functional studies predicted that both DHX and PrDHX were full agonists, neither ligand activated D_2-like presynaptic autoreceptors, which mediate inhibition of dopamine neuron firing, dopamine release, and dopamine synthesis (Kilts et al. 2002; Mottola et al. 2002). In addition, in vivo experiments showed that DHX was an antagonist of the physiological actions of the potent D_2 agonist apomorphine (Mottola et al. 2002). Although the in vitro functional characterization suggested that DHX had both D_1 and D_2 agonist properties, its behavioral effects were different from apomorphine or amphetamine. Interestingly, the behavioral effects of DHX appeared to be primarily D_1-like, even at very high doses (Darney et al. 1991).

These early in vitro/in situ data suggested that DHX and PrDHX had high intrinsic activity at postsynaptic D_2-like receptors but low intrinsic activity at presynaptic receptors (Mottola et al. 1991). Off-site actions were largely excluded by both receptor screening and competitive pharmacological studies (Mottola et al. 1992).

Although a D_4 contribution could be ruled out based on localization, it was possible that DHX and PrDHX were agonists at one dopamine receptor isoform (e.g., D_{2L}) but antagonists at another (e.g., D_{2S} or D_3). Interestingly, studies showed that DHX and PrDHX were agonists at D_{2L} receptors for the cAMP pathway, whereas they were antagonists at presynaptic autoreceptor functions. Taken together, these studies led to the hypothesis that DHX and PrDHX were D_2 functionally selective (Mottola et al. 1991).

Following the discovery and initial characterization of DHX, its functional selectivity was demonstrated in several model systems. For example, DHX was a full agonist at inhibiting adenylate cyclase in pituitary lactotrophs, and this activity was blocked by D_2 antagonists but not by D_1 antagonists. In addition, DHX had little intrinsic activity at D_2 receptors coupled to GIRK and was an antagonist at D_2 autoreceptors (Mottola et al. 2002). One advantage of the lactotrophs was that they only express products of the D_2 gene (DRD2; Bouthenet et al. 1991). We also examined the effects of DHX and PrDHX in mesencephalic-derived MN9D cells, where the transfection of the D_{2L} receptor has been shown to cause inhibition of adenylate cyclase and inhibition of dopamine release that is similar to dopamine neurons (O'Hara et al. 1996; Tang et al. 1994). Neither DHX nor PrDHX had effects in untransfected MN9D cells, but after D_{2L} transfection, both compounds (as well as the reference D_2 agonist quinpirole) were full agonists at inhibition of adenylate cyclase activity. Importantly, these agonist effects were blocked by D_2, but not D_1, antagonists. Although quinpirole caused a concentration-dependent, reversible depolarization-induced release of dopamine, neither DHX nor PrDHX inhibited dopamine release. Moreover, PrDHX actually antagonized the effects of quinpirole (Kilts et al. 2002). Taken together, these studies convinced us that functional selectivity was real.

The concept of functional selectivity was initially met with resistance because classical pharmacological theory did not allow for a molecule to be both a full agonist and pure antagonist at the same receptor (i.e., not having consistent intrinsic efficacy) (Stephenson 1956); however, studies had shown that GPCRs could have effects via different signaling partners (Kenakin 1990). Although the common theoretical conceptualization of receptors was that they existed in the form of discrete active states (De Lean et al. 1980; Leff et al. 1997), our conceptualization was of a dynamic system in which ligands could induce an essentially limitless number of conformational states of a target receptor, which could cause markedly different effects on receptor signaling partners (Mailman and Gay 2004; Mailman et al. 1997). Indeed, functional selectivity has sometimes been explained as the stabilization of novel discrete active states of a receptor. Our concept was that functionally selective ligands induce unique conformational states of a receptor that are distinct from those caused either by the endogenous ligand or by antagonists. In a sense, binding of the ligand provides the driving force needed for the receptor to assume conformations that would otherwise not be energetically favorable. Understanding the molecular mechanisms that mediate functional selectivity and the impacts on drug action in vivo are critical.

2.1.3 Functional Selectivity In Vitro Affects Pharmacological Effects In Vivo

Because the concept of functional selectivity was met initially with such resistance, studies demonstrating the relevance of functional selectivity to drug actions in vivo were necessary. Studies with dihydrexidine did not show the typical behavioral actions of a D_1/D_2 agonist (Darney et al. 1991), but this may be because the D_1 selectivity masked the D_2 effects. To avoid this issue, studies also examined PrDHX, which is much more D_2/D_1-selective (similar to apomorphine). Importantly, PrDHX showed full intrinsic activity at D_2-mediated inhibition of adenylate cyclase. Although classic pharmacology would have predicted that a compound with full intrinsic activity at D_2-mediated adenylate cyclase would have behavioral effects similar to apomorphine or the prototypical D_2 agonist quinpirole (i.e., locomotor inhibition at low doses and locomotor stimulation at higher doses) (Eden et al. 1991), PrDHX caused only modest locomotor inhibition across a wide range of doses, and there were no competing behaviors that might have interfered with locomotion (Smith et al. 1997). This finding provided the first evidence that functionally selective compounds would have novel pharmacological actions. The potential impact of a functionally selective ligand is illustrated in Fig. 1. In theory, a ligand should be able to discriminate between canonical functions mediated by different G protein heterotrimers and differentially affect long-term drug responses.

2.1.4 D_2 Functionally Selective Drugs and Schizophrenia

Chlorpromazine was discovered serendipitously approximately 60 years ago (Delay et al. 1952), and scientists soon realized that the antipsychotic effects were due to antidopaminergic actions (Carlsson and Lindqvist 1963), which were later shown to result from blockade of D_2 dopamine receptors (Creese et al. 1976). Although non-dopaminergic drugs are being tested, all current APDs have some degree of D_2 antagonism as part of their pharmacological profile. Classical APDs, however, elicit numerous side effects, and researchers are constantly searching for improved APDs. One of the novel hypotheses of interest to the field was that drugs with dopamine agonist properties might decrease dopamine neurotransmission and have dopamine antagonist-like effects (Tamminga and Carlsson 2002). Indeed, a high-affinity partial dopamine agonist that activated presynaptic D_2 autoreceptors and had low intrinsic activity at postsynaptic D_2 receptors could reduce dopamine neurotransmission. One of the most recently approved APDs, aripiprazole, was touted as the first high-affinity, low intrinsic activity partial D_2 agonist. Although the compound has effects on several other receptors, many of the leading researchers/clinicians in schizophrenia biology have taken to calling aripiprazole the first “dopamine stabilizer” because of its D_2 partial agonist properties (Lieberman 2004; Stahl 2001; Tamminga 2002). It should be noted that aripiprazole does not fit the characteristics of a selective presynaptic D_2-like agonist as was originally proposed (*vide supra*).

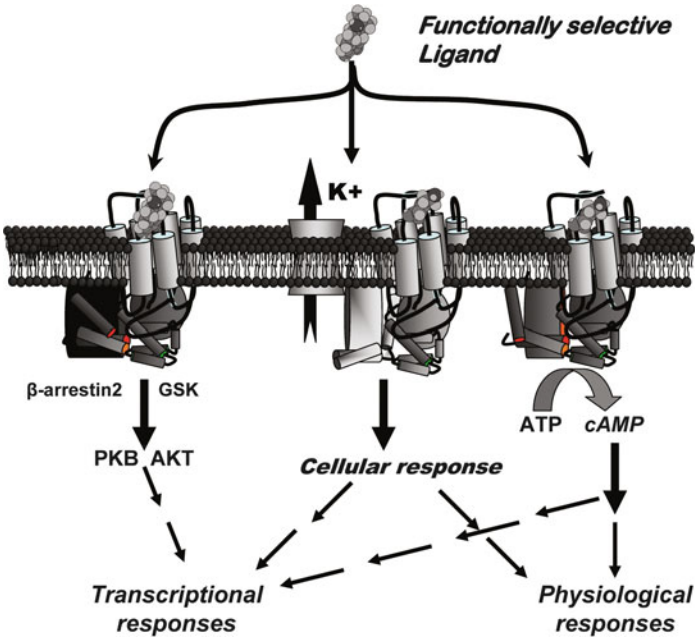

Fig. 1 The implications of functional selectivity at the dopamine D_2 receptor are illustrated in this *cartoon*. Functionally selective drugs, unlike dopamine, might differentially affect both canonical and noncanonical signaling pathways. This could result in differential acute effects, which is illustrated by the *center* and *right-hand* aspects of the figure. For example, a ligand would cause differential effects on mediators of acute action (e.g., the dopamine-induced hyperpolarization of a cell mediated via inward-rectifying potassium channels and acute actions of cAMP) as well as the longer term effects of drugs. Thus, changes in transcription initiated by cAMP on mechanisms like CREB could be altered by some drugs in a different manner than receptor-initiated changes in transcription initiated by β-arrestin2/Akt

The idea of a partial agonist is intriguing because all partial agonists are also partial antagonists. The positive symptoms of schizophrenia are mediated by excess dopaminergic transmission in mesolimbic areas, and the partial agonist properties of aripiprazole compete with dopamine and cause partial antagonism, which provides clinical benefit. Conversely, in situations where extracellular dopamine concentrations are low (e.g., in dopamine circuits involved in working memory), partial agonists (e.g., aripiprazole) can occupy additional receptors and cause partial activation. Although aripiprazole looks like a low-to-moderate intrinsic activity partial agonist in many model systems (Burris et al. 2002; Lawler et al. 1999; Shapiro et al. 2003), other available data suggest that aripiprazole is a functionally selective D_2 ligand rather than a simple partial agonist. For example, the intrinsic activity and potency of aripiprazole for the D_2-mediated inhibition of cAMP accumulation is dependent on the cell line being studied: the drug demonstrates weak partial agonist activity in the CHO-D_{2L} cell line but strong partial agonist activity in HEK-D_{2L} cells (Burris et al. 2002; Lawler et al. 1999;

Shapiro et al. 2003). Moreover, aripiprazole has been shown to have markedly different potencies at two D_{2L}-mediated functions within the same cell line (Urban et al. 2007b). Furthermore, aripiprazole completely antagonizes both D_2 agonist-mediated GTPγS binding and GIRK channel activity in some cell systems (Shapiro et al. 2003), whereas it is a full agonist in situ for D_2-mediated inhibition of tyrosine hydroxylase (Kikuchi et al. 1995).

The wide array of D_2-mediated intrinsic activities and/or potencies observed for aripiprazole in different systems cannot be explained by classic pharmacology and suggests that aripiprazole is functionally selective (Urban et al. 2007a). These in vitro findings can also be correlated with the actions of aripiprazole in vivo, which are irreconcilable with the partial agonist hypothesis. One of the clearest examples is the effect of aripiprazole in the unilaterally lesioned 6-hydroxydopamine (6-OHDA)-treated rat. Both full and partial dopamine agonists cause the 6-OHDA-lesioned rats to turn with high frequency in a tight contralateral fashion. The robust rotation in this model is a result of relative receptor/cellular hypersensitivity of the target receptors on the lesioned, dopamine-depleted side. As a partial agonist, aripiprazole should also cause contralateral rotation; however, this effect was not observed (Kikuchi et al. 1995). Another less direct example relates to Parkinson's disease (PD). Many PD patients develop psychotic side effects as a result of their use of levodopa and/or dopamine agonists (the latter largely working via D_2 receptors). Similar to the reasoning espoused for schizophrenia, aripiprazole (as a partial agonist) should be very useful in treating these psychotic symptoms when added to the dopaminergic regimen of a PD patient; however, aripiprazole not only lacks effectiveness in treating the psychoses, but also tends to worsen motor function (Friedman et al. 2006).

Although aripiprazole is a functionally selective D_2 ligand, aripiprazole also has actions at other receptors. Indeed, aripiprazole has high affinity for several receptors, including 5-HT_{1A}, and modest affinity for several others (Shapiro et al. 2003). Nonetheless, the interest in this compound revolves around its D_2 action. Because its intrinsic activity varies markedly depending on the signaling environment of the D_2 receptor (Lawler et al. 1999; Shapiro et al. 2003; Urban et al. 2007a), we believe the logical explanation to integrate the in vitro and in vivo data is functional selectivity at the D_2 receptor. If this hypothesis is true, a corollary is that compounds with similar D_2 partial agonist effects at adenylate cyclase might have very different clinical effects in treating psychoses. This latter hypothesis may be testable as other "partial agonists" (e.g., bifeprunox) are brought into clinical trials.

3 D_1-Like Signaling

D_1-like receptors couple to $G\alpha_{s/olf}$ and stimulate adenylate cyclase activity, which subsequently activates PKA and other signaling molecules. Although $G\alpha_s$ appears to mediate D_1-like receptor signaling, $G\alpha_{olf}$ also stimulates adenylate cyclase activity and is highly expressed in dopaminergic regions, such as the neostriatum, where there is little $G\alpha_s$ expression (Zhuang et al. 2000). Studies have also suggested that D_1 receptors couple to other heterotrimeric G proteins, such as

$G\alpha_o$ and $G\alpha_q$ (Jin et al. 2001; Kimura et al. 1995; Wang et al. 1995). In addition, D_1-like receptors can mediate signaling at a variety of voltage-gated ion channels as well as NMDA and $GABA_A$ receptors, either directly or indirectly, through actions on DARPP-32, the MAPK pathway, and other kinases and phosphatases. Moreover, there is evidence that dopamine receptors (and G proteins) can have other protein–protein interactions, such as receptor oligomerization or interactions with scaffolding or other regulatory proteins, which can also affect dopamine receptor signaling (Neve et al. 2004). D_1 receptor signaling can also occur through the $\beta\gamma$ subunits that form heterotrimers with $G\alpha_s$ or $G\alpha_{olf}$, but less is known about these signaling mechanisms. For example, $\beta\gamma$ subunits can play a selective role in D_1-like signaling as D_1 mediated, but not D_5 mediated, adenylate cyclase activity is attenuated by depletion of the $\gamma 7$ subunit (Wang et al. 2001). Finally, as is typical for GPCRs, ligands can induce dopamine receptor internalization (Ryman-Rasmussen et al. 2007, 2005), and a recent study demonstrated a new role of endocytosis and endocytic machinery in dopamine D_1 receptor signaling (Kotowski et al. 2011). It is too soon to know if this finding will impact the use of D_1 agonists in the treatment of negative and cognitive aspects of schizophrenia.

The signaling cascades that are activated by D_1 receptors can also have long-term effects on cellular function by regulating transcription. Indeed, D_1 agonists increase cAMP, and cAMP phosphorylates cAMP response element binding protein (CREB) at Ser133, which regulates the transcription of many genes that are important to a variety of drug responses (Andrisani 1999; Hyman et al. 1995; Minowa et al. 1996; Sands and Palmer 2008). In addition, D_1 receptor activation can affect proteins in the MAPK signaling pathway, such as ERK (Brami-Cherrier et al. 2002). Interestingly, transcriptional changes in MAPK signaling molecules may be able to improve the therapeutic profile of D_1 agonists. Developing a functionally selective drug that selectively activates signaling molecules and pathways associated with the desired effects can improve a drug's therapeutic profile. For example, D_1 agonists may have the potential to improve prefrontal cortical functions and working memory in schizophrenic patients. Indeed, SKF-81297 has been shown to improve recognition and memory by increasing the phosphorylation of CREB and DARPP32 in rat prefrontal cortex (Bateup et al. 2008; Hotte et al. 2006). Thus, developing functionally selective drugs that differentially activate aspects of CREB and DARPP32 signaling could have marked therapeutic utility.

Certain effects of novel drugs and potential D_1 ligands that have already been studied may not have been discovered because researchers may not have been examining the right pathway or using the right in vitro system to be able to observe effects. The concept of functional selectivity opens up exciting new opportunities for the development of many drugs, including APDs. Two decades ago, we found that D_1-binding sites in the amygdala were not associated with an appreciable stimulation of adenylate cyclase, which led us to hypothesize a novel species of D_1 receptor (Kilts et al. 1988; Mailman et al. 1986a, b). Molecular data over the next decade clearly demonstrated that these binding sites were actually the same D_1 receptors that are found in striatum, and the receptor activity was determined to

represent a nontraditional mechanism(s) of signaling (Leonard et al. 2003a, b). Today, functional selectivity promises to provide more exciting findings in the drug discovery and development realm, and schizophrenia is one area where a functionally selective D_1 ligand could have a tremendous impact.

3.1 Evidence for Functional Selectivity at D_1-Like Receptors

3.1.1 Possible Mechanisms of D_1-Receptor Signaling That Could Evoke Functional Selectivity

Despite promising therapeutic potential for D_1 receptor agonists, few efforts have been made to investigate functional selectivity at D_1-like receptors. In regards to schizophrenia, D_1 agonists may have therapeutic potential for negative symptoms and cognitive deficits. In addition, D_1 agonists may even reduce the side effects associated with current APDs. A clearer understanding of D_1-like signaling pathways is critical for the identification and design of functionally selective D_1 compounds. This problem is complicated, however, because the signaling pathways activated by dopamine D_1 receptors are dependent on several factors: the cellular machinery in a given cell or experimental system (e.g., G proteins, β-arrestins, and GRKs), differences in membrane dynamics (e.g., highly lipophilic neuronal cells vs. renal proximal tubular cells), and/or attenuation/potentiation of input signaling pathways (Mailman 2007; Mailman and Huang 2007; Neve et al. 2004). The most studied D_1-signaling cascade is the cAMP/PKA pathway. One signaling molecule in this pathway, DARPP32, can both inhibit and promote D_1 signaling, which provides an important mechanism for regulating dopaminergic signaling. Indeed, D_1-like receptor activation of PKA leads to a phosphorylation/dephosphorylation cycle of DARPP32 at Thr34 and Thr35, which results in inhibition of protein phosphatase 1 (PP1) (Greengard et al. 1999), whereas phosphorylation at Thr75 by Cdk5 results in DARPP32 inhibition of PKA. D_1-activated PKA can lead to the phosphorylation of other receptors in the cell (e.g., L-type Ca^{2+} channels and NMDA receptors) and inhibition of PP1, which prevents the dephosphorylation of many substrates, including the same receptors that are phosphorylated by PKA (Snyder et al. 1998). Although other pathways have been shown to be activated by D_1 receptors, many pathways are dependent on cAMP/PKA signaling.

The MAP kinase pathway, which plays important roles in growth and cell cycle control, may be a G protein-independent D_1-signaling pathway. Although few studies have investigated its role in D_1-like receptor signaling, arrestins have been shown to act as adaptor proteins for MAP kinase. For example, p-ERK has been found to form stable heterotrimeric complexes with the D_1 receptor and β-arrestin 2 (Chen et al. 2004). In addition, Nagai et al. (2007) revealed dose-dependent D_1 activation of ERK1/2 in the mouse prefrontal cortex that was blocked by a D_1 antagonist (but not a D_2 antagonist). Furthermore, β-arrestin 2 has been

suggested to play a role in D_1-mediated ERK signaling (Urs et al. 2011). The mechanism(s) responsible for D_1-MAP kinase activation is unclear, but evidence suggests a dependence on the β-arrestin scaffolding protein. In addition, D_1 effects on MAP kinases may link D_1 signaling with other neurotransmitters, such as glutamate. Studies have clearly shown that D_1 receptors activate ERK in striatal MSNs, but further studies must be carried out to gain a clearer understanding of the mechanisms that are involved.

D_1 dopamine receptors are also involved in calcium signaling. Calcium is a dynamic but tightly regulated second messenger pathway that is differentially controlled across non-nervous and nervous tissue. The slow IP_3-mediated pathway via phospholipase C predominates in non-excitable cells. In excitable cells, however, voltage-dependent Ca^{2+} channels (L, N, and P/Q type) play a greater role and balance Ca^{2+} intake/output from the cell. D_1-like receptors are positively coupled to L-type channels and negatively coupled to N and P/Q-type Ca^{2+} channels (Surmeier et al. 1995). Interestingly, studies have shown that D_1 receptors can interact directly with N-type calcium channels, and D_1 activation has been shown to inhibit N-type calcium channels (Kisilevsky et al. 2008). We previously mentioned that many D_1-mediated pathways are dependent on cAMP/PKA signaling, and this also appears to be the case for D_1-mediated inhibition of voltage-gated calcium channels (Fienberg et al. 1998). For example, D_1-stimulated L-type Ca^{2+} channels have been shown to lead to PKA-dependent potentiation and PKC-dependent suppression of currents in rat prefrontal cortical neurons (Young and Yang 2004).

3.1.2 Phospholipase C as a D_1 Signaling Mechanism

Phospholipase C (PLC) hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to produce 1,2-diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). The latter binds to the IP_3 receptor and stimulates the release of Ca^{2+} from intracellular stores within the endoplasmic reticulum. Diacylglycerol recruits protein kinase C (PKC) to the membrane, which leads to a variety of effects, including NF-κB activation and actin reorganization. Phospholipase C may be activated by both $G\alpha_q$ and $G\beta\gamma$, and all four members of the $G\alpha_{q/11}$ family (α_q, α_{11}, α_{14}, and α_{16}) have been shown to activate PLC-β isoforms (Hepler et al. 1993; Kozasa et al. 1993; Lee et al. 1992). In addition, $G\beta\gamma$ subunits can activate PLC-β, and the composition of specific $G\beta\gamma$ subunits affects the potency for PLC-$\beta\gamma$ activation (Boyer et al. 1994). Both $G\alpha_q$ and $G\beta\gamma$ play a role in PLC-β activation (either on their own or synergistically), and the finding that PLC-β has distinct sites for $G\alpha_q$ and $G\beta\gamma$ activation (Runnels and Scarlata 1999) has important consequences for functional selectivity. Moreover, if both cAMP/PKA and PLC signaling occur via D_1 receptors, then drug discovery efforts could potentially exploit specific signaling properties of ligands.

To truly test the functional selectivity of compounds, researchers must identify independent signaling pathways because signaling pathways that are dependent on

other pathways can confound the results. In addition, various in vitro systems are needed to properly test functional selectivity because the signaling machinery may be different in different cell lines (i.e., not all cell lines are appropriate for testing certain signaling pathways). For example, one study showed that D_1-linked PLC was dependent on PKA activation in LTK^- cells (Yu et al. 1996); however, the predominant PLC isoform that was believed to be involved (i.e., PLC-β2) is not expressed in LTK^- cells. The study concluded that PLC-γ was responsible for the observed activity, but different results may have been obtained if the model system contained PLC-β2. Although a recent study of D_1 effects on intracellular Ca^{2+} currents supported the idea of $G\alpha_q$-mediated PLC activation, this mechanism was found to be codependent on a cAMP/PKA signal (Dai et al. 2008). In addition, measurements of intracellular Ca^{2+} currents may be influenced by additional sources other than PLC stimulation. Indeed, similar data have been observed in other studies, and there is a strong possibility that changes in Ca^{2+} can result from a D_1-mediated non-PLC mechanism (Lin et al. 1995).

3.1.3 Implications and Complications of Purported D_1-Mediated PLC Signaling

Non-cyclase D_1-mediated signaling clearly occurs (Leonard et al. 2003a, b; Mailman et al. 1986a), and evidence for a cAMP/PKA-independent signaling pathway has been shown in studies of adenylate cyclase V-deficient mice (Iwamoto et al. 2003). Although 85–90 % of cyclase activity was abrogated in these mice, D_1-mediated locomotion was enhanced. Such findings are direct evidence for the possibility of discovering D_1 functionally selective compounds. Unlike the D_1 actions on cAMP/PKA, the importance of PLC in direct D_1 signaling is controversial. Indeed, several studies have suggested concurrent $G\alpha_{q/11}$ and $G\alpha_{s/olf}$ coupling to the D_1 receptor (Mannoury la Cour et al. 2007; Panchalingam and Undie 2000; Wang et al. 1995), and a recent report indicated differential coupling by SKF-83959 (Rashid et al. 2007b).

Our group originally (and mistakenly) hypothesized that these non-adenylate cyclase-linked effects might represent a D_1-like receptor from a different superfamily that had similar pharmacology to the known D_1-like receptors (Mailman et al. 1986a). We quickly determined that the non-adenylate cyclase effects were more likely to be generated by the same gene product utilizing different signaling machinery (Kilts et al. 1988; Leonard et al. 2003a, b). Interestingly, another group subsequently resurrected the hypothesis of a novel "D_1-like" receptor (Friedman et al. 1997; Undie et al. 1994), and those data are very relevant to the issue of D_1 functional selectivity.

The data in support of the hypothesis for a novel D_1-like receptor came from D_1 ligand activation of PLC; however, limitations in the designs of the studies that have supported this hypothesis have raised doubts about whether the signaling is really D_1 mediated. For reasons that are unclear, the concentrations of the drugs used in the published experiments have always been suprapharmacological

(10 μM or greater, orders of magnitude higher than the affinities of the compounds). Moreover, there are good correlations between the binding affinities of D_1 ligands and their potencies at activating adenylate cyclase, but these correlations were not observed between binding and PLC activation. Although functional selectivity can be expressed as large changes in potency and/or intrinsic activity (Gay et al. 2004; Mailman 2007; Mailman and Gay 2004; Urban et al. 2007a, b), the combination of a requirement for high drug concentrations and structure activity relationship discordance in studies demonstrating D_1-mediated PLC signaling may be a red flag.

To further investigate whether D_1 receptors can couple to $G\alpha_q$ and signal through PLC, similar studies to the previously published reports that showed D_1-mediated PLC signaling were repeated in D_1 knockout mice. Importantly, the D_1-mediated adenylate cyclase activity was abolished in the D_1 knockout mice (Friedman et al. 1997), but PLC activation was similar to the wild-type controls. The conclusion from this study was that this result was an evidence for a novel D_1 receptor (Friedman et al. 1997); however, an equally plausible explanation is that the PLC signaling was not D_1-mediated. In support of the latter explanation, none of the known or orphan GPCRs have been matched to this proposed new D_1-like receptor. Moreover, in D_1 knockout mice, there is a profound decrease in phenylbenzazepine-binding sites (Montague et al. 2001), which makes it highly unlikely that the pharmacological properties of benzazepines would be unaffected if this was a D_1 effect. Furthermore, the purported D_1-like $G\alpha_q$-coupled receptor does not react with a D_1 receptor antibody (Jin et al. 2001). Taken together, the evidence may favor the hypothesis that these PLC effects are mediated by a non-dopamine receptor-binding site that can be activated with low potency by one class of dopamine ligands (i.e., phenylbenzazepines) (Leonard et al. 2003a). Interestingly, a more recent study demonstrated that the PLC activity induced by benzazepines was abolished in D_5 knockout mice (Sahu et al. 2009).

In addition, several recent studies have suggested that phenylbenzazepine-based D_1 ligands may actually signal through the PLC pathway in a functionally selective fashion. For example, a functional D_1/D_2 dimer has been reported to be activated by one phenylbenzazepine (SKF-83959) but not another (SKF-83822). Interestingly, this correlates with the suggestion that SKF-83959 selectively activates D_1-linked $G\alpha_q$, whereas SKF-83822 selectively affects $G\alpha_s$ (Lee et al. 2004; Rashid et al. 2007b), and these studies support the importance of PLC/$G\alpha_q$ signaling through D_1 receptor heterodimers (e.g., with D_2) (Rashid et al. 2007a). The signaling of D_1/D_2 heterodimers has recently been reviewed (Hasbi et al. 2011), but the physiological relevance of D_1/D_2 heterodimer signaling is controversial because studies have shown that most striatal neurons do not coexpress D_1 and D_2 receptors (Valjent et al. 2009). Further studies are needed to clarify whether D_1 receptors can directly activate $G\alpha_q$ and signal through the PLC pathway. If the PLC pathway is important for D_1 signaling, then certain phenylbenzazepines (and possibly D_1 ligands of other chemical classes) may be highly functionally selective (Ryman-Rasmussen et al. 2007, 2005), and the PLC signaling pathway may provide a route to the development of novel drugs.

3.1.4 Direct Evidence for Functional Selectivity at the D_1-Like Receptors

Functional selectivity has been difficult to demonstrate for D_1-like dopamine receptors because of the lack of clear effectors coupled to the receptor. Nevertheless, one study investigated the adenylate cyclase activation and receptor internalization induced by a variety of structurally different D_1 agonists with various affinities for D_1 receptors (Ryman-Rasmussen et al. 2005). Interestingly, the Ryman-Rasmussen et al. study identified several D_1 agonists that activate adenylate cyclase with great efficacy but fail to cause receptor internalization. Importantly, internalization efficacy was found to be independent of agonist structural class and agonist affinity, suggesting that functional selectivity at D_1 receptors cannot be predicted by simple structural examination of D_1 agonists.

A subsequent study by Ryman-Rasmussen et al. (2007) compared the ability of dopamine and two structurally dissimilar agonists, A-77636 (chemically an isochroman) and dinapsoline (DNS; chemically an isoquinoline), to regulate receptor internalization and trafficking. Both A-77636 and DNS are full agonists at activating adenylate cyclase, and DNS exhibited a similar efficacy to dopamine in causing internalization, whereas A-77636 caused significantly greater internalization. An investigation of the post-endocytic agonist effects on receptor trafficking revealed significant differences in agonist regulation of receptor trafficking. Dopamine caused the D_1 receptor to recycle back to the cell surface within 1 h, whereas the D_1 receptor persisted intracellularly for up to 48 h after the removal of A-77636. Surprisingly, DNS caused the receptor to recycle back to the membrane after 48 h. Pulse-chase experiments and the use of actinomycin D to inhibit new protein biosynthesis demonstrated that cell surface recovery was not due to the synthesis of new proteins. Taken together, these data indicate that agonists target D_1 receptors to different intracellular trafficking pathways.

3.1.5 Potential Utility of D_1 Functionally Selective Drugs

The D_1-like receptors have been implicated as therapeutic targets for numerous CNS disorders, such as Parkinson's disease (Mailman et al. 2001; Taylor et al. 1991), schizophrenia, learning and memory dysfunctions (Arnsten et al. 1994; Goldman-Rakic et al. 2004), and attention deficit hyperactivity disorder (Heijtz et al. 2007). Importantly, D_1 agonists may play a critical role in the treatment of the negative and cognitive symptoms of schizophrenia, which are not very responsive to current drugs. One of the issues that has been associated with the development of a selective full D_1 agonist is side effects (e.g., hypotension and tachycardia) (Huang et al. 2001). Utilizing the concept of functional selectivity, however, we potentially can design a D_1 agonist that interacts with specific signaling pathways to enhance the beneficial effects while avoiding unwanted side effects. For example, sodium levels play a critical role in regulating blood pressure, and the hypotension and tachycardia that are observed with D_1 agonists result from excessive stimulation of peripheral D_1 receptors, which can influence sodium concentrations. Although the

D_1-linked signaling cascade(s) regulating sodium transport are not entirely clear, evidence suggests that D_1 receptors primarily modulate sodium resorption via the Na^+/H^+-exchanger and Na^+/K^+-ATPase (Hussain and Lokhandwala 1998). Thus, the design of a D_1 agonist that is less efficacious at these or other currently unidentified transduction pathway(s) could permit the use of high doses of a D_1 agonist in patients.

Although functional selectivity has considerable promise for the discovery and development of D_1 ligands, much more knowledge is required to take full advantage of functional selectivity. For example, instead of just determining the binding characteristics and whether a drug is an agonist or antagonist at D_1 receptors, researchers must understand which signaling pathways are activated by a given drug and which signaling pathways are critical for the desired effects of the drug. A thorough understanding of these issues will enable scientists to manipulate the chemical structures of novel D_1 ligands to selectively activate signaling pathways. Interestingly, studies have shown that major ligand structural differences cannot explain differences in functional selectivity at the D_1 receptor; thus, functional selectivity could be due to more subtle structural changes or to the G proteins and other signaling molecules that are coupled to D_1 receptors in various brain regions. With the acceptance of functional selectivity and the ability to selectively modulate cellular functions in a much more specific manner than previously imagined, researchers have questioned whether diseases could be treated by modulating signaling pathways rather than directly targeting receptors. This strategy has flaws, however, because many of the signaling pathways that are mediated by dopamine receptors have critical functions throughout the body; thus, just targeting the signaling pathway would likely result in many serious side effects. Indeed, functionally selective ligands that target dopamine receptors could be designed to affect a specific signaling pathway, but the effects could be localized to dopaminergic diseases by activating or inhibiting a specific pathway through dopamine receptors.

Superficially, a D_1 agonist seems counterintuitive for the treatment of schizophrenia; however, the differential localization and functional characteristics belie this intuition. In addition, functionally selective D_1 agonists might further improve the therapeutic index of drugs used to treat cognitive and/or negative domains of schizophrenia and related disorders. Interestingly, the primary function of almost all clinically used dopamine antagonists is the treatment of schizophrenia and other psychotic or manic disorders. On the other hand, all clinically used CNS-available dopamine agonists were designed as D_2 agonists, approved for a variety of disorders other than schizophrenia, and are contraindicated for use in schizophrenia. Thus, no clinically used CNS drug was designed as a D_1 agonist. Because the focus of dopaminergic therapy of schizophrenia has been aimed at D_2 receptors, the potential of full D_1 agonists has been underappreciated. Whereas several studies have demonstrated that D_1 antagonists would not be effective APDs (Den Boer et al. 1995; Karlsson et al. 1995), there is a large body of experimental research showing that D_1 agonists can improve working memory processes in the prefrontal cortex (Arnsten et al. 1994; Cai and Arnsten 1997; Castner et al. 2000; Goldman-Rakic et al. 2004; Hersi et al. 1995; Lidow et al. 1991; Schneider et al. 1994; Steele et al. 1997) as

well as other functions (Han et al. 1997; Shohamy and Adcock 2010). Importantly, the large body of data supporting the potential beneficial effects of D_1 stimulation in cognition and memory also show a clear dose-dependency for these effects. Indeed, higher doses of a D_1 agonist have been demonstrated to impair memory performance in aged monkeys (Castner et al. 2000). The involved mechanisms by which D_1 receptors affect memory and cognition are not fully understood, but a functionally selective D_1 ligand might be able to avoid the biphasic dose–response relationships and only activate the signaling pathway(s) that enhance cognition. Such examples illustrate how the elucidation of mechanisms of functional selectivity of dopamine receptor ligands may have clinical relevance as well as intrinsic heuristic value.

Although numerous D_2-like ligands have been the subject of clinical studies, the only reports of studies in humans for selective D_1 agonists are for DHX (Brewster et al. 1990; Lovenberg et al. 1989; Mottola et al. 1992) and ABT-431 (nee A83959) (Michaelides et al. 1995; Shiosaki et al. 1996). Both compounds have similar pharmacology and have been shown to have profound antiparkinson activity (Giardina and Williams 2001; Haney et al. 1999; Okumu et al. 2002; Rascol et al. 1999, 2001; Self et al. 2000). Both compounds have little oral bioavailability, and only DHX remains available for clinical testing (George et al. 2007; Mu et al. 2007) with a phase IIa study as a cognitive enhancer in schizophrenia currently ongoing (Slifstein et al. 2011). If positive results come from such studies, it will spur efforts to discover compounds with better pharmacokinetics and, possibly, functionally selective signaling properties.

4 Conclusion

Current APDs are relatively effective at treating the positive symptoms of schizophrenia, but unwanted side effects and a lack of efficacy in treating negative and cognitive symptoms have highlighted the need for new and improved APDs. Although newer generation APDs may have important therapeutic effects at receptors other than the dopamine receptor, all currently approved APDs share actions at D_2 receptors. With the growing acceptance of functional selectivity and in-depth mechanistic studies into the signaling pathways mediated by dopamine receptors, this is an exciting time for the discovery of APDs. Current high-throughput screening assays for novel APDs that only examine effects on the cAMP pathway may be missing potential therapeutic compounds. Drug discovery efforts should also examine other signaling pathways that are activated by D_1 and D_2 receptors and search for functionally selective compounds. The primary target for APDs is the dopamine receptor system, but a thorough understanding of the dopamine-mediated signaling pathways that are responsible for the specific effects of schizophrenia will help to focus drug discovery and development efforts. Although current APDs are effective at treating the positive symptoms of schizophrenia, they are not very effective at treating negative symptoms and cognitive deficits. In addition, current APDs have significant side effects. The improvements

that have been made from typical antipsychotics to atypical antipsychotics and newer functionally selective drugs, such as aripiprazole, highlight the possibility of improving APDs, and the design of novel functionally selective drugs holds promise for the treatment of schizophrenia.

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Serotonergic Mechanisms as Targets for Existing and Novel Antipsychotics

Herbert Y. Meltzer

Contents

Abstract A variety of serotonin (5-HT) receptors, especially 5-HT_{2A}, 5-HT_{1A}, 5-HT_6, 5-HT_7, and 5-HT_{2C}, have been postulated to contribute to the mechanism of action of atypical antipsychotic drugs (APDs), i.e., APDs which cause fewer

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extrapyramidal side effects (EPS) at clinically optimal doses, in contrast with typical APDs, which are more likely to cause EPS. This advantage, rarely disputed, has made such drugs the preferred treatment for schizophrenia and other indications for APDs. These 5-HT receptors are still of interest as components of novel multireceptor or stand-alone APDs, and potentially to remediate cognitive deficits in schizophrenia. Almost all currently available atypical APDs are 5-HT_{2A} receptor inverse agonists, as well as dopamine (DA) D_2 receptor antagonists or partial agonists. Amisulpride, an exceptional atypical APD, has 5-HT_7 antagonism to complement its DA $D_{2/3}$ antagonism. Some atypical APDs are also 5-HT_{1A} partial agonists, 5-HT_6, or 5-HT_7 antagonists, or some combination of the above. 5-HT_{2C} antagonism has been found to contribute to the metabolic side effects of some atypical APDs, whereas 5-HT_{2C} agonists have potential as stand-alone APDs and/or cognitive enhancers. This review will provide an update of current preclinical and clinical evidence for the role of these five 5-HT receptors in the actions of current APDs and for the development of novel psychotropic drugs.

Keywords Serotonin • Dopamine • Glutamate • GABA • Antipsychotic • Schizophrenia • Hallucinations • Memory • Phencyclidine

1 Introduction

The discovery of the antipsychotic properties of chlorpromazine and the attribution of its antipsychotic action and mechanism-driven side effects, such as parkinsonism and prolactin elevations to blockade of dopamine (DA) D_2 receptors, firmly established the role of DA D_2 receptor blockade as a reliable means of achieving an antipsychotic effect (see Meltzer and Stahl 1976; Miyamoto et al. 2005; Ginovart and Kapur 2012 for reviews). As will be discussed, the most widely used, and arguably the most clinically useful, antipsychotic drugs (APDs) target one or more of the 14 serotonin (5-HT) receptors in addition to their actions as DA D_2 receptor antagonists, e.g., clozapine, or DA D_2 partial agonists, like aripiprazole or bifeprunox. Of the 5-HT receptors targeted by these APDs, the 5-HT_{2A} receptor has been suggested to be the most important for antipsychotic efficacy (Meltzer et al. 1989). Effects upon 5-HT_{1A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors have also been suggested to contribute to effects upon psychosis, cognition, and some side effects, especially metabolic side effects such as weight gain. The regulatory effect of 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors on the activity of cortical and hippocampal pyramidal neurons, GABAergic interneurons, the dorsal and median raphe serotonergic neurons, substantia nigra, and ventral tegmental dopaminergic neurons, all of which are central to current hypotheses about the pathophysiology of schizophrenia is firmly established (Meltzer and Huang 2008). Nevertheless, the importance of 5-HT in the action of APDs is still rejected by some, in large part because of the view that fast dissociation of atypicals from the D_2 receptor is the basis for the low rate of extrapyramidal side effects (EPS) of the atypical APDs (Howes and Kapur 2009; Vauquelin et al. 2012). However, only

clozapine and quetiapine, because of their weak affinity for the D_2 receptor, can be shown to dissociate rapidly; many of the atypical APDs, e.g., risperidone, paliperidone, asenapine, iloperidone, ziprasidone, etc., because of their high affinity for the D_2 receptor, dissociate at rates equal to or more slowly than haloperidol, which makes the fast dissociation theory as a general mechanism, untenable (Gray and Roth 2007; Meltzer and Huang 2008). The rejection of the role of 5-HT receptors as contributing to low EPS also fails to take into account the abundant evidence that 5-HT_{1A} partial agonists diminish the EPS caused by undesirable dorsal striatal D_2 receptor blockade of both typical and atypical APDs, particularly the former (Prinssen et al. 2002; Depoortere et al. 2003; Kleven et al. 2005). Interest in the role of 5-HT in the mechanism of action of APDs was greatly stimulated by the hypothesis that two key clinical advantages of clozapine, fewer EPS and lack of elevation of serum prolactin levels, were dependent, in part, upon more potent 5-HT_{2A} than DA D_2 receptor antagonism (Meltzer et al. 1989; Arnt and Skarsfelt 1998). The most important initial evidence for this was the result of a comparison of the affinities for 5-HT_{2A}, and DA D_1 and D_2 receptors by APDs which differed in propensity to cause EPS (Meltzer et al. 1989), but earlier evidence had suggested the importance of the 5-HT_{2A} receptor blockade for some but not all atypical APDs (Altar et al. 1986). The APDs which convey greater risk for EPS such as parkinsonism and tardive dyskinesia, as well as enhanced secretion of prolactin, are exemplified by chlorpromazine and haloperidol. All such drugs share the ability to block limbic and cortical DA D_2 receptors, leading to their antipsychotic action, but the same mechanism also causes EPS due to blockade of D_2 receptors in the dorsal striatum and plasma prolactin elevations due to D_2 receptor blockade in prolactin-secreting cells in the anterior pituitary gland (see Meltzer and Stahl 1976; for review, Strange 2001). They are generally referred to as typical or first-generation APDs. The serotonergic agents are usually referred to as atypical APDs or second-generation APDs because of their lack of EPS. This distinction is of critical importance because EPS are important reasons for noncompliance and tardive dyskinesia is associated with diminished longevity due to associated health impairment and suicide risk (Margolese et al. 2005a, b).

Other clinical differences between typical and atypical APDs particularly clozapine have emerged and provided further impetus for interest in a possible role of 5-HT in explaining these differences. Clozapine, the prototypical atypical APD, was used as a first-line treatment in Europe despite side effects such as sedation, hypersalivation, tachycardia, and weight gain because of its low rate of EPS and not because of any awareness of a more favorable efficacy profile (see Gründer et al. 2009 for review). Clozapine was withdrawn from general use after the discovery in 1975 that its rate of agranulocytosis was many fold greater than that of other APDs, but was restored, for limited use, by selected clinicians (see Meltzer 1993; Gründer et al. 2009). It did not gain widespread appreciation as the "gold standard" treatment for schizophrenia (Volavka 2012) until it was shown to be effective to treat psychotic symptoms in a third of the 30 % of patients with schizophrenia who failed to respond to chlorpromazine or haloperidol within 6 weeks of initiating treatment (Kane et al. 1988), using 20 % improvement in

total psychopathology as the main measure of response; the response rate increases to 60–70 %, when treatment is continued for up to 6 months (Meltzer 1989). These findings, together with the hypothesis of relatively more potent 5-HT_{2A} antagonism as a major component of its action, led to the development of other APDs which were more potent 5-HT_{2A} than D_2 receptor antagonists, or D_2 partial agonists (Table 1). The affinities of 17 atypical APDs for the five 5-HT receptors discussed here, the DA D_1 and D_2 receptors, and the 5-HT_{2A}/D_2 ratio are given in Table 1. The majority of the data are obtained from the NIMH Psychoactive Drug Screening Program Web site and from human cloned receptors when available. For comparison purposes, the affinities of two atypical APDs, chlorpromazine and haloperidol, are also provided. With the exception of aripiprazole, amisulpride, and sulpiride, all of the atypical APDs have higher affinities for 5-HT_{2A} than for D_2 receptors, and thus the ratios of their K_i values are less than 1. For chlorpromazine and haloperidol, the ratios are 1.6 and 146, respectively. These findings are consistent with the hypothesis that typical APDs are more potent D_2 than 5-HT_{2A} antagonists, while the reverse is true for atypical APDs (Meltzer et al. 1989). The basis for the atypicality of amisulpride and sulpiride will be discussed subsequently. The variation in affinities for 5-HT_{1A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors of the atypical APDs is noteworthy, and will be discussed subsequently, since these receptors also contribute to the efficacy and/or side effects of these drugs.

A report that clozapine was able to improve some domains of cognition in schizophrenia (Hagger et al. 1993) further stimulated interest in the possible importance of 5-HT receptors in the action of atypical APDs, since studies of typical APDs provided minimal evidence for improvement in cognition [see Meltzer and McGurk (1999) for review]. Executive function, working memory, and cognitive flexibility are important functions of the prefrontal cortex (PFC) (Puig and Gulledge 2011), one of the two regions of the brain most closely related to cognitive impairment in schizophrenia, the other being the hippocampus (Volk and Lewis 2010; Wang et al. 2008). Both of these regions are heavily innervated by 5-HT neurons and express a wide variety of 5-HT receptors (Andrade 2011; Puig and Gulledge 2011). As will be discussed, the inhibitory effects of 5-HT_{1A} and excitatory effects of 5-HT_{2A} receptor stimulation appear to play a critical role in the mechanism of action of atypical APDs to improve cognition, certainly in some animal models of cognitive impairment in schizophrenia and possibly schizophrenia itself.

The goal of improving cognition in schizophrenia with pharmacologic agents is clearly one of the principal objectives of the quest for novel treatments for many psychiatric disorders but especially schizophrenia (Millan et al. 2012). As will be discussed, the efficacy of clozapine to improve cognition in patients with schizophrenia has been disputed by some, but the ability of clozapine and other atypical APDs, which are 5-HT_{2A} antagonists or partial 5-HT_{1A} agonists, or both, to produce greater improvement in animal models of cognitive impairment in schizophrenia than selective D_2 antagonists is generally accepted (Egashira et al. 2008;

Table 1 Receptor affinities (K_i, nM) of atypical and typical antipsychotic drugs

	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7	D_2	D_3	5-HT_{2A}/D_2
Aripiprazole	5.6[a]	4.6	181	574[a]	10[a]	0.95[a]	4.5	4.8
Asenapine	2.7[a, (13)]	0.07[a, (13)]	0.034[a, (13)]	0.25[a, (13)]	0.11[a, (13)]	1.3[a, (13)]	0.42[a, (13)]	0.054
Blonanserin	>100[(1)]	3.98[a, (1)]	26.4[a, (1)]	41.9[a, (1)]	>100[(1)]	14.8	0.49[(1)]	0.27
Chlorpromazine	2,610[b]	3.2	26	4.0[c]	20[c]	2.0[a]	5.0	1.6
Clozapine	105[a]	13[c]	29	17[a]	18[a]	431[a]	646	0.03
N-desmethylclozapine	13.9[a]	10.9[a]	11.9	9.4[(2)]	14.9[(2)]	115[a]	234	0.095
Haloperidol	2,600[(3)]	73	>10,000	4,561[c]	254[c]	0.5[(4)]	12	146
Iloperidone	93.2[c,a]	0.1[a]	147[c,a]	63.0[c,a]	112[a]	21.4[a]	14.0[a]	0.047
Lurasidone	6.38[a, (5)]	0.47[a, (5)]	415[d,(5)]	–	0.495[a, (5)]	0.994[a, (5)]	15.7[a, (5)]	0.47
Melperone	2,200[e, (6)]	32[b, (7)]	1,259[(2)]	1,254[(2)]	578[(2)]	200[(2)]	160[c,a]	0.16
Olanzapine	7,100[(3)]	3	24	6[a]	105[a]	7.5[(8)]	63	0.4
Paliperidone	638[a, (14)]	1.9[a, (14)]	48[a, (14)]	2,414[a,(14)]	2.7[a, (14)]	9.4[a, (14)]	2.6[a, (14)]	0.20
Quetiapine	431[a]	101[a]	1,500	1,297[(9)]	134[(9)]	567[(a)]	483	0.18
Risperidone	427[a]	0.19	95	659[c]	1.24[c]	1.58[(2)]	12.2	0.12
Sertindole	2,200[(3)]	0.2[(3)]	0.51[(3)]	5.4[(3)]	28[(3)]	0.45[(3)]	2.6[(3)]	0.44
Ziprasidone	37[(3)]	0.3[a]	68	61[a]	6[a]	4.0[(a)]	17	0.075
Zotepine	611[(a)]	2.6[c]	4.5	1.17[(2)]	1.78[(2)]	25[a]	17	0.10
Amisulpride	>10,000[a, (10)]	8,304[a, (10)]	>10,000[a, (10)]	4,154[a, (10)]	11.5[a, (10)]	3.0[a, (10)]	3.5[(10)]	2,768
Sulpiride	>10,000[c,a]	>10,000[(11)]	>10,000[(11)]	5,000[(2)]	5,000[(2)]	160[(12)]	8.05[c,a]	62.5

Atypical APDs; from NIMH Psychoactive Drug Screening Program (PDSP) http://www.pdsp.unc.edu, unless otherwise indicated

[a]Data from human cloned receptors

[b]Data from rat brain

[c]Average data from PDSP

[d]Data from porcine brain

[e](1) Kurumiya and Une (2008) unpublished, (2) Roth et al. (1994), (3) Arnt and Skarsfeldt (1998), (4) Roth et al. (1995), (5) Ishiyama et al., communicated as poster at CINP 2010, (6) Richelson and Souder (2000), (7) Roth et al. (1992), (8) Strange (2001), (9) Kongsamut et al. (1996), (10) Abbas et al. (2009), (11) Toll et al. (1998), (12) Grandy et al. (1989), (13) Chwieduk and Scott (2012), (14) Richtand et al. (2008), (15) Oka et al. (1993)

Matsumoto et al. 2008; Meyer et al. 2010; Neill et al. 2010), and has led to interest in other serotonergic mechanisms that may influence cognition (Meltzer et al. 2012). There has been relatively little study of the role of 5-HT_3 receptors in schizophrenia, and, in particular, its role in the action of APDs to ameliorate psychosis or cognitive impairment in schizophrenia, although there is some genetic evidence for an involvement of 5-HT_3 receptors in schizophrenia (Souza et al. 2010). The role of 5-HT_3 receptors in the PFC, particularly the superficial layers, has been reviewed elsewhere (Puig and Gulledge 2011). Here, the role of 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors in the mechanism of action of APDs as cognitive enhancers, not just as antipsychotic agents, will be the major focus.

2 The 5-HT_{2A} Receptor as a Target for Antipsychotic Drug Action

2.1 Neurobiology of 5-HT_{2A} Receptors

5-HT_{2A} receptors are present throughout the mammalian brain, with the highest density in the frontal cortex. They are located on apical dendrites of most cortical pyramidal neurons, as well as on many large and medium-size parvalbumin- and calbindin-containing GABAergic interneurons which inhibit cortical and hippocampal pyramidal neurons (Jakab and Goldman-Rakic 1998). The pyramidal and GABAergic neurons in the cortex, hippocampus, and ventral striatum are of fundamental importance for the neural functions which underlie reality testing, executive function, and selective response to sensory inputs (Goldman-Rakic and Selemon 1997; Lewis et al. 2005). Using single-cell RT-PCR, it has been demonstrated that almost all pyramidal neurons express detectable levels of 5-HT_{2A} and 5-HT_{2c} receptor mRNA, with half expressing both (Vysokanov et al. 1998). 5-HT_{2A} receptor stimulation leads to depolarization and enhanced spontaneous glutamatergic excitatory postsynaptic currents (EPSCs) in layer V pyramidal neurons (Araneda and Andrade 1991; Aghajanian and Marek 1997). 5-$HT_{2A/C}$ receptor activation has also been shown to reduce dendritic excitability and may negatively modulate activity-dependent dendritic synaptic plasticity via effects upon Na^+ and Ca^{++} channels (Carr et al. 2002) which has implication for the ability of 5-$HT_{2A/2C}$ receptor to regulate both the dorsal raphe (DR) and ventral tegmental area (VTA; Vázquez-Borsetti et al. 2011). Thus, atypical APDs which are 5-HT_{2A} antagonists may distally modulate serotonergic and dopaminergic neurotransmission through 5-HT_{2A} receptor blockade in the PFC, presumably decreasing the activity of neurons receiving direct cortical inputs from the DR and VTA, as well as the thalamus and other cortical regions. By this means, the PFC may simultaneously coordinate the activity of dopaminergic and serotonergic systems needed to sustain cognitive function, something not possible with selective D_2 antagonists. It should be noted that 5-HT_{2A} receptors are also present on the cell bodies of DA neurons in

the substantia nigra and VTA, as well as other non-dopaminergic VTA neurons (Doherty and Pickel 2000; Ikemoto et al. 2000). The VTA 5-HT_{2A}-immunoreactivity is dendritic as well as axonal. Only 40 % of the 5-HT_{2A}-labeled dendritic profiles also contained the catecholamine marker tyrosine hydroxylase. Thus, 5-HT_{2A} receptors may be important for the postsynaptic activation of non-dopaminergic neurons (Doherty and Pickel 2000).

A major hypothesis concerning the pathophysiology of schizophrenia is hypoglutamatergic function (see Coyle and Tsai 2004 for review). This hypothesis rests largely on clinical studies of the effect of *N*-methyl-D-aspartate (NMDA) receptor antagonists such as dizocilpine (MK-801), phencyclidine (PCP), and ketamine to mimic the cognitive impairments associated with schizophrenia in normals, to cause psychosis in some normals, and to exacerbate schizophrenia. 5-HT_{2A} receptors have been shown to be highly important modulators of NMDA receptors (see Meltzer et al. 2011 for a more detailed review). Using single slices of mouse cortex, the transport and dynamic regulation of NMDA receptors in pyramidal neurons in cortex have been shown to be oppositely regulated by both 5-HT_{2A} and 5-HT_{1A} receptors (Yuen et al. 2005). Metabotropic glutamate$_{2/3}$ ($mGlu_{2/3}$) receptor agonists may have antipsychotic effects on their own but especially in combination with 5-HT_{2A} receptor antagonists. 5-HT_{2A} and $mGlu_2$ receptors co-localize in cortical pyramidal neurons and form a heterodimer complex which were suggested to produce functionally relevant inhibition of 5-HT_{2A} agonist-induced signaling in cortex (González-Maeso et al. 2008). However, a more recent study (Delille et al. 2012), using HEK-293 cells which co-express both receptors, reported no relevant effects on signaling as assessed with intracellular cAMP levels after treatment with $mGlu_2$ agonists, antagonists, and positive allosteric modulators or 5-HT_{2A} hallucinogenic and non-hallucinogenic agonists and antagonists (Delille et al. 2012). $mGluR_{2/3}$ agonists, like 5-HT_{2A} inverse agonists, decrease 5-HT_{2A} agonist-induced head twitch (Gewirtz and Marek 2000) and excitatory postsynaptic potentials (Marek et al. 2000). LY2140023, an oral prodrug of LY404039, a selective agonist for $mGlu_{2/3}$ receptors which had an antipsychotic profile in some animal studies, was found to be an effective antipsychotic in an olanzapine-controlled study (Patil et al. 2007). Further clinical trials of this mechanism are under way. Coadministration of subeffective doses of the mGlu2/3 receptor agonist LY379268 and the 5-HT_{2A} receptor antagonist M100907 (0.2 mg/kg) in rats produced a synergistic inhibitory effect on both amphetamine- and dizocilpine (MK-801)-induced locomotor activity as well as a reduction in MK-801-induced DA efflux in the nucleus accumbens. It was suggested that a single compound having both $mGlu_{2/3}$ receptor agonist and 5-HT_{2A} receptor antagonist activity or coadministration of two compounds selective for these receptors could be superior in terms of efficacy and/or reduced side-effect liability relative to an $mGlu_{2/3}$ receptor agonist alone (Fribourg et al. 2011; Uslaner et al. 2009). Based upon the studies of Horiguchi et al. (2011b), the same could apply to the combination of an $mGlu_{2/3}$ agonist and an atypical APD which had potent 5-HT_{2A} antagonist properties.

The ability of 5-HT_{2A} receptor blockade to modulate glutamatergic currents may contribute to the procognitive effects of atypical APDs and selective 5-HT_{2A} inverse agonists. More recently we found that the $mGluR_{2/3}$ agonist, LY379268 alone (1 and 3 mg/kg), did not improve the subchronic PCP-induced deficit in novel object recognition (NOR) (Horiguchi et al. 2011b), despite evidence that these doses of LY379268 attenuate acute PCP-induced hyperlocomotion (Cartmell et al. 1999; Swanson and Schoepp 2002; but see Henry et al. 2002). However, coadministration of LY379268 with subeffective doses of atypical APDs and 5-HT_{2A} inverse agonists significantly reversed the PCP-induced NOR deficit (Horiguchi et al. 2011b).

There is evidence for a chemical and functional interaction between 5-HT_{2A} receptors and D_2 receptors in brain which may help to explain why they are able to diminish psychosis in many, but not all individuals, and why combined DA D_2 and 5-HT_{2A} receptor antagonism is synergistic, despite the fact that they signal through different mechanisms, the $G_{q/11}$ protein and the $G_{i/o}$ protein, respectively. Studies in HEK cells expressing both receptors suggested that these two receptors can physically interact possibly due to formation of a receptor heterocomplex (Albizu et al. 2011). D_2 receptor activation increased the affinity of the hallucinogen (+ or −)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI) for 5-HT_{2A} receptors. Furthermore, 5-HT_{2A} receptor expression was shown to be necessary for the D_2 receptor antagonists to block the NMDA noncompetitive antagonist, MK-801-induced locomotor activity, a model for its psychotomimetic potential (Albizu et al. 2011). However, as will be discussed, D_2 receptor antagonists are much less potent than 5-HT_{2A} receptor antagonists to block the locomotor effects of NMDA receptor antagonists.

Both preclinical and clinical evidence suggest that the potent 5-HT_{2A} receptor blockade of atypical APDs is relevant to the low EPS profile of clozapine and related atypical APDs (Kruzich and See 2000; Meltzer and Huang 2008). The selective 5-HT_{2A} inverse agonist, M100907, was reported to block haloperidol-induced catalepsy (Ishikane et al. 1997). Clozapine is not cataleptic at any dose. There is a significant separation of the ED_{50} doses for catalepsy and antipsychotic action in amphetamine-induced locomotor activity or prepulse inhibition (PPI) for all atypical APDs. This is not the case for typical APDs (Meltzer et al. 2003).

It has been suggested that 5-HT_{2C} rather than 5-HT_{2A} receptor blockade is the basis for the low EPS profile of atypical APDs (Creed-Carson et al. 2011). This issue is discussed in the section on 5-HT_{2C} receptors.

Because of the high incidence of abuse of cocaine by patients with schizophrenia (Winklbaur et al. 2006), the role of 5-HT_{2A} receptor stimulation and blockade in the action of cocaine is of particular interest. Locomotor activity stimulated by systemic cocaine is attenuated by local administration of the selective 5-HT_{2A} inverse agonist, M100907, into the VTA, but not the shell of the nucleus accumbens (McMahon et al. 2001). Clozapine, in particular, has been found to decrease abuse of cocaine in schizophrenia (Buckley et al. 1994), while amperozide, a 5-HT_{2A} antagonist, with no D_2 receptor blocking properties, which stimulates the release of DA in the nucleus accumbens when given acutely (Kimura et al. 1993), but reduces basal DA efflux

when given chronically, and inhibits amphetamine-induced DA release in the nucleus accumbens (Ischikawa and Meltzer 1992), also has potent inhibitory effects on cocaine craving in rodents (McMillen et al. 1993).

Growth factors such as brain-derived neurotrophic factor (BDNF) are another possible basis for differentiating typical and atypical APDs via a 5-HT_{2A}-dependent mechanism (Vaidya et al. 1997). BDNF may be important to schizophrenia through its ability to regulate survival, differentiation, synaptic strength, and neuronal morphology in the cerebral cortex and hippocampus. Diminished BDNF levels have been reported in some postmortem studies of schizophrenia brain (Issa et al. 2010). Risperidone, an atypical APD, was found to be much less neurotoxic to primary neurons in culture, compared to haloperidol, by a BDNF mechanism that was due in part to 5-HT_{2A} receptor blockade (Ukai et al. 2004).

2.2 *Central Effects of Selective 5-HT_{2A} Antagonists*

Whereas drugs which stimulate 5-HT_{2A} receptors may be hallucinogenic, e.g., lysergic acid diethylamide (LSD) and DOI (Silva and Calil 1975), M100907 and other selective 5-HT_{2A} receptor inverse agonists, e.g., pimavanserin (ACP-103) and SR43469B, either alone or in combination with antagonists of D_2 and other receptors have been found to be effective in various animal models of psychosis. These models include (a) blockade of PCP- and MK-801-induced locomotor activity (Gleason and Shannon 1997; Martin et al. 1997, 1998); (b) blockade of amphetamine-induced locomotor activity and inhibition of the firing of VTA dopaminergic neurons (Schmidt et al. 1995); (c) blockade of both the local (intramedial PFC) and systemic administration of DOI to increase the firing rate and burst firing of DA neurons and DA release in the VTA and mPFC (Bortolozzi et al. 2005); (d) blockade of MK-801-induced PPI in the rat (Varty et al. 1999); and (e) prevention of the disruption in the rat by DOI of PPI of startle in the rat (Sipes and Geyer 1995, 1997). M100907 has been found to diminish the increase in DA efflux in the nucleus accumbens produced by haloperidol (Liegeois et al. 2002) or *S*-sulpiride (Ichikawa et al. 2001). The combination of raclopride, a D_2 receptor antagonist, and M100907, a selective 5-HT_{2A} antagonist, but not M100907 alone, blocks the conditioned avoidance response, an accepted model of antipsychotic efficacy (Wadenberg et al. 1998). In support of this, Gardell et al. (2007) demonstrated that ACP-103 potentiated the ability of a subeffective dose of haloperidol or risperidone needed to block amphetamine- or MK-801-induced hyperactivity. ACP-103 has also been shown to potentiate the effect of both haloperidol and risperidone to enhance cortical DA efflux in rats, which presumably is related to the ability to improve cognitive impairment (Li et al. 2005). Thus, 5-HT_{2A} inverse agonism appears to play a role in attenuation of experimental psychosis, perhaps through modulation of cortical serotonergic inputs onto dopaminergic neurons in the nucleus accumbens, and therefore have potential as adjunctive therapy when combined with drugs that possess some degree of DA antagonism.

2.3 Role of 5-HT$_{2A}$ Receptor Antagonism in the Antipsychotic and Cognitive Enhancing Effects of Atypical Antipsychotic Drugs

High affinity for 5-HT$_{2A}$ compared to DA D$_2$ receptors (referred to here as the 5-HT$_{2A}$-D$_2$ ratio) is a robust, but not exclusive, basis for identifying APDs which are "atypical," i.e., at clinically effective doses produce significantly less motor symptoms in clinical use than do typical APDs (Meltzer et al. 1989; Schotte et al. 1996; Meltzer and Huang 2008). It should be noted that lack of elevation of serum prolactin levels is not a feature of all atypical APDs, with risperidone and its metabolite, paliperidone, producing the largest prolactin elevation of any APD, by a mechanism as yet unknown (Zhang et al. 2005). In vitro 5-HT$_{2A}$–D$_2$ ratio and in vivo occupancy data in rodents and, to the extent it exists, PET and SPECT studies in humans, of most atypical APDs, including asenapine, blonanserine, clozapine, iloperidone, lurasidone, *N*-desmethylclozapine, olanzapine, paliperidone (9-hydroxyrisperidone), perospirone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine, are consistent with the 5-HT$_{2A}$-D$_2$ ratio model. Aripiprazole meets the criteria for an atypical APD because of its minimal EPS at clinically effective doses (Argo et al. 2004). Its mechanism of action is different from, but consistent with that of the clozapine-derived atypical APDs, as it is a partial DA D$_2$ agonist. It has higher affinity for the D$_2$ receptor than for the 5-HT$_{2A}$ receptor, but functionally, it reduces the activity of the D$_2$ receptor so that its affinity should not be directly compared with that of D$_2$ receptor antagonists (Swainston et al. 2004).

The atypical APDs listed above are inverse agonists at the 5-HT$_{2A}$ receptor, i.e., they block constitutive activity (spontaneous signaling in the absence of agonist) of the 5-HT$_{2A}$ receptor, as well as agonist-stimulated activity (Weiner et al. 2001). Acute or chronic administration of atypical APDs, as well as the relatively selective 5-HT$_{2A}$ antagonist ritanserin, downregulates the density of 5-HT$_{2A}$ receptors in most brain regions (Andree et al. 1986; Leysen et al. 1986; Matsubara and Meltzer 1989; Steward et al. 2004). Interestingly, subchronic PCP also downregulates cortical 5-HT$_{2A}$ receptors, which was interpreted as a compensatory action to negate the deleterious effects of NMDA receptor blockade (Steward et al. 2004).

A recent study found a much more diverse effect of 5-HT$_{2A}$ antagonists on 5-HT$_{2A}$ receptor protein levels, a more sensitive measure than previous radioligand-based studies whose results might have been affected by residual drug, pseudoirreversible binding, and receptor inactivation (Yadav et al. 2011). After chronic administration to C57BL/6J mice, the 5-HT$_{2A/2C}$ inverse agonist SR43468B was found to increase 5-HT$_{2A}$ protein level in brain. Two atypical APDs, clozapine and olanzapine, downregulated, and four selective 5-HT$_{2A}$ receptor inverse agonists with variable degrees of 5-HT$_{2C}$ antagonism, M100907, M11939, pimavanserin, and altanserin, had no effect. In contrast, ketanserin, which is similar to the four selective 5-HT$_{2A/2C}$ antagonists, but with more 5-HT$_{2C}$ antagonism than the others, also increased 5-HT$_{2A}$ protein levels. Interestingly, SR46349B was found to enhance PCP-induced locomotor activity while clozapine and olanzapine treatment had the opposite effect.

These differences were attributed to functional selectivity and were suggested to parallel clinical responses to these agents (Yadav et al. 2011). However, both M100907 and SR43469B do have significant antipsychotic efficacy (Meltzer et al. 2004; see Meltzer et al. 2012 for review).

Another group of atypical APDs are D_2/D_3 antagonists (e.g., amisulpride) or D_2/D_3 antagonist–partial agonist (cariprazine) which lack potency as 5-HT_{2A} antagonists or inverse agonists, but have potent effects on other serotonin receptors which may be relevant to their antipsychotic or procognitive properties, or both. Amisulpride is also a 5-HT_7 antagonist (Abbas et al. 2009); it has been widely used in Europe as both an APD and, at lower doses, an antidepressant, for the last two decades but is not available in the USA. Cariprazine, along with its complex D_2/D_3 effect, is also a potent 5-HT_{2B} antagonist with weaker 5-HT_{1A} partial agonist properties to complement its D_2/D_3 antagonism–partial agonism (Gyertyán et al. 2011; Kiss et al. 2010). Its efficacy as an APD for patients with schizophrenia was demonstrated in several successful controlled clinical trials. The evidence for the potential for D_3 antagonism to contribute to an atypical APD was equivocal until selective D_3 antagonists were shown to counteract the cataleptogenic effects of haloperidol (Gross and Drescher 2012 for review). A number of typical APDs are as, or nearly as, potent D_3 as D_2 antagonists, e.g., chlorpromazine and haloperidol, but may not sufficiently block D_3 receptors in vivo because of the high affinity of DA for the D_3 receptor (Gross and Drescher 2012) and lack distinguishing serotonergic properties which might overcome the burden of extensive D_2 receptor blockade. There are some selective D_3 compounds without D_2 affinity which have shown some promise in models of cognitive impairment in schizophrenia, e.g., S33804 (Gross and Drescher 2012; Watson et al. 2012). Other D_2/D_3 antagonists with atypical properties are being developed, but these have some combination of 5-HT_{2A}/5-HT_{2C} and 5-HT_6 antagonist properties or 5-HT_{1A} partial agonism (Garzya et al. 2006; Homan et al. 1998). A series of compounds with high D_3 affinity, low D_2 affinity, and potent 5-HT_{1A} partial agonism and 5-HT_{2A} antagonism, has been reported to have atypical properties, but it is unclear that the activity of these compounds is related strongly to D_3 antagonism (Butini et al. 2009). No selective D_3 antagonist which has been tested clinically in controlled trials has been shown to be an effective APD, but it is unclear that sufficient blockade of D_3 receptors was achieved to provide an adequate test of this possibly important mechanism of action.

Atypical APDs, including amisulpride, have modest effects to improve some domains of cognition (Woodward et al. 2005; Wagner et al. 2005). The ability of the 5-HT_{2A}/D_2 antagonists to increase DA and acetylcholine (ACh) efflux in PFC and hippocampus, which depends, in part, on their serotonergic actions, may contribute to this (Kuroki et al. 1999; Ichikawa et al. 2002a; Huang et al. 2012). No studies have been published on the ability of amisulpride to enhance cortical DA or ACh efflux. However, the closely related substituted benzamide, sulpiride, does enhance the efflux of DA in rat cortex and nucleus accumbens (Ichikawa et al. 2001). The combination of a saturating dose of a 5-HT_{2A} inverse agonist/antagonist with a dose of a D_2 antagonist which only partially blocks D_2 receptors

leads to increased DA release in the frontal cortex (Liegeois et al. 2002; Bonaccorso et al. 2002; Li et al. 2005). 5-HT_7 antagonism and 5-HT_{1A} partial agonism can also potentiate the ability of lurasidone, an atypical APD, to enhance cortical DA efflux (Huang et al. 2012). In addition, the atypical APDs enhance efflux of ACh in the PFC and hippocampus of rodents (Parada et al. 1997; Ichikawa et al. 2002a; Shirazi-Southall et al. 2002; Chung et al. 2004). It is possible that this effect may also contribute to their ability to improve cognition. However, an in vivo imaging method for muscarinic receptor activation indicated that clozapine and olanzapine administration led to blockade of frontal cortical M_1 receptors despite the release of ACh (Nguyen et al. 2010). Presumably, atypical APDs which increase cortical and hippocampal ACh efflux will also enhance nicotinic receptor activation, which may well have value for improving cognition and negative symptoms (Wallace and Porter 2011). However, olanzapine and clozapine are the only two atypical APDs which are muscarinic antagonists. Thus, the other atypical antipsychotics that enhance ACh efflux should lead to muscarinic as well as nicotinic receptor stimulation.

There is extensive evidence that atypical APDs related to clozapine ameliorate the NOR deficit in rodents that follows a subchronic PCP regimen, whereas typical APDs do not, even when augmented with 5-HT_{2A} inverse agonists or 5-HT_{1A} partial agonists (Snigdha et al. 2010; Meltzer et al. 2011). For example, clozapine, risperidone, quetiapine, perospirone, or sertindole, but not haloperidol, when administered acutely or once daily for 2 weeks attenuated the NOR deficit following subchronic PCP exposure in mice (Hashimoto et al. 2005) or rats (Grayson et al. 2007; Hagiwara et al. 2008; Tanibuchi et al. 2009; McLean et al. 2010). Similar differences between clozapine and haloperidol have been reported for improving acute MK-801-induced NOR deficits (Karasawa et al. 2008). We have reported recently that a single dose of the atypical APDs, lurasidone, melperone, *N*-desmethylclozapine, and risperidone, but not haloperidol, significantly reversed impairment in NOR subsequent to 7 days treatment with PCP 2.0 mg/kg i.p. bid (Snigdha et al. 2010; Horiguchi and Meltzer 2012; Horiguchi et al. 2011a, b). In addition, the combination of ACP-103 or M100907, with subeffective doses of lurasidone, melperone, risperidone, restored NOR performance in rats treated previously with subchronic PCP. M100907 was ineffective when combined with haloperidol (Snigdha et al. 2010). Furthermore, pretreatment with haloperidol, 0.1 mg/kg, negated the ability of risperidone to reverse the effect of subchronic PCP on NOR, without impairing locomotor activity, indicating the importance of the 5-HT_{2A}-D_2 ratio for this memory-improving effect of atypical APDs (Snigdha et al. 2010). The selective 5-HT_{2A} inverse agonists, M100907 and ACP-103, alone, at doses that fully occupy 5-HT_{2A} receptors (Kehne et al. 1996; Vanover et al. 2006) did not reverse the effects of subchronic PCP on NOR (Snigdha et al. 2010). In contrast with these negative results in the PCP model in rodents, Gozzi et al. (2010), using pharmacological magnetic resonance imaging, found that the disruptive effects of acute treatment with PCP on the fronto-temporo-hippocampal patterns of rat brain corticolimbic activity were markedly attenuated by pretreatment

with M100907, but not by the D_1 antagonist SCH 23390. They interpreted their results to rule out a significant contribution of DA in the functional changes mapped in favor of a key role of cortical 5-HT_{2A} receptors in modulating glutamate-mediated cognitive performance. Furthermore, M100907 and ACP-103 alone are sufficient to block the locomotor stimulating effects of acute PCP and these selective 5-HT_{2A} inverse agonists also block the effect of NMDA receptor antagonists on the firing rates of pyramidal neurons (Wang and Liang 1995). These results suggest that blockade of 5-HT_{2A} receptors may be sufficient to produce an antipsychotic effect but not to improve cognition by this mechanism alone. The inability of low-dose haloperidol plus ACP-103 to reverse the effect of subchronic PCP treatment on NOR indicates that the combination of D_2 and 5-HT_{2A} receptor blockade is insufficient to reverse the effects that follow subchronic PCP exposure. As will be discussed, 5-HT_{1A} agonism may be contributing significantly to the ability of some of the atypical APDs related to clozapine to reverse the impairment in various types of cognitive impairment that follows subchronic PCP treatment.

There is extensive recent interest in the role of cytokine-mediated inflammation in both the psychosis and cognitive impairment in schizophrenia, based in part, but not only, upon the evidence for inflammation affecting neurodevelopment in animal models of schizophrenia and the increased risk for schizophrenia conveyed by maternal infections and birth complications (Nawa and Takei 2006; Nichols 2009). 5-HT and its precursor tryptophan are involved in the regulation of immune function (Mössner and Lesch 1998). In particular, 5-HT_{2A} receptors have been shown to have an exceptional action upon the actions of the proinflammatory cytokine, tumor necrosis factor-alpha (TNFα; Yu et al. 2008). Activation of 5-HT_{2A} receptors in primary aortic smooth muscle cells by DOI rapidly inhibits a variety of TNF-α-mediated proinflammatory markers, including the interleukin (IL)-6 and NFκB gene expression (Yu et al. 2008). Atypical and typical APDs differ on their ability to promote the stimulation of pro-and anti-inflammatory cytokines from various peripheral and presumably central sites (Chen et al. 2012). It has been suggested that blockade of 5-HT_{2A} receptors by atypical APDs may be proinflammatory and contribute to weight gain and atherosclerotic heart disease (Nichols 2009). Whether there is a connection between inflammation and efficacy or side effects of atypical APDs based on serotonergic differences among these agents will require extensive research to unravel.

2.4 5-HT_{2A} Receptors, 5-HT_{2A} Receptor Blockade and Antipsychotic Activity: Clinical Evidence

Supporting the importance of 5-HT_{2A} receptor blockade, decreased density of 5-HT_{2A} receptors and decreased levels of 5-HT_{2A} receptor mRNA in various cortical and hippocampal regions have been demonstrated in postmortem

studies of patients with schizophrenia (see Matsumoto et al. 2005 for review), possibly the results of downregulation of these receptors to diminish the effect of 5-HT_{2A} receptor stimulation (Burnet et al. 1996). This finding suggests that the decreases in cortical 5-HT_{2A} receptor density result from alterations at the level of transcription. Recent PET studies have also shown decreased density of 5-HT_{2A} receptors in frontal cortex of drug-naïve patients with first episode schizophrenia or drug-naïve patients with prodromal symptoms and behaviors characteristic of patients with a high risk of conversion to first episode psychosis (Rasmussen et al. 2011; Hurlemann et al. 2008). The increased risk for schizophrenia in the adult offspring of women who contract an influenza infection has been linked to the 5-HT_{2A} receptor. The offspring of mice with maternal exposure to influenza virus show increased head-twitch responses to hallucinogens. The frontal cortexes of mice born to influenza virus-infected mothers have upregulated 5-HT_{2A} receptors and altered cortical 5-HT_{2A} receptor-dependent signaling pathways (Moreno et al. 2011).

5-HT_{2A} receptor blockade has been found to diminish psychosis in both acutely psychotic chronic schizophrenia patients and L-DOPA-induced psychosis in patients with Parkinson's disease (Meltzer et al. 2010). Ritanserin, a 5-$HT_{2A/2C}$ antagonist, was effective in treating acutely psychotic schizophrenia patients in a small, open trial (Wiesel et al. 1994). As previously mentioned, another 5-$HT_{2A/2C}$ selective antagonist, SR 46349B (Rinaldi-Carmona et al. 1992), was not significantly different from haloperidol in treating acutely psychotic patients with schizophrenia in a double blind, randomized clinical trial with haloperidol as active comparator (Meltzer et al. 2004). Similar results have been found with M100907 (Potkin S, personal communication, December 2011). However, the latter results have only been presented at scientific congresses and not peer reviewed. Pimavanserin, a selective 5-HT_{2A} inverse agonist (Vanover et al. 2006; Li et al. 2005), potentiated the ability of risperidone to improve psychotic symptoms in acutely psychotic patients with schizophrenia (Meltzer et al. 2012). Doses of clozapine, quetiapine, and melperone which are ineffective in treating schizophrenia have been found to be effective and tolerable in the treatment of L-DOPA psychosis (see Meltzer et al. 2010 for discussion). At these doses, e.g., clozapine 12.5–50 mg/day, the only shared pharmacology is blockade of 5-HT_{2A} receptors. Melperone lacks 5-HT_{1A} partial agonism or 5-HT_{2C} receptor affinity. Quetiapine has too weak an effect as a 5-HT_{1A} partial agonist to attribute its antipsychotic properties in L-DOPA psychosis to this mechanism. Pimavanserin, which is highly selective for 5-HT_{2A} receptors compared to SR46349B and is lacking in affinity for D_2 receptors, was also effective as monotherapy in the treatment of L-DOPA psychosis in a placebo-controlled, double blind trial (Meltzer et al. 2010). Sufficient D_2 receptor blockade to achieve control of psychosis under these conditions is highly unlikely and would have caused severe motor side effects, which it did not. The results of Phase 3 trials of pimavanserin for the treatment of L-DOPA psychosis should be available in 2012.

3 The 5-HT$_{1A}$ Receptor as a Target for Antipsychotic Drug Action

3.1 *Neurobiology of 5-HT$_{1A}$ Receptors in Atypical Antipsychotic Drug Action*

5-HT$_{1A}$ receptors are particularly dense in the CA1 region and dentate gyrus of the human hippocampus, as well as in layer II of the cortex (Hoyer et al. 1986). Kargieman et al. (2012) recently demonstrated that the ability of clozapine to prevent PCP-induced disruption of cortical rhythms was diminished in 5-HT$_{1A}$ knockout mice or following pretreatment with the 5-HT$_{1A}$ antagonist, WAY-100635. However, clozapine's efficacy in this model in 5-HT$_{2A}$ knockout mice was not different from wild-type mice. 5-HT$_{1A}$ agonism often achieves the same functional effect as 5-HT$_{2A}$ antagonism in animal models of antipsychotic activity (see Meltzer and Huang 2008, Sumiyoshi et al. 2008; Newman-Tancredi 2010), e.g., decreasing catalepsy due to D$_2$ receptor blockade or blockade of conditioned avoidance response and amphetamine-induced locomotor activity (Wadenberg 1992). Some atypical APDs, including aripiprazole, bifeprunox, clozapine, lurasidone, perospirone, quetiapine, and ziprasidone, are 5-HT$_{1A}$ partial agonists, and, as such, may either function as agonists or antagonists, depending upon the availability of endogenous 5-HT$_{1A}$ receptor density and brain region (Kalkman et al. 2001; Newman-Tancredi et al. 1998; Newman-Tancredi 2010). However, some actions in animal models which are relevant to efficacy in schizophrenia of even those atypical APDs such as olanzapine and risperidone which lack significant affinity for 5-HT$_{1A}$ receptors, e.g., the release of cortical DA or ability to reverse the deleterious effects of subchronic PCP on memory in rodents, are inhibited by a selective 5-HT$_{1A}$ antagonist, e.g., WAY-100635 (Ichikawa et al. 2001, 2002a, b; Assié et al. 2005; Rollema et al. 1997; Ichikawa et al. 2001, 2002b; Chung et al. 2004; Diaz-Mataix et al. 2005; Horiguchi et al. 2011a, b).

3.2 *5-HT$_{1A}$ Receptor Contribution to Antipsychotic Drug Effects on Cognitive Function*

There is both preclinical and clinical evidence for the potential of 5-HT$_{1A}$ partial agonists to improve cognition in schizophrenia and possibly other neuropsychiatric disorders. Stimulation of 5-HT$_{1A}$ receptors in brain has been suggested to be an important target for improvement of cognitive impairment in schizophrenia (Meltzer and McGurk 1999; Bantick et al. 2001). This suggestion is consistent with the theory that diminished DA release in the cortex and hippocampus might be an important cause of cognitive impairment (Goldman-Rakic and Selemon 1997). As previously discussed, atypical APDs related to clozapine enhance cortical DA (and ACh) release. This effect has been suggested to be due, in part, to their 5-HT$_{1A}$

receptor agonist properties or secondary to 5-HT efflux due to combined blockade of 5-HT_{2A} and D_2 receptors. WAY-100635, a 5-HT_{1A} antagonist, blocks the effect of atypical APDs to increase DA release. Furthermore, selective 5-HT_{1A} receptor partial agonists increase rat cortical DA release (Ichikawa et al. 2001, 2002a, b). Gronier (2008) demonstrated that systemic administration of the 5-HT_{1A} agonist 8-OH-DPAT activated VTA DA neurons by diminishing a GABA B-dependent inhibitory effect on descending cortical glutamatergic innervation of the VTA neurons. This hypothesis was supported by Lladó-Pelfort et al. (2012); however, these authors suggested a GABA A, rather than GABA B, involvement. The effect of 5-HT_{1A} agonists to reduce the transport of NMDA receptors along pyramidal neurons, leading to diminution of NMDA currents, may be another means by which 5-HT_{1A} agonists might affect the cognition-disrupting effects of NMDA receptor antagonists (Yuen et al. 2005, 2008).

Subchronic treatment with PCP significantly decreased the density of 5-HT_{1A} receptors in mouse hippocampus but not cortex (Hagiwara et al. 2008). 5-HT_{1A} agonists have been reported to reverse the cognitive impairment in NOR following withdrawal of the NMDA noncompetitive antagonist PCP. The ability of three atypical APDs perospirone, aripiprazole, and lurasidone to block the effects of subchronic PCP on NOR was blocked by pretreatment with WAY-100635, indicating a requirement for 5-HT_{1A} receptor stimulation to reverse the effect of PCP on this measure (Hagiwara et al. 2008; Nagai et al. 2009; Horiguchi and Meltzer 2012). Furthermore, we have now tested the effect of the selective 5-HT_{1A} partial agonists, tandospirone and buspirone, on the NOR deficit that follows subchronic PCP treatment (Horiguchi and Meltzer 2012). Tandospirone significantly reversed the NOR deficit following subchronic PCP; this effect of tandospirone was blocked by pretreatment with WAY-100635. The effect of buspirone to reverse the effect of PCP was much weaker than that of tandospirone. The difference in efficacy in this model between tandospirone and buspirone may be due to the difference in the 5-HT_{1A} partial agonism of these compounds. It has been reported that tandospirone is almost a full agonist for 5-HT_{1A} receptors and more potent as a 5-HT_{1A} agonist than buspirone (Tanaka et al. 1995; Newman-Tancredi et al. 1998). The ability of tandospirone to improve NOR in rats treated previously with PCP was also blocked by pretreatment with haloperidol, 0.1 mg/kg, as was the case for risperidone and lurasidone (Snigdha et al. 2010; Horiguchi and Meltzer 2012). Shin et al. (2010) reported that Parishin C, a natural product, which is a 5-HT_{1A} partial agonist, at doses of 50 and 100 mg/kg ip, when administered with PCP for 14 days to mice, attenuated the deleterious effects of PCP on NOR, forced swimming time, and social interaction. The effect of Parishin C was antagonized by WAY-100635 during the withdrawal period from PCP, indicating that the action of Parishin C treatment was mediated through 5-HT_{1A} agonism. The combination of the selective DA D_1 receptor antagonist SCH 23390 with WAY-100635 was needed to block the effect of aripiprazole to reverse impairment in NOR in mice (Nagai et al. 2009). This result implicates stimulation of both DA D_1 and 5-HT_{1A} receptors in the beneficial effects of aripiprazole on the NOR deficit seen after prior subchronic PCP treatment. There have been no studies of the effect

of acute administration of 5-HT_{1A} agonists on the cognitive impairment or locomotor stimulation due to PCP or MK-801.

Scorza et al. (2010) concluded that 5-HT_{1A} receptor effects of clozapine were not related to its antipsychotic action since the ability of clozapine to block the effects of MK-801 to increase locomotor activity, a model of its antipsychotic potential, did not differ in 5-HT_{1A} knockout and wild-type mice (Scorza et al. 2010). Bifeprunox is a 5-HT_{1A} partial agonist, D_2 antagonist, without appreciable 5-HT_{2A} antagonist properties (Casey et al. 2008) which was considered to be less effective than aripiprazole which has both 5-HT_{1A} and 5-HT_{2C} partial agonism and 5-HT_{2A} antagonism to complement its D_2 receptor partial agonism. Novel atypical APDs which combine D_2 antagonism and 5-HT_{1A} partial agonism, in lieu of 5-HT_{2A} antagonism, are in development for the treatment of schizophrenia, e.g., F15603, which is a potent 5-HT_{1A} partial agonist, D_2 and D_4 antagonist, with weak affinity for 5-HT_{2A} receptors, and has the properties of an atypical antipsychotic drug (Depoortere et al. 2007; Bruins Slot et al. 2009). However, there are no clinical data of which we are aware with this compound. As will be discussed, there is evidence for 5-HT_{1A} partial agonists to enhance cognition in patients with schizophrenia as augmenting agents. Whether there are advantages to atypical APDs which have both 5-HT_{2A} inverse agonism and direct or indirect 5-HT_{1A} agonism over atypical APDs which have 5-HT_{1A} agonism and lack sufficient 5-HT_{2A} antagonism is unknown.

There is also evidence that stimulation of 5-HT_{1A} receptors leads to worsening and blockade of 5-HT_{1A} receptors leads to improvement in specific types of cognitive performance in rodents (Elvander-Tottie et al. 2009; Meneses and Perez-Garcia 2007). Thus, the 5-HT_{1A} antagonist WAY-100635 attenuated the deficit in a radial arm maze reference memory task produced by MK-801 (Boast et al. 1999). However, subchronic administration of WAY-100635 did not improve impairment in NOR in mice induced by subchronic treatment with PCP (Hagiwara et al. 2008; Nagai et al. 2009; Horiguchi and Meltzer 2012). Acute WAY-100635 administration also did not impair NOR in normal rats nor did it attenuate the subchronic PCP-induced NOR deficit (Horiguchi and Meltzer 2012). Subchronic treatment with PCP which impairs various forms of cognitive function has been reported to increase 5-HT_{1A} receptor binding in the medial–prefrontal and dorsolateral–frontal cortex of rats and to decrease D_1 receptor density in the medial and lateral caudate–putamen (Choi et al. 2009). This effect may be the basis for the ability of subchronic PCP treatment to enhance the ability of 5-HT_{1A} receptors to regulate NMDA receptors in a subset of PFC pyramidal neurons (Gu et al. 2007). These two effects of subchronic PCP may explain why the 5-HT_{1A} agonist tandospirone was able to reverse the impairment in NOR produced by subchronic PCP (Horiguchi and Meltzer 2012). Tandospirone has been reported to be effective to improve some domains of cognition in some patients with schizophrenia (Sumiyoshi et al. 2000, 2001a, b). This finding is the best available evidence for the role of 5-HT_{1A} agonism to improve cognition in schizophrenia but only a relatively small number of subjects were studied and only some domains of cognition improved.

Hahn et al. (2012) recently collected 5-HT_{1A} receptor binding data in normal subjects indicating an important modulatory effect of 5-HT_{1A} receptors on the default mode network (DMN), the resting brain state that is important for declarative memory and theory of mind. The DMN is the brain state demonstrable by its consistent deactivation during cognitive-demanding tasks, especially those requiring focused attention. The functional connectivity in the DMN has been reported to be abnormal in schizophrenia, as well as other psychiatric disorders (Salvador et al. 2010). The two key areas which linked 5-HT_{1A} receptor binding potential and DMN were the retrosplenial cortex and the posterior cingulate cortex, both important for schizophrenia. Because of the direct and indirect effects of atypical APDs on 5-HT_{1A} receptors discussed previously, studies of the DMN in patients treated with atypical APDs or 5-HT_{1A} partial agonists or antagonists require careful interpretation. Whether the effects of tandospirone and atypical APDs on cognition in schizophrenia are due, in part, to the effect of 5-HT_{1A} receptor stimulation requires careful study.

In summary, preclinical studies suggest that 5-HT_{1A} partial agonism contributes to the mechanism of action of atypical APDs to improve cognition in subchronic PCP or MK-801 induced models of cognitive impairment in schizophrenia. It may also contribute to their antipsychotic activity. The intrinsic activity of the 5-HT_{1A} partial agonists is of fundamental importance in this regard. Those that are too weak to initiate appropriate signaling, e.g., buspirone, have been disappointing clinically. Although bifeprunox, a 5-HT_{1A} partial agonist combined with D_2 partial agonism was disappointing in clinical trials in schizophrenia, it may still be worthwhile to bring to clinical trials a drug which combines 5-HT_{1A} partial agonism with D_2 antagonism providing the intrinsic activity of the 5-HT_{1A} component is sufficiently potent.

4 The Role of the 5-HT_{2C} Receptor in Antipsychotic Drug Action

4.1 Neurobiology of 5-HT_{2C} Receptors

The 5-HT_{2C} receptor is a 7-transmembrane G protein-coupled receptor present throughout the brain, including the VTA, nucleus accumbens, and PFC, including most pyramidal neurons (Hoyer et al. 1986; Vysokanov et al. 1998). The absolute density of 5-HT_{2C} receptors in mouse brain and the relative density of 5-HT_{2C} to 5-HT_{2A} receptors in mice is low compared to that of the rat, and especially man, requiring caution in interpreting studies of drugs affecting these receptors, in mice (Dougherty and Aloyo 2011). 5-HT_{2C} antagonism enhances DA efflux in the cortex and nucleus accumbens (Di Matteo et al. 1998; Meltzer and Huang 2008; Di Matteo et al. 1999; De Deurwaerdère and Spampinato 1999). The enhancement of cortical DA release by 5-HT_{2C} antagonism might be expected to be procognitive. Conversely, 5-HT_{2C} agonists, which suppress nucleus accumbens DA efflux, would be expected to have an antipsychotic action, a hypothesis which is supported by

preclinical and some clinical data. We have previously reported that WAY-163909, a selective 5-HT_{2C} agonist, suppressed DA efflux in the rat nucleus accumbens without inhibiting in the striatum and that MK-212, which is also an agonist at 5-HT_{2C} receptors, decreases the efflux of DA in wild-type but not 5-HT_{2C} receptor knockout mice (Huang et al. 2011). Suppression of cortical DA efflux would not be expected to have a beneficial effect on cognition.

Since the 5-HT_{2C} receptor is constitutively active, that is, it does not require stimulation by an agonist to be activated and to couple with signaling systems, it can regulate dopaminergic activity under basal as well as stimulated conditions (Barker et al. 1994; De Deurwaerdère et al. 2004; Leggio et al. 2009). Multiple forms of the 5-HT_{2C} receptor are present in brain because its mRNA can be edited after transcription at any or all of five adenosine sites. These forms differ in functional activity, with the more edited forms being less active constitutively (O'Neil and Emeson 2012). Many atypical APDs, among them asenapine, clozapine, fluperlapine, olanzapine, risperidone, sertindole, tiospirone, ziprasidone, and zotepine, are inverse agonists at rat and human 5-HT_{2C} receptors in vitro (Roth et al. 1992; Herrick-Davis et al. 2000; Rauser et al. 2001). On the other hand, some typical APDs (e.g., chlorpromazine, thioridazine, spiperone, thiothixene) are 5-HT_{2C} neutral antagonists, as indicated by their ability to reverse inverse agonist effects of clozapine at the 5-HT_{2C} receptor (Roth et al. 1992; Herrick-Davis et al. 2000; Rauser et al. 2001). The importance of differences between inverse agonists and neutral antagonists has not been investigated thoroughly. It may be that the ability to block constitutive activity of 5-HT_{2C} receptors conveys important advantages. Aripiprazole was found to be a 5-HT_{2C} partial agonist, with its intrinsic activity varying as a function of the editing of 5-HT_{2C} receptors (Zhang et al. 2006). It was found to be a full agonist at the unedited INI form of the 5-HT_{2C} receptors in Chinese hamster ovary (CHO) cells and a partial agonist at the partially edited VNI and fully edited VSV isoforms.

There is indirect evidence for enhanced mesolimbic DA release in response to an amphetamine challenge in drug-naive patients with schizophrenia which has been interpreted as evidence that patients with schizophrenia during an acute episode have increased presynaptic dopaminergic activity (Laruelle 1998; Abi-Dargham et al. 2009). If so, the ability of 5-HT_{2C} agonists to reduce DA release from terminals of VTA neurons in mesolimbic areas would be expected to have an antipsychotic effect. The selective 5-HT_{2C} agonist WAY-163909 (Dunlop et al. 2005) has been shown to have an antipsychotic profile in rodents, including much more potent inhibition of PCP- than amphetamine-induced hyperlocomotion (Marquis et al. 2007). WAY-163909 also reversed MK-801 but not amphetamine-induced deficit in PPI (Marquis et al. 2007). There are, as yet, no reported clinical trials with this compound. Because of functional selectivity of 5-HT_{2C} agonists (Cussac et al. 2008), it would be of interest to develop and test several such compounds. Several promising highly selective 5-HT_{2C} agonists with the ability to block PCP-induced impairment of PPI have recently been reported (Kozikowski et al. 2010). 5-HT_{2C} agonists should also be anorexigenic (Bays 2009), and, thus, of help to the many patients with schizophrenia or bipolar disorder who are overweight or obese due to poor diet, lack of exercise, and the side effects of some

psychotropic drugs, including some atypical APDs, and possibly a greater level of insulin-resistance than the general population. There have been four studies of editing of 5-HT_{2C} receptor mRNA in postmortem dorsolateral PFC of patients with schizophrenia, with inconclusive results. As reviewed by O'Neil and Emeson (2012), methodological deficiencies in these studies, especially undersampling of the number of clones for each form of the 5-HT_{2C} receptor, precludes drawing any conclusion about possible abnormalities in editing of the 5-HT_{2C} receptor mRNA in this region with the available data.

The 5-HT_{2C} neutral antagonists, SB228357 and SB242084, have been reported to reverse haloperidol-induced catalepsy in rats (Reavill et al. 1999; Creed-Carson et al. 2011). In both studies, the 5-HT_{2A} inverse agonist M100907 was without effect on haloperidol-induced catalepsy. Furthermore, in rats treated chronically with haloperidol, SB242084 but not M100907 attenuated the development of vacuous chewing movements, a proxy for tardive dyskinesia. Both studies suggested 5-HT_{2C} antagonism might be more important than 5-HT_{2A} antagonism for identifying atypical APDs. As can be seen in Table 1, seven of the atypical APDs referred to as serotonin–dopamine antagonists, aripiprazole, blonanserine, iloperidone, lurasidone, melperone, paliperidone, and ziprasidone, have very weak affinities for 5-HT_{2C} compared to 5-HT_{2A} receptors, ruling out 5-HT_{2C} antagonism as a common mechanism for low motor side effects. Seven others, asenapine, clozapine, *N*-desmethylclozapine, olanzapine, quetiapine, sertindole, and zotepine, are relatively potent 5-HT_{2C} antagonists compared to their 5-HT_{2A} antagonism.

5-HT_{2C} antagonism may contribute to their low EPS profile. Pimavanserin, another selective 5-HT_{2A} inverse agonist, but with greater affinity for 5-HT_{2C} receptors than M100907, was recently reported to diminish the EPS produced by haloperidol, 2 mg/day, in acutely psychotic patients with schizophrenia (Meltzer et al. 2012). Further study of the role of these two 5-HT receptors in diminishing EPS is needed.

4.2 The Effect of 5-HT_{2C} Receptor Agents on Cognitive Deficits

In addition to the possible importance of 5-HT_{2C} receptors for antipsychotic action and their more certain role in weight gain, there is also evidence for their importance for cognition. By correlating performance in the 5-choice serial reaction time (5-CSRT) task (a measure of attentional and executive function) with NMDA receptor antagonism-induced increases in glutamate and 5-HT in the PFC, Calcagno et al. (2009) demonstrated that 5-HT_{2A} antagonism and 5-HT_{2C} agonism recversed the NMDA receptor competitive antagonist (+/−)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP)-induced cognitive deficits observed in the 5-CSRT task, and that these effects are related to concomitant inhibition of prefrontal cortical glutamate and 5-HT release (Calcagno et al. 2009). These results suggest that combined 5-HT_{2C} agonism and 5-HT_{2A} antagonism present a promising mechanism for pharmacological treatment of psychosis and for the reversal of cognitive deficits in schizophrenia. However, as noted above, some atypical APDs are at least in vitro 5-HT_{2C} antagonists. This action may diminish their ability to improve cognition.

5-HT_{2C} agonists, e.g., lorcaserin, stimulate weight loss by decreasing energy intake (Martin et al. 2011). As 5-HT_{2C} antagonism is undesirable because of its positive effect on appetite (Somerville et al. 2007), it would appear desirable to develop APDs which are 5-HT_{2C} agonists, along with other useful actions, e.g., weak D_2 receptor antagonism or partial agonism, 5-HT_{2A} antagonism, and 5-HT_{1A} partial agonism. Down-regulation of the 5-HT_{2C} receptor was found in the alpha-calcium/calmodulin-dependent protein kinase II (alpha-CaMKII+/−) heterozygous mouse which has impaired neuronal development in the dentate gyrus of the hippocampus, severe deficits in working but not declarative memory as well as increased locomotor activity (Yamasaki et al. 2008). We have identified alstonine, a natural product used to treat psychosis in Nigeria, as a 5-HT_{2C} agonist in studies involving administration of alstonine to rats following subchronic treatment with PCP (Meltzer HY and Horiguchi M, unpublished data). The effect of alstonine to reverse the impairment in NOR produced by subchronic PCP was blocked by the 5-HT_{2C} inverse agonist, SB2060553, but not the 5-HT_{2C} neutral antagonist, SB242084. This finding provides further evidence for the importance of the constitutive activity of the 5-HT_{2C} receptors to the effects of NMDA receptor antagonists.

Linck et al. (2012), after learning of these findings, reported confirmatory evidence. In their studies, alstonine prevented MK-801-induced impairment in working memory and hyperlocomotion. These effects were blocked by the 5-$HT_{2A/2C}$ antagonist ritanserin.

However, it should be noted that stimulation of 5-HT_{2C} receptors has also been reported to promote psychosis-like behavior, at least in animal models. Canal et al. (2010) reported that the head twitch response (HTR), considered by many to be a behavioral proxy for hallucinations (Willins and Meltzer 1997; Canal et al. 2010) produced by the indole hallucinogen DOI was reduced approximately 50 % in 5-HT_{2C} knockout mice compared to their littermates. Further, pretreatment of both the C57BL/6J and DBA/2J strains of mice with either the 5-HT_{2C} receptor inverse agonist SB206553 or neutral antagonist SB242084 reduced the HTR by 50 % in the wildtype mice so that there was no longer a difference in the DOI-induced HTR between the wildtype and knockout mice strains. It was concluded that the HTR to DOI in mice is strongly modulated by 5-HT_{2C} receptor activity and that both, 5-HT_{2A} and 5-HT_{2C} receptor stimulation, rather than just 5-HT_{2A} receptor stimulation, may be important for head twitch and potential hallucinogenesis. Functional selectivity of 5-HT_{2C} receptor agonists may explain these apparently incompatible views about 5-HT_{2C} agonism.

5 The Role of the 5-HT_6 Receptor in Antipsychotic Drug Action

5-HT_6 receptors are expressed largely in the striatum, olfactory tubercle, nucleus accumbens, cerebral cortex, and hippocampus, which would suggest importance for schizophrenia and antipsychotic drug action (Ward et al. 1995). Their role in relation to schizophrenia, cognition, motor side effects, and obesity has recently

been reviewed in detail (Arnt and Olsen 2011; Marazziti et al. 2011). Some APDs, including clozapine, olanzapine, and sertindole, are relatively potent 5-HT_6 receptor antagonists (Monsma et al. 1993; Roth et al. 1994; Kohen et al. 1996; Arnt and Skarsfeldt 1998; Boess et al. 1998). The 5-HT_6 antagonist, SB-285585, significantly blocked the 5-hydroxytryptophan-induced increase in catalepsy in haloperidol-treated mice, suggesting the importance of this receptor to the low EPS profile of the atypical APDs, which are 5-HT_6 antagonists (Ohno et al. 2011). However, selective 5-HT_6 antagonists are ineffective in animal models of psychosis such as amphetamine-induced increase in locomotor activity (Gravius et al. 2011) or PCP-, apomorphine- or LSD-induced disruption in PPI (Leng et al. 2003).

There is considerable evidence from animal studies for a role for 5-HT_6 antagonists to improve cognition in animal models of schizophrenia as well as Alzheimer's disease. The selective 5-HT_6 antagonists, Ro 04-6790 and Lu AE58054 attenuated the acute MK-801-induced and subchronic PCP-induced deficits in NOR in rat, respectively (Pitsikas et al. 2008; Arnt et al. 2010) and improved NOR in normal rats (Gravius et al. 2011). Several novel 5-HT_6 antagonists were effective to improve NOR in scopolamine-treated adult Wistar rats (de Bruin et al. 2011). The scopolamine-induced deficit in working memory was prevented by the 5-HT_6 antagonist SB-271046 (Da Silva Costa-Aze et al. 2012). 5-HT_6 antagonists have been shown to increase acetylcholine efflux in rat cortex (Riemer et al. 2003). The effect of the 5-HT_6 antagonist SB-724457 alone and as augmentation of risperidone, which lacks potent 5-HT_6 antagonism, on cognitive function and some neurophysiologic measures in normal subjects included increased somnolence, a significant increase in the maximum plasma concentration of risperidone, and an increase of absolute EEG alpha and beta power. No significant effects of SB-742457 alone were found.

Further study of the influence of 5-HT_6 antagonists in patients with schizophrenia is still of interest (Liem-Moolenaar et al. 2011).

6 5-HT_7 Receptors and Antipsychotic Activity: Amisulpride, a 5-HT_7 Antagonist

The 5-HT_7 receptor is a G-protein-coupled receptor positively coupled to adenylyl cyclase. The highest density of 5-HT_7 receptor expression is present in the thalamus, hippocampus, and frontal cortex, suggesting a possible importance for schizophrenia (Plassat et al. 1993; Martín-Cora and Pazos 2004; Hedlund and Sutcliffe 2004). Further, the 5-HT_7 receptor has been shown to be involved in learning and memory (Hedlund and Sutcliffe 2004; Thomas and Hagan 2004). Serendipitously, several atypical APDs, including amisulpride, asenapine, clozapine, lurasidone, and risperidone, were found to have high affinity for this receptor (Roth et al. 1994; Abbas et al. 2009; Hedlund 2009; Ishibashi et al. 2010; Shahid et al. 2009). The 5-HT_7 antagonist, SB-269970, was recently reported to block amphetamine- and PCP-induced locomotor activity, although not as robustly as the 5-HT_{2A} antagonist,

M100907 (Waters et al. 2011). A series of compounds with potent affinity for 5-HT_7, as well as various DA receptors, have recently been reported to have antipsychotic activity (Zajdel et al. 2012).

The effect of a subeffective dose of lurasidone to enhance cortical DA efflux, which may be relevant for its ability to improve cognition and possibly negative symptoms and depression, was enhanced by the 5-HT_7 antagonist, SB-269970 (Huang et al. 2012). In vivo administration of the 5-HT_7 receptor antagonist (SB-269970) or lurasidone produced a significant and selective enhancement of NMDA receptor-mediated synaptic responses and surface expression of NR2A and NR2B subunits whereas the D_2 receptor antagonist haloperidol failed to do so (Yuen et al. 2012). There have been a number of studies of the effect of 5-HT_7 receptor antagonists or deletions on models of psychosis such as PCP-, ketamine-, or amphetamine-induced locomotor activity; some studies indicate that 5-HT_7 receptor deletion by mutation or pharmacologic blockade has antipsychotic drug-like activity in these models and others not (Pouzet et al. 2002; Semenova et al. 2008; Galici et al. 2008). Thus, PCP-induced disruption of PPI, which has been used to characterize APDs, was reduced in 5-HT_7 knockout compared to wildtype mice (Semenova et al. 2008). The hyperlocomotion induced by ketamine, an NMDA receptor antagonist, is another model of psychosis; it is also attenuated by the selective 5-HT_7 inverse agonist, SB-269970 (Galici et al. 2008). However, amisulpride, which has significant 5-HT_7 antagonist properties (Abbas et al. 2009), only weakly blocked MK-801-induced locomotor activity (Millan et al. 1999).

Several preclinical studies have attempted to test the possible relevance of 5-HT_7 receptors to the cognitive impairments in schizophrenia using NMDA receptor antagonist-treated rodents. Meneses (2004) reported that the 5-HT_7 antagonists SB-269970 and DR4004 reversed MK-801-induced memory deficits in an autoshaping Pavlovian/instrumental learning task. Moreover, SB-269970 improved reversal learning deficits induced by subchronic PCP in rats (McLean et al. 2009). SB-269970, as well as amisulpride, but not sulpiride, which has much weaker affinity for 5-HT_7 receptors than amisulpride, but similar affinities for D_2 and D_3 receptors, significantly reversed the subchronic PCP-induced NOR deficit (Horiguchi et al. 2011a). Further, AS19, a selective 5-HT_7 agonist, blocked the ameliorating effects of amisulpride in the NOR model of declarative memory (Horiguchi et al. 2011a). It was also reported that the ability of lurasidone to reverse the effects of PCP on NOR was potentiated by SB-269970 (Horiguchi et al. 2011a). The selective 5-HT_7 antagonist SB-656104-A administered before or after the NMDA receptor antagonist MK-801, significantly reversed impairment in learning and memory as assessed by the passive avoidance test. SB-656104-A administered post-training also counteracted the effect of MK-801 to impair performance in the Morris water maze test, suggesting a role of the 5-HT_7 receptor in memory consolidation (Horisawa et al. 2011). These data suggest that 5-HT_7 blockade may be a possible target for treatment of cognitive impairment in schizophrenia.

7 Conclusions

5-HT_{2A} receptors are important targets for APDs as well as to diminish EPS. There is robust and diverse evidence from basic and clinical studies for the importance of 5-HT_{2A}, as well as 5-HT_{1A}, 5-HT_6, 5-HT_7, and 5-HT_{2C} receptors, to various effects of specific atypical APDs. The 5-HT_{2A} antagonist property of many atypical APDs, in particular, contributes to their antipsychotic action and low EPS risk. While atypical APDs have been shown to be more effective than selective D_2 antagonists to improve cognition in rodents whose cognition is impaired following the withdrawal of NMDA receptor antagonists, it is still controversial whether atypical APDs can improve some domains of cognition in schizophrenia. 5-HT_{1A} partial agonism appears to be an important direct and indirect effect of many atypical APDs, and the possible basis for development of a novel class of atypical APDs, which have weak D_2 receptor antagonist properties. 5-HT_6 and 5-HT_7 antagonism may be useful to improve cognition but do not appear to have antipsychotic action. 5-HT_{2C} agonism may be useful to treat psychosis and to improve cognition in schizophrenia.

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Managing the Prodrome of Schizophrenia

W. Wolfgang Fleischhacker and Alexander M. Simma

Contents

Abstract It is a well-known fact that managing schizophrenia patients as early as possible has a positive impact on the psychopathological and psychosocial outcomes of the disorder. Identifying people at risk for this serious disorder before its outbreak has become a major research aim in the past decade. Consequently, the intuitive notion that intervening at this early stage, before a diagnosis of schizophrenia is established, could be a preventive measure has been scientifically studied. In this context, a number of interventions, both pharmacological and psychosocial, have been evaluated in prospective controlled clinical trials. Amisulpride, olanzapine, risperidone, omega-3 fatty acids, and antidepressants have been compared to placebo or other control interventions and have been found somewhat helpful. With the exception of omega-3 fatty acids, however, the original positive findings were not maintained in follow-up studies. In addition, the rates of conversion to psychosis, although generally lower in the experimental treatment groups, were also reasonably low in the control groups. Similar findings have been established in psychotherapy trials.

All evidence taken together makes it difficult to justify specific interventions at the prodromal stage of schizophrenia from the perspective of preventing or delaying the

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onset of the disorder. On the other hand, as many of the affected individuals suffer considerably, symptomatic treatment certainly is called for even though the evidence whether it should be pharmacological or psychosocial is not yet available.

Keywords Schizophrenia • Prodrome • High risk • Prevention • Antipsychotics • Antidepressants • Omega-3 fatty acids • Psychotherapy • CBT • Early intervention • Prophylaxis

1 Introduction

Schizophrenia is a serious mental disorder with a global lifetime risk of around 1 % of the population. For most of those affected, it is a lifetime illness associated with psychosocial impairments and a considerable negative impact on individual patients' and their significant others' quality of life as well as on indirect and direct health care cost. The World Health Report has ranked schizophrenia as number three on its list of disabling diseases (World Health Organization 2001).

Research in the past two decades has convincingly demonstrated that treating schizophrenia patients as early as possible not only improves the prognosis of the disorder to a considerable extent on a psychopathological and psychosocial level (Dell'osso and Altamura 2010) but also very likely reduces the negative impact of the disorder on the disease process regarding brain pathology (Malla et al. 2011). It is therefore imperative to manage schizophrenia as early as possible.

In the past decade, the interest in identifying people at risk for schizophrenia and reducing the risk that these individuals develop full-blown schizophrenia has been revived. All over the world, early detection and intervention centers have surfaced and the concept of basic symptoms, consisting of self-perceived thought and perception deficits, originally put forward by Gerd Huber et al. in Bonn in the 1950s (Gross and Huber 1985), has seen a renaissance. Various new descriptions and definitions were coined, such as for instance: At Risk Mental States (ARMS), Attenuated Psychotic Symptoms (APS) Brief Limited Intermittent Psychotic Symptoms (BLIPS), Ultra High Risk Individuals (UHR), all defined in Yung et al. (2004), Early Initial Prodromal States (EIPS, Ruhrmann et al. 2003), and Late Initial Prodromal States (LIPS, Ruhrmann et al. 2003). Most of these definitions include some cognitive deficits, psychotic symptoms which are not substantial, long, or persistent enough to fulfill full criteria for schizophrenia as well as objective and subjective functional impairment. A genetic risk may or may not be present as well. These definitions are, at least in part, based on earlier studies, which, through an elaborate systematic approach, attempted to retrospectively identify the symptoms preceding the outbreak of schizophrenia. This research has also identified depressive and negative symptoms before illness onset.

The psychosis task force of the American Psychiatric Association (APA) charged with revising diagnostic criteria for DSM-5 has put forward the suggestion to include an "Attenuated Psychosis Syndrome" as a diagnostic entity into the new American classification system, although this suggestion is still up for debate (http://www.dsm5.org).

Ideally, identifying individuals at risk for schizophrenia before the outbreak of the illness offers the opportunity of secondary preventive efforts which would spare these persons the grave psychosocial and neurobiological consequences of full-blown schizophrenia. Studies to this end have been and are being conducted in centers all over the world. Results from published prospective, mostly randomized, controlled clinical trials and conclusions which can be currently drawn from these will be discussed in the following chapters.

2 Interventional Controlled Clinical Trials

Since the turn of the century a number of controlled clinical trials have been conducted with the general aim to reduce the risk of conversion from a risk state to psychosis. Pharmacological, psychotherapeutic, or a combination of both measures have been applied. For the purpose of this book, the focus is on pharmacological interventions; psychotherapy studies are briefly summarized at the end of the chapter. Moreover, all of the studies described below have used slightly different definitions of the prodrome as well as somewhat different outcome criteria. The latter are detailed in the following chapters and in Table 1, the interested reader is referred to the original publications for the former.

2.1 Pharmacological Interventions

The available studies are summarized in Table 1. Pat McGorry et al. (2002) conducted the pioneering trial in their Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne. This was a randomized non-blinded study in which 59 patients were treated with either needs-based supportive psychotherapy or a combination of behavioral therapy (CBT) with low-dose oral risperidone. After 6 months of treatment 10 % of the patients in the experimental group (CBT + risperidone) met criteria for first episode psychosis as opposed to 36 % in the control group, constituting a significant difference with a number needed to treat (NNT) of four. Due to the fact that three additional patients converted to psychosis after an additional 6-month observation period, the statistical difference between groups was lost. However, when including adherence to risperidone into the equation, the difference between supportive psychotherapy and the specific intervention groups was maintained. Symptoms improved in both groups and functional levels were reported to remain stable, with no between group differences in either case. Only four patients suffered from minor side effects of risperidone which were relieved in all cases by dose reduction. A 3-year follow-up of almost 70 % of the participants of this study failed to demonstrate group differences regarding transition rate, level of symptomatology, or functioning but the authors found moderate

Table 1 Controlled pharmacological treatment trials in patients at risk for psychosis

Authors	Design	Experimental interventions	Control interventions	*n*	Length of intervention in months (follow-up)	Results
McGorry et al. (2002), Phillips et al. (2007)	Prospective randomized	CBT + risperidone	Needs-based supportive psychotherapy	59	6/(12)/(36)	6 mo: reduced conversion rates 12, 36 mo: no difference
Yung et al. (2011)	Prospective randomized double blind	CBT + placebo; CBT + risperidone	Needs-based supportive psychotherapy + Pbo	115	12/18	Low overall conversion rates, no group differences
McGlashan et al. (2006)	Prospective randomized double blind	Olanzapine + supportive psychoeducation	Pbo + supportive psychoeducation	60	12/(24)	No group differences in conversion rates, less positive prodromal sx on olanzapine, more weight increase on olanzapine
Ruhrmann et al. (2007)	Prospective randomized	Amisulpride + supportive psychoeducation	Supportive psychoeducation	124	24	More improvement of BS, APS, BLIPS on amisulpride, conversion rates not analyzed
Cornblatt et al. (2007)	Prospective naturalistic	Antipsychotics and Antidepressants according to "best practice guidelines" (polypharmacy common)	–	48	>6 (Ø 30.5)	Better adherence on antidepressants, differences regarding conversion rates not analyzed
Amminger et al. (2010)	Prospective randomized double blind	Omega-3 fatty acids + needs-based psychotherapy	Pbo + needs-based psychotherapy	81	3 (12)	Reduced conversion rate on Omega-3 fatty acids, sustained at follow-up

CBT cognitive behavioral therapy, *APS* attenuated psychotic symptoms, *Pbo* placebo, *BLIPS* brief limited intermittent psychotic symptoms, *BS* basic symptoms, *mo* months, *sx* symptoms

levels of psychiatric morbidity in a significant proportion of individuals and a continuing need and desire for care (Phillips et al. 2007).

The Melbourne group (Yung et al. 2011) also attempted to replicate their encouraging findings in a larger group of patients using a similar design as in their original study, comparing CBT and risperidone, CBT and placebo, and supportive therapy and placebo in 115 young people at ultra high risk for developing a psychotic disorder. In addition, they followed 78 persons who had not agreed to be randomized in an open, noninterventional manner. Only 7 % of the individuals in the study groups and 5.1 % of the observational group developed a psychotic disorder at the 6-month endpoint. Differences between groups concerning the main outcome conversion to psychosis were small and nonsignificant, most likely due to the low number of converters.

McGlashan et al. (2006) used a randomized double blind design to evaluate the effect of olanzapine on delaying, respectively preventing, conversion in individuals with prodromal symptoms. In four Prevention through Risk Identification Management and Education (PRIME) clinics 31 individuals received 5–15 mg olanzapine/day over the course of a 1-year study period and were compared with 29 persons on placebo. All were then followed for an additional year on no treatment. In the olanzapine group 16 % developed psychosis compared to 38 % on placebo, the group difference amounted to a trend level ($p = 0.08$). The NNT of 4.5 was comparable to the one reported by McGorry et al. (2002). All conversions in the olanzapine group occurred in the first month of treatment, while individuals on placebo converted continuously. Olanzapine reduced prodromal positive symptoms significantly more than placebo, but these symptoms worsened again when medication was discontinued. Two adverse events were prominent and different between groups. Patients on olanzapine more commonly were affected by fatigue (29 % vs. 3.4 % on placebo) and weight gain (61.3 % vs. 17.2 % on placebo). Patients on olanzapine gained almost 9 kg. Extrapyramidal symptoms did not differ between groups.

Ruhrmann et al. (2007) used a somewhat different approach in their study comparing a supportive needs-focused intervention with and without amisulpride in 124 individuals with putative prodromal symptoms. Rather than evaluating conversion rates, their main outcome criterion was the improvement in various prodromal symptoms including Attenuated Positive Symptoms (APS), Brief Limited Intermittent Psychotic Symptoms (BLIPS), and Basic Symptoms (BS). They found an advantage of amisulpride (mean dose 118.7 mg/day) over the non-pharmacological intervention in a 12-week treatment trial regarding BS, APS, BLIPS and full-blown psychotic symptoms. They also found more improvement regarding negative and depressive symptoms as well as global functioning in individuals treated with amisulpride. The main side effect of amisulpride was a non-dose-dependent increase in prolactin levels. Ruhrmann et al. (2007) make the point that patients with prodromal signs or symptoms should not only be managed to reduce the risk of conversion to psychosis but also to treat their subjective suffering.

Based on previous trials of polyunsaturated omega-3 fatty acids (PUFAs) in patients suffering from chronic schizophrenia which have led to ambiguous results and on evidence which indicates reduced concentrations of unsaturated fatty acids

in schizophrenia patients, Amminger et al. (2010) conducted a clinical trial investigating the potential protective effect of PUFAs in ultra high risk individuals. Omega-3 PUFAs play an important role in the membrane composition of neurons (Fenton et al. 2000) and have been shown to increase glutathione concentrations in the temporal lobes of first episode patients (Berger et al. 2008). Such effects may impact upon the risk to develop schizophrenia in two ways: on one hand via a neuroprotective, antioxidant route and on the other hand by modifying membrane permeability in dopaminergic and serotonergic neurons (Piomelli et al. 1991). In order to test this hypothesis, the authors compared a four times daily intake of capsules containing high concentrations of fish oil (700 mg eicosapentaenoic acid (EPA), 480 mg docosahexaenoic acid (DHA), 7.6 mg tocopherol (Vitamin E), and 220 mg other omega-3 fatty acids) with placebo capsules containing the same amount of vitamin E as well as 1 % of fish oil to imitate the taste of the active treatment. The double blind treatment protocol was continued for 12 weeks and patients were then followed up after 12 months. At follow-up the cumulative conversion rate was 4.9 % in the omega-3 group and 27.5 % in the placebo group ($p = 0.007$) amounting to an NNT of four. Next to the differences in conversion rates, positive, negative, and total symptoms as well as functioning also differed between fish oil and placebo. In addition to these encouraging results, two other details stand out: the high acceptance rate (76.4 %) and the low number of drop outs (6.2 %). It is most interesting to note that differences were apparent after 1 year despite the fact that the length of treatment only amounted to 3 months. Since fish oil capsules were tolerated extremely well, these findings, if replicated, would appear to hold considerable advantages over treatments with psychotropic drugs such as antipsychotics from an acceptance and safety perspective.

A different approach was employed by Cornblatt et al. (2007) who followed patients of the Zucker Hillside Hospital Recognition and Prevention (RAP) clinic in a prospective naturalistic study. Patients in this clinic were treated according to best practice guidelines by attending clinicians and assessed independently by the research team. The published report focuses on a sample suffering from Attenuated Positive Symptoms (APS) which were treated for at least 8 weeks with psychotropic drugs (commonly polypharmacy) and could be followed for at least 6 months (or until conversion). The main research questions were (1) which drugs are most commonly described against APS and (2) the efficacy of these medications on APS and adherence in young outpatients.

Antidepressants (as monotherapy, or in combination, or together with mood stabilizers) were most commonly used (in 42 % of the adolescent patients). They were usually well accepted and associated with reasonably low non-adherence rates (20 %). In contrast, adherence problems amounted to around 60 % in patients who were treated with second generation antipsychotics. Eleven of twelve patients who converted to psychosis were non-adherent. Given the naturalistic non-randomized design, a direct comparison of antidepressants and antipsychotics regarding the conversion rate was not possible, but Cornblatt et al. (2007) argue that antidepressants may exert their action via an indirect reduction of the basic vulnerability for schizophrenia by directly impacting on stress coping mechanisms.

In summary, all of the available clinical trials which have studied pharmacological interventions have demonstrated at least symptomatic improvements. The evidence concerning a positive impact on conversion rates to psychosis is less solid especially regarding a true prophylactic effect. Moreover, initial positive effects appear to dissipate over time. Further trials are needed to consolidate the available evidence and to answer the question whether pharmacological treatments merely postpone the onset of the disorder or truly prevent it.

2.2 Psychosocial Interventions

While the authors of the studies reviewed in the paragraphs above have focused on the assessment of the efficacy of pharmacological treatments, a number of groups have specifically researched psychosocial interventions, mostly evaluating the same outcomes, namely conversion to psychosis, symptomatic improvement, and psychosocial adaptation. In this context it is important to note that in three of the antipsychotic trials (McGorry et al. 2002; Ruhrmann et al. 2007; Yung et al. 2011) antipsychotics were combined with a psychotherapeutic intervention.

Similarly, Nordentoft et al. (2006) studied young individuals with features of schizotypal disorder and randomized them to either standard treatment or Integrative Therapy (IT) consisting of elements of the assertive community treatment model, social skills training, and psychoeducation. Pharmacotherapy was based on the clinical judgment of the treating psychiatrist and evenly distributed among the two treatment groups. The authors found significantly reduced conversion rates to schizophrenia spectrum diagnoses in the IT group.

Convergent findings were reported from studies that had evaluated cognitive behavioral therapy without concomitant antipsychotics vis-à-vis more unspecific supportive treatment measures. Morrison et al. (2004) in the UK, Addington et al. (2011a) in Canada, as well as Bechdolf et al. (2012) in Germany have performed such studies. With the exception of Addington et al. (2011a), who found no group differences, probably due to small sample size and generally low conversion rates, all of these trials demonstrated lower conversion rates in the experimental treatment group, supporting the hypothesis that specific psychotherapeutic interventions also reduce or delay the risk of converting to full-blown psychosis in individuals suffering from prodromal symptoms. Bechdolf et al. (2012), who also reported fewer conversions in an Integrated Psychological Intervention group, found no advantage of this treatment over supportive counseling after 1 year of treatment (Bechdolf et al. 2007) concerning social adjustment.

Patients accepted entering psychotherapy trials more readily than studies which offered pharmacological treatments and dropouts tended to be less frequent as well. In the only follow-up study available so far (Morrison et al. 2007) the main group differences found in their original 2004 report were not sustained. Interestingly, no study as yet has compared the effects of CBT to those of antipsychotics.

3 Discussion

All of these reports have demonstrated some advantages of whatever specific experimental treatment was studied over placebo or unspecific control interventions. These findings have been used to argue for treating people who are at risk for psychotic disorders before a definitive diagnosis of schizophrenia has been established. On the other hand, all of these studies have also demonstrated that the majority of patients on placebo or in the unspecific control condition did not meet diagnostic criteria for a psychotic disorder after an observation period of at least 1 year. This finding has sparked a debate that mainly focuses on two issues: Firstly, whether the proposed criteria for ultra high risk subjects or an attenuated psychosis syndrome (or whatever other term is used to define this group) really represent a clinically meaningful and valid concept and, secondly, whether such individuals should be treated prophylactically with either medication or psychotherapy or both.

When considering both issues, one is struck by a recent paper that has reported that despite the fact that a large number of individuals meeting risk criteria do not develop psychosis even if they are not treated, a considerable percentage suffer from a number of other psychiatric conditions, including anxiety and mood disorders, leading to disease burden and functional impairment (Addington et al. 2011b). In addition, a significant portion of those followed up improve and would no longer be considered symptomatic. These observations would argue that the proposed criteria are rather unspecific and only partially helpful in identifying patients who go on to develop a psychotic disorder.

The story becomes even more complicated when specifically considering the management strategies for persons meeting the proposed risk criteria. Although all interventions which have been evaluated so far have demonstrated some efficacy, a major concern is that around 60–80 % of all persons meeting the various at risk criteria do not convert to psychosis and would therefore be treated unnecessarily with measures that have a risk for side effects and are costly. In addition, potential positive effects appear to be short-lived. Even though one may argue about the adverse events of psychotherapy and the cost of omega-3-fatty acids, an additional risk remains for all of these interventions, namely the potential to induce stigma and discrimination which people suffering from mental health problems still incur. This stigma includes the potentially unjustified and damaging labeling of “at risk” individuals with a serious mental illness.

The fact that all of the currently available clinical trials have explored relatively short follow-up periods, generally amounting to about 1 year, presents another limiting factor in the attempt to translate findings derived from these studies to prophylactic measures of clinical utility. This concern is underscored by a recent report, documenting a conversion risk of 36 % 3 years after the emergence of prodromal symptoms (Fusar-Poli et al. 2012). Nevertheless, people who suffer from symptoms such as the ones mentioned above deserve attention and treatment even if not fulfilling any diagnostic criteria. Management options will range all the way

from supportive psychotherapy to specific psychopharmacological interventions but will need to be seen as symptomatic rather than prophylactic. Whether, in addition to reducing the risk of conversion to psychosis, the underlying disease process can also be affected by such interventions will have to be a topic of future research.

Studies which will identify risk factors that go beyond descriptive psychopathology by including neurobiological risk variables should help to enhance predictive power for conversion rates which will ultimately allow to target prophylactic interventions to specifically identified individuals. First studies applying neuroimaging methods provide promising preliminary evidence to this end (Koutsouleris et al. 2011; Howes et al. 2011).

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Metabolic Consequences of Antipsychotic Therapy: Preclinical and Clinical Perspectives on Diabetes, Diabetic Ketoacidosis, and Obesity

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Contents

Abstract Antipsychotic drugs, particularly second-generation antipsychotics (SGAs), have reduced the burden to society of schizophrenia, but many still produce excessive weight gain. A significant number of SGAs also act directly to impair glycemic control causing insulin resistance, impaired glucose tolerance and type 2 diabetes, and also rarely diabetic ketoacidosis (DKA). Schizophrenia itself is almost certainly causal in many endocrine and metabolic disturbances, making this population especially vulnerable to the adverse metabolic consequences of treatment with SGAs. Hence, there is an urgent need for a new generation of antipsychotic drugs that provide efficacy equal to the best of the SGAs without their

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liability to cause weight gain or type 2 diabetes. In the absence of such safe and effective alternatives to the SGAs, there is a substantial clinical need for the introduction of new antipsychotics without adverse metabolic effects and new antiobesity drugs to combat these metabolic side effects. We discuss the adverse metabolic consequences of schizophrenia, its exacerbation by a lack of social care, and the additional burden placed on patients by their medication. A critical evaluation of the animal models of antipsychotic-induced metabolic disturbances is provided with observations on their strengths and limitations. Finally, we discuss novel antipsychotic drugs with a lower propensity to increase metabolic risk and adjunctive medications to mitigate the adverse metabolic actions of the current generation of antipsychotics.

Keywords Antipsychotics • Diabetes • Diabetic ketoacidosis • Metabolic dysfunction • Obesity • Weight gain

Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
DKA	Diabetic ketoacidosis
FGA	First-generation antipsychotic
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide-1
HDL-C	High-density lipoprotein-cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
IOTF	International obesity task force
LDL-C	Low-density lipoprotein-cholesterol
SGA	Second-generation antipsychotic
SSRI	Selective serotonin reuptake inhibitor

1 Introduction

Numerous studies have reported that natural and unnatural deaths are increased significantly in schizophrenia. Cardiovascular disease (CVD) is a common cause of mortality, accounting for more than 30 % of deaths in these subjects. Studies report CVD mortality to be increased nearly fourfold in schizophrenia patients aged 18–49 years (Mortensen and Juel 1993; Osborn et al. 2007), demonstrating that CVD risk in schizophrenia has an early onset, together with a doubling of risk in 50–75 year olds. Patients with schizophrenia are particularly at risk from the CVD risk factors of obesity, hyperglycemia, dyslipidemia, and smoking-related disease, because they are more likely to have an unhealthy lifestyle (lack of exercise and poor diet) than the general population (Brown et al. 1999). They are reported to

have around three times more intra-abdominal fat than control subjects (Ryan et al. 2004) and 40–80 % have a body mass index (BMI) $\geq$ 20 % above normal. An estimated 75 % of schizophrenic patients are smokers (Newcomer 2005).

This review describes the effects of antipsychotic drugs on various metabolic risk factors, including weight, adiposity, and glycemic control. The contribution from these metabolic factors to the unacceptably high rates of cardiovascular morbidity and mortality suffered by patients with schizophrenia and related disorders is discussed. Since much has already been written about the relationship between antipsychotics and weight gain (e.g., Allison et al. 1999a, b; Newcomer 2005; Lieberman et al. 2005; Reynolds and Kirk 2010; De Hert et al. 2011c) about their metabolic side effects (Reynolds and Kirk 2010; De Hert et al. 2011c), we will focus more on insulin resistance and type 2 diabetes. We review the strengths and limitations of animal models of antipsychotic-induced metabolic disturbances. Finally, we describe the merits of antipsychotic drugs with lower cardiovascular risk and adjunctive medications to mitigate the adverse metabolic actions of the current generation of antipsychotics.

2 Metabolic Dysregulation and Cardiovascular Risk

2.1 Obesity

Obesity predisposes an individual to developing dyslipidemia, hypertension, proinflammatory atherogenesis, prediabetes (i.e., insulin resistance and impaired glucose tolerance), and type 2 diabetes (Mokdad et al. 2001; Pi-Sunyer 2002). Together, they increase cardiovascular morbidity and mortality (Montani et al. 2002; Beckman et al. 2002; Flack et al. 2003; Rashid et al. 2003; Law et al. 2003) and are implicated in cancer (International Obesity Task Force [IOTF] 2010), sleep apnoea, arthritis, gout, and gallstones (Wolk et al. 2003; Felson 1996; Bhole et al. 2010; Heshka and Heymsfield 2001). As discussed in this review, antipsychotic-induced weight gain is a major disincentive to treatment in patients.

2.2 Prediabetes, Type 2 Diabetes, and Diabetic Ketoacidosis

Type 2 diabetes (non-insulin dependent) causes increased cardiovascular morbidity, renal damage, neuropathy, and blindness. Many factors including obesity, visceral adiposity, and release of proinflammatory peptides reduce the ability of insulin to promote uptake of blood glucose into liver and skeletal muscle (insulin resistance). To maintain glucose homeostasis, pancreatic β-cells increase their release of insulin (hyperinsulinemia). As the disease progresses, insulin resistance gradually increases and pancreatic insulin secretion can no longer maintain glycemic control, resulting in

glucose intolerance and type 2 diabetes. In later stages, secretion of insulin by the pancreas declines dramatically (van den Oever et al. 2010; Abdul-Ghani and DeFronzo 2010; DeFronzo 2010; Herman and Kahn 2006). Management of type 2 diabetes with sulphonylurea drugs that promote insulin secretion may also contribute to loss of pancreatic β-cell function. The final stage of Type 2 diabetes is characterised by a profound loss of pancreatic β-cell mass whereby insulin secretion is reduced to the point at which individuals need to use injectable insulin to control blood glucose levels. Hypoinsulinemia also reduces insulin-mediated inhibition of lipolysis in adipose tissue, which can lead to diabetic ketoacidosis (DKA) (Eledrisi et al. 2006). Since type 1 diabetes is characterized by autoimmune-mediated loss of pancreatic β-cell function causing profound insulin deficiency, DKA is far more prevalent in this form of the disease. In the absence of insulin, hepatic glucose production rapidly increases whilst fatty acids are metabolized to ketone bodies, resulting in low blood pH (ketoacidosis). When the liberation of ketone bodies resulting in a low blood pH (ketoacidosis) is combined with glucose-induced osmotic diuresis, which depletes blood of potassium and sodium, it sets up a self-perpetuating, cycle of ionic dysregulation and dehydration that can lead to coma and death. Although DKA is rare, the use of atypical antipsychotic drugs is believed to have increased its incidence (Henderson 2001; Jin et al. 2002; Wilson et al. 2003; Reist et al. 2007).

3 Metabolic Dysregulation Associated with Schizophrenia

Evidence suggests that subjects with schizophrenia and schizo-affective disorders are similarly metabolically compromised in terms of glycemic control (insulin resistance, impaired fasting plasma glucose (FPG) [prediabetes], or type 2 diabetes). Although lifestyle factors and obesity unequivocally contribute, studies in first-degree relatives have shown that there is a strong contribution to impaired glycemic control (Spelman et al. 2007).

In a small clinical study comparing insulin resistance using a glucose tolerance test in drug-free, nondiabetic schizophrenic subjects and healthy volunteers, insulin sensitivity in individuals with schizophrenia was 42 % lower (Cohn et al. 2006). Moreover, a compensatory increase of insulin secretion was not present, indicating they had considerably greater risk of developing type 2 diabetes. Although this finding was not consistent across all studies (e.g., Spelman et al. 2007), the inability of insulin release to compensate for hyperglycemia may explain why schizophrenic subjects are prone to DKA when treated with second-generation antipsychotics (SGAs). Ryan et al. (2003) found that mean FPG and insulin concentrations were significantly higher in young, non-obese schizophrenia sufferers than the controls. Insulin resistance calculated by the homeostasis model assessment (HOMA-IR) was also significantly greater in the schizophrenic subjects. Finally, Spelman et al. (2007) performed a study in young, normal weight subjects, who fulfilled the criteria for first-episode, drug-naïve schizophrenia. Using a glucose challenge

test, plasma glucose and fasting insulin concentrations, insulin secretion, and HOMA-IR were all significantly greater in schizophrenic subjects and first-degree relatives than in controls. Impaired glucose tolerance was present in 11 % of patients with schizophrenia, 18 % of nonschizophrenic relatives, and in none of the healthy control subjects.

Although these studies were performed on small groups of subjects (because the number of newly diagnosed cases of schizophrenia not receiving medication is relatively small), the results consistently show that individuals with schizophrenia are much more likely to be prediabetic or to have type 2 diabetes than the general population. The fact that these metabolic disturbances are not necessarily linked to obesity and are present in nonschizophrenic, first-degree relatives (Spelman et al. 2007) indicates there is a strong genetic component. Moreover, this state of affairs exists even before patients are exposed to the cardiometabolic liabilities of treatment with first-generation antipsychotics (FGAs) or SGAs.

4 Adverse Metabolic Effects Associated with the Use of Antipsychotic Drugs

4.1 Effects of Antipsychotic Drugs on Bodyweight

As long ago as 1974, an Editorial in the British Medical Journal reported unusual patterns of weight gain with chlorpromazine. Interestingly, the article stated that this side effect occurred only rarely when other FGAs were used to treat schizophrenia. In the 1980s, reports of weight gain associated with use of depot formulations of FGAs started to appear (Johnson and Breen 1979; Silverstone et al. 1988). However, it was the introduction of the prototypical SGA clozapine that was linked to a high incidence of obesity (Cohen et al. 1990; Leadbetter et al. 1992). Meltzer's hypothesis that clozapine's unique profile as an antipsychotic drug derived from the ratio of its affinities for D_2 and 5-HT_2 receptors (Meltzer et al. 1989; Meltzer 1989) prompted the rapid discovery and development of the SGAs that currently dominate the treatment of schizophrenia. Allison et al. (1999b) produced the first systematic meta-analysis of the relative propensities of a wide range of FGAs and SGAs to induce weight gain. It established beyond doubt that many SGAs had much greater liability to cause substantial increases in bodyweight than the preceding FGAs. The article by Allison and colleagues contained a widely reproduced graph of corrected mean weight change at 10 weeks with molindone being weight-neutral and olanzapine and clozapine at the opposite end of the weight gain spectrum. Possibly excepting clozapine and ziprasidone, it has been frequently reported that weight gain plateaus on longer term antipsychotic treatment and differences for individual drugs become less pronounced (Stanton 1995; Haddad 2005; Gentile 2006). Although our analysis is not comprehensive, in Fig. 1a we ranked the weight changes for various FGAs and SGAs in studies where treatment ranged from 12 weeks to several years.

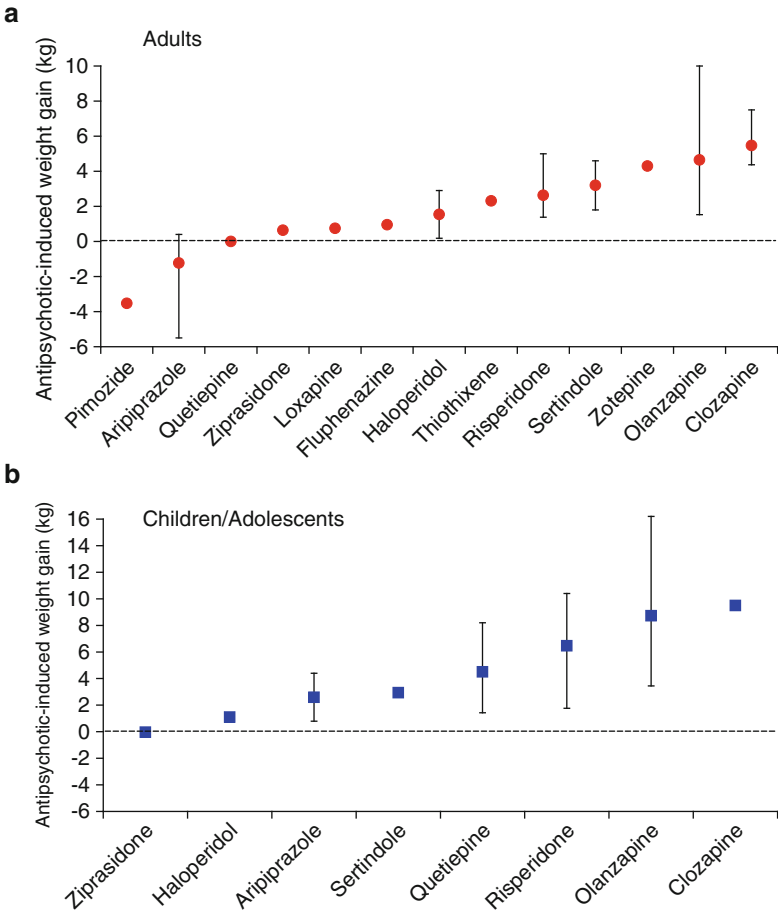

Fig. 1 Liability of various FGAs and SGAs to elicit weight gain. Data for adults are taken from studies with ≥12 week drug exposures. Ranges are shown where results were taken from several sources; Daniel et al. (1998), Allison et al. (1999b), Wetterling (2001), Ratzoni et al. (2002), Bobes et al. (2003), McQuade et al. (2004), Chrzanowski et al. (2006), Keck et al. (2007), De Hert et al. (2007), Kane et al. (2009), Correll et al. (2009), and De Hert et al. (2011a, b)

These results represent a time frame that is different from those reported by Allison et al. (1999b). Our analysis shows that clozapine, olanzapine, sertindole, zotepine, and risperidone cause the greatest weight gain in adults. Taking ≥7 % increases in bodyweight as clinically significant for cardiometabolic risk, Newcomer (2005) revealed that the percentage of subjects meeting this criterion was 41 % for olanzapine, >20 % for clozapine, 23 % for quetiapine, and 18 % for risperidone compared with 12 % for haloperidol. Similar findings were published by Bobes et al. (2003).

Mean bodyweight change data have also given rise to the misconception that certain SGAs, e.g., ziprasidone and aripiprazole, do not cause clinically significant weight gain. As reported by Newcomer (2005), 10 % of patients treated with

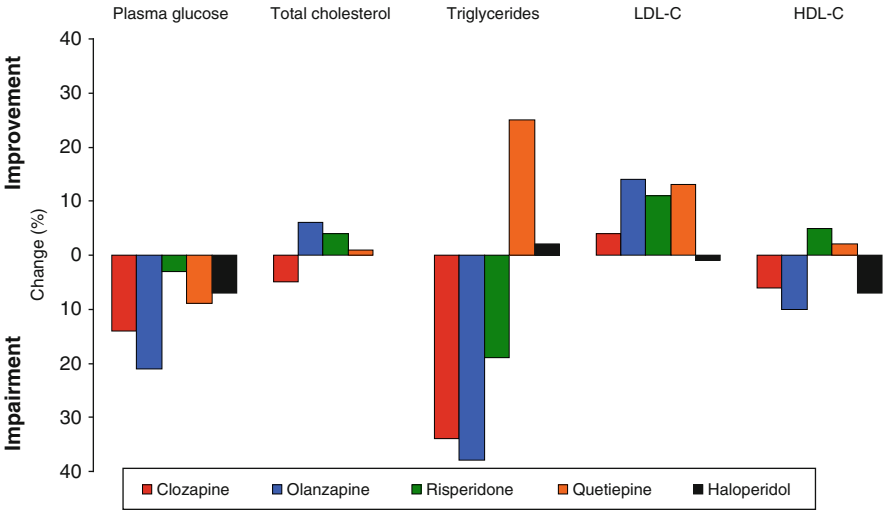

Fig. 2 Impact of various antipsychotic drugs on obesity-related cardiometabolic risk factors. Changes in the parameters are represented as percentage improvements or impairments relative to baseline. Data sourced from Wirshing et al. (2002)

ziprasidone experienced $\geq$7 % weight gain compared with 4 % of subjects on placebo. Similarly, Keck et al. (2006) reported that 13 % of patients on aripiprazole experienced $\geq$7 % weight gain compared with 0 % of control subjects.

Figure 1b shows weight change produced by antipsychotic drugs in children and adolescents. Once again, the drugs causing the greatest weight gain were clozapine and olanzapine. Since the data were taken from different sources, the assumption that clozapine induced more weight gain than olanzapine is misleading. In fact, in the trial by Fleischhaker et al. (2008), the rank order of weight gain was olanzapine $>$ clozapine $>$ risperidone. It is evident that SGAs pose a significant obesity risk in children/adolescents. Results with first-time use of SGAs in children/adolescents are even more troubling. Correll et al. (2009) reported mean increases in bodyweight after 11 weeks treatment of 4.4–8.5 kg for olanzapine, quetiapine, risperidone, and aripiprazole compared with 0.2 kg in the control group.

As obesity exacerbates cardio-metabolic risk factors, antipsychotic-induced weight gain would be predicted to have similar deleterious metabolic effects. However, the SGAs also produce unexpected changes in cardio-metabolic risk factors (Fig. 2). As examples, all of the SGAs reduce plasma LDL-C concentrations, and although clozapine, olanzapine, and risperidone increase plasma triglycerides, paradoxically quetiapine reduces them. In this regard, ziprasidone appears to be relatively benign with small reductions in both the fasting concentrations of glucose and triglycerides and no deleterious effects on waist circumference, blood pressure, or HDL-C (Meyer et al. 2008).

From this representative evidence, the SGAs have much greater propensity to induce clinically significant weight gain than the FGAs. Although some SGAs are worse than others, none is entirely devoid of risk.

4.2 Insights from Animal Models of Antipsychotic-Induced Weight Gain

There has been considerable debate on whether rodent models of antipsychotic-induced weight gain have "construct" and "translational" validity. This is because antipsychotics causing weight gain in humans frequently do not produce this effect in rodents and vice versa. During the development of sibutramine (Meridia®, Reductil®) in the late 1990s, we explored rodent models of neuroleptic-induced weight gain at a very early stage to evaluate whether this antiobesity drug would be effective in treating this adverse event.

We employed adult, outbred (Sprague–Dawley or Wistar), female rats maintained on reversed-phase lighting with free access to high fat diet. The rationale for selecting females was because they are relatively weight stable and a high fat diet was chosen as schizophrenia patients often eat unhealthy "junk food" (Brown et al. 1999). Although in many respects, the experimental conditions that we employed appear very similar to those used by other research groups, as will be discussed in this section, the subtle differences can have a substantial impact on the experimental outcome. The results from published studies and our own work on antipsychotic-induced weight gain in rodents, together with some of the key experimental conditions employed, are reported in Table 1.

As shown in Table 1 and Fig. 3b, administration of olanzapine to female rats consistently produces increases in bodyweight, and in some experiments, hyperphagia and/or increased adiposity. In many of these studies, the translational validity of the model has been tested using ziprasidone, one of the SGAs with the lowest propensity to cause weight gain in the clinic, as the negative control. Although ziprasidone has been reported not to increase the bodyweights of rats and mice in a substantial number of studies, weight gain has been observed in others (Table 1; Fig. 3c). It is important to note that this is often dependent on the dose used and duration of treatment (Fig. 3c). Various other FGAs and SGAs, e.g., haloperidol, sulpiride, and risperidone that cause moderate weight gain have also been studied in rodents. Again, the data are conflicting with most researchers observing weight gain, but a significant minority reporting either no effect or a mixed outcome (Table 1). The effects of these antipsychotics on the comorbid endpoints of hyperphagia and increased adiposity were similarly inconsistent across studies (Table 1). Clozapine is associated with a high risk of substantial weight gain (Allison et al. 1999b; Newcomer 2005), and although it has not been extensively investigated, its effects on hyperphagia, weight gain, and adiposity have also been determined in female rats. Cooper et al. (2008) investigated a wide range of doses (Table 1) and observed that this SGA did not increase bodyweight; at some doses, it even caused weight loss without altering food intake. The only reported adverse metabolic outcome was increased adiposity at certain doses (Cooper et al. 2008). In our model, we also found that clozapine did not cause weight gain but did produce hyperphagia when given acutely (Fig. 3a). Only at very high doses which caused sedation, was weight loss observed (Fig. 3a). Although such findings have

Table 1 Summary of the findings from various rodent models of antipsychotic weight gain

Female rats (juvenile)							
Drug	Dose and route	Duration	Diet	Weight	Hyperphagia	Adiposity	Author
Haloperidol	0.5 mg/kg ip	21 days	HF	↑	±	↑	Fell et al. (2005b)
Olanzapine	4 mg/kg ip	21 days	HF	↑	±	↑	
Risperidone	0.5 mg/kg ip	21 days	HF	↑	±	↑	
Sulpiride	10 mg/kg ip	21 days	HF	↑	↑	↑	
Ziprasidone	2.5 mg/kg ip	21 days	HF	±	±	±	
Female rats							
Drug	Dose and route	Duration	Diet	Weight gain	Hyperphagia	Adiposity	Author
Olanzapine	2 mg/kg ip	22 days	CD	↑	↑	↑ (NS)	Fell et al. (2007)
Risperidone	0.5 mg/kg ip	22 days	CD	±	±	±	
Ziprasidone	2.5 mg/kg ip	22 days	CD	±	±	±	
Olanzapine	0.5, 1, 4 mg/kg ip	21 days	SLC	↑	↑	↑	Fell et al. (2004a)
Olanzapine	2 mg/kg ip	28 days	HF	↑/↓	↑/↓	±	Fell et al. (2008)
Risperidone	0.5 mg/kg ip	28 days	HF	↑/±	↑/↓	±	
Ziprasidone	2.5 mg/kg/ip	28 days	HF	±	±	±	
Olanzapine	1, 2, 4 mg/kg ip bid	20 days	SLC	↑	↑/±	↑/±	Cooper et al. (2005)
Olanzapine	4 → 20 mg/day po	33 days	SLC	↑	↑	↑	Albaugh et al. (2006)
Clozapine	4 → 8 mg/day po	13 days	SLC	±	ND	±	
Olanzapine	1.75 mg/day sc osmotic pump	28 days	SLC	↑	↑	↑	Lykkegaard et al. (2008)
Clozapine	0.25–0.5, 1–4, 6, 12 mg/kg ip bid	20 days	SLC	↓	±	↑	Cooper et al. (2008)
Olanzapine	3 mg/kg po	21 days	HF	↑	↑	ND	RenaSci
Clozapine	1, 3, 10 mg/kg po	21 days	HF	±	↑	ND	
Ziprasidone	3, 10 mg/kg po	21 days	HF	↑/±	±	ND	
Haloperidol	0.1, 0.5, 1.0 mg/kg ip	21 days	SLC	↑	±	ND	Fell et al. (2004b)
Risperidone	0.1, 0.5, 1.0 mg/kg ip	21 days	SLC	↑	↑	ND	
Ziprasidone	1, 2.5 mg/kg ip	28 days	SLC	±	±	ND	Fell et al. (2005a)
Olanzapine	1.75 mg/day sc osmotic pump	14 days	SLC	↑	↑	ND	Wallingford et al. (2008)

(continued)

Table 1 (continued)

Olanzapine	3 mg/kg po bid	24 days	SLC	↑	↑	ND	Stefanidis et al. (2009)
Olanzapine	5, 20 mg/kg po	7 days	LP	↑	±/↑	ND	Pouzet et al. (2003)
Haloperidol	0.08, 0.31 mg/kg po	7 days	LP	↑	±	ND	
Sulpiride	20 mg/kg ip	21 days	HF	↑	↑ (?)	ND	Baptista et al. (1998)
Risperidone	0.5 mg/kg	12 days	HF	↑	↑	ND	Baptista et al. (2002a)
Sulpiride	20 mg/kg	12 days	HF	↑	↑	ND	
Olanzapine	2 mg/kg po bid	7 days	SLC	↑	ND	ND	Kalinichev et al. (2006)
Ziprasidone	2, 6, 10 mg/kg po bid	7 days	SLC	↑	ND	ND	
Olanzapine	4 mg/kg ip bid	20 days	SLC	↑	ND	ND	Goudie et al. (2002)
Male rats							
Drug	Dose and route	Duration	Diet	Weight	Hyperphagia	Adiposity	Author
Risperidone	0.125, 0.25, 0.5 mg/kg sc	16 days	HF	±	±	ND	Baptista et al. (2002a)
Clozapine	10 mg/kg sc	28 days	SLC	↓	↓	±	Smith et al. (2008a)
Haloperidol	0.25 mg/kg sc	28 days	SLC	↓	↓	±	
Quetiapine	10 mg/kg sc	28 days	SLC	±	±	↑	
Sulpiride	20 mg/kg ip	21 days	HF	±	±	±	Baptista et al. (2002b)
Olanzapine	5, 20 mg/kg po	21 days	LP	±/↓	±	ND	Pouzet et al. (2003)
Haloperidol	0.08, 0.31 mg/kg po	21 days	LP	±	±	ND	
Olanzapine	1, 2, 4 mg/kg ip bid	20 days	SLC	↓	±	↑	Cooper et al. (2007)
Olanzapine	0.1, 0.5 2 mg/kg po in diet	42 days	MF	↑	↑	ND	Minet-Ringuet et al. (2006)
Olanzapine	1 mg/kg po in diet	21 says	MF	↑	↑	ND	
Ziprasidone	10 mg/kg po in diet	21 days	MF	±	±	ND	
Haloperidol	1 mg/kg po in diet	21 days	MF	±	±	ND	
Olanzapine	1 mg/kg po in diet	35 days	MF	±	ND	↑	Minet-Ringuet et al. (2007)
Ziprasidone	10 mg/kg po in diet	35 days	MF	±	ND	±	
Haloperidol	1 mg/kg po in diet	35 days	MF	±	ND	±	
Olanzapine	5, 7.5,10 mg/kg po in diet	42 days	MF	↑/±	↑/±	↑	Shobo et al. (2011a)
Olanzapine	0.5, 1,2 mg/kg in diet	Acute	SLC	ND	↑	ND	

Ziprasidone	1.25, 2.5, 5 mg/kg in diet	42 days	MF	±	±	±	
Ziprasidone	0.3, 1, 3 mg/kg ip	Acute	SLC	ND	±	ND	
Female mice							
Drug	Dose and route	Duration	Diet	Weight gain	Hyperphagia	Adiposity	Author
Olanzapine	6 mg/kg po bid	28 days	SLC	↑	↑	↑	Cope et al. (2005)
Quetiapine	15, 30 mg/kg po bid	28 days	SLC	↑	↑	±	
Risperidone	0.125, 0.25 mg/kg po bid	28 days	SLC	↑	↑	±	
Ziprasidone	7, 10.5 mg/kg po bid	28 days	SLC	↑	↑	±	
Olanzapine	4 → 8 mg/day po	18 days	SLC	±	ND	ND	Albaugh et al. (2006)
Clozapine	4 → 8 mg/day po	18 days	SLC	±	ND	ND	
Risperidone	4 mg/kg po bid	21 days	LF	↑	↑	ND	Cope et al. (2009)
Male mice							
Drug	Dose and route	Duration	Diet	Weight gain	Hyperphagia	Adiposity	Author
Olanzapine	1.0, 1.5 mg/kg sc osmotic pump	42 days	MF	±	±	±/↑	Shobo et al. (2011b)

ND not determined, ± no change, ↑ increase, ↓ decrease, *SLC* standard laboratory chow, *HF* high fat diet, *MF* medium fat diet, *CD* cafeteria diet.

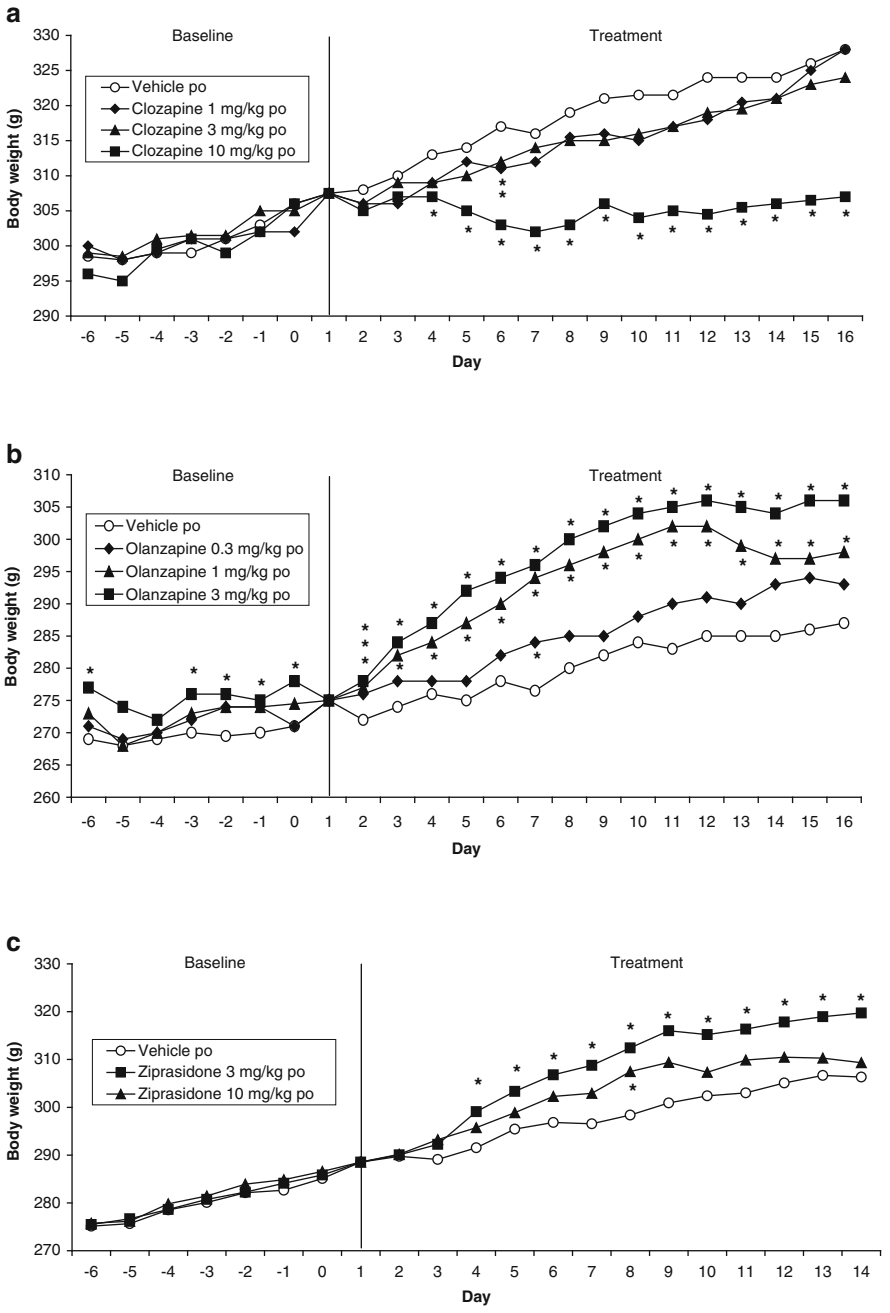

Fig. 3 Effects of repeated administration of (**a**) clozapine, (**b**) olanzapine, or (**c**) ziprasidone on bodyweight in female rats maintained on a high fat diet. Female rats were maintained in reversed-phase lighting and on a high fat diet. Drug treatment commenced Day 1. Results are adjusted means; $n = 10$. Data analyzed by ANCOVA with bodyweight on Day 1 as covariate. Multiple comparisons versus control group by Dunnett's test. Significant differences versus controls $^*p < 0.05$. Data on file RenaSci

prompted many researchers to dismiss rodent models as having little value in predicting the effects of antipsychotic drugs on weight, differences in protocols may have influenced experimental outcomes and contributed to the inconsistencies in the data. In addition to defining the optimal experimental conditions, this analysis has also examined the results to determine whether there are more predictive outcomes than simply measuring changes in bodyweight.

With the exception of studies published by Cope et al. (2005, 2009), Albaugh et al. (2006) and Shobo et al. (2011b), all experiments on weight gain have been conducted in rats. Although data in mice are limited, the observation that all antipsychotics, including ziprasidone, induced weight gain and hyperphagia (Cope et al. 2005) together with the finding that olanzapine failed to induce weight gain in two studies (Albaugh et al. 2006; Shobo et al. 2011b) clearly indicates that there is less differentiation between adverse metabolic actions of antipsychotic drugs in the mouse than in the rat.

When female rats are used, olanzapine consistently produces increases in bodyweight, and in the majority of studies, weight gain is observed with antipsychotics that have a moderate liability for weight gain in humans, e.g., risperidone, haloperidol, and sulpiride. The credibility of the model is generally questioned because ziprasidone has been reported to increase bodyweight or to produce equivocal outcomes (Table 1; Fig. 3c). Clozapine appears to be the most serious anomaly in the model. It causes weight gain in humans, but although it caused hyperphagia, it did not cause weight gain in our hands (Fig. 3a). It has even been reported to induce weight loss (Cooper et al. 2008). Although there are some notable dissentions (Shobo et al. 2011a, b), the majority view is that male rats are not suitable for modeling the effects of antipsychotic drugs on bodyweight because olanzapine and many other antipsychotics known to produce weight gain in man fail to produce this effect in them (Table 1).

The choice of dose, dosing intervals, route of administration, and duration of treatment are all factors that potentially influence experimental outcomes. A wide range of dose routes has been employed including oral, intraperitoneal and subcutaneous, with the drugs being given as discrete doses once or twice daily, or continuously by mixing the drug in the animals' food or via osmotic mini-pumps. The duration of dosing ranged between 7 and 42 days. From the data in Table 1, weight gain with olanzapine has been observed across a wide range of doses and dosing routes. Furthermore, changes in these variables do not provide an obvious explanation for the discordant findings obtained with ziprasidone and antipsychotic drugs that evoke moderate weight gain in humans. However, the duration of dosing does appear to have a significant influence on the outcome. Thus, in the case of ziprasidone, although some initial weight gain does occur in rats, tolerance tends to develop later in the study (Figure 3c), and for this reason drugs should be administered for a period of at least 14 days. With the exception of Fell et al. (2008), all studies report that excessive weight gain is maintained throughout treatment with antipsychotics that cause weight gain in humans. In several studies, (e.g., Pouzet et al. 2003; Cooper et al. 2005), the effects of the antipsychotic drugs on bodyweight and related comorbidities show an inverted U-shaped dose

relationship, which is discussed later. When administered once daily, we observed that the lighting phase influenced the actions of antipsychotic drugs on food intake. When female rats were maintained on reversed-phase lighting and drugs were administered just prior to the dark cycle, they induced hyperphagia, but this effect disappeared when rats were dosed prior to the light cycle. Rats are predominantly nocturnal feeders and these drugs have their greatest effect when given before the animals consume most of their daily diet.

On the basis of the results in Table 1, increased bodyweight in rats is not predictive of whether antipsychotics have potential to cause weight gain in humans. On the basis of the results presented in Table 1, an increase in bodyweight is not a definitive endpoint to determine whether antipsychotic drugs have the potential to cause weight gain in humans. Based on results obtained with olanzapine, antipsychotics with the potential to cause marked weight gain in humans will induce weight gain in rats, together with hyperphagia and/or increased adiposity. Other factors that distinguish olanzapine from antipsychotics with a lower propensity to cause obesity are increased weight gain in rodents across a range of doses and no evidence of tolerance to weight enhancement when the drug is given for prolonged periods. Conversely, antipsychotics with lower potential to induce obesity in humans, e.g., risperidone, haloperidol, and sulpiride, generally induce some degree of weight gain in rodents without producing hyperphagia or increased adiposity. The data reveal that female rats are more susceptible to the weight enhancing actions of antipsychotic drugs than males, but on the other hand, the possibility that hyperphagia will be recorded for an antipsychotic that causes moderate weight gain in humans is increased.

Reduced energy expenditure and/or decreased basal metabolic rate also significantly contribute to weight gain and there is evidence to show that both are influenced by antipsychotic administration. Stefanidis et al. (2009) reported that olanzapine produced a sustained increase in the bodyweight of female rats during 23 days treatment, even though hyperphagia was only apparent for ten of them. However, dark-phase activity and non-shivering thermogenesis in brown adipose tissue were decreased (Stefanidis et al. 2009). Similarly, risperidone-induced weight gain in female mice was associated with increased food intake and reduced locomotor activity (Cope et al. 2009).

Returning to the lack of dose-dependency for the actions of some antipsychotics on bodyweight, because changes in bodyweight are mediated by the effects of these drugs on feeding, locomotor activity and metabolic rate, it is probable that the relative contribution of each varies according to the dose of antipsychotic thereby accounting for the lack of a linear dose-response relationship. For example, although a sedative dose of a SGA is likely to reduce exercise and basal metabolic rate, it may also reduce food intake to such an extent that weight loss not gain occurs.

Finally, when assessing the translational validity of the models, it is important to define the positive and negative control responses. Ziprasidone is mostly used as a comparator with no propensity to cause weight gain in humans. Whilst this assessment is correct based on average data, in reality this drug simply causes less weight gain than most other antipsychotics. Furthermore, there is a significant minority of

ziprasidone-treated subjects whose weight increases substantially (Simpson et al. 2005; Hoffmann et al. 2010).

After taking all of these factors into account, the hypothesis that antipsychotic-induced weight gain in humans can be modeled by measuring the effects of these drugs on bodyweight in rodents must be treated with caution. However, olanzapine-induced weight gain in female rats is dose-dependent, and persistent. In addition, olanzapine and clozapine have been reported to induce hyperphagia when given acutely and increased adiposity when given repeatedly. We hypothesize that if these additional endpoints are employed, particularly induction of hyperphagia, the predictive validity of the model would be much improved. Although not definitively proven, the results in Table 1 suggest that by employing all three criteria, olanzapine can be differentiated not only from ziprasidone but also from antipsychotics that have the potential to cause moderate weight gain.

4.3 Antipsychotic Drugs and Type 2 Diabetes

The negative impact of the FGAs and SGAs on glycemic control can be subclassified into at least two major categories:

1. Indirect induction/exacerbation of hyperinsulinemia and insulin resistance/impaired glucose tolerance (prediabetes) as a secondary consequence of antipsychotic-induced weight gain and dyslipidemia.
2. The idiosyncratic, de novo induction of type 2 diabetes (possibly leading to DKA) by antipsychotic drugs.

Mechanisms responsible for these aspects of impaired glycemic control are probably not identical and reflect multiple pharmacological actions.

There is an increased risk of developing insulin resistance, impaired glucose tolerance, or type 2 diabetes with FGA treatment (Scheen and de Hert 2007; Smith et al. 2008b; De Hert et al. 2008; Yood et al. 2009; Nielsen et al. 2010; Vidarsdottir et al. 2010). A meta-analysis of 11 studies reported that overall relative risk for type 2 diabetes was higher for SGAs compared with FGAs (Smith et al. 2008b). De Hert et al. (2008) reported significantly more subjects with abnormal glucose levels after treatment with SGAs compared with FGAs. However, Nielsen et al. (2010) did observe that the hazard ratio for developing type 2 diabetes was similar for midpotency FGAs compared with clozapine or olanzapine and the chance of developing the disease within 3 months of treatment initiation was similar for low-potency FGAs and the SGAs. Part of the reason for this apparent discordance is because some analyses grouped all SGAs into a single cohort and there are marked differences between them in terms of adverse effects on glycemic control (Table 2). Clozapine and olanzapine have the greatest adverse impact on glycemic control and pose the highest risk of causing type 2 diabetes (Wirshing et al. 2002; Scheen and de Hert 2007; Yood et al. 2009; Nielsen et al. 2010; Newcomer 2005). Ziprasidone and aripiprazole are relatively benign in terms of adverse effects on glycemic control (Newcomer 2005; Scheen and de Hert 2007; Yood et al. 2009;

Nielsen et al. 2010). With midranked SGAs, i.e., quetiapine and risperidone, some studies demonstrate that their negative influence on glycemic control is not substantially different from olanzapine and clozapine (Scheen and de Hert 2007; Lambert et al. 2006), whilst others reported it was similar to the low risk SGAs or the FGAs (Wirshing et al. 2002; Yood et al. 2009).

Obesity is a major causal factor in pre-diabetes and Type 2 diabetes across the whole of the demographic range and it can, therefore, be concluded that antipsychotic-induced weight gain contributes to the increased incidence of glycemic dysregulation in subjects treated with SGAs. This view is supported by the observation that clozapine and olanzapine are not only the SGAs with the greatest liability for weight gain, but also are the most likely to produce glycemic dysregulation and Type 2 diabetes. Although there is a reasonably good association between weight gain and adverse changes in glycemic control and/or newly diagnosed type 2 diabetes (Scheen and de Hert 2007; Haupt et al. 2007; Kim et al. 2010), BMI is thought to contribute only 25–33 % of the variance in insulin resistance in patients treated with SGAs (Kim et al. 2010). Kim et al. (2010) observed that although the slopes of the linear correlation between fasting plasma glucose concentration and BMI were not significantly different for individuals on risperidone or aripirazole compared with controls, the curve for olanzapine deviated significantly, indicating it has a weight-independent action to increase insulin resistance. Where obesity is not linked to drug treatment, progression of insulin resistance and impaired glucose tolerance to type 2 diabetes generally takes several years. Evidence for SGAs as an independent causal factor in the development of glycemic disturbances comes from the finding that many cases of hyperglycemia occur within 6 weeks of starting antipsychotic treatment (Cohen 2004; Newcomer 2005; Saddichha et al. 2008), development of type 2 diabetes is most prevalent in the first 6 months (Cohen 2004), and the disease is frequently reversible when antipsychotic drugs are switched or discontinued (Cohen 2004; De Hert et al. 2007).

Possible direct effects of SGAs on glycemic control have been investigated by hyperinsulinemic/euglycemic clamp studies in human volunteers (Sowell et al. 2002, 2003; Sacher et al. 2008; Vidarsdottir et al. 2010), where they were infused with high levels of insulin to promote glucose tissue disposition together with glucose to maintain plasma glucose concentration. Although the data are not totally consistent, the evidence indicates that SGAs directly impair glycemic control. Vidarsdottir et al. (2010) compared the effects of 8 days administration of the SGA, olanzapine, against the FGA, haloperidol, in young healthy male volunteers. Neither drug altered bodyweight or fasting plasma insulin or FPG. However, in a hyperinsulinemic clamp experiment, subjects receiving olanzapine had significantly decreased glucose uptake, indicating it reduced insulin action and glucose disposal. Haloperidol was without effect. These results suggested that olanzapine impaired glycemic control by a rapid mechanism independent of weight gain. Sacher et al. (2008) compared the effect of 10 days administration of olanzapine or ziprasidone in young healthy male volunteers. At the end of treatment, there was a small (0.6 kg) weight increase in the olanzapine subjects but no change in the ziprasidone group. Fasting plasma concentrations of insulin, but not glucose, were increased by olanzapine. Olanzapine decreased glucose uptake in a hyperinsulinemic clamp, indicating reduced insulin

Table 2 Relative liability of various atypical antipsychotics to cause type 2 diabetes and diabetic ketoacidosis (DKA)

	Warning in the product label		Number of cases[a]			Odds ratio relative to:	
Antipsychotic drug	Hyperglycemia	Diabetes	Type 2 diabetes	DKA	Deaths	FGAs	No drug
Clozapine (Clozaril®)	Yes	Yes	384 (323)[b]	73[b]	23[b]	1.37[c]	7.44[c]
Olanzapine (Zyprexa®)	Yes	Yes	237 (188)[b]	80[b]	15[b]	1.26[c]	2.31[c]
Risperidone (Risperdal®)	Yes	Yes	131 (78)[b]	16[b]	4[b]	1.07[c]	1.20[c]
Quetiapine (Seroquel®)	Yes	Yes	46 (34)[b]	21[b]	11[b]	1.22[c]	1.00[c]
Ziprasidone (Geodon®)	Yes	Yes	ND	0	ND	ND	ND
Aripiprazole (Abilify®)	Yes	Yes	ND	2[d,e]	ND	ND	ND

ND no data, *FGA* first-generation antipsychotic.
[a]Number of de novo cases of type 2 diabetes shown in parentheses.
[b]*Sources*: Newcomer (2005).
[c]Newcomer (2007a, b).
[d]Church et al. (2005).
[e]Reddymasu et al. (2006).

sensitivity and impaired glucose disposal. None of these parameters was altered by ziprasidone, consistent with other findings (Newcomer 2005; Scheen and de Hert 2007; Yood et al. 2009; Nielsen et al. 2010; Vidarsdottir et al. 2010). Sowell et al. (2002) administered olanzapine or risperidone to adults for 15–17 days where they increased bodyweight by ~3 kg and the fasting plasma concentration of insulin but not glucose compared with the placebo group. In a hyperglycemic clamp study, insulin secretion was not impaired by administration of either olanzapine or risperidone. However, insulin sensitivity was reduced 18 % by both drugs, although only olanzapine's effect was statistically significant. Impaired insulin responsiveness and increased fasting insulin support the hypothesis that these SGAs adversely affect glycemic control. Decreased insulin responsiveness and increased fasting plasma insulin concentrations correlated with bodyweight (Sowell et al. 2002), but of itself this does not imply causality, only that SGAs are responsible for both metabolic effects. Olanzapine and risperidone were administered for 21–23 days to healthy volunteers before a hyperinsulinemic clamp (Sowell et al. 2003) and they increased weight by 1.6–2.0 kg. Olanzapine raised fasting plasma insulin and glucose compared with baseline. No changes in glucose uptake were observed in the clamp experiment, but enhanced excursions of meal-induced plasma insulin and glucose were found. Experience of treating first episode psychosis with SGAs mirrors human volunteer studies with reports of clinically meaningful increases in fasting plasma concentrations of glucose and insulin (De Hert et al. 2008; Graham et al. 2008).

The minority of studies where glycemic markers were measured in children/adolescents do not reveal substantial metabolic disturbances (De Hert et al. 2011a).

The risk of schizophrenia patients developing DKA whilst taking SGAs is high for clozapine and olanzapine, moderate for risperidone and quetiapine, and low for ziprasidone and aripiprazole (Table 2). The pharmacological mechanism of the SGAs that is responsible for progression of diabetes to DKA is unlikely to be mediated via weight gain or insulin resistance. It is more likely to be a direct action that rapidly suppresses insulin secretion in susceptible individuals. There is a substantial amount of clinical evidence to support this view. Several studies have reported that pancreatic β-cell function is impaired in schizophrenic subjects and certain SGAs, e.g., clozapine and olanzapine, can further suppress insulin secretion (Henderson et al. 2005a; Cohn et al. 2006; Chiu et al. 2006).

4.4 Insights from Animal Models on the Effects of Antipsychotic Drugs, Pancreatic β-Cell Function and Glycemic Control

Olanzapine and clozapine, but not risperidone or ziprasidone, dose dependently antagonized the carbachol enhancement of glucose-stimulated insulin release from perifused pancreatic islets in vitro; an effect mediated by muscarinic M_3 antagonism (Johnson et al. 2005). In contrast, none of the antipsychotics altered pancreatic insulin secretion in response to normal physiological concentrations of glucose (Johnson et al. 2005; Melkersson and Jansson 2005). In vitro studies have demonstrated that some drugs, particularly clozapine, reduced insulin-stimulated glucose uptake into adipocytes (Vestri et al. 2007). Although *in vitro* experiments have shown that various antipsychotic drugs do not influence glucose-stimulated insulin release from rat pancreatic islets, there is compelling *in vivo* evidence to demonstrate that they have direct actions that have a substantial influence on the release of insulin. In hyperglycemic clamp experiments (Chintoh et al. 2009), clozapine and olanzapine reduced insulin secretion, whilst ziprasidone reduced the first phase of this response. Therefore although pancreatic insulin secretion was normal in response to a physiological glucose concentration (~8.0 mM) (Johnson et al. 2005; Melkersson and Jansson 2005), when faced with a glucose load, β-cell function was clearly impaired (Chintoh et al. 2009).

In vivo hyperinsulinemic/euglycemic clamp experiments and complementary in vitro studies showed that acute administration of various antipsychotics, particularly clozapine and olanzapine, increased peripheral insulin resistance (Vestri et al. 2007; Houseknecht et al. 2007; Chintoh et al. 2009). Houseknecht et al. (2007) reported that clozapine, not other atypical antipsychotics, reduced insulin-stimulated glucose uptake into skeletal muscle in vitro but increased glucose uptake into liver and adipocytes. In contrast, Vestri et al. (2007) reported that clozapine and risperidone decreased insulin-stimulated glucose uptake into adipocytes. Clozapine and olanzapine, but not risperidone, ziprasidone, or haloperidol, were also shown to increase hepatic glucose production in vivo (Houseknecht et al. 2007; Chintoh et al. 2009). Various antipsychotics, especially clozapine, reduced insulin-stimulated

glucose uptake into skeletal muscle in vivo (Houseknecht et al. 2007; Chintoh et al. 2009). Savoy et al. (2010) showed antipsychotic-induced increases in plasma glucose to be inhibited by the ganglionic blocker, hexamethonium, indicating central activation of the sympathetic nervous system to the liver (Savoy et al. 2010) and/or muscarinic antagonism of parasympathetic drive (Houseknecht et al. 2007).

The results reveal a multiplicity of mechanisms whereby atypical antipsychotics could cause glycemic dysregulation, e.g., increased peripheral insulin resistance, enhanced hepatic glucose production, and reduced pancreatic insulin secretion. Although clozapine, olanzapine, and possibly risperidone appear to carry the greatest risk, other antipsychotic drugs may not be free of safety concerns.

Adverse effects after acute exposure to certain antipsychotics do not appear to ameliorate on repeated treatment. Experiments have investigated the effect of repeated administration where no weight gain occurred, providing insights into their direct effects on glycemic control and also where increased weight and adiposity did contribute to the adverse metabolic effects.

Male rats have generally been used in these experiments because they are generally resistant to the weight promoting effects of the FGAs and SGAs. However, not all studies in female rats have observed weight gain with antipsychotic drugs and they have also made a significant contribution to research in this area. Chintoh et al. (2008) infused olanzapine for 29 days in female rats, and although there was no hyperphagia or weight gain, increased visceral adiposity occurred. Using a hyperinsulinemic/euglycemic clamp, prolonged olanzapine treatment increased hepatic glucose production and decreased peripheral glucose utilization, indicating reduced sensitivity to insulin. In contrast to clinical data, hyperglycemic clamp experiments revealed no increase in insulin secretion, but this is consistent with in vitro observations with olanzapine (Johnson et al. 2005). Cooper et al. (2007) administered olanzapine for 20 days to male rats, which did not increase bodyweight or alter fasting plasma concentrations of glucose or insulin. Although these experiments suggested olanzapine had no deleterious effect on glycemic control independent of weight gain, more sensitive measures of glycemic control, e.g., glucose or insulin challenge tests, were not performed. Several other SGAs, including risperidone, quetiepine, and clozapine, did not induce weight gain in male rats (Baptista et al. 1998, 2002a, b; Smith et al. 2008a, 2009). Glucose tolerance tests revealed that repeated administration of sulpiride, quetiapine, or clozapine, but not risperidone, enhanced plasma glucose and insulin (Baptista et al. 1998, 2002a, b; Smith et al. 2008a, 2009). These results demonstrate that antipsychotic drugs impair glucose tolerance and decrease insulin action, consistent with clamp experiments (Chintoh et al. 2008). Risperidone was the exception because no impairment of glucose tolerance was observed after repeated administration (Baptista et al. 2002a).

Studies where antipsychotics produced weight gain have been mostly performed in female rats. The findings are similar to those where bodyweight was not increased. Repeated administration of olanzapine increased fasting insulin concentrations in female rats (Cooper et al. 2005; Albaugh et al. 2006; Lykkegaard et al. 2008) and male mice (Coccurello et al. 2009). Increased insulin resistance (Cooper et al. 2005; Coccurello et al. 2009) and impaired glucose tolerance were

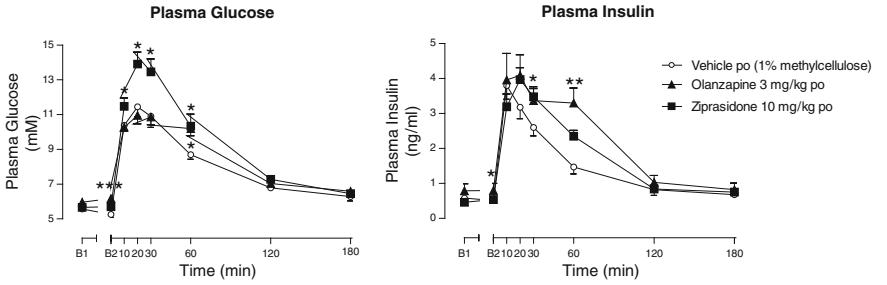

Fig. 4 Effects of repeated administration of olanzapine or ziprasidone on glucose tolerance of female Sprague–Dawley rats maintained on a high fat diet. Female rats were maintained in reversed-phase lighting on a high fat diet. After an overnight fast, (Day 15 of dosing) a baseline blood sample was taken, followed 15 min later by vehicle/drug. A second sample was collected after ~45 min followed by oral glucose challenge (2 g/kg D-glucose). Results are means adjusted for differences in bodyweight on Day 1 and bleeding order ± SEM, $n = 10$. Multiple comparisons versus controls were by a multiple t-test for olanzapine and a Williams' test for ziprasidone. Significant differences versus controls $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$. Data on file RenaSci

also found (Albaugh et al. 2006; Lykkegaard et al. 2008; Coccurello et al. 2009). In obese animals, risperidone, quetiapine, and clozapine all impaired glucose tolerance (Baptista et al. 2002a; Smith et al. 2009). Sulpiride was the exception because although it produced significant weight gain, an oral glucose tolerance test revealed a decrease in the excursion of plasma glucose with no change in plasma insulin (Baptista et al. 2002a). In our laboratory, we repeatedly administered olanzapine, which caused significant weight gain, and ziprasidone, which did not. After 15 days, both SGAs increased fasting plasma insulin and impaired glucose tolerance (Fig. 4). However, with olanzapine, the dysregulation was predominantly due to increased plasma insulin, whereas ziprasidone caused a marked increase of plasma glucose (Fig. 4).

Smith et al. (2009) observed that perturbations in glycemic control caused by quetiapine and clozapine were reversed after 7 days of their withdrawal.

In summary, SGAs have rapid and direct actions to impair glycemic control by mechanisms independent of weight gain. However, increased adiposity and obesity resulting from repeated administration exacerbate the dysregulation in glycemic control.

5 Drug Treatments for Antipsychotic-Induced Metabolic Dysregulation

5.1 Clinical Data

A wide range of pharmacological interventions to manage antipsychotic-induced weight gain have been studied. However, the relatively small size of many studies

is a major difficulty in assessing their relative efficacy. A meta-analysis of 32 placebo-controlled, clinical trials showed that only 5 of 14 drugs produced significant weight loss, i.e., the antiobesity drugs, sibutramine, *d*-fenfluramine, and topiramate, the insulin sensitiser, metformin, and the selective noradrenaline reuptake inhibitor, reboxetine. The average placebo-subtracted weight reductions produced by these drugs was 2.0–3.0 kg (Maayan et al. 2010). However, weight loss was enhanced when drug treatment was combined with behavioral therapy (Wu et al. 2008). In addition to reductions in abdominal obesity, weight-related improvements in glycemic control and plasma lipid profiles were reported (Maayan et al. 2010). The effect of stimulant medication in children and adolescents with ADHD, who were receiving SGAs for management of their behavioral disorders, has been determined (Penzner et al. 2009). The stimulants did not reduce weight gain or improve other cardio-metabolic risk factors. Since stimulants decrease food intake by enhancing adrenergic and dopaminergic neurotransmission, while antipsychotics are potent D_2 and α_1-adrenergic receptor antagonists (Peroutka et al. 1977; Svensson 2003), this outcome is consistent with their mutually antagonistic pharmacological properties.

Overall, where positive effects were reported with drug treatments, reductions in bodyweight have been relatively modest. In most instances when used as a preventative measure, the drugs did not abolish antipsychotic weight gain, and when used to treat the condition they failed to return weight to its starting-point. These data clearly reveal a significant unmet need especially when two of the clinically effective drugs, i.e. sibutramine and *d*-fenfluramine, have now been withdrawn.

5.2 Insights from Animal Models

Olanzapine-induced weight gain in rats has been used to predict the efficacy of various drugs to prevent antipsychotic-induced weight gain. The potential usefulness of sibutramine is consistent with reports that it is only moderately effective clinically (Henderson et al. 2005b; Maayan et al. 2010) as it only partially prevented olanzapine-induced weight gain in female rats on a high fat diet (Fig. 5a). Since increased noradrenergic neurotransmission via α_1-adrenoceptors plays a major role in sibutramine's action (Jackson et al. 1997) and antipsychotics are generally potent α_1-adrenergic antagonists (Peroutka et al. 1977; Svensson 2003), these conflicting pharmacological mechanisms explain its limited efficacy. We have shown that the 5-HT_6 partial agonist, E-6837, not only abolished olanzapine-induced weight gain in female rats, but also markedly reduced bodyweight below baseline (Heal et al. 2008; Fig. 5b).

Lyraglutide abolished olanzapine-induced weight gain in female rats but did not reduce bodyweight below baseline values (Lykkegaard et al. 2008). This glucagon-like peptide (GLP)-1 agonist also prevented olanzapine-induced increased insulin resistance (Lykkegaard et al. 2008). The anticonvulsant, zonisamide, and the SSRI, fluoxetine, prevented olanzapine-induced increases in both weight (Wallingford

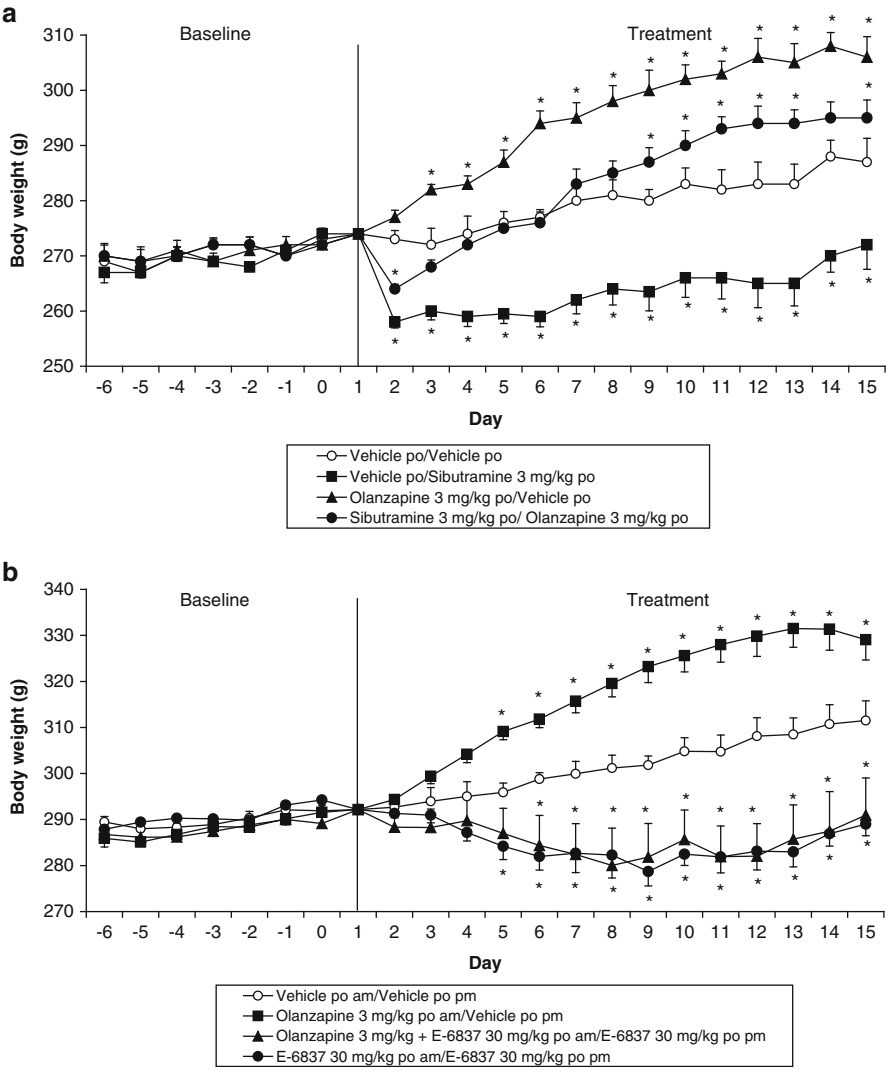

Fig. 5 Effect of repeated administration of (**a**) sibutramine or (**b**) the 5-HT_6 receptor partial agonist, E-6837, on olanzapine-induced weight gain in female rats maintained on a high fat diet. Female rats were maintained on reversed-phase lighting regime and a high fat diet. Drug treatment commenced Day 1. Results are adjusted means; $n = 10$. SEMs are calculated from residuals of the statistical model. Data analyzed by ANCOVA with bodyweight on Day 1 as covariate. Multiple comparisons versus the control group are by Dunnett's test. Significant differences versus control group, $*p < 0.05$. (**a**) Data on file RenaSci, (**b**) Heal et al. (2008)

et al. 2008; Perrone et al. 2004) and non-fasted plasma glucose in rats (Wallingford et al. 2008). Although compounds evaluated in rodents are relatively few, there is reasonable correlation between clinical and preclinical data. Therefore, olanzapine

may be a useful compound to employ in the preclinical profiling of potential new treatments for antipsychotic weight gain and metabolic dysregulation.

6 Summary and Future Directions

The reviewed evidence incontrovertibly demonstrates that many SGAs produce excessive weight gain and obesity. Furthermore, a significant number also have direct actions to impair glycemic control, thereby causing insulin resistance, impaired glucose tolerance, and type 2 diabetes (possibly leading to DKA). Schizophrenia is almost certainly causal in many endocrine and metabolic disturbances, making this population especially vulnerable to the adverse metabolic consequences of treatment with SGAs. Specific SGAs, e.g., aripiprazole and ziprasidone, may have a lower propensity for adverse metabolic effects, but they are not without risk. There is a widely held view that aripiprazole and ziprasidone are less clinically effective in treating schizophrenia than olanzapine or risperidone, and in addition, there are other safety factors to be taken into consideration. For example, ziprasidone causes QTc prolongation. Hence, there is an urgent need for a new generation of antipsychotic drugs that provide efficacy at least equal to olanzapine or risperidone, without their unwanted effects.

We have refrained from speculating on the pharmacological mechanisms responsible for the adverse effects of the SGAs on bodyweight and/or glycemic control as it is beyond the scope of this review. However, mechanisms such as 5-HT_{2C}, H_1, or M_3 receptor antagonism may contribute to their metabolic side effects. Clinical experience with both the FGAs and SGAs indicates that D_2 receptor antagonism, the therapeutic mechanism of almost all antipsychotics, may lead to the adverse effects of these drugs on bodyweight and glycemic control.

Pharmacological treatments for antipsychotic-induced weight gain are at best moderately effective, with metformin offering the dual benefits of weight reduction and improved insulin sensitivity. Clinical experience with antiobesity drugs and appetite suppressants is that they are generally poorly effective at managing weight gain caused by antipsychotics, unsurprising in view of the mutually antagonistic pharmacological mechanisms involved. In the absence of safe and effective alternatives to SGAs, there is substantial unmet clinical need for the introduction of new drugs to combat their adverse metabolic side effects. Preclinical experiments have mirrored the moderate efficacy of current antiobesity drugs in preventing antipsychotic-induced weight gain, but in the case of the GLP-1 agonist, lyraglutide, or the 5-HT_6 partial agonist, E-6837, have also revealed the existence of pharmacological mechanisms that are unlikely to be neutralised by the actions of the SGAs.

Predicting the liability of new antipsychotic drug–candidates to induce weight gain is still a major challenge for preclinical research. However, the situation is not as bleak as sometimes painted. First, there is evidence to demonstrate that all antipsychotic drugs are capable of causing substantial weight gain in patients; it

is only the percentage of subjects and magnitude of effect that varies across the SGAs. Hence, weight gain in rodent models induced by drugs like ziprasidone and aripiprazole is not the proof-of-concept failure that it is often stated to be. Second, predictive validity of the rodent models would be markedly improved if the effects of compounds are determined over a wide range of doses, and in addition to bodyweight, other metabolic endpoints, e.g., hyperphagia and visceral adiposity, are also measured.

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Medical Needs in the Treatment of Psychotic Disorders

F. Markus Leweke, Thorsten M. Odorfer, and J. Malte Bumb

Contents

Abstract Schizophrenia and psychotic disorders represent psychiatric disease patterns characterized by remarkable impairment arising from alterations in cognition, perception, and mood. Although these severe illnesses have been known for more than 100 years, psychopharmacological treatment of their characteristically broad spectrum of symptoms as well as patients' quality of life, compliance, and time to relapse still remain a challenge in everyday clinical practice. In the following, we will provide a brief synopsis of first-generation antipsychotics (FGAs) followed by a detailed description of current second-generation

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antipsychotics (SGAs) along with their effects and side effects to evaluate unmet needs in the treatment of schizophrenia and psychotic disorders.

Overall, drug profiles differ concerning their efficacy, associated side effects, cost, and mechanism of action. Thus, a shared decision-making process taking all these factors into account is necessary to develop an effective treatment based on currently approved compounds. To date, however, the spectrum of options is limited and only serves a limited proportion of patients. In addition, certain symptoms do not respond well to currently available strategies or respond only at the price of considerable side effects leading to reduced compliance and adherence in a substantial number of cases.

Unmet needs in the field of antipsychotic treatment are found in a wide range of areas starting from efficacy, safety and tolerability, compliance and adherence, and continuing to stage-dependent and more personalized approaches.

Keywords Medical needs • First- and second-generation antipsychotics • Schizophrenia • Compliance • Patient adherence • Quality of life • Side effects

1 Background

In 1908, Eugen Bleuler coined the term schizophrenia for a group of mental disorders previously conceptualized by Emil Kraepelin. More than a hundred years later, the clinical understanding and classification of psychoses in general and schizophrenia in particular have undergone some evolutionary changes. Today, schizophrenia refers to a clinical syndrome in patients suffering from a broad range of symptoms including positive (e.g., paranoid delusions, auditory hallucinations), negative (e.g., blunted affect, social withdrawal) and more general symptoms (e.g., anxiety), as well as cognitive impairment with an onset mostly in earlier periods of life (Insel 2010).

Considering the total number of 16.8 million disability-adjusted life years (DALYs) due to schizophrenia worldwide, the huge medical and social dilemma caused by this illness becomes obvious (Collins et al. 2011). Short- and long-term recovery rates are fairly low: only about 14 % in 5 years (Robinson et al. 2004) and 16 % in 25 years (Harrison et al. 2001). Compared to the general population, the mortality rate of schizophrenic patients is up to 2.5 times higher (Saha et al. 2007). In a European sample of patients suffering from schizophrenia, less than one-fifth were able to work (Marwaha et al. 2007). All aforementioned facts underscore the substantial necessity to improve current therapeutic options in general and psychopharmacological approaches in particular.

The development of first- and second-generation antipsychotics has provided substantial progress in the treatment of psychosis and schizophrenia. Although their side-effect profile has improved, current antipsychotics are far from offering an ideal treatment option for a substantial number of patients. Most second-generation antipsychotics (SGAs) are causing less extrapyramidal side effects (EPS) (Weiden

2007). However, there are still a number of severe adverse effects such as weight gain, induced metabolic syndrome, and cardiovascular side effects (De Hert et al. 2011) limiting their long-term use due to increased morbidity and mortality (Weinmann et al. 2009). Furthermore, there are also less dangerous side effects such as hyperprolactinemia (Bostwick et al. 2009) and sexual dysfunction (Costa et al. 2006), which may impair patients' compliance. Finally, cognitive functioning is still poorly addressed by current antipsychotics (Hori et al. 2006). This has become even more obvious as more standardized assessments like the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (Kern et al. 2004) have become available reflecting, e.g., executive dysfunction, disrupted attention and vigilance, as well as memory processes and patients' problem-solving ability.

Admittedly, most modern antidopaminergic drugs ameliorate the acute clinical syndrome especially regarding positive symptoms. Unfortunately, they fail to promote stable remission, with a particular insufficiency to ameliorate cognitive impairment and negative symptoms, leading to the patients' long-term disability (Insel 2010). In the following, we will briefly summarize the current state of the art of antipsychotic therapy and will try to define the medical need for better antipsychotics.

2 Current Antipsychotics

Numerous studies have investigated FGAs and SGAs analyzing and comparing them both with regard to their effectiveness in patients with chronic schizophrenia and their effects on patients' quality of life. Among these, two sophisticated trials stand out particularly due to the absence of any sponsorship by the industry: the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and CUtLASS 1 (Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study) studies (Jones et al. 2006; Lieberman et al. 2005).

In patients with chronic schizophrenia, CATIE demonstrated a marginal superiority of olanzapine compared to quetiapine, risperidone, ziprasidone, and the FGA perphenazine pertaining to time to discontinuation of treatment for any cause, because of the adverse effects. Moreover, the efficacy of perphenazine was comparable to that of quetiapine as well as that of risperidone and ziprasidone (Lieberman et al. 2005). With the exception of clozapine, the CUtLASS trial revealed no significant improvements when using SGAs (olanzapine, quetiapine, risperidone, or ziprasidone) in comparison to FGAs (e.g., sulpiride, trifluoperazine, haloperidol) with regard to quality of life, psychotic symptoms (measured by comparison of Positive and Negative Syndrome Scale scores), or associated costs of care at 1-year follow-up (Jones et al. 2006). However, various authors have discussed several limitations to the large-scale CATIE study, e.g., its selection of chronic patients has to be taken into account when more general conclusions on the efficacy of SGAs are drawn from its data. In particular, the study was criticized for the doses of the SGAs administered, the selection of patients (on average about 15 years of illness and

around 75 points on the PANSS) representing an in-part non-responding population of chronic schizophrenia patients who have been treated with a variety of antipsychotics prior to participation in the study. While a lack of efficacy may explain non-adherence to available medications as exemplified by the CATIE results, it still remains an open question whether perphenazine with its high dopamine D_3 receptor affinity is an appropriate representative of first-generation drugs to be compared with SGAs (Gross and Drescher 2012).

The effectiveness of the SGAs amisulpride, olanzapine, quetiapine, and ziprazidone in comparison with low-dose haloperidol in first-episode schizophrenia and schizophreniform disorder was investigated in a multi-company sponsored trial (EUFEST). Kahn et al. (2008) reported that symptom reduction was around 60 % for all of these antipsychotics while patients on SGAs were less likely to discontinue medication during a 1-year follow-up when compared to haloperidol.

Numerous other studies not only compared FGAs and SGAs with regard to compliance and patients' adherence to therapy but also investigated methods to improve compliance (for review please see Ascher-Svanum et al. 2008; Dolder et al. 2002; Puschner et al. 2005). In these trials, noncompliance rates of approximately 41 % (Lacro et al. 2002) and 55 % (Fenton et al. 1997) were observed.

Noncompliance has mainly been attributed to the patients' lack of understanding of their disease, substance abuse, insufficient patient follow-up, and inadequate therapeutic relationships (Ascher-Svanum et al. 2008; Fenton et al. 1997). Compliance and adherence to therapy, on the other hand, can clearly be regarded as reliable predictors of successful antipsychotic therapy (Bebbington 1995) and are therefore of special interest. In line with these findings, high relapse rates of noncompliant patients have been reported (Puschner et al. 2005). However, the phenomenon of noncompliance is not exclusively seen in association with antipsychotics or psychopharmacological treatment but is also frequently seen in other therapeutic areas (Leucht et al. 2012a; Osterberg and Blaschke 2005). Besides these observations, a recent meta-analysis underlined the beneficial effect of antipsychotic maintenance treatment in schizophrenia. Leucht et al. (2012b) found significantly reduced relapse rates at 1 year of 27 % with drug treatment vs. 64 % on placebo.

2.1 First-Generation Antipsychotics

In the early 1950s, Charpentier synthesized chlorpromazine, the initial first-generation antipsychotic (FGA), which was introduced in the clinic by Delay and Deniker in 1952 (Ban 2007). In the subsequent years, many chlorpromazine-like antipsychotics, both low- and high-potency FGAs, followed. Traditionally, schizophrenic patients have been treated with these drugs, which are predominantly effective in improving acute and/or exacerbated positive symptoms, including thought disorders and both delusions and hallucinations. On the other hand, the administration of FGAs is clearly limited by their adverse effects. One of the potentially most severe

effects is the risk of tardive dyskinesia with an incidence of approximately 5 % per year in adults and 25–30 % in elderly patients (Tarsy et al. 2011).

Blockade of dopaminergic transmission may induce both hyperprolactinaemia and EPS, while interference with serotonergic, cholinergic, and histaminergic actions may lead to weight gain. Among the anticholinergic side effects are dry mouth, urinary retention, constipation, tachycardia, and visual disturbance. Noradrenergic side effects are postural hypotension, disturbances of sexual functions, and nasal congestion. Due to their antihistaminic action, many FGAs have a sedative effect (Beaumont 2000).

Chlorpromazine and haloperidol in particular have been used as the main comparator drugs in clinical trials investigating SGAs. Adams et al. (2007) reviewed 50 studies conducted in the 1970s. Within this context, chlorpromazine's antipsychotic efficacy was shown in short-, medium-, and long-term trials. Although in comparison to placebo, chlorpromazine caused significantly more adverse effects such as sedation, EPS, hypotonia, and weight gain, the chlorpromazine groups nevertheless presented lower dropout rates compared to placebo.

There are few randomized controlled trials comparing chlorpromazine and haloperidol. In summary, there is a tendency to favor haloperidol in terms of efficacy but overall the data are not convincing. Regarding haloperidol, a systematic review of 21 clinical trials including 1519 subjects favored the compound over placebo with regard to clinical short- and medium-term improvement. Unfortunately, many haloperidol recipients suffered from severe EPS (Joy et al. 2006) and consequently there were high dropout rates in these trials because of these or other clinically relevant adverse effects.

More recent information on trials comparing haloperidol with SGAs is given in the following section.

2.2 Second-Generation Antipsychotics

Second-generation antipsychotics (SGAs) are preferred by many clinicians because of their advantage in reducing the incidence of EPS, such as akinesia, akathisia, hyperkinesia, hypertonia, tremor, and drug-induced chronic dyskinesia (Correll et al. 2004). Moreover, it was hoped that they would be superior in treating negative or cognitive symptoms of schizophrenia. However, if there are advantages for these antipsychotics, it is not clear that they are clinically relevant (Leucht et al. 2009). Therefore, the choice of SGA largely rests with the side-effect profile which needs to be considered in the context of the individual patient (for example, by choosing a drug with minimal weight gain for a person at risk for metabolic syndrome).

During the last two decades, numerous trials have been performed aiming at head-to-head comparisons of FGAs and SGAs. In principle, SGAs differ from FGAs by modified receptor binding profiles. Meltzer and Massey (2011) provide a thorough description of SGA receptor activities, showing for instance that amisulpride may have a special impact by antagonizing serotonin 5-HT_7-receptors

as well as dopamine D_3-receptors, thereby potentially ameliorating cognitive deficits. In general, clinical comparisons between several SGAs have shown that despite different receptor binding profiles differences in their efficacy are minimal.

Regarding positive symptoms (Fig. 1), all compounds are effective in about 70 % of the cases (Beitinger et al. 2008). However, criteria for response and remission as well as adequate thresholds for defining these measures of efficacy are still controversial (van Os et al. 2006). Efficacy-related outcomes between olanzapine, amisulpride, and clozapine (Mortimer et al. 2004, 2007; Naber et al. 2005; Peuskens et al. 2007), measured by the Clinical Global Impression (CGI), the Positive and Negative Syndrome Scale (PANSS) total score and its positive and negative symptoms subscores, the Brief Psychiatric Rating Scale (BPRS) total score, and the Scale for the Assessment of Negative Symptoms (SANS) total score, showed no significant difference between the groups. Several studies were able to demonstrate olanzapine's superiority in ameliorating positive symptoms when compared to aripiprazole (Komossa et al. 2010b), quetiapine (Atmaca et al. 2003; Leucht et al. 1999; McEvoy et al. 2006; Sacchetti and Valsecchi 2003; Stroup et al. 2006), and risperidone (Dollfus et al. 2005; Jayaram et al. 2007; McEvoy et al. 2006; Robinson et al. 2006; Tran et al. 1997).

Only sparse data exist comparing SGAs in patients with predominantly negative symptoms (Fig. 2). Data derived from the PANSS also failed to show a significant difference between these drugs with regard to negative and positive symptoms, although there is evidence that low-dose amisulpride (50–300 mg/day) may be superior in alleviating negative symptoms (Leucht et al. 2011). While Breier et al. (2005) found significant differences in PANSS negative subscore, favoring olanzapine over ziprasidone, Stroup et al. (2006) documented no difference between ziprasidone and olanzapine.

Clozapine remains the first choice in the treatment of refractory patients while there is no sufficient empirical support for such an approach for other SGAs or any of the FGAs (Leucht et al. 2011). Clozapine was equally effective as olanzapine, quetiapine, risperidone, and ziprasidone in improving BPRS total score. In terms of PANSS total and subscores, no differences between clozapine and olanzapine or risperidone could be documented (Asenjo Lobos et al. 2010).

Finally, clozapine may have the advantage of reducing suicide attempts in schizophrenia (Meltzer et al. 2003). While the group of SGAs is rather heterogeneous with regard to mortality, clozapine was associated with a substantially lower mortality than other antipsychotics in a population-based cohort study (FIN11 study) (Tiihonen et al. 2009). Overall, long-term treatment with antipsychotics is associated with lower mortality compared with no antipsychotic use and SGAs are not associated with a higher mortality than FGAs.

In general, there has been substantial criticism concerning clinical trials comparing different SGAs since the results seem to be biased by the sponsor's influence on trial design (Heres et al. 2006). Taking this aspect into account, it becomes questionable if there is a clinically relevant difference in efficacy between current SGAs with the exception of clozapine and possibly amisulpride (negative symptoms). Thus, the acute and long-term side-effect profile of each compound may be a decisive factor when choosing the appropriate SGA in individual patients.

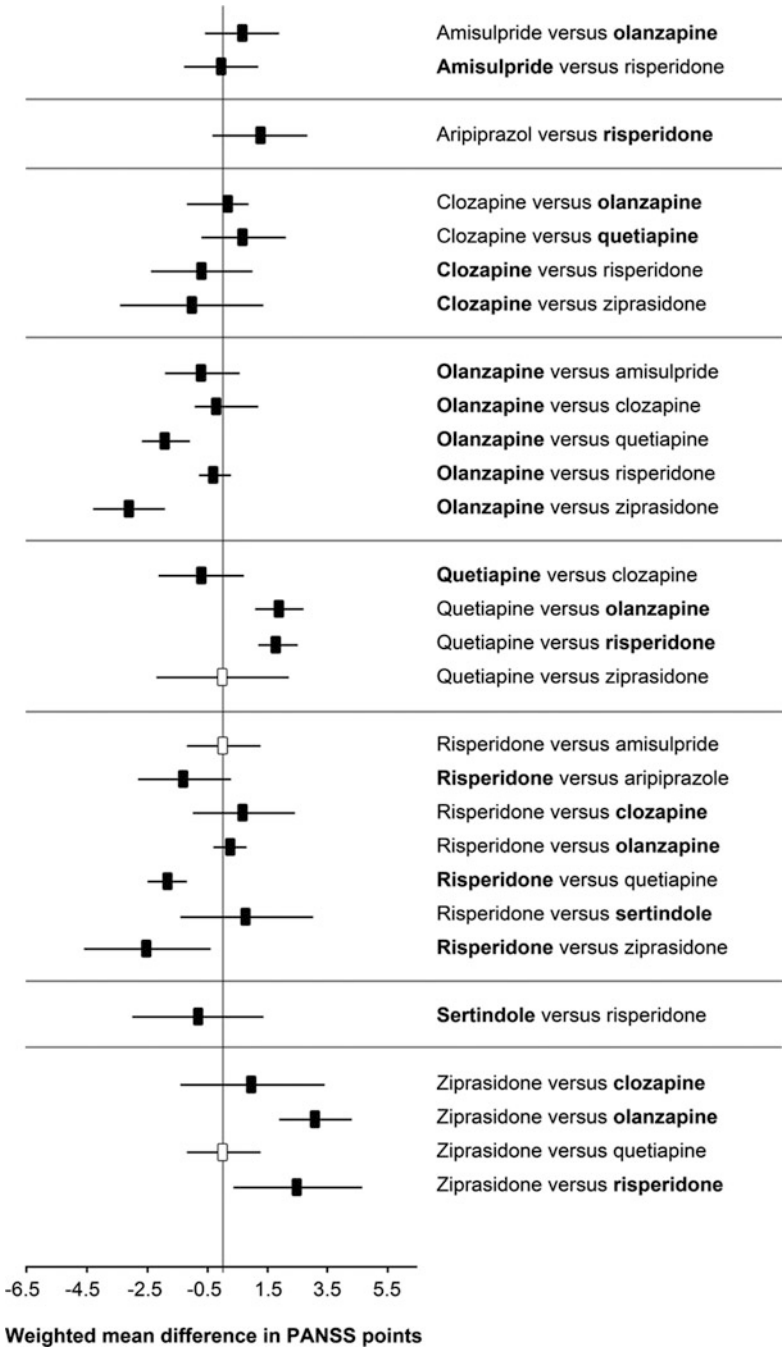

Fig. 1 Meta-analytic comparisons of the efficacy of SGAs on positive symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS) positive sub-score (adapted from Leucht et al. 2009). Preferable drug is *marked in bold*

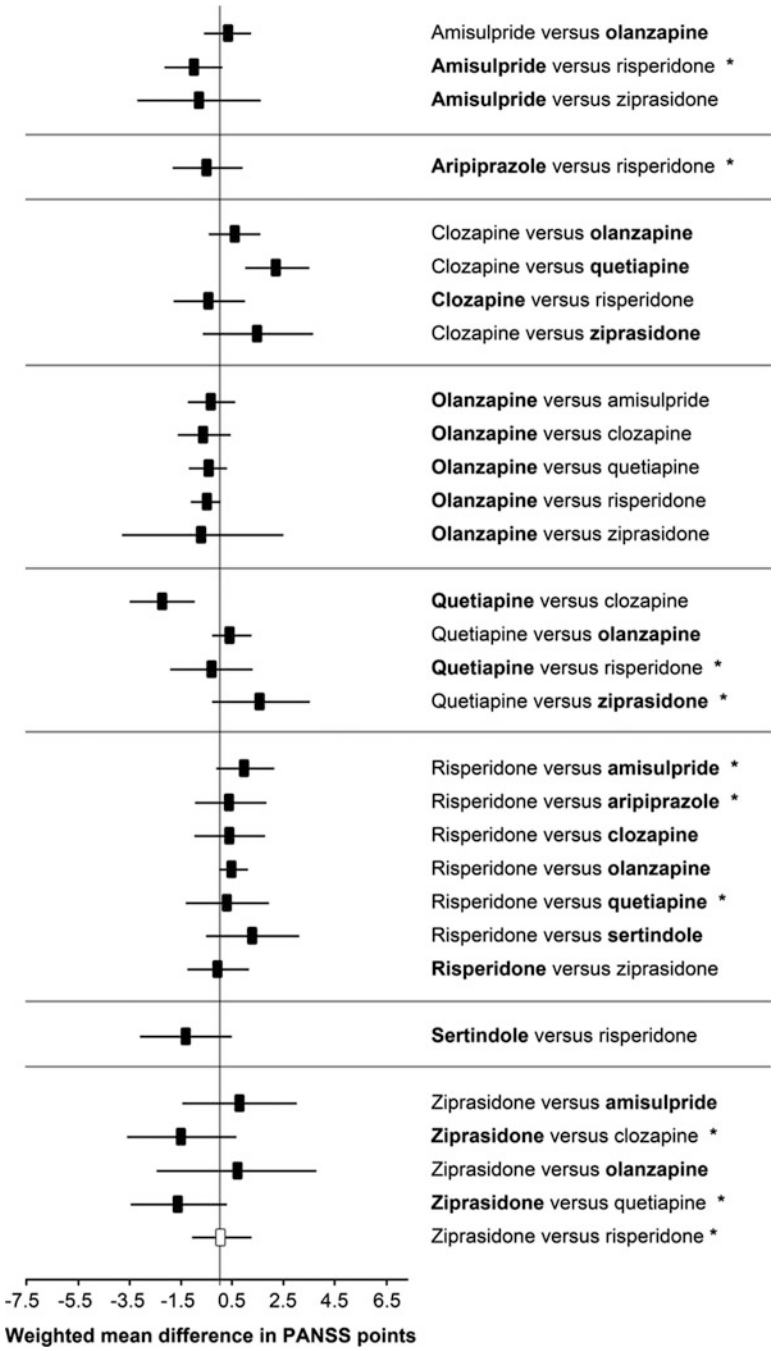

Fig. 2 Meta-analytic comparisons of the efficacy of SGAs on negative symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS) negative subscore (adapted from Leucht et al. 2009). Preferable drug is *marked in bold*. Differences to Fig. 1 (PANSS positive subscale) are marked with an *asterisk*. Noteworthy: Only amisulpride, clozapine, olanzapine, and risperidone have been shown to be more efficacious than first-generation antipsychotics in addressing negative symptoms (Leucht et al. 2009)

Although post-psychotic depressive episodes did not represent a focus in recent research, it seems that in this respect SGAs carry a particular advantage over FGAs, which is also highly relevant for the overall quality of life in schizophrenia and time to remission (Dollfus et al. 2005). While some more recent studies (Peluso et al. 2012) claim no difference between FGAs and SGAs regarding the risk for tardive dyskinesia there is evidence that the use of SGAs as a group is associated with a respective lower risk of about 0.8 % in adults (Correll et al. 2004).

Regarding side effects (Table 1), insomnia, somnolence, weight gain, and constipation are significantly lower in patients treated with amisulpride than in those treated with olanzapine (Mortimer et al. 2004). In contrast with many other SGAs like clozapine, risperidone, and, of course, olanzapine, amisulpride may be associated with fewer diabetogenic effects like new-onset diabetes, exacerbation or worsening of an existing diabetes, and a significantly lower risk of body weight gain. Compared with olanzapine, the SGA aripiprazole is better tolerable in terms of metabolic effects and sedation (McQuade et al. 2004). Furthermore, aripiprazole is associated with a lower risk of sinus tachycardia and blurred vision as compared to, for example, risperidone. While aripiprazole is comparable to risperidone in causing dystonia and cholesterol and/or prolactin increases, it has been shown to trigger QTc prolongations less frequently than risperidone (Chan et al. 2007; Komossa et al. 2009).

In general asenapine is well tolerated, with a dropout rate similar to that of placebo plus an improvement in time to relapse or impending relapse (Kane et al. 2011). The most common treatment-related adverse events with asenapine were insomnia, headache, and somnolence (Buchanan et al. 2012). Adverse effects including changes in weight, glucose and lipid levels, orthostatic hypotension, QTc interval prolongation, and alteration of prolactin levels were quite similar to that of placebo. Only EPS were documented more commonly in the asenapine than in the control group (Potkin 2011).

Clozapine represented the first in the class of SGAs associated with a very low incidence of EPS. In light of the approximately 1 % risk of drug-induced agranulocytosis, special drug monitoring is strictly mandatory. Patients receiving clozapine were experiencing EPS as often as patients in the placebo arm, although overall clozapine had a more sedative effect (Leucht et al. 2011). With respect to adverse effects, alterations of white blood counts occurred more frequently in participants receiving clozapine compared with those given FGAs, including haloperidol and chlorpromazine (Essali et al. 2009; Rosenheck et al. 2000). Moreover, drowsiness, hypersalivation, or temperature increases were more common in clozapine-treated patients who at the same time experienced fewer EPS, as mentioned above.

Olanzapine is associated with significantly more (greater) weight gain and increase of glucose levels than amisulpride and, similarly, with more (greater) prolactin increase, weight gain, cholesterol increase, and sedation than aripiprazole (Komossa et al. 2010a). No differences were documented between the olanzapine and clozapine groups concerning most of the described adverse effects (Tollefson et al. 2001). Compared to quetiapine, olanzapine was associated with more EPS, prolactin increase, sexual dysfunction, weight gain, and glucose increase (McEvoy

Table 1 Frequency of side effects of some first- and second-generation antipsychotics

	Amisulpride	Aripiprazole[b]	Clozapine[c]	Olanzapine	Quetiapine[d]
Agranulozytosis	No/less	No/less	High	No/less	No/less
Anticholinergic	No/less	No/less	High	Moderate	No/less
EPMS/TD	Low	No/less[a]	No/less[a]	No/less[a]	No/less[a]
Hyperglycaemia	No/less	No/less	High	High	Moderate
Hyperlipidaemia	No/less	No/less	High	High	Moderate
Hypersalivation	No/less	No/less	High	No/less	No/less
Orthostatic dysregulation	No/less	No/less	High	Low	Moderate
Prolactin increase	High	No/less	No/less	No/less	No/less
QTc prolongation	No/less	No/less	No/less	No/less	No/less
Sedation	No/less	No/less	High	Low	Moderate
Seizures	No/less	No/less	Moderate	No/less	No/less
Weight gain	Low	No/less	High	High	Moderate

Adapted from (Burlon 2007), additional information included from Arif and Mitchell (2011), Citrome (2010), McDonagh et al. (2010), Potkin (2011)
[a]Akathisia
[b]Dizziness and headache
[c]Myocarditis
[d]Sedation, oral hypoesthesia, bitterness, or disguise

et al. 2006). Unfortunately, these facts are based on insufficient data only. Because of its severe metabolic side effects such as weight gain and associated increases in cholesterol and glucose, the administration of olanzapine in the treatment of patients with high risk of developing a metabolic syndrome or in overweight patients, individuals suffering from diabetes, or those with high cholesterol levels must be scrutinized carefully limiting its use in daily practice (Komossa et al. 2010a).

Quetiapine has been shown to induce movement disorders to the same extent as placebo (Copolov et al. 2000; Hellewell 2002; Peuskens and Link 1997). It may also induce constipation and low blood pressure and appears to cause dizziness. Dry mouth and sleepiness are possibly more prevalent in patients treated with quetiapine compared with placebo and FGAs, such as chlorpromazine or haloperidol (Srisurapanont et al. 2004). Concerning adverse effects, quetiapine recipients suffer less often from EPS and prolactin-associated side effects than patients treated with either risperidone (McEvoy et al. 2006; Zhong et al. 2006) or ziprasidone (Lublin et al. 2009).

With risperidone, there were significantly more adverse effects such as EPS, weight gain, and increased prolactin levels (Rattehalli et al. 2010) than observed in the placebo group (Umbricht and Kane 1995). It was reported that risperidone induces weight gain more often and it also appears more likely to cause rhinitis than control drugs (e.g., haloperidol). No differences were observed between risperidone and controls regarding gastrointestinal, cardiovascular, and sexual side effects (Ceskova and Svestka 1993; Heck et al. 2000; Peuskens 1995).

Dyspepsia, nausea, dizziness, and somnolence represent commonly described adverse events of ziprasidone. These events occurred significantly less often in placebo groups (Daniel et al. 1999; Keck et al. 1998). In addition, ziprasidone recipients were more likely to experience abdominal pain, constipation, and had a higher incidence of

EPS than with placebo. Otherwise, the incidence of EPS was significantly lower compared with FGAs (haloperidol) (Daniel et al. 1999; Keck et al. 1998).

Interestingly, the discussion about the use of FGAs and their potential advantages over SGAs has recently been revived. Based on the idea that some advantages of SGAs might be due to relatively lower dosages compared to FGAs, low-dose FGAs have been suggested as an alternative, more cost-effective approach. This view, which to some extent is supposedly supported by the CATIE trial, is questionable for a number of reasons. To name only two, FGAs have not been shown to be more effective than SGAs while at the same time carrying a less favorable side-effect profile. Despite the fact that SGAs also still induce a large number of side effects, up to now they are suggested to be superior to FGAs in inducing less tardive dyskinesia (Luft and Taylor 2006). There is currently no convincing evidence that FGAs are superior to SGAs in any aspect other than costs.

Besides the potential bias in relation to sponsorship of a trial (see above), we want to address some additional, partly serious limitations of the referenced trials. First of all, some of the specified clinical trials were carried out in a rather limited number of subjects with patient groups that must be considered too small. As mentioned earlier, haloperidol often serves as comparator substance for either other FGAs or newer SGAs. More explicit comparisons to other antipsychotic agents are often lacking. Moreover, dosages varied and were either fixed or flexible. Finally, described dropout rates appeared clearly too high (about 50 % for most of the test substances, even SGAs, versus approximately 65 % for placebo), indicating that the problem of patients dropping out early during the study is still a matter of concern.

2.3 Off-Label Use

It is noteworthy to briefly address areas of need with regard to current drug treatment for schizophrenia. First, not all psychotic syndromes may be classified schizophrenia. Thus, there is a clinical need to investigate current SGAs and future antipsychotics adding to the limited experience with SGAs for nonschizophrenic psychotic syndromes.

There is also a substantial need to better understand the potential benefits from, e.g., antidepressants or mood stabilizers in schizophrenia. For example, antidepressants are often used in schizophrenia to affect negative symptoms but the evidence is still limited (Möller 2004).

Finally, there is urgent need for additional empiric data evaluating antipsychotic polypharmacy (Stahl and Grady 2004).

3 The Ideal Prototype Antipsychotic

Today, a number of potential mechanisms of action have been identified or hypothesized that may be targeted to ameliorate psychotic symptoms, affect, and cognition in psychosis and schizophrenia. However, in this evolving field, it seems

premature to select specific pharmacodynamic properties or rule out others for future investigational compounds.

An ideal drug for schizophrenia should be curative: it should reverse the underlying disease processes and restore the patient to health. In other words, we would like to have not just "antipsychotics" but "antischizophrenics" (see Bespalov et al. 2012). No such drug is on the horizon and it may be a tall order to identify such a compound in the near future, especially since the disorder is now commonly conceptualized as a neurodevelopmental illness. However, recent experience has shown that even severe genetic neurodevelopmental disorders such as Rett syndrome can be completely reversed in animal models. Therefore, the search for a curative and preventive therapy should continue, using the improved tools of modern translational neuroscience (Meyer-Lindenberg 2010).

Even if symptom control is accepted as the goal, an ideal antipsychotic agent should improve any kind of positive *and* negative symptoms, reduce behavioral disorders such as aggression and agitation, and ameliorate mood symptoms and of course cognitive functioning. Especially, amendments of negative symptoms, cognitive functioning, and relapse still are challenges in the therapy of schizophrenic patients. Subsequently, we must not forget other measurable endpoints of psychopharmacological treatment such as quality of life, subjective sensitivities, or compliance. In addition, the majority of patients should fully remit rather than merely respond to the treatment. The burden of the illness in terms of social disintegration including unemployment needs to be significantly affected by the ideal antipsychotic.

Besides an ideal antipsychotic does not cause adverse side effects, such as EPS or tardive dyskinesia, and does not enhance the risk for weight gain, sedation and both metabolic and cardiovascular adverse events. Furthermore, these agents should not elevate plasma prolactin levels and induce associated sexual dysfunction (e.g., erectile dysfunction or amenorrhea). In general, the side-effect profile should be close or equal to placebo.

The ideal antipsychotic should address stage-specific problems of initial prodromal or at ultra-high-risk patients, first-episode schizophrenia, recurrent episodes, chronic cases, and treatment resistance (Burlon 2007). It needs to be of low toxicity and safe when combined with other drugs.

However, these and further requirements for modern antipsychotics seem not to be accomplishable in a single compound and more specific drugs fulfilling certain expectations are much more likely than one individual "super compound."

4 Medical Needs of Future Antipsychotics

Based on the description of current pharmacological options in the treatment of schizophrenia given above, it becomes obvious that several aspects in the treatment of this disorder need to be addressed.

4.1 Efficacy

When focusing on the efficacy of current antipsychotics, the relatively high rate of about 30 % of patients remaining treatment resistant (Beitinger et al. 2008) and an even higher rate of only partially responding patients needs to be addressed (Freedman 2003; Honer et al. 2009). Criteria for response and remission in schizophrenia remain much more restricted than with, e.g., depression. Certain authors support a 20 % improvement in the PANSS as sufficient response. However, such a response will leave the average acute patient on a level of symptoms (including positive symptoms) coming close to a prodromal state of psychosis. It seems highly likely that this may in part be due to the limited spectrum of the mechanisms of action of current antipsychotics that primarily focus on antidopaminergic and serotonin receptor blocking properties. Additional candidate mechanisms hopefully broadening the spectrum of approved mechanisms of action will be discussed elsewhere in this book.

Adding to the first point, there is an even more inferior effect of the majority of FGAs and SGAs on negative symptoms. There are few such as clozapine and amisulpride showing moderate effects in this regard. However, as these symptoms are most relevant for the long-term functional outcome of the disease, this is a vital issue to address with next-generation antipsychotics.

Related to this requirement, it is of particular importance to target cognitive decline in schizophrenia, an issue that has been a topic on the agenda for many years. SGAs provide an improvement in this area that seems to be more or less limited to certain domains for each compound. Furthermore, the clinical relevance of these improvements is marginal (Kane and Correll 2010).

While patients resistant to other antipsychotics are regularly treated with clozapine, up to now, only few treatments have been investigated for those 40–70 % of patients who fail on clozapine or are only partially responsive (Kontaxakis et al. 2005). These more or less completely treatment-resistant patients require innovative future treatment options.

One important issue to address in this context is the urgent need to find more objective and reliable markers for treatment effects other than rating scales because biological markers may allow for the detection of a likely treatment response prior to clinical improvement. In addition, they may support the identification of subgroups of patients showing a better response to a certain treatment. This would allow for a more individualized treatment and prevent a failure to detect the beneficial effects of a certain compound in a minority of patients because other subgroups of patients may not or only marginally benefit, thus leading any clinical trial to a negative result.

While there is general agreement on the necessity to improve efficacy for the entire spectrum of symptoms in schizophrenia, more personalized approaches seem necessary to achieve this goal (Basile et al. 2002).

Comorbid psychiatric syndromes are another challenge for new pharmacological strategies. While certain antipsychotics like clozapine (Green et al. 2003) or

quetiapine (Potvin et al. 2006) seem to reduce craving for alcohol and/or cannabis use, this is still an unmet need and not conclusively investigated topic. Although SGAs seem favorable in terms of post-psychotic depression, this issue has to remain in the focus of future drug development.

4.2 Safety and Tolerability

There is a substantial need to improve side-effect profiles in antipsychotic treatment. Even though SGAs have improved the situation to some extent, a wide range of adverse reactions starting from extrapyramidal symptoms to weight gain and metabolic effects, to sedation, and to an increase in prolactin levels and sexual dysfunction still represent major problems in the treatment of schizophrenia.

While tardive dyskinesia is suggested to occur less frequently with SGAs, there is still a risk for developing long-term, severely disabling movement disorders due to antipsychotic treatment. For FGAs, the cumulative lifetime dosage of antipsychotics has been demonstrated to be related to the risk of tardive dyskinesia (Lieberman et al. 1988). Thus, there may be a chance that the risk to develop tardive dyskinesia due to FGAs may be overestimated using current dosages and that low-dose treatment may be associated with a more favorable side-effect profile in this respect.

Moreover, the reduced life expectancy of schizophrenia patients has to be addressed. It is likely that higher mortality in schizophrenia is not only due to adverse effects of medication (e.g., metabolic syndrome; see Heal et al. 2012). To meet these goals, future antipsychotics have to be designed with a particular emphasis on an optimized side-effect profile (Correll 2011). In addition, combination therapies including strategies emerging from internal medicine and other disciplines must be considered and investigated. The often-used combination therapy of antipsychotics and other psychopharmacological drugs needs to be explored in studies that can evaluate its effectiveness and adverse effects.

4.3 Approaches in Subpopulations

There is a substantial need to provide solutions for adolescent patients suffering from psychosis/schizophrenia (Ardizzone et al. 2010) as well as a similar need to develop antipsychotics that may be used in the elderly without an increase of morbidity or even mortality. This includes drug-interaction profiles compatible not only with other psychiatric medication but also with pharmacotherapeutic approaches for other somatic disorders (Hiemke and Pfuhlmann 2012). In addition, evidence is needed to guide and justify the frequent use of antipsychotics beyond their approved indications in the elderly and other groups of patients (e.g., movement disorders).

4.4 Stage-Dependent Approaches

Recent interest in the development of preventive approaches in the treatment of psychosis and schizophrenia (Ruhrmann et al. 2012) sheds light on the field of stage-dependent approaches, where initial at-risk states, first and recurrent episodes of schizophrenia, as well as more chronic courses need to be differentiated and may allow for more specific and less side effect-prone approaches to the disease. Beyond this point, it may well be that a differentiation between the acute phase and maintenance treatment may help to improve the outcome. In this concept, underlying basic symptoms will become the primary target of preventive or maintenance treatment rather than related and potentially resulting symptoms apparent in the acute phase of the disease. Thus, less side-effect prone and limiting treatment strategies may be developed leading to a substantially increased adherence and relapse prevention.

4.5 Personalized Approaches

While research into pharmacogenomic and other markers to identify individual traits providing aids to select the most effective pharmacological strategy has been around for quite some time, the limited number of mechanisms of action may have hindered more specific interventions on an individual basis. Recent biomarker research has pointed to additional ways to predict individual response to treatments and potentially related neurobiological needs of patients (Kaddurah-Daouk et al. 2007). The plethora of new neurochemical and other biomarkers may make way for more successful strategies in such a direction and should be part of the investigation in new compounds from the very beginning.

4.6 Drug Delivery

Among unmet needs for antipsychotics remains the route of administration of antipsychotics. While oral and intramuscular ways of administration and long-lasting preparations are available, the emergency and initial rapid administration is certainly an expandable field. There is a lack of intravenous preparations of SGAs as well as alternative ways to reliably deliver emergency medication in a less intrusive way (e.g., pulmonary) often experienced as somehow traumatic by patients. Although this does not directly belong to novel pharmacological developments, it is noteworthy that addressing those problems that may be solved in a not too distant future seems not to be on the agenda.

4.7 Sustainability

While most unmet needs in the treatment of schizophrenia have been focused on the issues stated above, one major improvement of antipsychotic therapy would be a sustained effect that would actually provide a cure rather than a control of

symptoms. Our limited understanding of the pathophysiological bases of this disease which seems to represent a group of diseases sharing similar syndromic features may bring this goal out of current reach. This is, however, what we still should aim to achieve in the future.

5 Conclusions

Antipsychotics are an essential part of the treatment of psychosis and schizophrenia. Although clear progress has been made in the recent decades, their use is often affected by limited efficacy, an individually unacceptable side-effect profile, unspecific action in terms of the stage of the disease, the lack of individualization, and a failure to provide a cure rather than a mere improvement or remission of symptoms only. In addition, gender- and age-specific aspects as well as a variety of modern routes of administration need to be addressed. New approaches need to address these issues to solve respective unmet needs in the treatment of psychotic disorders.

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Antipsychotics in the Treatment of Bipolar Disorder

Jaskaran Singh, Guang Chen, and Carla M. Canuso

Contents

Abstract Atypical antipsychotics have an important role in the acute and maintenance treatment of bipolar disorder. While robust evidence supports the efficacy of these agents in the treatment of mania and in the prevention of manic relapse, few atypical antipsychotics have shown efficacy in the treatment or prevention of depressive episodes. These agents pose a lower risk of extrapyramidal side effects compared to typical neuroleptics, but carry a significant liability for weight gain

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and other metabolic side effects such as hyperglycemia and hyperlipidemia. More comparative effectiveness studies are needed to assess the optimal treatment regimens, including the relative benefits and risks of antipsychotics versus mood stabilizers. The exploration of the molecular mechanisms of antipsychotics has helped to shed further light on the underlying neurobiology of bipolar disorder, since these compounds target systems thought to be key to the pathophysiology of bipolar disorder. In addition to modulating monoaminergic neurotransmission, atypical antipsychotics appear to share properties with mood-stabilizing agents known to alter intracellular signal transduction leading to changes in neuronal activity and gene expression. Atypical antipsychotic drugs have been shown to exhibit neuroprotective properties that are mediated by upregulation of trophic and cellular resilience factors. Building on our understanding of existing therapeutics, especially as it relates to underlying disease pathology, newer "plasticity enhancing" strategies hold promise for future treatments of bipolar disorder.

Keywords Bipolar disorder • Atypical antipsychotics • Monoamines • Signal transduction • Cellular resilience • Neuroplasticity

1 Introduction

Bipolar disorder is a common, chronic, recurrent mental illness that affects the lives and functioning of millions of individuals worldwide. High rates of relapse, chronicity, lingering residual symptoms, sub-syndromes, cognitive and functional impairments, psychosocial disability, and diminished well-being are unfortunately common occurrences in bipolar disorder (Goodwin and Jamison 2007; Levy and Manove 2011). Recent studies have shown the efficacy of several atypical antipsychotics, both as monotherapy and in combination with mood stabilizers such as lithium and valproate, for the treatment of acute mania, manic relapse prevention, and acute bipolar depression (Calabrese et al. 2005a, b; Surja et al. 2006; Thase et al. 2006; Tohen and Vieta 2009).

In this review, we discuss contemporary research with antipsychotics in bipolar disorder including clinical treatment, neuroimaging, genetic association studies, and molecular and preclinical pharmacological studies. This research has elucidated some of the cellular and molecular effects of antipsychotics that include their antidopaminergic effects, as well as other mechanisms of action. We conclude by highlighting key achievements, shortcomings and unmet medical needs, as well as emerging new targets and next steps forward. An understanding of the neurobiology of this complicated and multifactorial disease is still developing, yet critical for the future development of targeted therapies.

2 Clinical Studies

2.1 Introduction to Clinical Studies

Antipsychotic medications have a long history in the treatment of bipolar disorder, especially in the management of acute mania and depressive episodes with psychotic features (Gentile 2007). Conventional antipsychotics, such as chlorpromazine and haloperidol, have been reported to be effective in up to 70 % of patients with acute mania, particularly in those with psychomotor agitation (Cousins and Young 2007; Tohen and Vieta 2009; Vestergaard 1992). Additionally, retrospective reports suggest that conventional agents are effective in the maintenance treatment of bipolar disorder (Cousins and Young 2007). While efficacious, use of these drugs has been limited by their neurological side effects. These untoward effects may be of particular concern in bipolar disorder, as patients with affective illness appear to be especially vulnerable to acute extrapyramidal side effects and tardive dyskinesia (Gao et al. 2008). Further, several reports suggest that conventional antipsychotics have depressogenic potential (Kusumakar 2002).

The introduction of atypical antipsychotics held the promise of fewer neurological side effects and the potential for greater utility in bipolar disorder. Over the past decade nearly all of the drugs within this class have been systematically studied, either as monotherapy or adjunctive therapy to a mood stabilizer, both in acute mania as well as in maintenance therapy (Tables 1 and 3). As a result, most of these agents have been approved for these indications by health authorities around the world. More recently, some of these agents have been studied in bipolar depression (Tables 1 and 3). Current treatment guidelines include atypical antipsychotics as first-line treatment in bipolar disorder (APA 2002; Beckford-Ball 2006; Giese 2009; Toprac et al. 2006).

Despite the widespread use of atypical antipsychotics in bipolar disorder, there are limited data on the relative efficacy of (1) the various agents within the class; (2) atypical versus conventional antipsychotics; and (3) atypical antipsychotics compared to mood stabilizers, such as lithium or valproate. Likewise, there are little data on the comparative safety of atypical antipsychotics in this patient population. This section provides a review of the randomized placebo-controlled trials of atypical antipsychotics in bipolar disorder and recent meta-analyses of these agents in acute mania.

2.2 Clinical Studies in Acute Mania

Table 1 provides a summary of randomized placebo-controlled trials of atypical antipsychotics in acute mania, when used either as monotherapy or adjunctive therapy to mood stabilizers. Aripiprazole, asenapine, olanzapine, quetiapine, and risperidone have demonstrated efficacy and got health authority approval in the

Table 1 Atypical antipsychotics in the treatment of acute mania: placebo-controlled, randomized monotherapy, and adjunctive therapy studies

Atypical antipsychotic	Study	Comparator	*N*	YMRS Baseline	YMRS Change from Baseline	*P*-value vs. placebo
Monotherapy trials						
Aripiprazole	Keck et al. (2007)	Aripiprazole	123	28.2	−8.2	0.002
		Placebo	122	29.7	−3.4	
	Sachs et al. (2006)	Aripiprazole	137	28.8	−12.5	≤0.001
		Placebo	135	28.5	−7.2	
	McQuade et al. (2003)	Aripiprazole	129	27.8	−10.8	NS
		Aripiprazole	127	27.9	−10.0	NS
		Placebo	130	28.3	−10.1	
Asenapine	McIntyre et al. (2010)	Asenapine	189	28.3	−10.8	≤0.0001
		Olanzapine	188	28.6	−12.6	≤0.0001
		Placebo	103	29.0	−5.5	
	McIntyre et al. (2009)	Asenapine	183	29.4	−11.5	≤0.01
		Olanzapine	203	29.7	−14.6	≤0.0001
		Placebo	94	28.3	−7.0	
Olanzapine	Tohen et al. (1999)	Olanzapine	50	28.66	−10.3	0.02
		Placebo	66	27.65	−4.9	
	Tohen et al. (2000)	Olanzapine	54	28.76	−14.8	<0.001
		Placebo	56	29.43	−8.1	
Paliperidone	Vieta et al. (2010)	Paliperidone	195	27	−13.2	<0.001
		Quetiapine	193	28	−11.7	<0.001
		Placebo	106	27	−7.4	
Quetiapine	McIntyre et al. (2005)	Quetiapine	101	34	−12.3	≤0.01
		Haldol	98	32.3	−15.7	≤0.001
		Placebo	100	33.1	−8.3	
	Bowden et al. (2005)	Quetiapine	107	32.7	−14.6	<0.001
		Lithium	98	33.3	−15.2	<0.001
		Placebo	95	34	−6.7	
Risperidone	Hirschfeld et al. (2004)	Risperidone	127	29.1	−10.6	<0.001
		Placebo	119	29.2	−4.8	
	Khanna et al. (2005)	Risperidone	146	37.1	−22.7	<0.001
		Placebo	144	37.5	−10.5	
	Smulevich et al. (2005)	Risperidone	153	32.1	−15.1	<0.001
		Haloperidol	144	31.3	−13.9	<0.001
		Placebo	138	31.5	−9.4	
Ziprasidone	Keck et al. (2003)	Ziprasidone	131	27	−12.4	<0.001
		Placebo	66	26	−7.8	
	Potkin et al. (2005)	Ziprasidone	137	26.19	−11.1	<0.01
		Placebo	65	26.42	−5.6	
Adjunctive therapy trials						
Aripiprazole[a]	Vieta et al. (2008a, b)	Aripiprazole	253	23.2	−13.3	0.01
		Placebo	131	23.0	−10.7	
Asenapine	Calabrese et al. (2010)	Asenapine	155		−9.7	≤0.05
		Placebo	163		−7.7	

(continued)

Table 1 (continued)

Atypical antipsychotic	Study	Comparator	*N*	YMRS Baseline	YMRS Change from Baseline	*P*-value vs. placebo
Olanzapine[a]	Tohen et al. (2002)	Olanzapine	220	23.31	−13.1	0.003
		Placebo	114	22.67	−9.1	
Paliperidone	Berwaerts et al. (2011)	Palperidone	150	27	−14.3	NS (0.16)
		Placebo	150	27	−13.2	
Quetiapine	Mullen et al. (2003)	Quetiapine	104	NA	−16.5	NS
		Placebo	96	NA	−14.3	
	Sachs et al. (2004)	Quetiapine	81	31.5	−13.8	0.021
		Placebo	89	31.1	−9.9	
Risperidone	Sachs et al. (2002)	Risperidone	51	28	−14.3	0.009
		Haloperidol	50	27.3	−13.4	<0.003
		Placebo	47	28	−8.2	
	Yatham et al. (2003)	Risperidone	69	29.3	−19.5	NS (0.377)
		Placebo	73	28.3	−17.1	
Ziprasidone[b]	Weisler et al. (2003)	Ziprasidone	99	NA	−0.7	NS
		Placebo	99	NA	−0.7	

YMRS Young mania rating scale
Adapted from Perlis et al. (2006)
[a]All studies or primary endpoints at 3 weeks with the exception of Tohen et al. (4 weeks) and Vieta et al. (6 weeks)
[b]Studies of ziprasidone used the Mania Rating Scale

United States (US) and Europe (EU) for use in acutely manic adults with and without psychosis, as either mono- or adjunctive therapy. All adjunctive trials included subjects who had inadequate response to current treatment with a mood stabilizer, although the study of quetiapine also included subjects who may not have received an adequate course of treatment with lithium or valproate prior to randomization (Sachs et al. 2004). Ziprasidone has demonstrated efficacy and got approved US and EU indications as a monotherapy for acute mania (Bowden et al. 2010). Most pivotal trials of atypical antipsychotics in acute mania included subjects with mixed episodes (with the exception of quetiapine) (Bowden et al. 2005). However, only aripiprazole, olanzapine, and risperidone have been studied in subjects with rapid-cycling bipolar disorder (Zupancic 2011). Aripiprazole, olanzapine, quetiapine, and risperidone have demonstrated efficacy and safety in children and adolescents and are indicated for the treatment of acute mania in pediatric bipolar disorder (Chang 2008; Fraguas et al. 2010; Scheffer et al. 2011).

Few studies exist that directly compare the efficacy of the various atypical antipsychotics in acute mania. Perlis and coworkers conducted a meta-analysis of randomized placebo-controlled, mono- and adjunctive therapy trials of atypical antipsychotics published through 2004 (Perlis et al. 2006). Little difference between agents was observed in efficacy scores versus placebo or in differential response rates among the individual atypical antipsychotics whether used alone or adjunctive to a mood stabilizer. The three monotherapy studies that included active

comparators suggest that atypical antipsychotics had similar efficacy scores compared to lithium and haloperidol, a typical antipsychotic (Yildiz et al. 2011). As expected, the meta-analysis confirmed that adjunctive therapy with an atypical antipsychotic provides additional benefit over monotherapy with a mood stabilizer. Another meta-analysis suggests that antipsychotics are more effective than anticonvulsants when used as monotherapy (Cipriani et al. 2011). However, the relevant question of whether the combination of atypical antipsychotic and mood stabilizer is clinically superior to atypical antipsychotic alone remains unanswered. Nonetheless there appears to be a clear role for atypical antipsychotics in the treatment of acute mania, with a large body of data giving clinicians evidence for use as monotherapy or in combination with a mood stabilizer, in patients with pure and mixed mania, and in those with and without psychosis.

2.3 Clinical Studies in Acute Agitation

Intramuscular (IM) formulations of both aripiprazole and olanzapine are approved for the acute treatment of agitation associated with manic or mixed episodes of bipolar I disorder. In a placebo-controlled study of 291 agitated inpatients with manic or mixed episodes, both 9.75 and 15 mg doses of IM aripiprazole were superior to placebo in reducing acute agitation 2 h post-dose, as measured by the PANSS Excited Component (PEC). Likewise, 10 mg of IM olanzapine was superior to placebo in reducing the PEC 2 h post-dose in a study of 201 acutely agitated inpatients with a manic or mixed episode (Wagstaff et al. 2005). The efficacy for the two appears to be similar (Kinon et al. 2008).

2.4 Clinical Studies in Acute Treatment of Bipolar Depression

Table 2 summarizes the placebo-controlled, randomized monotherapy and adjunctive therapy studies of atypical antipsychotics in the acute treatment of bipolar depression. Quetiapine is the only atypical antipsychotic indicated as a monotherapy for treatment of acute bipolar depression, with efficacy demonstrated in a population of bipolar I and II subjects (Thase et al. 2006). Little is known whether other atypical antipsychotics would be effective as monotherapy in bipolar depression, though two studies of aripiprazole in this population were negative. The combination of olanzapine and fluoxetine is also approved for the acute bipolar I depression. While olanzapine monotherapy did show superiority over placebo, the magnitude of antidepressant effect was greatest with the olanzapine–fluoxetine combination (Tohen et al. 2003). Additionally, an open-label follow-up study of olanzapine–fluoxetine combination showed little risk of inducing mania (Corya et al. 2006).

Table 2 Atypical antipsychotics in the treatment of bipolar depression: placebo-controlled, randomized monotherapy, and adjunctive therapy studies

Atypical antipsychotic	Study	Comparator	*N*	MADRS baseline	MADRS change from baseline	*P*-value vs. placebo
Monotherapy trials						
Aripiprazole	Thase et al. (2008)	Aripiprazole	177	29.1	−12.0	NS
		Placebo	164	28.5	−11.4	
	Thase et al. (2008)	Aripiprazole	176	29.56	−12.3	NS
		Placebo	178	29.35	−11.8	
Quetiapine	Calabrese et al. (2005a, b)	Quetiapine (300 mg)	170	30.3	−16.7	<0.001
		Quetiapine (600 mg)	172	30.4	−16.4	<0.001
		Placebo	169	30.6	−10.3	
	Thase et al. (2006)	Quetiapine (300 mg)	155	29.9	−16.0	<0.001
		Quetiapine (600 mg)	161	31.1	−16.9	<0.001
		Placebo	151	29.6	−11.9	
Combination therapy trials						
Olanzapine-fluoxetine combination (OFC)	Tohen et al. (2003)	OFC	86	30.8	−18.5	<0.001
		Olanzapine	370	32.6	−15.0	0.002
		Placebo	377	31.3	−11.9	

MADRS Montgomery-Asberg depression rating scale
Adapted from Cruz et al. (2009)

2.5 *Clinical Studies in Maintenance Treatment of Bipolar Disorder*

Table 3 summarizes the randomized placebo-controlled trials of atypical antipsychotics as maintenance therapy in bipolar I disorder. Aripiprazole and long-acting risperidone have shown efficacy in the maintenance treatment of bipolar I disorder as mono- and adjunctive therapy (Popovic et al. 2010; Rybakowski 2005; Smith et al. 2007). Olanzapine has proven efficacy as a monotherapy in preventing mood episodes (Weisler et al. 2010), whereas quetiapine and ziprasidone have only been shown to prevent such relapses when given in combination with a mood stabilizer (Vieta et al. 2011).

Although the study designs differed among the pivotal trials for the various atypical antipsychotics, all trials employed a randomized discontinuation after a period of stabilization. While studies of all of the agents included subjects stabilized from an acute manic or mixed state, maintenance studies of quetiapine also included subjects stabilized from acute depressive episodes. The adjunctive study of long-acting injectable risperidone also enrolled euthymic patients and patients stabilized from hypomanic and depressed states.

Table 3 Atypical antipsychotics in the maintenance treatment of bipolar disorder: placebo-controlled, randomized monotherapy, and adjunctive therapy studies

Atypical antipsychotic	Study	Treatment regimen	Comparator	*N*	*P* value vs. placebo for time to recurrence	*N* (%) relapsed overall	*N* (%) relapsed manic	*N* (%) relapse depressed
Aripiprazole	Keck et al. (2007)	Monotherapy	Aripiprazole	78	0.005	19 (24.4)	6 (7.7)	9 (11.5)
			Placebo	83		36 (43.4)	19 (22.9)	11 (13.3)
	Marcus et al. (2011)	Adjunctive	Aripiprazole	168	0.014	25 (17)	7 (5)	14 (10)
			Placebo	169		43 (29)	19 (15)	18 (13)
Olanzapine	Tohen et al. (2006)	Monotherapy	Olanzapine	225	<0.001	105 (46.7)	27 (12)	68 (30.8)
			Placebo	136		109 (80.1)	44 (32)	53 (39)
Quetiapine	Vieta et al. (2008a, b)	Adjunctive	Quetiapine	336	<0.001	62 (18.5)	36 (10.7)	26 (7.7)
			Placebo	367		180 (49.0)	96 (26.2)	84 (22.9)
	Suppes et al. (2009)	Adjunctive	Quetiapine	310	<0.001	63 (20.3)	22 (7.1)	41 (13.2)
			Placebo	313		163 (52.1)	61 (19.5)	102 (32.6)
Long-acting injectable risperidone	Quiroz et al. (2010)	Monotherapy	LAI	154	<0.001	42 (27.3)	22 (14.3)	20 (13.0)
			Risperidone	149		76 (51.0)	62 (41.6)	14 (9.4)
			Placebo					
	Macfadden et al. (2009)	Adjunctive	LAI Risperidone	65	0.010	15 (23.1)	5 + 2 mixed (10.8)	8 (12.3)
			Placebo	59		27 (45.8)	12 + 4 mixed (27.1)	11(18.6)
Ziprasidone	Bowden et al. (2010)	Adjunctive	Ziprasidone	127	0.010	25 (19.7)	7 + 2 mixed (7.1)	16 (12.6)
			Placebo	113		36 (32.4)	14 + 6 mixed (17.7)	16 (14.2)

Although data from most maintenance trials of atypical antipsychotics show greater differences between the active treatment and placebo groups in the number of manic relapses compared to the number of depressive relapses, only the long-term study of quetiapine showed a treatment effect of delaying both manic and depressive relapses (Vieta et al. 2008a, b; Weisler et al. 2010). However, it is important to note that these maintenance trials were not designed to conclude that atypical antipsychotics are more effective in preventing mania than depression. In general, these trials were powered to detect a drug–placebo difference only in the total number of relapses. Moreover, most subjects entered the maintenance phase after an acute manic or mixed episode, thereby biasing the outcome towards more manic episodes.

Little data exist on the comparative long-term efficacy of atypical antipsychotic monotherapy versus mood stabilizers in preventing relapses. Olanzapine, however, has been compared to both lithium and valproate in two separate randomized controlled trials (Suppes et al. 2005a, b; Tohen et al. 2005). Both of these studies showed similar rates of *overall* relapses in subjects receiving olanzapine and each of the mood stabilizers; however, olanzapine appeared to be more effective than lithium in preventing *manic* relapses (13.8 % vs. 23.4 %, $p = 0.002$) (Tohen et al. 2005).

2.6 Tolerability and Safety in Clinical Studies

Table 4 summarizes the safety profiles of the various atypical antipsychotics in patients with bipolar disorder. While this newer generation of agents has a lower risk of extrapyramidal side effects, they carry a significant risk of weight gain and other metabolic side effects, such as hyperglycemia and hyperlipidemia. Weight gain may be particularly problematic in the bipolar patient population, especially if it is additive to the weight gain caused by mood stabilizers. Certain agents, such as olanzapine, have an increased potential for weight gain and hyperlipidemia, and these effects may be more pronounced in adolescents compared to adults (olanzapine prescribing information). Additionally, the sedation associated with some atypical antipsychotics may be especially bothersome to patients who are students or are employed.

2.7 Summary of Clinical Data

A relatively large body of evidence now exists to support the efficacy of atypical antipsychotics in various stages of bipolar disorder. As a class, these drugs appear to be effective in the treatment of acute mania. Indeed, several treatment guidelines have recommended atypical antipsychotic monotherapy as a first-line treatment for acute mania (APA 2002; Suppes et al. 2005a, b), and several studies suggest that the

Table 4 Summary of evidenced-based information on the safety of atypical antipsychotics for uses in bipolar disorder

Drug	Risk of ECG alterations	Risk of weight gain	Risk of other metabolic events	Risk of EPS	Risk of increasing serum prolactin levels
Aripiprazole	–	±	–	±	–
Asenapine	–	+	–	±	–
Olanzapine	–	++	++	±	++
Quetiapine	–	++	NA/I	±	–
Risperidone	–	++	NA/I	++	++
Ziprasidone	±	NA/I	NA/I	NA/I	NA/I

EPS extrapyramidal symptoms; *NA/I* no available data or insufficient data; ± indicates that the drug shows a higher risk of inducing the event compared with placebo; + indicates that the drug shows a higher risk of inducing the event when compared with placebo or one active comparator (either first-generation antipsychotic or mood stabilizer); ++ indicates that the drug shows a higher risk of inducing the event when compared with two different active comparators (either first-generation antipsychotics or mood stabilizers); – indicates that the drug shows a risk of inducing the event that is not different to that shown by placebo
Adapted from Gentile (2007)

combination of an atypical antipsychotic plus a mood stabilizer is more effective than a mood stabilizer alone, especially in patients inadequately responsive to mood stabilizers. Yet, it is not clear if an antipsychotic adjunctive to a mood stabilizer is superior to an antipsychotic alone. Intramuscular formulations of certain atypical antipsychotics are effective in the treatment of acute agitation associated with mania (Kinon et al. 2008; Tran-Johnson et al. 2007). Quetiapine is the only antipsychotic monotherapy to demonstrate efficacy in acute bipolar depression, whereas olanzapine in combination with fluoxetine appears to be effective in bipolar depression with little risk of inducing mania (Benyamina and Samalin 2012). Either of these treatments may have utility in acutely depressed patients requiring rapid treatment response. Most of the atypical antipsychotics have demonstrated the ability to prevent relapse of a mood episode after stabilization from a manic or mixed state, with clear benefit in preventing manic relapses.

The decision to use an atypical antipsychotic in a patient with bipolar disorder, as well as the selection of a particular agent, will depend on factors other than efficacy alone, such as safety, tolerability, compliance, and cost (Perlis et al. 2006). The atypical antipsychotics carry the risk of weight gain and metabolic abnormalities, sedation, and other side effects, some of which may be compounded when used in combination with mood stabilizers. Long-acting injectable risperidone may be a particularly valuable treatment option for bipolar patients with a history of poor medication compliance (Walburn et al. 2001). While pharmacoeconomic factors may also play a role in treatment selection, there are now several generic atypical antipsychotics available.

Further comparative effectiveness trials of atypical antipsychotics are still needed to best evaluate the full utility and value of these agents in clinical practice. Specifically, more data are needed to determine the relative acute efficacy of atypical antipsychotic versus mood stabilizer monotherapy, as well as atypical

antipsychotic monotherapy versus atypical antipsychotic plus a mood stabilizer. Moreover, far fewer agents have demonstrated efficacy for preventing depressive relapse and additional research is needed to establish effective treatments for this phase of the illness.

Atypical antipsychotics have broadened the pharmacological armamentarium for the treatment of bipolar disorder. Furthermore, the exploration of the molecular mechanisms of antipsychotics has helped to shed greater light on the underlying neurobiology of the condition. The subsequent section of this chapter reviews the putative pharmacological mechanisms of antipsychotics, including their effect on monoaminergic neurotransmitters and signaling cascades implicated in the control of neuroplasticity, and cellular resilience.

3 Mechanisms of Antipsychotics in the Treatment of Bipolar Disorder

3.1 Introduction to Mechanisms of Action

As described above, many antipsychotics have been shown to have an antimanic effect, and some of the atypical antipsychotics have also been shown to have antidepressant effects as monotherapy (e.g., quetiapine) or as an adjunct to an antidepressant (e.g., aripiprazole and olanzapine). The primary mechanism of action of antipsychotics is via blockade of dopamine D_2 receptors. Atypical antipsychotics also block serotonin 5-HT_2 receptors and may restore the dampened firing rate of norepinephrine (NE) neurons produced by selective 5-HT reuptake inhibitors, thereby enhancing their antidepressant activity (Blier and Blondeau 2011). In addition, antipsychotics have differing activity on α-adrenoceptors, muscarinic receptors, and histamine receptors. Beyond their effects on neurotransmission, atypical antipsychotics alter intracellular signal transduction and exhibit neuroprotective properties that are mediated by upregulation of trophic and cellular resilience factors.

3.2 Role of Dopamine

The role of dopamine in bipolar disorder has been reviewed extensively (Berk et al. 2007; Cousins et al. 2009; Goodwin 2007; Kapur and Mann 1992). In summary, dopaminergic pathways have been implicated in the core symptoms of bipolar disorders. Historically, dopaminergic models of bipolar disorder were simplistic, dichotomous models suggesting mania as a hyperdopaminergic state and depression as a hypodopaminergic state. However, such a model fails to explain the complexity of the illness and various symptoms or comorbid conditions

(e.g., psychotic symptoms during bipolar depression episodes or attentional deficits during manic episodes). Nonetheless, studies of regional dopaminergic pathways and cell signaling pathways have provided some insight into the pathophysiology of bipolar disorder, as these pathways subserve many of the physical and psychological processes known to be altered in this condition.

Bipolar disorder is a highly heritable illness. Genes encoding the dopamine transporter (DAT), SLC6A3, and rs27072 (Kato 2007; Pinsonneault et al. 2011) have been implicated bipolar disorder, although not consistently (Sklar et al. 2011). Brain imaging studies have not consistently shown any direct evidence of increased or reduced dopaminergic activity, dopamine transporter (DAT) activity, or striatal D_2 dopamine receptor binding in bipolar disorder (Pearlson et al. 1995). Interpretation of neuroimaging findings of the dopaminergic system in bipolar illness is hampered by the fact that subjects were assessed during different phases of illness, bipolar depression, mania or during a euthymic state, as well as while medicated and drug-free in the few studies conducted (Nikolaus et al. 2009).

Dopaminergic psychostimulants, such as amphetamine and methylphenidate, can lead to euphoria or can mimic hypomania. High doses, particularly when taken repeatedly, can cause a number of symptoms including alterations in drive, motivation, impulsivity, and sleep, as well as a full manic episode. Interestingly, these symptoms can be attenuated with treatment with antipsychotics, lithium, or valproate (Berk et al. 2007; Kapur and Mann 1992). Lithium and valproate at therapeutically relevant concentrations have been shown to modulate dopaminergic activity by attenuating the downstream pathways activated by dopamine receptors as shown by studies using forskolin-raised cAMP concentrations which were inhibited by lithium, valproate, and carbamazepine, both in vitro and in vivo (Montezinho et al. 2006). Data from pharmacological interventions support the role of dopamine in bipolar disorder, with most of the antipsychotics having shown antimanic activity (reviewed above).

3.3 Role of Serotonin and Norepinephrine

As discussed above, a few atypical antipsychotics have been shown to improve depressive symptoms. In addition to their affinity to D_2 receptors, atypical antipsychotics are also characterized by their affinity for 5-HT_{2A} and 5-HT_{2C} receptors and effects on norepinephrine (NE) transmission. Potent α_2-adrenergic antagonist activity has been reported for aripiprazole, quetiapine, risperidone, and paliperidone. Blier and others have proposed that blockade of these autoreceptors on the cell body of NE neurons and their terminals can lead to enhanced NE neurotransmission. This effect may be seen especially with norquetiapine, an active metabolite of quetiapine, potentially conferring antidepressant effects while the D_2 blockade may prevent a switch to mania (Blier and Blondeau 2011; Jensen et al. 2008; McIntyre et al. 2009; Prieto et al. 2010).

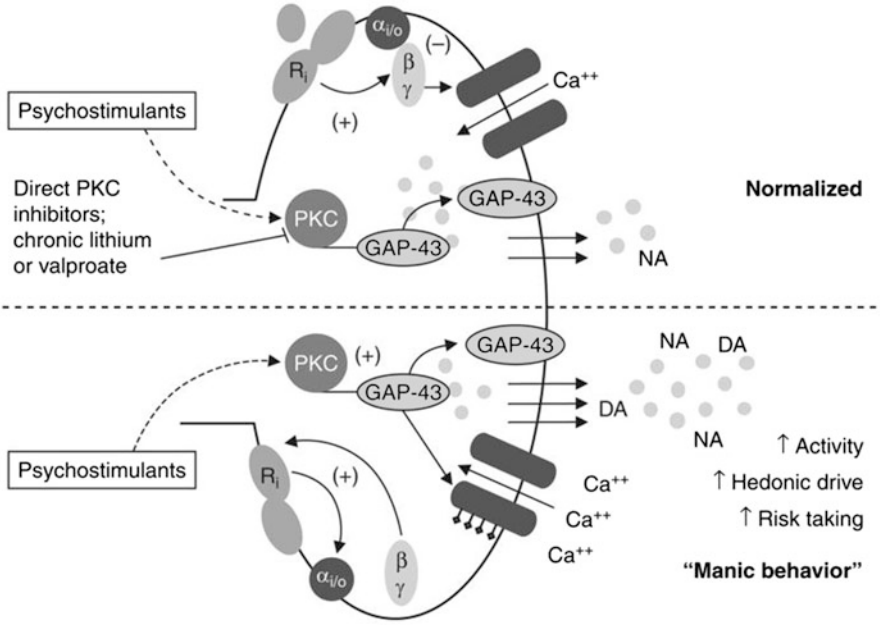

Fig. 1 Protein kinase C (PKC) in the pathophysiology and treatment of manic behavior. *DA* dopamine; *GAP-43* growth-associated protein of 43 kDa; *NA* noradrenaline (norepinephrine); ↑ indicates increased. Figure adapted from Zarate and Manji (2009)

3.4 Signal Transduction Pathways

Activation or blockade of dopaminergic receptors results in changes in intracellular signal transduction leading to alterations in neuronal activity and gene expression. Protein kinase C (PKC) has generated considerable interest as a common target for mood stabilization. Lithium has been shown to act directly on pathways involving phospholipase2 (PLA2), and lithium and valproate on PKC pathways (Fig. 1) (Zarate and Manji 2009). Based upon this hypothesis that PKC is a common target, a number of studies have demonstrated the potential involvement of PKC in the pathophysiology and treatment of bipolar disorder (reviewed in Zarate and Manji 2009). Most critically a number of small proof of concept studies with tamoxifen, a PKC inhibitor, demonstrated a fast onset of efficacy in acute mania (Amrollahi et al. 2011; Yildiz et al. 2008; Zarate et al. 2007), thus corroborating the PKC hypothesis of mania. Although tamoxifen also has antiestrogenic effects, studies with other antiestrogen compounds such as medroxyprogesterone or clomiphene did not attenuate the amphetamine-induced behavioral changes in an animal model of mania that are attenuated by tamoxifen, suggesting that the antiestrogenic effect of tamoxifen is unlikely to contribute to its antimanic property (Pereira et al. 2011). Chronic administration of clozapine and haloperidol has previously been shown to reduce PKC activity in discrete brain areas, e.g., the hippocampus (Dwivedi and

Pandey 1999), which may be relevant for the mechanism of antipsychotic drugs and may in part play a role in the antimanic activity of antipsychotics mediated through PKC inhibition (Zarate and Manji 2009). A recent meta-analysis of the efficacy of antimanic agents supports a larger effect size of tamoxifen compared to antipsychotics (Yildiz et al. 2011). These data add support to the relevance of PKC as a target in bipolar disorder and warrants further studies (DiazGranados and Zarate 2008; Zarate and Manji 2009).

3.4.1 Akt/GSK-3 and Wnt Pathway

Akt is a protein kinase (also known as protein kinase B) that is involved in multiple cellular functions including metabolism, cell stress, cell-cycle regulation, and apoptosis. Akt has a basic role in regulating neuronal cell size and survival (Freyberg et al. 2010). Regulation of Akt by phosphorylated phosphatidylinositol has been associated with the action of insulin, insulin-related peptides (e.g., insulin-like growth factor), and neurotrophins (e.g., nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin (NT)-3) that exert their biological function by stimulating receptor tyrosine kinase (Beaulieu and Gainetdinov 2011). Activation of Akt via phosphorylation by the intracellular kinases PDK1 (3-phosphoinoitide-dependent protein kinase 1) and rictor-mTORC2 (mammalian target of rapamycin complex 2) leads to phosphorylation of other molecules including GSK-3, which plays a significant role in glucose metabolism and in differentiation and development, intracellular trafficking, modulation of synaptic plasticity, apoptosis, and regulation of gene transcription.

In addition to the Akt/GSK-3 pathway, signaling through the Wingless (Wnt) pathway is also of relevance. Wnt proteins are important mediators of cell–cell communication and are involved in diverse cellular processes, including the development of the CNS and play a crucial role in modulation of synaptic plasticity and in neurogenesis and in maintaining and protecting neuronal connections throughout the entire life span (Inestrosa and Arenas 2010). Activated GSK3 promotes β-catenin (a downstream mediator on Wnt signaling) and inhibits protein synthesis. DISC1, one of the most consistently reported risk mutations in schizophrenia and a risk factor for mood disorders (Lipina et al. 2011), regulates adult progenitor cells through GSK-3–β-catenin signaling. Mice lacking DISC1 in the dentate gyrus exhibited schizophrenia-like and depression-like behavior that could be normalized by treatment with a GSK-3 inhibitor (Lipina et al. 2011).

Dopamine-mediated decreases in Akt activity are considered to be mediated by postsynaptic dopamine D_2 receptors. Activation of dopamine D_2 receptor by dopamine or amphetamines leads to recruitment of beta-arrestin 2 and Akt along with the phosphatase PP2A, which dephosphorylates and consequently inactivates Akt, leading to an increase in GSK-3 activity. GSK-3 is constitutively active in resting cells, requiring phosphorylation by kinases such as Akt to inactivate it (Beaulieu et al. 2009). Disruption of Akt's regulation of GSK-3 activity in the brain may also play a role in dysregulation of brain function in schizophrenia and mood disorders (Freyberg et al. 2010).

There is increasing evidence that Akt and GSK-3-related intracellular signaling may at least partially be responsible for the ability of antipsychotic medications to treat symptoms of psychosis and may be a common mechanism for antipsychotics, mood stabilizers, and antidepressants. Some atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, aripiprazole) and typical antipsychotics (e.g., haloperidol) have been shown to either activate Akt or mimic Akt activity by increasing the phosphorylation of its substrates GSK-3 (Roh et al. 2007). However, differences between haloperidol and atypical antipsychotics have emerged in the kinetics of Akt/GSK-3 phosphorylation, the levels of proteins expressed following drug exposure, and the pathway that is preferentially activated (i.e., Akt vs. Wnt pathway signaling) (Roh et al. 2007). Treatment with either haloperidol or clozapine led to phosphorylation of GSK-3α and GSK-3β in rat frontal cortex (Roh et al. 2007). However, whereas levels of phosphorylated Akt1 returned to baseline within 1 hour following acute haloperidol exposure, Akt remained phosphorylated after a similar acute clozapine treatment. The prolonged duration of the effect of clozapine on Akt relative to a typical antipsychotic such as haloperidol may account for its greater effect on downstream molecules in the Wnt pathway (Sutton and Rushlow 2011). In addition, GSK-3 activity is regulated by 5-HT neurotransmission, through the activation of 5-HT_{2A} receptors. It is therefore possible that atypical antipsychotics, which are antagonists of dopamine D_2 receptors and serotonin 5-HT_{2A} receptors, might inhibit GSK-3 activity by acting on dopamine and 5-HT receptor functions (Beaulieu et al. 2007).

Lithium exerts some of its biochemical and behavioral effects by interfering with a β-arrestin signaling complex involved in the regulation of Akt and GSK-3. Lithium's effects on circadian rhythms and mood stabilization have been suggested to be mediated through direct inhibition of GSK-3 at therapeutically relevant concentrations (Gould et al. 2006). Valproate and lamotrigine (but not carbamazepine) have also been shown to indirectly inhibit GSK-3, and this mechanism has been demonstrated by various techniques to result in mood stabilizer-like behavior in rodent models (Gould et al. 2006, O'Brien and Klein 2007). The action of SSRIs and other 5-HT-related antidepressants on GSK-3 as well as the apparent antidepressant-like action of GSK-3 inhibitors in behavioral tests are strongly suggestive of an involvement of GSK-3 in the effects of antidepressants. In summary, in both animal models and the clinical population, GSK-3 manipulation appears to have antidepressant, antipsychotic, and antimanic effects.

Downstream targets of Akt and/or GSK-3 in the action of psychotropic drugs need to be identified and investigated. Whether the role of the Akt/GSK-3/Wnt signaling cascade in mediating behavioral outcomes and actions of psychotropic drugs is confined to certain brain areas is of interest to explore. Interestingly the $mGlu_{2/3}$ agonist, LY379268, which has demonstrated preliminarily clinical antipsychotic efficacy, has also been shown to target Akt and Wnt signaling (Sutton and Rushlow 2011). It is tempting to speculate that this pathway may play a pivotal role in the therapeutic action of antipsychotics.

3.4.2 Neurotrophic Signaling Cascades

Neurotrophins (NTs), a family of peptide growth factors for nerve and glial cells, influence cell cycle, growth, differentiation and survival of neurons and thereby regulate synaptic plasticity in the adult brain. Members of the NT family include NGF, BDNF, NT-3, NT-4, NT-5, and NT-6. BDNF and other neurotrophic factors are necessary for the survival and function of neurons; thus, sustained reductions of these factors could affect neuronal viability.

Endogenous neurotrophic factors have traditionally been viewed as increasing cell survival by providing necessary trophic support. However, it is now clear that their survival-promoting effects are mediated largely by inhibiting cell death (apoptosis) cascades (Lee et al. 2001). Increasing evidence suggests that neurotrophic factors inhibit cell death cascades by activating the extracellular-regulated kinase (ERK) signaling pathway [cyclic adenosine monophosphate (cAMP) response element binding (CREB) is directly phosphorylated and activated by phospho-ERK1/2], the phospholipase C (PLC) cascade, and the phosphoinositide 3-kinase (PI3K)/Akt pathway.

Atypical antipsychotic drugs have been shown to exhibit neuroprotective properties that are mediated by upregulation of trophic factors (Lieberman et al. 2008). Quetiapine reverses the stress-induced decrease in hippocampal BDNF (Fumagalli et al. 2004) and prolongs neuronal survival similar to that shown with antidepressants. Quetiapine and olanzapine have been shown to elicit trophic effects in cultured neuronal cells by activation of Akt and ERK, which could indicate mitogenic and neuroprotective effects (Di Benedetto et al. 2011). Although antidepressants and antipsychotics both increase neurogenesis, the effect of antidepressants is restricted mainly to the subgranular zone (SGZ) of the dentate gyrus, with no impact on subventricular zone (SVZ) of the lateral ventricles in the forebrain (Samuels and Hen 2011). However, antipsychotic drugs have been reported to promote neurogenesis in both the SGZ and SVZ (Newton and Duman 2007). Additionally, haloperidol, a typical antipsychotic drug and potent D_2 receptor antagonist, significantly increases cell proliferation in the SVZ, resulting in new neurons in the olfactory bulb and non-neuronal cells in the striatum (Deutch et al. 1995). The striatal cell proliferation would explain the caudate enlargement (Newton and Duman 2007) that has been reported with long-term administration of typical antipsychotic drugs but not atypical agents. Despite the robust SVZ neurogenesis, antipsychotic drugs with high D_2 receptor specificity do not seem to increase hippocampal proliferation. In contrast, atypical antipsychotic drugs that exhibit affinity for serotonin receptors increase SGZ neurogenesis in addition to non-neuronal proliferation in the frontal cortex (Newton and Duman 2007). Whether atypicals are still able to induce SVZ proliferation is somewhat controversial as some studies report this effect (Green et al. 2006) while others do not (Councill et al. 2006).

The overlap that is seen in proliferation profiles of SSRI antidepressants and atypical antipsychotic drugs, particularly with 5-HT_2 inhibitory activity, is striking

(Nasrallah et al. 2010) but still only correlative, with the precise underlying mechanism remaining unclear. Studies with specific serotonin agonists and antagonists have shed light on some of these mechanisms. The role of D_2 receptors in haloperidol-induced proliferation was addressed by generating D_2 receptor null mice that do not exhibit an increase in neural stem cells with haloperidol administration (Newton and Duman 2007). These data also suggest that dopamine signaling via activation of D_2 receptors has an anti-proliferative effect, which is overcome by the antagonistic effect of haloperidol (Newton and Duman 2007). However, there is still significant controversy regarding the contribution of D_2 receptors, as D_3 receptor activation was earlier shown to stimulate adult SVZ (Merlo et al. 2011) and substantia nigra (Collo et al. 2008) neurogenesis.

3.4.3 The Bcl-2 Family of Proteins

The B-cell lymphoma protein (Bcl-2) family includes pro- (such as Bax and Bad) and anti-apoptotic (such as Bcl-2 and Bcl-xL) proteins (Youle and Strasser 2008). Several preclinical studies have shown that atypical antipsychotics, including olanzapine, risperidone, and quetiapine upregulate levels of Bcl-2 or Bcl-xL in the brain after chronic administration (Hammonds and Shim 2009; He et al. 2004, 2006; Keilhoff et al. 2010; Luo et al. 2004). The mechanism through which atypical antipsychotics upregulate Bcl-2 is still largely unknown. However, Bcl-2 effects of atypical antipsychotics illustrate that atypical antipsychotics and mood stabilizers can produce similar intracellular actions, and this might explain in part the efficacy of atypical antipsychotics in the treatment of mood episodes and in the prevention of recurrence.

These Bcl-2 family proteins are known to play essential roles in apoptosis. They also play non-apoptotic regulatory roles in mitochondrial function, endoplasmic reticulum stress, calcium homeostasis, neurite growth, axonal regeneration, AMPA receptor trafficking and synaptic plasticity (Chen et al. 2010; Hunsberger et al. 2009; Jiao and Li 2011; Jonas 2006, 2009; Kim et al. 2008; Li and Jope 2010; Youle and Strasser 2008). Chen et al. (1999) found that upregulation of Bcl-2 in the brain is a common effect of two structurally distinct mood stabilizers, lithium and valproate. They also determined that the upregulation is at least in part through activation of the ERK MAP kinase (Creson et al. 2009; Einat et al. 2003; Yuan et al. 2001). The ERK activation led to activation of CREB, a transcription factor, and upregulation of bcl-2 gene transcription (Creson et al. 2009; Einat et al. 2003; Yuan et al. 2001). The follow-up studies from their group and others show that mood stabilizers also enhance cellular function of Bcl-2, including neuronal protection against death-inducing insults, neurite and axonal growth, calcium signaling, and mitochondrial function (Chen et al. 2010; Hunsberger et al. 2009; Machado-Vieira et al. 2011). The same group also demonstrated that lithium and valproate upregulated another Bcl-2-related protein, BAG1, and modulated a BAG1 unique function, glucocorticiod receptor translocation to nuclei (Zhou et al. 2005). Their follow-up behavioral studies show that Bcl-2 proteins including Bcl-2, BAG1,

BI-1, and tBid are sufficient to modulate behavioral outcomes in a wide range of rodent models of mood disorders (Chen et al. 2010; Einat et al. 2005; Hunsberger et al. 2011; Lien et al. 2008; Maeng et al. 2008; Malkesman et al. 2011). The paradigms include the forced swim test, tail suspension test, learned helplessness paradigm, anhedonia-like deficits induced by serotonin and catecholamine depletion, amphetamine-induced hyperlocomotion, and amphetamine-induced behavioral sensitization. Human postmortem brain studies reveal lower levels of Bcl-2 (Kim et al. 2010), higher levels of Bax and Bad (Kim et al. 2010), and lower levels of ERK pathway components in cortical tissues from bipolar patients (P. Yuan et al. 2010). These coherent data indicate the possible role of Bcl-2 dysfunction in bipolar disorder. Some studies also revealed lower levels of Bcl-2 (Jarskog et al. 2000); a higher ratio of Bax vs. Bcl-2 (Jarskog et al. 2004), and lower levels of ERK/MAP kinase pathway components in the postmortem brain tissues from schizophrenia patients (Yuan et al. 2010). These data suggest that Bcl-2 dysfunction is a common intracellular arbiter of both illnesses, though the Bcl-2 dysfunction might reside in different neuronal circuitries and/or different cell types in these two different illnesses.

3.5 Summary of Preclinical Studies and Future Directions

A considerable body of evidence supports abnormalities in the regulation of cellular plasticity cascades as an integral part of the neurobiology underlying bipolar disorder. Many of these pathways play critical roles in immediate synaptic plasticity, and in long-term cell growth/atrophy and cell survival/cell death. Indeed, the atrophic changes observed in multiple cell types (neurons and glia), as well as the reversibility of the changes with treatment, support a role for intracellular plasticity cascades. It is likely that the major defect is in the ability to regulate neuroplastic adaptations to perturbations (both physiological and pathophysiological) and the inability to handle "normal loads" (neurochemical, hormonal, stress-induced, pharmacologically induced, etc.) without failing or invoking compensatory adaptations that overshoot and predispose to oscillations.

Antipsychotics appear to affect a number of these targets, underlying their utility in mood disorders. Newer "plasticity enhancing" strategies that may have utility in the treatment of mood disorders include inhibitors of glutamate release, N-methyl-D-aspartate antagonists, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid potentiators, and PKC inhibitors. Indeed, such potential next-generation drugs, in addition to treating the core symptoms of bipolar disorder, might be able to target other important aspects of the illness. These aspects include enhancing cognition independent of any improvement in mood symptoms, and preventing or reversing epigenetic factors that may have long-term negative impacts on the course of the illness. The development of novel therapeutics holds much promise for the long-term treatment of severe mood disorders and for improving the lives of the many who suffer from them.

4 Conclusions

Atypical antipsychotics have an important role in the acute and maintenance treatment of bipolar disorder. While a large body of evidence supports the efficacy of these agents in the various stages of bipolar disorder, more comparative effectiveness studies are needed to assess the optimal treatment regimens, including the relative benefits and risks of antipsychotics versus mood stabilizers. The growing understanding of the underlying neurobiology of bipolar disorder, along with the ability of atypical antipsychotics to target key pathophysiological pathways of this condition, suggests that these medications exert their therapeutic effect through a variety of mechanisms. Further, the development of novel "plasticity-enhancing" therapeutics brings hope for the future treatment of patients with bipolar disorder.

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The Pharmacogenetics of Antipsychotic Treatment

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Contents

Abstract There is substantial interindividual variability in the effects of treatment with antipsychotic drugs not only in the emergence of adverse effects but also in symptom response. It is becoming increasingly clear that much of this variability is due to genetic factors; pharmacogenetics is the study of those factors, with the eventual goal of identifying genetic predictors of treatment effects. There have been many reported associations of single nucleotide polymorphisms (SNPs) in candidate genes with the consequences of antipsychotic drug treatment. Thus variations in dopaminergic and serotoninergic genes may influence positive and negative symptom outcome, respectively. Among the adverse effects, tardive dyskinesia and weight gain have been the most studied, with some consistent associations of functional SNPs in genes relating to pharmacological mechanisms. Technological advance has permitted large-scale genome-wide association studies (GWAS), but

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as yet there are few reports that replicate prior findings with candidate genes. Nevertheless, GWAS may identify associations which provide new clues relating to underlying mechanisms.

Keywords Schizophrenia • Negative symptoms • Positive symptoms • Adverse effects • Association studies • Candidate gene • Single nucleotide polymorphism • Receptors • Weight gain • Extrapyramidal side effects

1 Introduction

Severe mental illness—schizophrenia, bipolar disorder and major depressive disorder—represents a huge burden to society in general and health care in particular. This fact reflects the limited efficacy of current treatment; pharmacotherapy of depression often achieves response rates of little more than 50%, while even lower proportions of patients with schizophrenia achieve adequate response to their antipsychotic drug treatment.

Antipsychotic drugs are widely prescribed, to over 1% of western populations. Primarily these are patients with schizophrenia, but the drugs are increasingly used in bipolar disorder, and may also be used in treating (often with little in the way of an evidence base) a variety of behavioral problems from autism in childhood to psychosis associated with various neurodegenerative and dementing disorders. While a proportion of people with schizophrenia respond well to antipsychotic drug treatment, a similar proportion (approximately one third) show little amelioration of their symptoms, while the remainder present varying degrees of symptom improvement. Treatment adherence is inevitably one factor that contributes to this substantial individual variability, although patients taking their medication as prescribed can still show profound differences in response. There is little understanding of the underlying reasons for these differences, although accumulating evidence over the past 15 years is pointing to a substantial contribution from genetic factors to the response to drug treatment.

Similar variability is also seen in the occurrence and severity of adverse effects of antipsychotic drug treatment. It remains unclear what underlies the individual differences in the emergence of extrapyramidal side effects such as the chronic and often irreversible tardive dyskinesia (TD), or of drug-induced weight gain and related effects including higher incidence of metabolic syndrome, although again genetic factors appear to play an important role.

Thus pharmacogenetics, the study of the influence of genetic variation on the effects of drug treatment, has much to offer in identifying what may underlie these differences in the consequences of antipsychotic treatment. The pharmacogenetics of antipsychotic drugs has received substantial research effort over the past decade, driven by an awareness of the varied and often limited effectiveness of these drugs both in controlling symptoms of schizophrenia and in inducing adverse effects.

1.1 Concepts and Approaches

Studies of siblings and twin pairs have provided some evidence in support of genetic factors influencing the emergence of certain side effects following antipsychotic drug treatment. A series of first degree relatives concordant for schizophrenia also showed concordance for the presence or absence of TD (Youssef et al. 1989). Weight gain following antipsychotic treatment has been studied in pairs of siblings and monozygotic twins, with greater concordance in the twin pairs being interpreted as evidence for drug-induced weight gain having a strong genetic contribution, estimated at 60–80% (Gebhardt et al. 2010). Treatment responses to clozapine (Vojvoda et al. 1996) and olanzapine (Mata et al. 2001) have also shown strong concordance in monozygotic twin pairs.

Implicit in the search for genetic associations with the outcome of antipsychotic drug treatment is that such associations may enable us to identify genetic predictors of side effects or treatment response. In addition, the results of pharmacogenetic studies can inform, as they are informed by, the pharmacological mechanisms underlying these effects of antipsychotics. Thus, the starting point for pharmacogenetic investigation would usually be a concern over a particular limitation of the drug treatment. Having identified the target problem, a phenotype, early approaches then investigated variations in the DNA (genotype) of one or a small number of "candidate" genes for study. Choice of candidate genes is hypothesis-driven, whereby genes are usually selected on the basis of their coding for a protein that is known to be, or is potentially, involved in pharmacokinetic or pharmacodynamic aspects of drug action. Identification of sites of variation in these genes, primarily single nucleotide polymorphisms ("SNPs") or insertion/deletion sequences provide the factors for association of genotype with phenotype.

Genetic factors could influence drug action at several levels, and I have previously suggested (Reynolds 2007) that pharmacogenetic associations can be considered to be in groups dependent on the mechanism of the drug–gene interaction:

1. genes influencing pharmacokinetic processes, such as the CYP metabolic enzymes, or MDR1 (ABCB1) coding for P-glycoprotein;
2. genes known or thought to be directly involved in the mechanisms of drug action, such as those for the dopamine D_2 receptor and, for most newer antipsychotics, the 5-HT_{2A} receptor;
3. genes that may indirectly modify the primary pharmacological mechanism, such as those involved in second messenger function, such as G-protein subunit beta3, or receptors relating to interacting neurotransmitter systems;
4. genes that are involved in disease pathology and which may therefore determine how responsive the disease may be to pharmacotherapy. These might include genes for disease risk or disease modifying factors such as catechol-O-methyltransferase (COMT) or dysbindin1.

Genetic polymorphisms may have a direct effect on the function of the gene product. Clearly, a SNP in the coding region of the gene leading to a change in the

amino acid sequence (a missense or non-synonymous mutation) is likely to influence gene function through an effect on protein structure. This might, in the case of a receptor for example, affect agonist affinity or the disposition of the protein in the neuronal membrane. SNPs outside the coding region can still affect gene function; thus upstream 5′ SNPs in the promoter sequence of the gene could influence the binding of transcription factors and hence the extent and/or control of gene expression, resulting in changes in, for example, receptor density. Other SNP sites might influence mRNA stability, or affect the binding of miRNA, each of which could result in changes in the expression and availability of gene product.

SNPs that are relatively close to one another tend to be inherited together; these are referred to as being in linkage disequilibrium (LD). Haplotype analysis may then employ multiple SNPs in LD in an attempt to increase genetic association with a clinical phenotype. Other approaches are increasingly being used; gene–gene interaction is studied in recognition of the fact that the effects of polymorphisms in different genes may interact to influence the phenotype, while gene–environment interaction acknowledges the environmental contribution to phenotype and its potential in modifying, or being modified by, the influence of genetic factors. In a sense, of course, pharmacogenetics is the study of gene–environment interactions where the environmental factor is drug treatment.

Technological advance has driven pharmacogenetic approaches beyond the study of single sites of variation, such as SNPs or insertion/deletion sequences, in candidate genes to the application of genome-wide association studies (GWAS). These hypothesis-free approaches investigate many (e.g., one million) SNPs across the whole of the genome and offer great power in identifying novel genetic associations unconstrained by prior hypotheses, which are inevitably founded on a limited understanding of the underlying mechanisms. However, GWAS are not without limitations; they generally employ tagging SNPs, selected on the basis of position in the genome sequence, rather than polymorphisms of known, or potential, functionality that may be chosen in candidate gene studies. They also have their own problems associated with the difficulties of data handling (where a sample of several hundred subjects can produce over 10^8 individual results) and appropriate statistical analysis and interpretation.

2 The Target Phenotypes and Candidate Genes

This section will briefly address the symptoms and side effects that remain a problem with current antipsychotic drugs and identify some of the major hypothesis-driven approaches to understanding their genetic influences. Although our knowledge of the underlying mechanisms is often very limited, what we know of the pharmacological processes involved has provided indications of what genes might be worthy of investigation. These candidate genes will not be comprehensively listed, but the major genes of interest will be briefly mentioned, particularly where they have given rise to further pharmacogenetic study. This will concentrate

on genes particularly related to pharmacodynamic mechanisms, although pharmacokinetic genes are also strong candidates for influencing both symptom response and adverse effects in a drug-specific manner. Functional variants in metabolic enzymes, notably the widely studied cytochrome P450 enzymes, can influence drug concentrations, availability and the ratio of active drug to metabolites (both active and inactive). Similarly, any functional genetic variability in the p-glycoprotein pump, which acts to remove xenobiotics and many drugs from the brain, can also influence drug availability at sites of action. All such effects on drug disposition will inevitably have effects on drug action, whether they are in the relief of symptoms or in the emergence of side effects; influence on the latter is a commonly reported consequence of genetic variability in cytochrome P450 enzymes for several antipsychotic drugs (Arranz and de Leon 2007). To some extent the effects of pharmacokinetic variability can be ameliorated by dose titration, although this may only be true when the pharmacology is uncomplicated by the presence of active metabolites.

2.1 Symptom Response

Clearly the response to drug treatment of the disease symptoms is an important target for pharmacogenetic study, given the high proportion of patients who suffer from residual symptoms of schizophrenia. This inadequate response to treatment is more apparent in subgroups of symptoms; while antipsychotic drugs are often effective at controlling the positive psychotic symptoms, they are less able to ameliorate the negative and cognitive features of schizophrenia. These features include social withdrawal, blunted mood, lack of self-care, and a range of cognitive deficits which, along with depressed mood, are the symptoms that are most problematic in integrating the patient into society.

It is generally considered that the primary antipsychotic mechanism involves antagonist action at the dopamine D_2 receptor. Thus, polymorphisms in this gene (DRD2) have been widely investigated in respect of symptom response, as have the related D_2-like receptor genes DRD3 and DRD4. Similarly, the 5-HT_{2A} receptor is a major drug target proposed to differentiate the atypical antipsychotics from the older drugs. The pharmacological mechanisms underlying antipsychotic drug effects on negative and cognitive symptoms are far from clear, however. It has been suggested that the drug action at 5-HT_{2A} receptors is also responsible for some improved efficacy of the atypical antipsychotics on negative symptoms, although the supporting evidence for this clinical effect is very limited (Lieberman et al. 2005), as is our understanding of the underlying mechanism. Nevertheless, there is some indication that 5-HT systems are involved in models of cognitive dysfunction in schizophrenia (Neill et al. 2010; Meltzer and Massey 2011) as well as in symptom amelioration by newer antipsychotic drugs (Meltzer and Massey 2011), providing candidature for HTR2A and other serotonergic genes such as HTR1A, HTR2C, HTR6, and SLC6A4.

There is, however, increasing evidence of the importance of glutamate neurotransmission in cognitive dysfunction in schizophrenia (Tamminga 2006), and more generally in the pathology of the disease itself (Kantrowitz and Javitt 2010). The cognitive deficits of schizophrenia are modeled by chronic administration of glutamate/NMDA receptor antagonists, and this provides a series of candidate genes, from the NMDA receptor subunit proteins to other glutamate receptors and metabolic enzymes.

The unique efficacy of clozapine in the treatment of otherwise non-responsive patients has resulted in clozapine being a prime target for pharmacogenetic investigation. In addition to its clinical importance, this work has a pragmatic advantage of sample availability and regular patient monitoring in retrospective studies, due to the necessity for blood monitoring for the potentially fatal side effect of agranulocytosis. A pharmacological basis for the clinical efficacy of clozapine remains elusive; among the receptor mechanisms implicated, in addition to the 5-HT_{2A} receptor antagonism common to most atypical antipsychotics, are effects at α_2-adrenoceptors, 5-HT_{1A} receptors and dopamine D_1 receptors, although no single receptor action is likely to explain clozapine's action in full (Reynolds 2004).

2.2 *Adverse Effects*

A consequence of dopamine D_2 receptor antagonism, essential for the antipsychotic effects of current drugs, is an inhibition of dopaminergic function in regions of the brain controlling motor function. This results in the extrapyramidal side effects (EPS), which include the relatively immediate effects of akathisia, dystonia, and parkinsonism, believed to be consequences of acute inhibition of dopaminergic neurotransmission *via* antipsychotic drug antagonism of the D_2 receptor, as well as tardive dyskinesia (TD), a severe problem associated with chronic treatment which may be irreversible. The avoidance of EPS has driven the development of the second generation of antipsychotic drugs; it is proposed that 5-HT_{2A} receptor antagonism may contribute to the lower propensity for EPS shown by some these drugs, although other mechanisms may also be involved. 5-HT_{2C} receptors are also important in the pharmacology and physiology of dyskinesias. Thus, genes associated with dopamine and 5-HT_2 receptors are strong candidates; others, particularly those relating to TD, have been proposed from further theories relating to the possible underlying mechanism(s). These mechanisms include, in addition to receptor-mediated effects, damage associated with oxidative free radicals, implicating genes involved in free radical scavenging such as that for a superoxide dismutase (SOD2).

Dopamine D_2 receptor antagonism has a further consequence of disinhibiting the release of prolactin, resulting in galactorrhoea; much of the work in this area has focused on risperidone, which among the commonly used antipsychotics has the greatest effect on prolactin. These drug effects on the hypothalamic–pituitary–gonadal axis can have further consequences, including amenorrhoea and, potentially,

osteoporosis in some patients, as well as contributing to sexual dysfunction. DRD2, as well as genes involved in the serotonin system and in estrogen function, are among those implicated in these adverse effects seen with several antipsychotic drug treatments. Prolactin secretion occurs following inhibition of dopamine receptors in the pituitary gland; this is accessed directly by drugs in the blood without the restriction of an effective blood–brain barrier. Thus, drugs that are poorly penetrant or substrates for the p-glycoprotein pump, such as risperidone and amisulpride, are likely to affect receptors in the pituitary to a greater extent than in the brain. The major p-glycoprotein gene (ABCB1) is thus a further candidate for effects on prolactin.

Of the other limiting side effects, weight gain and, to a lesser extent, its related metabolic consequences have been investigated in some detail. Here the candidate genes derive from the underlying receptors considered to mediate drug effects on food intake (Reynolds and Kirk 2010), notably but not exclusively the serotonin 5-HT_{2C} and histamine H_1 receptor. In addition, further candidates are provided by the various mechanisms involved in the control of food intake and body weight. These include circulating hormones such as leptin and adiponectin, the hypothalamic neuropeptides, the cannabinoid system and factors involved in glucose and lipid disposition and metabolism (Reynolds and Kirk 2010).

Other problematic side effects include sedation, little studied in pharmacogenetics but considered to relate to antagonism at histamine H_1 receptors, and postural hypotension, for which α_1-adrenoceptor antagonism by many of the antipsychotic drugs is thought to be responsible (Reynolds 2004). QT interval prolongation, involving disturbance of potassium channel function, is a concern with some antipsychotics occasionally, but not inevitably, resulting in the arrhythmia of *torsades de pointes* and, potentially, a sudden cardiac death. Another rare but also potentially fatal side effect is that of agranulocytosis, a particular limitation of treatment with clozapine.

3 Pharmacogenetic Findings

3.1 Scope and Limitations

This chapter reports and comments on the work that reflects progress in, and the current status of, the field of antipsychotic pharmacogenetics. It will not be a comprehensive review of all the various pharmacogenetic results relating to individual differences in the effects of antipsychotic drug treatment, but will provide examples as well as reference to more specific review articles; many single unreplicated findings will not be reported, although some of potential interest will be mentioned. Furthermore, there will be a bias here towards pharmacodynamic rather than pharmacokinetic influences on drug action, driven by the value of pharmacogenetics in informing pharmacological and physiological mechanisms.

Both the casual reader and the systematic reviewer may be struck by the paucity of consistently reproducible findings in the pharmacogenetic studies reported. There are many reasons for this. One particularly important factor is that many studies are underpowered to identify what are often relatively small effects; this factor will inevitably introduce variability of results between studies. Other factors include differences in sample ethnicity, with the inevitable differences in genetic make-up between different ethnic samples. Different drug treatments may be associated with different pharmacogenetic influences, and published literature may give an impression that there are drug-specific pharmacogenetic associations.

A major goal of pharmacogenetics is to inform drug selection, and thus a genetic test that identifies e.g., responders specific to particular drug treatments would be of huge value in guiding prescribing practice. However, there is little evidence for this to be the case in antipsychotic drug treatment, with the possible exception of clozapine. Authors occasionally forget that finding a significant genetic association of the effects of one drug, not reaching significance in patients on another drug, is very different from demonstrating a statistically significant difference between two drugs in the genetic influences on their effects. In fact, as discussed below, some results indicate that several genetic associations with response and with side effects can generalize across drug treatments.

There are other differences between samples that may introduce inconsistencies; a drug effect, whether response to treatment or a side effect, emerging in first-episode and previously drug-naïve patients may well have differences in underlying pharmacological mechanisms, and hence differences in pharmacogenetic influences, from equivalent effects in patients with a chronic treatment history. Furthermore, the clinical phenotypes measured may often be complex and multi-factorial, composed of several physiological responses under different genetic control mechanisms. In the case of symptom response, this problem will be discussed in more detail below.

The important independent CATIE trial of the relative effects of several antipsychotic drugs (Lieberman et al. 2005) has provided a very valuable sample source for pharmacogenetics, given the rigorous and comprehensive assessments undertaken in a large series of people with schizophrenia. Although it is not without limitations, pharmacogenetic studies from this trial are beginning to yield interesting and novel findings, some of which will be discussed here.

3.2 Pharmacogenetic Findings: Symptom Response

Many of the earlier reports assessing genetic associations with antipsychotic treatment response concentrated on the most obvious candidate genes with some replicated, if not totally consistent, findings of polymorphisms in three receptors: dopamine D_2, dopamine D_3, and serotonin 5-HT_{2A}, being associated with response to treatment (reviewed by Reynolds et al. 2006a, b; Malhotra et al. 2004).

The association of DRD2 with response has been confirmed more recently in a systematic review (Zhang et al. 2010), although overall association of DRD3 remains weak and inconsistent (e.g., Hwang et al. 2010; Xuan et al. 2008). Other dopaminergic factors have been investigated in relation to the pharmacogenetics of drug response. The dopamine transporter (DAT) gene has shown both positive (with clozapine) and negative (with risperidone) associations (Xu et al. 2008; Zhang et al. 2007), but there are no convincing results indicating an influence of SNPs in the dopamine D_1 or D_4 receptors on treatment response.

A review of association studies with SNPs in the 5-HT_{2A} receptor gene concluded that results indicate some weak association with antipsychotic response as well as with psychosis itself (Serretti et al. 2007). Some further supporting data for this association with drug response have emerged from several more recent small studies including one employing the methodologically more rigorous transmission disequilibrium test (Benmessaoud et al. 2008). Nevertheless, the effect is a small one and not consistently obtained. The same is true for genes for other markers of serotonergic function. The 5-HT transporter gene (SLC6A4), with what is perhaps the most studied polymorphism in psychiatry, the insertion/deletion (ins/del) sequence in the promoter region (Lesch et al. 1996), is associated with antipsychotic response in some (e.g., Dolzan et al. 2008; Wang et al. 2007) but not all (Lee et al. 2009) studies. A SNP in the 5-HT_{1A} receptor gene has also been shown to have effects on treatment response (Mossner et al. 2009; Reynolds et al. 2006a, b; Wang et al. 2008). Both SLC6A4 and HTR1A genes code for proteins that control presynaptic activity of the serotonin neuron; the major SNPs investigated in each case appear to directly influence gene expression. Thus promoter sequence SLC6A4 SNPs including the ins/del polymorphism of SLC6A4 and the SNP found within the insertion sequence (Hu et al. 2006) influence SLC6A4 expression and activity, while the −1019 C/G promoter SNP in HTR1A affects a transcription factor binding site, again influencing expression of the 5-HT_{1A} receptor and its control, as well as being associated with suicide and diagnosis of depression (Lemonde et al. 2003).

In developing the opportunities for genetic testing, it seems more valuable to differentiate groups of symptoms in terms of their response to treatment. As mentioned above, the negative features of the disease respond poorly to antipsychotic drugs and it is these features, rather than the positive symptoms, that are more important in determining functional recovery in patients. A minority of outcome studies have assessed separately the responses of positive and negative symptoms to drug treatment, despite the established differences in the effects of antipsychotics on these symptom clusters. However, where separate responses have been assessed, it appears that the majority of genes associated with positive symptom response are of dopamine receptors, while effects on negative symptoms are more associated with serotoninergic genes, in particular the 5-HT_{1A} and 5-HT_{2A} receptors. Updating earlier observations (Reynolds 2007), we find that more recent results confirm this impression (Table 1), with notably few anomalies. This is notwithstanding the differences between samples in terms of treatment history (drug-naïve, or previously treated) and ethnicity. These findings may seem

Table 1 Some reported associations differentiating positive and negative symptom response to antipsychotic drugs—influence of dopamine and serotonin genes

	Polymorphism	Association with symptom subgroup:	References
Dopamine D_2 receptor (*DRD2*)	Ser311cys	*Positive*	Lane et al. (2004)
	Taq1A	*Positive*	Suzuki et al. (2000)
Dopamine D_3 receptor (*DRD3*)	Ser9gly	*Negative*	Lane et al. (2005)
	Ser9gly	*Positive*	Reynolds et al. (2005)
	−205A/G, Ser9gly	*Positive*	Staddon et al. (2002)
	Ser9gly and others	*Positive*	Adams et al. (2008)
Norepinephrine transporter (*SLC6A2*)	1287 G/A, −182 T/C	*Positive*	Meary et al. (2008)
5-HT_{2A} receptor (*HTR2A*)	102 T/C	*Negative*	Lane et al. (2002)
	−1438A/G	*Negative*	Hamdani et al. (2005)
	−1438A/G	*Negative*	Ellingrod et al. (2003)
5-HT_{2C} receptor (*HTR2C*)	−759 C/T	*Negative*	Reynolds et al. (2005)
5-HT_{1A} receptor (*HTR1A*)	−1019 C/G	*Negative*	Reynolds et al. (2006a, b)
	−1019 C/G	*Negative*	Mossner et al. (2009)
	−1019 C/G	*Negative*	Wang et al. (2008)
5-HT transporter (*SLC6A4*)	HTTLPR ins/del	*Negative*	Vazquez-Bourgon et al. (2010)

surprising on first sight, given the variety of different genes involved. However this multiplicity of genetic factors points to common mechanistic pathways; for example, changes in the expression and activity of both 5-HT_{1A} receptors and the 5-HT transporter are likely to affect serotonergic activity at the synapse, consequences of which may be mediated by post-synaptic receptors such as 5-HT_{2A}. A similar but unconfirmed observation has been seen for another 5-HT receptor gene, HTR3E (Schuhmacher et al. 2009). However it is notable that the results for catechol-O-methyltransferase (COMT) indicate association solely with negative symptom improvement (discussed below). Nevertheless, the overall results strongly suggest that the dopamine and serotonin neurotransmitter systems are implicated separately in drug response of the two syndromes, while the exact mechanisms of their involvement remain elusive. Certainly, there is evidence that selective serotonin uptake inhibitors may be useful in the relief of negative symptoms in some patients (Silver 2004).

In one study identifying a relatively strong effect of a 5-HT_{1A} gene SNP explaining much of the variance in negative symptom response in first-episode patients (Reynolds et al. 2006a, b), there was also an effect on depressive symptom response, differentiated from that on negative symptoms. This finding is unsurprising, given the established association of this SNP with depression (Lemonde et al. 2003) and its treatment (Lemonde et al. 2004). An association with negative symptoms and depression has been found for the 5-HT transporter gene in patients receiving antipsychotics, although the influence of treatment on this finding was not determined (Goldberg et al. 2009). However it is notable that few pharmacogenetic studies have

investigated separately the depression syndrome in schizophrenia, although it is an important determinant of relapse in patients receiving antipsychotics (Tollefson et al. 1999).

The unique efficacy of clozapine has attracted substantial investigation into the genetic basis of response to treatment with this drug. However, at least 50% of patients not otherwise responding to antipsychotic drug treatment benefit from clozapine; much early work on antipsychotic pharmacogenetics addressed this problem. Arranz et al. (2000) studied a range of candidate genes, primarily chosen on the basis of the known pharmacology of clozapine. They looked for association of response with 19 polymorphisms in ten genes associated with monoamine neurotransmission; six polymorphisms in genes for the 5-HT_{2A} and 5-HT_{2C} receptors, the 5-HT transporter, and the histamine H_2 receptor together gave a (retrospective) sensitivity of 96% in identifying clozapine responders. The strongest components in this profile of polymorphisms are two SNPs in the HTR2A gene: one synonymous (silent) 102 T/C in linkage disequilibrium with a promoter SNP (-1438A/G) with functional activity (Parsons et al. 2004) and one nonsynonymous his452tyr. These findings have not been consistently replicated (Malhotra et al. 2004), but they nevertheless led to the establishment of a pharmacogenetic test for clozapine response. However, this test is no longer available and a confirmatory prospective trial to assess the predictability and value in practice of such pharmacogenetic testing for drug response has yet to be undertaken. Reflecting our incomplete understanding of the unique efficacy of clozapine, a consistent pharmacogenetic finding that might relate selectively to clozapine response still eludes us. Many pharmacogenetic studies, including some cited in this chapter, have been carried out on cohorts of clozapine-treated subjects, but as yet there is no evidence for distinct clozapine-specific pharmacogenetic associations with response.

The positive and replicated findings with SNPs in these dopamine and serotonin genes, reviewed more extensively elsewhere (Zhang and Malhotra 2011), are reassuring in terms of our very limited understanding of pharmacological mechanisms, but are strongly influenced by a research bias towards testing these more obvious hypotheses. Variation in these genes can still only explain a small percentage of the variance in response, and further factors inevitably contribute to antipsychotic-induced improvement in symptoms. Those further factors might include SNPs in a wide variety of other factors potentially influencing neuronal function, including other neurotransmitter receptors, enzymes and transporters, as well as second messenger systems or signaling pathways. This potentially involves many hundreds of further candidate genes, of which just one example is the SNP in the G-protein beta3 subunit gene (GNB3), involved in receptor signal transduction, and which reportedly shows weak association with symptom response (Müller et al. 2005; Anttila et al. 2007; Kohlrausch et al. 2008). However, there are few associations with symptom response outside the genes involving dopamine and serotonin systems that have been consistently replicated.

Concentrating on symptom subgroups, few other pharmacogenetic findings are specifically associated with positive symptom improvement, although many other

genetic associations with undifferentiated symptom response may primarily reflect the (generally relatively greater) improvement in positive symptoms. The latest and strongest single gene risk factor for schizophrenia, ZNF804A, is also interestingly a determinant of positive symptom response (Mossner et al. 2011).

There are some other genetic associations with drug-induced changes in the more problematic negative and cognitive symptoms in schizophrenia. These associations include the val/met COMT polymorphism (Bertolino et al. 2007; Fijal et al. 2009; Weickert et al. 2004), which has a strong effect on enzyme activity and thereby influences dopamine (and norepinephrine) concentrations in the cortex where this enzyme, rather than neuronal transport, is primarily responsible for synaptic removal of catecholamine neurotransmitters. The glutamate metabotropic receptor-3 gene, a further risk factor for schizophrenia, has been reported as having SNPs associated with response (Fijal et al. 2009), particularly of negative symptoms (Bishop et al. 2005), although a following study showed an association not with negative symptom response but with treatment-refractory schizophrenia (Bishop et al. 2011). Dysbindin1 (DTNBP1), another gene with an established association with schizophrenia and implicated in neuronal and synaptic development as well as dopamine receptor function, also shows association with treatment response in refractory schizophrenia (Zuo et al. 2009).

Other genes involved in neuronal development have been implicated in antipsychotic drug response. This is not as specific a statement as it might first seem; a very large number of genes expressed in the brain can potentially influence neuronal development including many related to, for example, serotonin or glutamate neurotransmitter function. However, an interesting model-based approach (Webb et al. 2008) found that several SNPS in the developmental gene EN1 (*engrailed1*) are associated with antipsychotic response in the CATIE trial. This study used datasets for schizophrenia risk genes and for mouse SNPs affecting prepulse inhibition, which is consistently deficient in schizophrenia and reversed by antipsychotic drug treatment, to generate candidates of which only EN1 was significant.

Some similar approaches, using relatively unbiased and independent methods to select candidate genes, have identified other associations. Homer-1, a gene associated with glutamatergic transmission and identified as a candidate from animal studies of gene expression following haloperidol administration, shows SNP associations with response to treatment (Spellmann et al. 2011). A similar approach (Ikeda et al. 2010) with a risperidone mouse administration study coupled with a GWAS for risperidone response identified several novel candidates, of which PDE-7 was found to have association both with disease, internally replicated, and with treatment response. Unfortunately, despite the apparent validity of these approaches, there appears to be little consistency between them. Such criticism, to which much of the pharmacogenetic literature is susceptible, can always be countered by highlighting the differences between study samples in ethnicity, drug treatment and other such factors, but it remains a problem for the generalizability of any findings.

Even within a sample, where the phenotype is identical between studies, different approaches can yield very different results. Thus the CATIE trial has been very

valuable in providing a large set of data on the consequences of antipsychotic treatment of a carefully controlled and rigorously assessed sample. The results of one very focused study have been mentioned above. A further investigation of a large series of 118 candidate genes (Need et al. 2009) identified several significant associations with change in the Positive and Negative Syndrome Scale (PANSS), the numbers of which were roughly in line with the expected false discovery rate (22 of 2,769 SNPs reached significance at $p < 0.01$). Seven of the significant SNPs were in glutamate receptor genes, which might be of more interest were it not for the fact that such genes were represented by over 1,000 of the SNPs studied. Nevertheless, these authors also identified significant association with SNPs on HTR2A, DRD3, the nicotinic receptor alpha7 subunit gene, and the excitatory amino acid transporter 4 gene (SLC1A6) among other candidates.

A GWAS study of the same sample has provided very different results, with the strongest effect on change in PANSS shown with a SNP in an inter-gene sequence on chromosome 4; other novel results close to the significance threshold were in ANKS1B, CNTNAP5, and TRPM1, all of which are potentially involved in neuronal development or neurotransmission (McClay et al. 2011b). How exactly they might be involved in drug response is far from clear; however, certainly replication as candidate genes in other samples is needed. The same group has looked at neurocognition as an outcome measure of response in this series (McClay et al. 2011a), finding significance in several genes of which the top two are EHF (a transcription factor with little evidence for a neuronal role) and SLC26A9 (a chloride ion transporter). Interpretation of these findings is not straightforward, although more reassuring are the findings of (somewhat weaker) association with DRD2 and ANKS1B, the latter also found to be associated with negative symptom response in the previous analysis.

Iloperidone is an antipsychotic that was recently approved (in the USA) and has undergone substantial pharmacogenetic study during its phase III trials. One investigation involved a GWAS that identified six SNPs in six genes contributing to drug treatment response (Lavedan et al. 2009); these data were re-analyzed in a retrospective assessment to identify response-dependent genetic subgroups of patients (Volpi et al. 2009b). How specific these findings are to iloperidone remains unclear; these authors report that the six SNPs did not significantly associate with ziprasidone response, although another group observed that two of the genes (XKR4 and GRIA4) were also associated with risperidone response (Fijal et al. 2011).

3.3 Pharmacogenetic Findings: Adverse Effects

3.3.1 Acute Motor Side Effects

Although they remain a concern with many antipsychotic drug treatments, particularly the earlier typical drugs, parkinsonian and other acute extrapyramidal symptoms have not been widely studied in terms of their genetic risk factors.

This situation may be because they are not considered as limiting effects, being adequately addressed by additional anticholinergic medication, or that more recently developed drugs have rendered them far less common. Nevertheless, several studies have investigated candidate genes such as dopamine and 5-HT_2 receptors. Despite several negative reports indicating no significant association of parkinsonian symptoms with dopamine receptor SNPs (Dolzan et al. 2008; Gunes et al. 2007) one recent study in Afro-Caribbean subjects showed association of polymorphisms in D_2 with rigidity and 5-HT_{2C} with bradykinesia (Al Hadithy et al. 2008). This result certainly emphasizes the value of differentiating the components of EPS that are likely to involve different pathophysiological mechanisms. A small study has shown association of undifferentiated EPS with 5-HT_{2A} and 5-HT_{2C} receptor SNPs (Gunes et al. 2007), confirmed for 5-HT_{2C} (Gunes et al. 2008).

A GWAS using a subgroup from the CATIE cohort failed to identify any SNPs meeting the fairly strict criteria for significant association with parkinsonism, but identified a few possible genes deserving further study (Alkelai et al. 2009). A further study of the full CATIE cohort yielded top associations of parkinsonism with two intergene SNPs and one on ZNF202, a transcription factor controlling PLP, a myelin protein (Aberg et al. 2010a). There was no replication of findings from any of the "promising candidates" from the previous study, indicating the sensitivity of these approaches to subtle differences in methodology and sample.

3.3.2 Tardive Dyskinesia

TD has been the subject of a large number of studies since the initial application of pharmacogenetics to antipsychotic drug effects. It is an important and limiting side effect, although its incidence is less frequent with the newer antipsychotic drugs. But the number of studies may as much reflect the fact that this is a relatively easily assessed side effect, which can be determined on the abnormal involuntary movements scale (AIMS) or as dichotomized categories.

Early studies inevitably focused on the dopamine receptors implicated in the control and modulation of motor function, often the same receptors as are implicated in symptom response. Pharmacogenetic findings have been reviewed comprehensively elsewhere (Zhang and Malhotra 2011; Thelma et al. 2008; Arranz and de Leon 2007) and consistently emphasize the role of dopamine D_2 and D_3 receptors, as well as several enzymes involved in drug metabolism, notably CYP2D6 and CYP1A2. Such pharmacokinetic influences will inevitably be dependent on the drug involved and its related metabolic pathways.

There is also some evidence from inconsistently replicated studies that both 5-HT_{2A} and 5-HT_{2C} receptor SNPs are associated with TD. This reflects the role serotonin systems have in motor function and its disturbances, both directly and in modifying dopaminergic influences. In particular, SNPs in both HTR2A and HTR2C have been, somewhat inconsistently, found to be associated with TD (reviewed in Zhang and Malhotra 2011). Interestingly, there are indications of additive, and perhaps synergistic, gene effects with interactions reported between SNPs in DRD3 and HTR2C (Segman et al. 2000) and DRD3 and SOD2

(Zhang et al. 2003b). The latter study involves the gene for an important enzyme involved in protection from reactive oxygen species, manganese superoxide dismutase (SOD2), which has a reported association with TD although recent meta-analysis could not confirm association with SOD2 or another gene (NQO1) involved in protection from free radical damage (Zai et al. 2010).

Again these candidate gene studies contrast profoundly with the findings from GWAS. The one SNP found to reach the (very conservative) significance for AIMS in the CATIE study was in an intergene region (Aberg et al. 2010a). Another study used the CATIE data to identify "promising SNPs" for further investigation in a second cohort and found association with the GLI2 gene, a transcription factor reportedly involved in dopaminergic embryogenesis (Greenbaum et al. 2010). Two further reports of smaller but internally replicated GWAS from the same group identified separately association of TD with HSPG2 (heparin sulfate proteoglycan 2) (Syu et al. 2010) and with DPP6 (Tanaka et al. 2011), each gene demonstrating possible pathophysiological involvement in animal studies; the first finding has recently been supported, albeit somewhat weakly, by a candidate gene study in two further cohorts (Greenbaum et al. 2011). A different approach, again using the Japanese sample cohorts, was to undertake pathway association analysis which, with multiple genes involved in GABAergic neurotransmission, has provided evidence for this system being involved in the development of TD (Inada et al. 2008).

The inconsistent results are disappointing but may to some extent reflect heterogeneity in the phenotype; there may be different pathophysiological influences on orofacial and limb/trunk dyskinesias, with differing pharmacogenetic influences (e.g., Lerer et al. 2005). The multiplicity of single gene associations with TD strongly indicates an unrealized potential for further investigation of gene–gene interactions and multiple gene effects on TD.

3.3.3 Weight Gain and Metabolic Effects

The first study to demonstrate a clear, and relatively strong, pharmacogenetic association of a candidate gene with antipsychotic drug-induced weight gain investigated a 5-HT_{2C} receptor promoter polymorphism (−759 C/T) in drug-naïve Chinese patients. After 10 weeks treatment there was a highly significant difference in which those patients carrying the minor T allele (22% of the sample) were protected from substantial (>7 %) weight gain caused by risperidone or chlorpromazine with a relative risk of 3.45 (Reynolds et al. 2002). This has, despite some failed replications, also been observed in several further studies including a European first-episode cohort receiving risperidone or olanzapine (Templeman et al. 2005), in chronic patients receiving olanzapine (Ellingrod et al. 2005) and in patients receiving clozapine (Miller et al. 2005; Reynolds et al. 2003). Thus the findings generalize to different drugs, including those with both high (clozapine and olanzapine) or low (risperidone) affinity for the 5-HT_{2C} receptor. The −759 C/T polymorphism, along with other promoter region polymorphisms of the 5-HT2C receptor gene with which it is in linkage disequilibrium, appears to be functional in influencing gene expression (Hill and Reynolds 2007, 2011).

Another candidate gene demonstrating a positive association with antipsychotic drug-induced weight gain is that of leptin. This gene has a promoter region polymorphism influencing the secretion of leptin and which is associated with obesity (Mammes et al. 2000). In two drug-naïve populations also investigated for a 5-HT_{2C} receptor association, antipsychotic weight gain was associated with this −2548A/G polymorphism (Templeman et al. 2005; Zhang et al. 2002), although in each study its influence on weight gain emerges later than that of the HTR2C SNP, which may differentiate effects on initial and longer-term fat deposition. Unpublished calculations from the combined leptin and HTR2C genotype effect reported by Templeman et al. (2005) indicate that, along with baseline measures of BMI, this genetic variability can account for over 25 % of the variance in weight gain. Interestingly, these authors reported that both the HTR2C and leptin SNPs influence leptin secretion, supporting a role for leptin in the mechanism of antipsychotic drug-induced weight gain.

Recent advances in the pharmacogenetics of antipsychotic-induced weight gain have been reviewed comprehensively (Lett et al. 2011); here I shall highlight just some of these findings. While the 5-HT_{2C} receptor and leptin genes have accumulated the most consistent evidence in support of their roles as risk factors for antipsychotic-induced weight gain, a large number of further candidate genes have been investigated, notably those for receptors that may mediate some of the metabolic effects of antipsychotic drugs. Unsurprisingly, there have been many negative findings, including importantly SNPs in genes for the dopamine D_2 (Zhang et al. 2003a) and histamine H_1 receptors (Hong et al. 2002), although both of these also have more recent positive reports (Lencz et al. 2010; Vehof et al. 2011).

Other candidates that have demonstrated replicated positive associations with weight gain on antipsychotic drugs include the α_{2A}-adrenoceptor (Park et al. 2006) and the G protein beta3 subunit genes (Bishop et al. 2006; Wang et al. 2005). Evidence for an effect of HTR2A SNPs on antipsychotic-induced weight gain has been inconsistent, although haplotype study carried out on patients treated with olanzapine showed that HTR2A and HTR2C SNPs, in combination with SNPs in GNB3 and the ß$_3$-adrenoceptor, were significantly associated with olanzapine-induced weight gain, with significant additive effects (Ujike et al. 2008). BDNF has a role in the regulation of food intake and there is a reported association of the functional val66met SNP in males (Zhang et al. 2008). Very recently, SNPs in the melanocortin4 receptor gene, a risk factor for obesity, have been shown to be associated with antipsychotic-induced weight gain in both treatment-naïve and chronic subjects (Lett et al. 2011). Another risk factor for obesity, the FTO gene, is not associated with initial weight gain in first-episode patients (Perez-Iglesias et al. 2010) but in as yet unpublished findings we observed that it is associated with body mass in chronic patients where the effect of the FTO gene appears greatly enhanced after long-term treatment with antipsychotic drugs.

Results from GWAS and other multiple SNP approaches contrast substantially with those from such studies of single candidate genes. The first genome-wide linkage study was successful in identifying a possible genetic indicator underlying antipsychotic drug-induced obesity (Chagnon et al. 2004). These authors identified

linkage in the region of the gene for pro-melanin-concentrating hormone, which is involved in the hypothalamic control of food intake; a subsequent study identified association of obesity in patients treated with olanzapine with a polymorphism in this candidate gene (Chagnon et al. 2007).

Genetic factors in genes that influence serum lipids, such as those for apolipoprotein and lipoprotein lipase, have been studied in one report, with small associations with weight gain being identified (Smith et al. 2008). A DNA microarray candidate-gene approach has led to the identification of further genetic factors that might contribute to antipsychotic-induced hyperlipidemia, with polymorphisms in genes for acetyl-coenzyme A carboxylase α and neuropeptide Y emerging as promising candidates (de Leon et al. 2008). Antipsychotics interact with genes controlled by sterol regulatory binding element protein transcription factors (Ferno et al. 2005), and a strong association has been identified between antipsychotic-induced weight gain and polymorphisms in one of these transcription factors, also a risk gene for obesity, insulin-induced gene 2 (Le Hellard et al. 2009), although this has not been fully replicated (Tiwari et al. 2010).

There has been relatively little investigation into the genetic factors determining the individual differences in liability to antipsychotic drug-induced diabetes. There are at least two different processes here: that associated with the often acute onset, reversible diabetes occurring independent of elevations in body fat mass and underlying the rare occurrences of ketoacidosis, and that which is a long-term consequence of obesity and the development of metabolic syndrome. The first acute effect has not been investigated genetically; the latter has been studied primarily in terms of the emergence of metabolic syndrome. One study reported an association with the leptin SNP, but not with the 5-HT_{2C} receptor (Yevtushenko et al. 2008); however, an interaction between the two polymorphisms was observed. Another group did find, and replicated, association of metabolic syndrome with another 5-HT_{2C} receptor SNP (Risselada et al. 2010a) and with the α_{2A}-adrenoceptor gene (Risselada et al. 2010b).

The CATIE cohort has been studied with respect to a variety of metabolic outcomes (Adkins et al. 2011). Unfortunately, none of the genes associated with the 21 significant SNPs identified have previously been found to associate with metabolic consequences of antipsychotic drug treatment. However two of these genes, MEIS2 and PRKAR2B, respectively, associated with risperdone effects on waist and hip circumference and clozapine effects on triglycerides, have reportedly been previously implicated in metabolic function (Adkins et al. 2011). Here again, more gene–gene interaction analysis as well as further large studies are urgently needed to resolve the inconsistences and replicate novel findings.

3.3.4 Prolactin Secretion and Its Consequences

The main candidate gene for effects on hyperprolactinemia is that for the dopamine D_2 receptor, and several studies have demonstrated an association of DRD2 SNPs with prolactin concentrations following antipsychotic treatment (Young et al. 2004; Zhang et al. 2011; Calarge et al. 2009), albeit with some inconsistencies between

the effects of the various SNPs investigated. Although there have been studies of other candidates including the enzyme CYP2D6, responsible for metabolism of risperidone and some other antipsychotics, and the p-glycoprotein pump (ABCB1), these genes have not shown consistent associations with prolactin concentrations. The associated DRD2 polymorphisms have been shown to be associated with some of the consequences of hyperprolactinemia (Calarge et al. 2009), including the inadequately studied problem of sexual dysfunction (Zhang et al. 2011). However the latter authors indicate that despite the association between a DRD2 SNP and male sexual dysfunction following antipsychotic treatment, dopamine D_2 receptor-mediated hyperprolactinemia does not fully explain the sexual side effects of antipsychotic treatment.

3.3.5 Other Side Effects

Clozapine is unique in its efficacy but is restricted by its liability to cause agranulocytosis. This side effect has been investigated in both GWAS and candidate gene analyses; of the various findings (Opgen-Rhein and Dettling 2008), a very strong (O.R. = 16.9) association with a SNP in HLA-DBQ1 has been identified which is of potential value in prognostic clinical assessment (Athanasiou et al. 2011).

Two further major concerns of antipsychotic drug treatment deserve some mention as target phenotypes in pharmacogenetic studies. One is QT interval prolongation; a GWAS study of iloperidone's effect identified association with SNPs in several genes of relevance to cardiac function (Volpi et al. 2009a), while studies on the CATIE cohort (Aberg et al. 2010b) found association with other genes, including one, SLC22A23, of particular relevance to ion transport.

Sedation has received very little attention despite its importance as a consequence of antipsychotic drug treatment. One study has investigated the α_{1A}-adrenoceptor as a candidate gene and found only weak and non-significant associations with side effects including sedation (Saiz et al. 2008).

4 Concluding Remarks

For more than the past decade much effort has been spent in attempting to determine the genetic predictors of the effects of antipsychotic drugs, not only their positive effects on symptom response but also their many and various adverse effects. These studies have often responded to topical concerns, including the increasing emphasis on the importance of negative and cognitive symptoms in determining outcome, and the recognition of the contribution of metabolic side effects such as weight gain to both treatment adherence and further iatrogenic morbidity. It is clear that, despite this effort, identification of the major genetic contributors to the consequences of antipsychotic drug treatment still eludes us. This is, at least in part, due to the fact that only very rarely will variability in the

consequences of antipsychotic treatment depend on genetic polymorphisms in single genes; most effects will be polygenic in nature. Future work will need to overcome the many limitations and discrepancies between studies that are apparent in the current literature. One problem that is rarely acknowledged in pharmacogenetic studies, particularly of cohorts of subjects with chronic schizophrenia, is that of non-adherence to treatment, making blood monitoring of drug a valuable component of any study. There will also need to be a greater recognition that gene–gene interactions and even, as is increasingly apparent in understanding disease pathogenesis, gene–environment interactions may be important in understanding properly the risk factors contributing to poor response or the emergence of adverse events.

Thus, notwithstanding some past attempts at commercialization and one possible exception for clozapine-induced agranulocytosis mentioned above, we still have some way to go before the application pharmacogenetics to predictive clinical testing becomes a valuable reality. Nevertheless, the pharmacogenetics of antipsychotic drugs has progressed enormously, and new findings are beginning to take us towards a better understanding of the mechanisms underlying the effects of these drugs. As the technology develops and genotyping of large numbers of SNPs in large samples becomes cheaper and more accessible, findings from further GWAS will, we hope, converge to give us consistent results. Industry-sponsored drug trials have already contributed useful GWAS findings (e.g., Lavedan et al. 2009); further such studies can reap the benefit of the well-characterized phenotype data that controlled clinical trials provide, although the often highly restrictive inclusion criteria may limit how easy it is to generalize from such findings. More valuable perhaps are studies of first-episode patients initially naïve to drug treatment; recognition of the importance of effective early intervention in psychosis has identified such cohorts ripe for pharmacogenetic study. Consistent and convergent findings from such studies will open up opportunities for predictive genetic testing, once their validity and, importantly, utility in the clinic are established.

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Interactions and Monitoring of Antipsychotic Drugs

Christoph Hiemke and Bruno Pfuhlmann

Contents

Abstract As a consequence of individualized antipsychotic pharmacotherapy, many patients need more than a single drug, since they do not respond sufficiently to monotherapy. Other patients suffer from comorbid diseases and therefore require additional drugs from other pharmacological classes. Drug combinations, however, can give rise to pharmacokinetic and/or pharmacodynamic drug–drug interactions. Evaluation of pharmacokinetic interactions with antipsychotic drugs must consider substrate, inhibitor, and inducer properties for the cytochrome P450 (CYP) isoenzymes of all combined drugs. For consideration of pharmacodynamic interactions, special attention must be given to effects on dopamine D_2, histamine H_1, and acetylcholine M_1 receptors and on cardiac potassium channels. Additive pharmacological actions of combined drugs on these target structures can induce

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adverse reactions such as extrapyramidal symptoms, drowsiness, metabolic disturbances leading to weight gain and cardiac problems, cognitive impairment, delirium, or ventricular arrhythmia. Measuring plasma concentrations, i.e., therapeutic drug monitoring (TDM), is valuable to adjust antipsychotic medication when drug combinations contain inhibitors or inducers that alter plasma concentrations of the antipsychotic drugs. Amalgamating the broad knowledge on drug–drug interactions and using appropriately the option to monitor plasma concentrations in blood will help to apply complex combination therapies with antipsychotic drugs with maximal efficiency and safety.

Keywords Drug–drug interactions • Cytochrome P450 • Therapeutic drug monitoring • Plasma concentration • Pharmacokinetics • Pharmacodynamics

1 Introduction

The aim of antipsychotic drug treatment is to attain maximal reduction of positive and negative symptoms of schizophrenia without causing adverse effects during the acute phase of the illness and to prevent relapses or recurrences during continuation and maintenance therapy. To achieve these goals, drug choice and dosage must be optimized for each patient individually. As a consequence of individualized antipsychotic drug therapy, many patients require more than a single drug. When monotherapy is not sufficiently effective, remission is incomplete or chronic symptoms persist, there is a need of additional drugs. Side effects induced by antipsychotic drugs such as dystonia may also require additional drug treatment. Moreover, patients who suffer from comorbid diseases may require drugs from other classes. Under every day conditions of antipsychotic drug therapy, polypharmacy is more common than monotherapy (Faries et al. 2005; Freudenreich and Goff 2002; Goodwin et al. 2009). Drug combinations, however, can give rise to drug–drug interactions. In daily clinical routine of polypragmasy, it is not common use to check any possible combination for potential drug–drug interaction risks. Most drug combinations are not critical, many combinations are even useful or required, and many combinations have only a low risk for adverse events. Nevertheless, one must be aware that drug–drug interactions endanger patients who take multiple medications (Köhler et al. 2000). Among elderly patients who are often treated with many drugs, drug–drug interaction is a significant factor that leads to hospitalization due to drug toxicity (Juurlink et al. 2003).

To keep the risk associated with drug combinations on a minimum level it is necessary to understand the principles of drug–drug interactions and to know highly interacting drugs and contraindicated combinations of individual drugs. This holds also true for antipsychotic drugs. With regard to drug interactions, scientific knowledge has markedly advanced. Neurotransmitter receptor profiles have been

characterized in detail for most antipsychotic drugs (Richelsen and Souder 2000). Substrate properties of antipsychotic drugs for cytochrome P450 (CYP) enzymes are now quite well known. Moreover, many drugs from multiple drug classes were identified as inhibitors or inducers of CYP isoforms. In addition to metabolic enzymes, transporters of the solute carrier (SLC), and ATP-binding cassette (ABC) superfamilies, especially the efflux transporter subtype ABCB1 (P-glycoprotein, P-gp) is an important dterminant for absorption, distribution, and excretion of drugs including antipsychotics (DeGorter et al. 2012; Moons et al. 2011). P-gp is also expressed in capillary endothelial cells in the brain and protects it against blood-borne toxic influences and thus participates in the function of the blood–brainbarrier. Some antipsychotics such as risperidone or aripiprazole are substrates of P-gp (Cascorbi 2011). P-gp expression has an impact on the CNS availability of these drugs which has pharmacodynamic consequences (Kirschbaum et al. 2011). So far, however, evidence is lacking that P-gp in the blood–brainbarrier is a target of drug–drug interactions. According to actual knowledge, neurotransmitter receptors and CYP isoenzymes are the major players that precipitate drug–drug interactions. In spite of the broad knowledge, prediction of potential drug–drug interaction problems is often neglected in clinical practice when treating individual patients. Interpretation is a complex task, since more than 30 antipsychotic drugs differ markedly with regard to their receptor profiles and their metabolic properties related to CYP isoenzymes. This review deals with mechanisms that are involved in interactions with antipsychotic drugs and that have practical relevance. It also explains the value of therapeutic drug monitoring (TDM) for the guidance of antipsychotic pharmacotherapy under concomitant medication.

2 Drug–Drug Interaction Mechanisms

Drug interactions occur when a patient takes two or more medications concurrently and when the effectiveness, tolerability, or toxicity of one drug is altered. There are a number of possible interaction mechanisms. They are divided into two general categories: pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions consist of changes in the absorption, distribution, metabolism, or excretion of a drug and/or metabolites. Pharmacodynamic interactions may occur when two drugs act at the same or interrelated receptors and signaling pathways. Drug–drug interactions can lead to adverse effects, but they may also have beneficial consequences. Under antipsychotic drug treatment, concomitant medication with anticholinergic drugs like trihexyphenidyl or biperiden mitigates extrapyramidal symptoms, and addition of an antidepressant drug may ameliorate negative symptoms. Most of the interactions with antipsychotic drugs, however, are a matter of drug safety.

2.1 Pharmacokinetic Drug–Drug Interactions

Pharmacokinetic drug interactions have consequences for the amount of the drug reaching its site(s) of action. They can occur during any pharmacokinetic phase, absorption, distribution, metabolism, or excretion (ADME). Most antipsychotic drugs are taken orally. Interactions during the absorption phase affect the influx of drugs from the gut into the blood stream. Examples are changes in gastrointestinal pH or gastrointestinal motility. Other example are interactions at the level of drug transporters. The availability of some antipsychotic drugs is limited by the action of drug efflux transporters in the endothelial cells (Cascorbi 2011). They eject drugs that have diffused across the gut lining back into the gut. A well-characterized and most important efflux transporter is P-gp. Risperidone, paliperidone, aripiprazole, ziprasidone, and also a number of typical antipsychotics are substrates of P-gp (Moons et al. 2011). Actually, however, it is not clear if a drug like verapamil that inhibits P-gp (Moons et al. 2011) has a clinically relevant effect on the pharmacological activity of these drugs. For carbamazepine and St. John's wort which induce both P-gp, some evidence is given that the availability of risperidone and paliperidone could be reduced (Dürr et al. 2000, summary of product characteristics for paliperidone). Overall, however, actual knowledge indicates that drug interactions during the absorption phase have little relevance for pharmacokinetic interactions with antipsychotic drugs.

The same holds true for the distribution phase which follows after absorption. In the body, lipophilic antipsychotic drugs are distributed via the circulation and thereby bound to plasma proteins. It was long believed that displacement from plasma proteins will cause an increase in drug effects, since only the unbound fraction is pharmacologically active. In practice, however, changes in plasma protein binding have little clinical relevance (Benet and Hoener 2002). The extraction of antipsychotic drugs into brain is the most efficient process and target structures have high affinity. Therefore, changes in the amount of binding to plasma proteins seem unlikely to alter the potency of antipsychotic drugs in vivo.

Most susceptible with regard to pharmacokinetic interactions of antipsychotic drugs are hepatic cytochrome P450 enzymes of the phase 1 metabolism. Among the multiple isoenzymes in the liver, CYP1A2, CYP2C19, CYP2D6, and CYP3A4 are practically relevant for the degradation of antipsychotic drugs. Substrate specificity differs between antipsychotic drugs (Table 1).

Inhibition or induction of metabolic enzymes may affect markedly the elimination of antipsychotic drugs when they are degraded preferentially by a single enzyme. An example is clozapine which is primarily degraded by CYP1A2. Changes in CYP1A2 activity affect clozapine concentrations in plasma and clinical effects. Drugs that are inhibitors of cytochrome enzymes involved in antipsychotic drug metabolism are listed in Table 2. Among them are several antipsychotic drugs. Perazine inhibits CYP1A2 and CYP2C19 and levomepromazine, melperone, perphenazine, and thioridazine CYP2D6. An example for an interaction effect is the occurrence of extrapyramidal symptoms under treatment with fluphenazine, which

Table 1 Enzymes involved in the degradation of antipsychotic drugs (Hiemke et al. 2011)

Drug (active metabolite)	Enzymes
Amisulpride	More than 90 % is excreted unmetabolized via the kidney
Aripiprazole (dehydroaripiprazole)	*CYP2D6, CYP3A4*
Asenapine	*N*-Glucuroronosyl-transferase and CYP1A2
Benperidol	Unclear
Bromperidol	*CYP3A4*
Chlorpromazine	*CYP1A2, CYP2D6*
Chlorprothixene	*CYP2D6*
Clozapine	*CYP1A2, CYP2C19*, CYP3A4
Flupenthixol	*CYP2D6*
Fluphenazine	*CYP2D6*
Fluspirilene	Unclear
Haloperidol	CYP2D6, *CYP3A4*
Iloperidone	*CYP2D6*, CYP3A4
Levomepromazine	CYP1A2, CYP2D6
Melperone	Unclear
Olanzapine	*N*-glucuronosyl-transferase, flavin monoxigenase, *CYP1A2*, CYP2D6
Paliperidone (= 9-Hydroxy-risperidone)	60 % excreted unmetabolized, different pathways
Perazine	CYP1A2, *CYP2C19*, CYP3A4, flavin monooxygenase
Perphenazine	CYP1A2, CYP2C19, *CYP2D6*, CYP3A4
Pimozide	CYP1A2, *CYP3A4*
Pipamperone	Unclear
Prothipendyl	Unclear
Quetiapine	*CYP3A4*
Risperidone	*CYP2D6*, CYP3A4
Sertindole	*CYP3A4, CYP2D6*
Sulpiride	Excreted unmetabolized via the kidney
Thioridazine	*CYP1A2*, CYP2C19, *CYP2D6*, CYP3A4
Ziprasidone	CYP3A4, Aldehyde oxidase
Zotepine	*CYP1A2*, CYP2D6, *CYP3A4*
Zuclopenthixol	*CYP2D6*

Major enzymes are indicated in italics. Inhibition of these enzymes will significantly increase the plasma concentration of the antipsychotic drug; induction (CYP1A2 or CYP3A4) will decrease the plasma concentration

is a preferential substrate of CYP2D6 (Zhou 2009). Paroxetine is a potent inhibitor of CYP2D6 (Spina et al. 2008). Comedication with paroxetine will lead to elevated plasma concentrations of fluphenazine, and thus enhance concentration-dependent side effects such as motor symptoms. When the antipsychotic drug has a broad safety margin, adverse events may not occur after addition of the inhibitor. However, when the safety margin is narrow, there is high risk for an adverse reaction. For risk reduction, combinations should be kept to a minimum. Another risk reducing strategy is adaptation of the dose, at best under control of plasma concentrations (Hiemke et al. 2011).

Table 2 Inhibitors of cytochrome P450 (CYP) isoenzymes that may give rise to pharmacokinetic drug interactions with antipsychotic drugs (Hiemke et al. 2011; Lynch and Price 2007; Spina et al. 2003)

CYP	Inhibitory drugs	Food, herbal drugs and life style
1A2	Cimetidine, ciprofloxacin, enoxacin, fluvoxamine, norfloxacin, perazine, propafenone	Infections
2C19	Felbamate, fluconazole, fluvoxamine, moclobemide, omeprazole, perazine	
2D6	Amiodarone, bupropion, cimetidine, fluoxetine, levomepromazine, melperone, metoclopramide, moclobemide, norfluoxetine, paroxetine, pergolide, perphenazine, propafenone, propanolol, quinidine, ritonavir, ropinirole, thioridazine	
3A4	Bromocriptine, cimetidine, cisapride, clarithromycin, diltiazem, erythromycin, indinavir, itraconazole, ketoconazole, miconazole, mifepriston, nelfinavir, norfluoxetine, ritonavir, saquinavir, simvastatine, troleandomycin, verapamil, voriconazole	Grapefruit juice

For inhibitors listed above, warnings are given in the summary of product characteristics or in vivo studies or case reports have shown that clinically relevant drug interactions may occur under combination with antipsychotic drugs

In case of discontinuation of an inhibitor of a combination treatment it must be assumed that the withdrawal will decrease the plasma concentration of the drug whose elimination was inhibited. Disinhibition bears the risk of symptom impairment or loss of action. Under such conditions, it can also be helpful to adapt the dose by monitoring the concentration of the antipsychotic drug in plasma.

For barbiturates it was long recognized that chronic treatment requires increasing the dosage to achieve the same hypnotic effect. It was found that this effect was due to increased activity of microsomal enzymes in the liver. This enhanced the extent of metabolism and excretion. Meanwhile, it has been clarified that the increase of enzyme activity is the result of enhanced enzyme protein synthesis possibly due to a pregnane X receptor-mediated stimulation of transcription (Ma et al. 2008). Inducers and enzymes that can affect the pharmacokinetics of other drugs are listed in Table 3. The major enzymes that are susceptible to induction are CYP1A2 and CYP3A4 (Zhu et al. 2010). In clinical practice, the most important inducers of CYP1A2 are polycyclic aromatic hydrocarbons that are present in cigarette smoke. Major substrates of CYP1A2 are clozapine or olanzapine. For CYP3A4, carbamazepine is the most important inducer. A susceptible substrate of CYP3A4 is quetiapine. For quetiapine it was found that the drug concentration in plasma decreases by about 90 % (Castberg et al. 2007; Nickl-Jockschat et al. 2009). This will lead to a loss of efficacy of the antipsychotic drug. Therefore, such combination should be avoided. When the effect is less pronounced, as it is for aripiprazole, (Nakamura et al. 2009), it may be sufficient to adapt the dose and thus avoid the occurrence of decreased antipsychotic drug activity.

As for the discontinuation of treatment with an inhibitor, discontinuation of the inducer should also be regarded with caution. When the enzyme inducing effect stops, enhanced synthesis of the induced isoenzyme will decrease to the baseline expression level. Accelerated elimination decreases within 3–6 days (Faber et al.

Table 3 Inducers of cytochrome P450 (CYP) isoenzymes (Hiemke et al. 2011; Pang et al. 2011; Spina et al. 2003; Sinz et al. 2008)

CYP	Inducing drugs	Food, herbal drugs and life style
1A2	Carbamazepine, rifampicin	Smoke, charcoal-broiled food, broccoli
2C19	Carbamazepine, Felbamate, modafinil, topiramate, rifampicin, St. John's Wort, phenytoin	
2D6	Unknown	Not inducible
3A4	Carbamazepine, efavirenz, dexamethasone, lovastatine, oxybutynin, rifabutin, rifampicin, St. John's Wort (hyperforin), phenobarbital, phenytoin, primidon	

For the above listed inducers, warnings are given in the summary of product characteristics or in vivo studies or case reports have shown that clinically relevant drug interactions may occur under combination with antipsychotic drugs

2005). Patients who were treated with clozapine or olanzapine and who stopped smoking were thus intoxicated due to decreased elimination of clozapine or olanzapine after stopping of smoking (Bondolfi et al. 2005; Cole et al. 2010; Lowe and Ackman 2010). The symptoms disappeared after dose reduction. To handle combinations with drugs that are enzyme inducers it is recommended to monitor plasma concentrations and adapt the dose about 1 week after start or stop of intake of the inducing drug.

The magnitude of pharmacokinetic drug–drug interactions depends on the genotype. The decrease in CYP1A2 activity observed after quitting of smoking is dependent on the CYP1A2*F genotype (Dobrinas et al. 2011). However, when a patient is under co-medication with ciprofloxacine, a strong inhibitor of CYP1A2, cessation of smoking will not affect the pharmacokinetics, independent of the genotype, since the enzyme activity is blocked by the antibiotic drug. In patients who are poor metabolizers of CYP2D6, an inhibitor of CYP2D6 does not effect changes in the pharmacokinetics of CYP2D6 substrates.

In drugs that are primarily eliminated via active secretion into the renal tubes, drug–drug interactions might occur during the excretion phase. Sulpiride and amisulpride are eliminated primarily through renal excretion (Rosenzweig et al. 2002). Drugs such as amidarone, clarithromycin, itraconazole, propafenone, or quinidine might inhibit this process. So far, however, reports on respective interactions with amisulpride or sulpiride are lacking. Most antipsychotic drugs, however, undergo phase 1 metabolism and subsequent conjugation to glucuronic acid. These drugs are not susceptible to interactions during the excretion process.

2.2 Pharmacodynamic Drug–Drug Interactions

Surveys of prescribing in psychiatric services internationally have identified the relatively frequent and consistent use of combined antipsychotics, usually for patients with established schizophrenia, with a prevalence of up to 50 % (Barnes

Table 4 Target structures which may be blocked by antipsychotic drugs and related therapeutic and adverse effects

Target structures	Therapeutic effects	Adverse effects
Adrenoceptors, α_1	Uncertain for α_1-adrenoceptors in the brain	Orthostatic hypotension, reflex tachycardia, dizziness
Adrenoceptors, α_2	Unknown	Facilitation of tachycardia or antagonism of antihypertensive effects of clonidine or methyldopa
Dopamine D_2 receptors	Antipsychotic effects, amelioration of positive symptoms	Extrapyramidal symptoms, akathisia, prolactin release, sexual dysfunction in man, disturbed thermoregulation, neuroleptic syndrome. Stimulation may induce nausea, vomiting or enhance sexual drive
Histamine H_1 receptors	Sedation and sleep	Sedation, delirium, weight gain
Cardiac potassium channels	None	QTc interval prolongation, torsades de pointes, arrhythmia
Acetylcholine M_1 receptors	Mitigation of extrapyramidal side effects	Disturbed accommodation, dry mouth, sinus tachycardia, obstipation, urinary retention, glaucoma, cognitive disturbances, delirium, or seizures
Acetylcholine M_3 receptors	Unknown	Elevated risk for type 2 diabetes
Serotonin 5-HT_{2D} receptors	Unknown	Unknown
Serotonin 5-HT_{2A} receptors	Inhibition may affect anxiety, negative symptoms, sleep, appetite	Unknown
Serotonin 5-HT_{2C} receptors	Inhibition may affect anxiety, negative symptoms, sleep, appetite	Inhibition may lead to weight gain and affect gastrointestinal functions and the regulation of body temperature

Modified after Richelsen and Souder (2000), Silvestre and Prous (2005) and Wenzel-Seifert et al. (2011)

Under combination of antipsychotic drugs and other drugs, overlapping target structure occupancy can give rise to pharmacodynamic drug–drug interactions with additive or antagonistic pharmacological effects

and Paton et al. 2011). It remains a matter of debate to what extent combination treatments are advantageous in comparison to antipsychotic monotherapy. More valid studies are required. On the other hand, it is well documented that the frequency of numerous unwanted effects (Table 4) increases (Tranulis et al. 2008).

Most drug–drug interactions that occur in vivo are pharmacodynamic interactions. This holds also true for antipsychotic drugs (Bender et al. 2004; Spina and deLeon 2007). Pharmacodynamic interactions are those where the effect of one drug is modified by the effect of the other drug at a common or at different sites of action. Actions can be additive or synergistic and thus intensify therapeutic effects or bring about toxic effects. Other ways of pharmacodynamic interactions

are antagonistic or opposing effects. Target structures of antipsychotic drugs and related effects are summarized in Table 4. With regard to pharmacodynamic interactions of antipsychotic drugs, abnormal extrapyramidal motor behavior, metabolic disturbances, cognitive impairment, or delirium are typical adverse reactions. These effects are mediated via dopamine D_2, histamine H_1, acetylcholine M_1, or serotonin 5-HT_2 receptors. Moreover, cardiac disturbances due to blockade of cardiac potassium channels (hERG) or other ion channels must be considered.

Additive *antidopaminergic effects* are mostly the result of co-prescription of more than one antipsychotic drug. They include extrapyramidal symptoms, endocrine effects, disturbed thermoregulation, and the neuroleptic syndrome. The prevalence of parkinsonism and tardive dyskinesia is thus enhanced under combination of different antidopaminergic drugs. This risk, however, is also increased under co-medication with lithium (Ghadirian et al. 1996). With regard to therapeutic outcomes it can be plausible to add a low dose of another antidopaminergic drug in case of insufficient suppression of positive symptoms by enhancing the antidopaminergic activity. This may occur under clozapine or quetiapine therapy. Both drugs have low affinity to dopamine receptors (Gross and Drescher 2012; Richelsen and Souder 2000).

QTc interval prolongation is reported for a number of old and new antipsychotic drugs, e.g., haloperidol, levomepromazine, melperone, pimozide, quetiapine, sertindole, thioridazine, or ziprasidone (van Noord et al. 2010; Wenzel-Seifert et al. 2011). QTc interval lengthening indicates prolonged ventricular repolarization that may lead to sudden death in severe cases, mostly under high concentrations of the drug. The prolonged repolarization results from a net decrease in repolarizing current by increased inward current or decreased outward current, whereby a specific potassium current, the rapid component of the delayed rectifier I_{Kr} plays a crucial role (Kannakeril and Roden 2007). This current is generated by potassium flow through the hERG ion channel which is susceptible to a blockade by various drugs including psychotropic drugs and various antipsychotics (Roden 2004). QTc prolongation can give rise to torsades de pointes and ventricular fibrillation (Tisdale et al. 2011; van Noord 2010). The risk for QTc prolongation and potentially fatal complications due to drug exposure seems also to be influenced by an underlying genetic predisposition for a "reduced repolarization reserve" (Roden and Viswanthan 2005). Additional risk factors are hypokalemia, bradycardia, female sex, or severe heart disease. Since drug-induced QTc prolongation seems to be concentration-dependent (Crumb et al. 2006; Roden and Viswanthan 2005; Unterecker et al. 2012), pharmacokinetic interactions may also be relevant in the pathogenesis of drug-induced long QT syndrome. When an antipsychotic drug with hERG blocking activity that leads to QTc prolongation is combined with another QTc-lengthening drug, the concomitant use has additive or even potentiating effects. For this reason the FDA has added a warning to the summary of product characteristics (SPC) of quetiapine against using this atypical antipsychotic in conjunction with drugs like quinidine, procainamide, amiodarone, sotalol, gatifoxacin, or moxifloxacin. Also for lithium, which is combined with many antipsychotic drugs, the potential of QTc prolongation must always be considered.

A combination of drugs which both exert hERG blocking properties and interact pharmacokinetically, as it is the case e.g., for the combination of olanzapine with the antibiotic ciprofloxacin, is particularly hazardous with respect to QTc prolongation due to a combination of pharmacokinetic and pharmacodynamic interactions (Letsas et al. 2006). Careful clinical supervision with obligatory electrocardiogram (ECG) recording is required when such combination treatments are necessary. The same holds true for other antipsychotic drugs with QTc-lengthening properties.

Weight gain and occurrence of a *metabolic syndrome* is a severe burden of new antipsychotic drugs (Heal et al. 2012). It is most prominent for clozapine, olanzapine, and thioridazine followed by paliperidone, risperidone, quetiapine, and sertindole (Newcomer 2007). The risk is lower for aripiprazole and ziprasidone (Mitchell et al. 2011). The metabolic syndrome includes a cluster of abnormalities such as a disturbed glucose and lipid status. Most prominent is weight gain leading to obesity (Baptista et al. 2004). The syndrome is associated with an increased risk of mortality. So far, limited evidence exists if polypharmacy has an impact on this side effect. A recent cross-sectional study revealed an increased risk of polypharmacy compared to monotherapy (Misawa et al. 2011).

Disturbed accommodation, dry mouth, sinus tachycardia, obstipation, urinary retention, glaucoma, impaired cognition, delirium, or seizures are typical clinical consequences of blockade of acetylcholine M_1 receptors. There are a number of drugs from different classes which all exhibit *anticholinergic activity*. A recent study analyzed anticholinergic activity of 107 medications (Chew et al. 2008). Among antipsychotic drugs marked anticholinergic activity was found for clozapine and thioridazine followed by chlorpromazine, olanzapine, and quetiapine. Under therapeutic doses, no measurable activity could be attributed to aripiprazole, haloperidol, perphenazine, risperidone, and ziprasidone. With regard to anticholinergic drug interactions one should avoid combinations of an antipsychotic and another drug when both exhibit anticholinergic activity. An example is the combination of clozapine and diphenhydramine.

Concerning antagonistic or opposing pharmacodynamic interactions, the combination of antipsychotic drugs and dopamine stimulating properties are the most relevant. Effects of antipsychotic drugs are antagonized by dopamine agonists and antipsychotic drugs dampen effects of dopamine-stimulating drugs. Such combination treatments can be required for patients with Parkinson's disease, e.g., when psychotic symptoms occur. However, the combination should be used with caution. L-Dopa-induced psychotic symptoms may be treated effectively with an antipsychotic drug, but it is more appropriate to reduce the dose of L-dopa.

3 Monitoring Blood Levels of Antipsychotic Drugs

In case of a pharmacokinetic interaction, the plasma concentration of the affected drug will change (Fig. 1). The concentration increases when the co-medication is an inhibitor and it decreases with a certain delay after concomitant medication with an

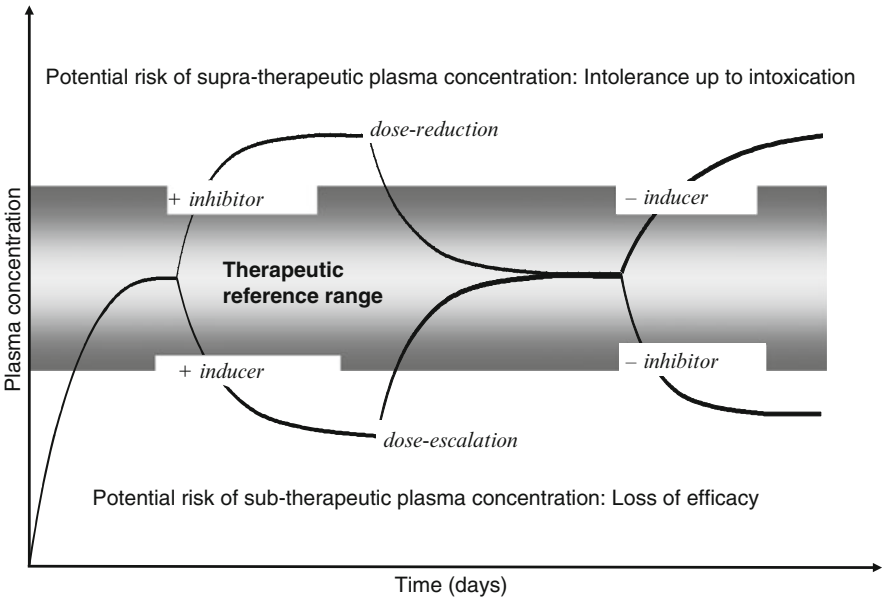

Fig. 1 Time-dependent in vivo plasma concentrations of a drug after addition or discontinuation of a second drug with either inhibiting or inducing properties on enzymes involved in the degradation of the affected drug

inducer. Opposite effects will occur when the intake of the inhibiting or inducing drug is stopped. Both situations can have problematic clinical consequences. When the drug concentration increases to supratherapeutic levels, toxic effects may result. When drug concentrations attain subtherapeutic levels, the potential risk is loss of action. For antipsychotic drugs, there are multiple examples reported in the literature that demonstrate these consequences.

Optimal drug concentrations can be re-established by changing the dose (Fig. 1). For antipsychotic drugs, dose adaptation should be guided by measuring plasma concentrations, i.e., by TDM. TDM is a valid tool for tailoring the dosage of the prescribed antipsychotic medication (Hiemke et al. 2011). Combination treatment with a drug known for its interaction potential is one of the strong indications for measuring plasma concentrations of antipsychotic drugs or other medications. It should also be mentioned that many pharmacokinetic drug–drug interactions have been found by TDM either by chance or by retrospective analysis of TDM data bases (Castberg et al. 2007; Jerling et al. 1994). TDM even enables the use of critical drug combinations such as clozapine and fluvoxamine safely. This combination can be helpful for an individual patient (Szegedi et al. 1999; Silver 2001), but without TDM it may lead to severe intoxications (Lu et al. 2000). In elderly patients TDM is particularly recommended; in these patients the elimination capacity is frequently reduced, and they may have a higher risk to develop side effects. Moreover, most of these patients take more than a single drug.

The best practice of TDM in psychiatry was recently described in the consensus guideline of the AGNP–TDM task force (Hiemke et al. 2011), an interdisciplinary expert group of the "Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie" (AGNP). Typical indications to use TDM for guidance of antipsychotic medication are the following:

- Dose optimization after initial prescription or after dose change
- Drugs, for which TDM is mandatory for safety reasons (e.g., clozapine)
- Suspected complete or partial non-adherence (non-compliance) to medication
- Lack of clinical improvement under recommended doses
- Adverse effects under recommended doses
- Combination treatment with a drug known for its interaction potential or suspected drug interaction
- TDM in pharmacovigilance programs
- Relapse prevention under maintenance treatment
- Recurrence under adequate doses
- Presence of a genetic particularity concerning drug metabolism (genetic deficiency, gene multiplication)
- Pregnant or breast-feeding patient
- Children and adolescent patient
- Elderly patient (>65 years)
- Individuals with intellectual disabilities
- Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
- Forensic patient
- Switching from an original preparation to a generic form (and vice versa)

When using TDM to guide antipsychotic drug therapy, it is assumed that there is a relationship between plasma concentrations and clinical effects. It is also assumed that there is a plasma concentration range of the drug which is associated with maximal effectiveness and safety, the "therapeutic window." This "therapeutic reference range" is defined as the range of medication concentrations which specify a lower limit below which a drug-induced therapeutic response is relatively unlikely to occur and an upper limit above which tolerability decreases or above which it is relatively unlikely that therapeutic improvement may be still enhanced (Hiemke et al. 2011). For many antipsychotic drugs, the therapeutic reference range is not merely based on classical pharmacokinetic and/or pharmacodynamics studies but also on in vivo receptor-binding studies using imaging techniques. Positron emission tomography (PET) enables quantification of the amount of dopamine receptor occupancy by antipsychotic drugs (Farde et al. 1988). It has also been shown that receptor occupancy correlates better with plasma concentrations of antipsychotic drugs than with daily doses (Kapur et al. 2000; Gründer et al. 2011). Studies combining TDM and functional imaging are particularly useful to establish an optimal plasma concentration range (Wong et al. 2007), although type and binding parameters of the used radioligands have to be considered for valid conclusions. According to PET studies optimal antipsychotic treatment outcome

occurs at 70–80 % of striatal dopamine D_2-like receptor occupancy by dopamine receptor antagonists (Gründer et al. 2011). Occupancies of more than 80 % are associated with an increased frequency of extrapyramidal side effects (Farde et al. 1992). This relationship seems to apply for classical as well as for most atypical antipsychotics. Therapeutic plasma concentrations reported from clinical studies could be confirmed by PET for a number of antipsychotics (for review see Gründer et al. 2011). They included classical antipsychotic drugs such as haloperidol (Farde et al. 1988) and perphenazine (Talvik et al. 2004) as well as second generation antipsychotics like risperidone (Medori et al. 2006) or olanzapine (Kapur et al. 1998). Only few newer antipsychotics challenge this concept: clozapine, quetiapine, and aripiprazole. For these drugs other properties must be taken into account, partial agonism for aripiprazole or preferential binding to extrastriatal dopamine receptors for clozapine and quetiapine (Gründer et al. 2003).

Due to the broad knowledge gained for the in vivo pharmacology of antipsychotic drugs during the last years (Talbot and Laruelle 2002), TDM has become the most helpful tool for optimization of the dosing of individual patients especially those under polypharmacy. It allows consideration of a patient's dopamine receptor pharmacology and his/her pharmacokinetic status. Both can be affected in case of drug–drug interactions.

4 Practical Issues for Handling and Monitoring of Interactions with Antipsychotic Drugs

Consideration of potential drug–drug interactions for a distinct combination of drugs in an individual patient and the decision if monitoring of the blood concentration of an antipsychotic drug could be valuable, requires compilation of complex information. Individual patients differ with regard to their genetic background, age, sex, disease state, and multiple other factors, and the more than 30 available antipsychotic drugs differ in their pharmacodynamic and pharmacokinetic properties. Evaluation of drug–drug interactions therefore requires consideration of the pharmacological profile of all drugs involved. Moreover, all pairs of drugs that may be derived from the list of drugs that are taken by the patient must be checked in theory for complete evaluation. The number of pairs and potential drug interactions (i) can be calculated from the number of combined drugs (n) as follows:

$$i = \frac{(n^2 - n)}{2}.$$

For a combination of 5 drugs this means that there are 10 possible drug–drug interactions; for 10 drugs, the number increases to 45 possible drug–drug interactions. In clinical practice, it is not common and not necessary to check any possible combination for drug interactions. It is essential, however, to identify signals in the list of drugs that may give rise to drug–drug interactions.

Pharmacokinetic signals are drugs that are inhibitors or inducers of CYP isoenzymes (see Tables 2 and 3). When the list of drugs also contains a substrate of the inhibited or induced enzyme, then it must be assumed that the drug can be affected. For consideration of pharmacodynamic interactions the list of drugs must be checked for overlapping target profiles that may lead to additive or antagonistic pharmacological actions.

For consideration of potential interactions with antipsychotic drugs relevant information is given below for 30 old and new antipsychotic drugs. The list is based on information reported in the summaries of product characteristics and the recently published reviews of Chew et al. (2008) for anticholinergic activity, Hiemke et al. (2011) for CYP- and TDM-related information and Wenzel-Seifert et al. (2011) for QTc prolongation. If recommended therapeutic ranges are mentioned they refer always to trough levels measured under steady-state conditions (Hiemke et al. 2011).

Amisulpride is a specific antagonist of dopamine D_2 and D_3 receptors and of serotonin 5-HT_7 receptors. Due to the dose-dependent prolongation of the QTc interval, combinations with medications which can induce torsades de pointes, such as quinidine, disopyramide, procainamide, amiodarone, or sotalol, are contraindicated. It has a bioavailability of 33–45 % after oral ingestion. The elimination half-life is 12–20 h. The drug undergoes little metabolism. Pharmacokinetic interactions have so far not been reported. The therapeutic reference range of plasma concentrations is 100–320 ng/mL.

Aripiprazole is a high-affinity partial agonist of dopamine D_2 and D_3 and serotonin 5-HT_{1A} receptors and an antagonist of 5-HT_{2A} and 5-HT_{2C} receptors. Combinations that require precautions for use are CNS depressants, antihypertensive, and hypotensive medication. The mean oral bioavailability is 87 % and the elimination half-life is 60–80 h. Aripiprazole is metabolized by CYP2D6 and CYP3A4 to dehydroaripiprazole and other metabolites. Aripiprazole is the predominant medicinal product. Plasma concentrations are significantly affected in combinations with inhibitors or inducers of CYP3A4 (Tables 2 and 3). TDM may then be of value for dose correction. The therapeutic reference range of aripiprazole plasma concentrations is 150–500 ng/mL.

Asenapine is a high-affinity antagonist at dopamine D_2 and D_3, serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6, and 5-HT_7 receptors, and at histamine H_1 receptors. The bioavailability of sublingual asenapine is 35 %. It is cleared predominantly by direct glucuronidation and to a lesser extent by CYP1A2. Following an initial rapid distribution phase, the mean terminal half-life is approximately 24 h. Dose adaptation under TDM control may be required under combination with CYP1A2 inhibitors such as fluvoxamine or inducers such as smoking (Tables 2 and 3). Therapeutically recommended plasma concentrations of asenapine are 2–5 ng/mL.

Benperidol is a butyrophenone derivative being about two times more potent at dopamine D_2 receptors with similar properties as haloperidol. Oral bioavailability is 50–60 % and its elimination half-life is about 5 h. Enzymes involved are unknown. It should not be combined with polypeptide antibiotics such as capreomycin or polymyxin B and be used with caution with drugs that prolong the QTc interval.

Pharmacokinetic interactions are not reported in the literature. The therapeutically recommended plasma concentration of benperidol is 1–10 ng/mL.

Bromperidol is a typical antipsychotic drug which blocks dopamine D_2 receptors with high affinity. Its elimination half-life is 20–36 h. It is mainly metabolized by CYP3A4. TDM-guided dose adaptation may be required under co-medication with CYP3A4 inhibitors (Table 2) or inducers (Table 3). Therapeutically recommended plasma concentrations of bromperidol are 12–15 ng/mL.

Chlorpromazine was the first drug available for effective treatment of schizophrenia patients. It is an antagonist with moderate affinity at dopamine D_2 receptors and serotonin 5-HT_6 and 5-HT_7 receptors. Its oral bioavailability is about 30 % and its elimination half-life is about 30 h. It is mainly metabolized by CYP1A2 and CYP2D6. TDM-guided dose adaptation may be required under co-medication with CYP1A2 and CYP2D6 inhibitors (Table 2). The recommended therapeutic reference range of chlorpromazine concentrations in plasma is 30–300 ng/mL.

Chlorprothixene is an antagonist with low affinity at dopamine D_2 receptors, moderate affinity at D_1 receptors, and high affinity at serotonin 5-HT_1, histamine H_1, and acetylcholine M_1 receptors. Caution is required for combinations with drugs exhibiting anticholinergic or QTc prolongation properties or with drugs affecting potassium blood levels. Its oral bioavailability is about 50 % and its elimination half-life is 8–12 h. Chlorprothixene is mainly metabolized by CYP2D6. TDM-guided dose adaptation may be required under comedication with CYP2D6 inhibitors (Table 2). The therapeutically recommended plasma concentration of chlorprothixene is 20–300 ng/mL.

Clozapine is the classical atypical antipsychotic. It is an antagonist with low affinity to dopamine D_1, D_2, D_3, and D_5 receptors, with high affinity to D_4, histamine H_1, serotonin 5-HT_{2A} and 5-HT_{2C}, acetylcholine M_1, M_2, and M_3, and α_2-adrenergic receptors. The most critical adverse reaction is agranulocytosis, a potentially life threatening event. The mechanism is unclear; nonetheless due to the possibility that causative factors may act synergistically, clozapine should not be used with other agents having the potential to suppress bone marrow function. Combinations with tricyclic depot antipsychotics are contraindicated. Because of reported severe adverse events, caution is advised for combinations with benzodiazepines. Due to clozapine's high anticholinergic activity, combinations with drugs exhibiting anticholinergic or proconvulsive properties should be avoided. Weight gain is frequently observed under clozapine. Therefore, clozapine should not be combined with other drugs leading to metabolic abnormalities. Severe cardiovascular effects of clozapine are attributed to its potential to block the hERG-encoded potassium channel (Lee et al. 2006). The oral bioavailability of clozapine is 50–60 % and its elimination half-life is 12–16 h. It is metabolized primarily by CYP1A2 and CYP2C19 with additional contribution of other CYP isoenzymes. Under combination with an inhibitor of CYP1A2 like fluvoxamine or ciprofloxacin (Table 2), TDM is mandatory for dose adaptation. Plasma concentrations can increase up to tenfold. During infections, plasma concentrations of clozapine should also be monitored, since they can be markedly increased (Jecel

et al. 2005; Pfuhlmann et al. 2009). TDM is also recommended when patients change smoking habits because of the inducing effects of smoke on CYP1A2 (Table 3). The therapeutic reference range of clozapine concentrations in plasma is 350–600 ng/mL.

Flupenthixol is a chiral, tricyclic antipsychotic drug. The active principle, *cis*-(Z)-flupenthixol, is an antagonist with high affinity to dopamine D_1, D_2, and D_3 and serotonin 5-HT_{2A} receptors and with low to very low affinity to H_1 and acetylcholine M_1 and M_2 receptors. It should not be combined with monoamine oxidase inhibitors, carbamazepine, phenytoin, propranolol, or polypeptide antibiotics. Due to QTc prolongation properties combinations with other drugs exhibiting these effects or affecting potassium blood levels should be supervised. The oral bioavailability of flupenthixol is 40–50 % and its elimination half-life is 20–40 h. It is metabolized primarily by CYP2D6. Under co-medication with CYP2D6 inhibitors (Table 2) the plasma concentration of flupenthixol will increase which enhances the risk of extrapyramidal symptoms. Under combination therapies the dose should be adapted under TDM control. The therapeutic reference range of *cis*-(Z)-flupenthixol concentrations in plasma is 1–10 ng/mL.

Fluphenazine is a high affinity antagonist at dopamine D_2, and histamine H_1, serotonin 5-HT_2 receptors, and α_1-adrenoceptors. It should not be combined with monoamine oxidase inhibitors or lithium, and caution is advised for combinations with sedating drugs. Combinations with drugs exhibiting QTc prolongation properties or affecting potassium blood levels must be carefully supervised. The oral bioavailability of fluphenazine is 20–30 % and its elimination half-life is about 16 h. It is metabolized primarily by CYP2D6. Combinations with inhibitors of CYP2D6 (Table 2) will lead to an increased plasma concentrations of fluphenazine which enhances the risk of extrapyramidal symptoms. TDM dose adaptation is recommended. The therapeutic reference range of fluphenazine concentrations in plasma is 1–10 ng/mL.

Fluspirilene is a potent antagonist at dopamine D_2 and D_3 receptors and a weak D_2 receptor antagonist. It has moderate to low affinity to serotonin 5-HT_2, histamine H_1, and acetylcholine M_1 and M_2 receptors. Combinations with antihistamines like diphenhydramine may lengthen QTc intervals. It is used as depot and has a half-life of 1–2 weeks. Enzymes involved in the metabolism are unknown. The therapeutic reference range of fluspirilene concentrations in plasma is 0.1–2.2 ng/mL.

Haloperidol antagonizes with high-affinity dopamine D_2 receptors and to some extent α_1-adrenoceptors. Combination with other high-affinity dopamine receptor ligands should be avoided due to the risk of extrapyramidal symptoms or tardive dyskinesia. Combinations with sedating drugs should also be used cautiously. Due to QTc-lengthening properties of haloperidol combinations with drugs exhibiting also QTc prolongation or affecting potassium blood levels must be carefully supervised. The oral bioavailability of haloperidol is about 60 % and its elimination half-life is 3–12 h. It is metabolized primarily by CYP3A4 and to a lesser degree by CYP2D6. Under combinations with inhibitors of CYP3A4 (Table 2) haloperidol plasma concentrations may increase. They will decrease by

adding inducers of CYP3A4 (Table 3). The dose should therefore be adapted under TDM control. The therapeutic reference range of haloperidol concentrations in plasma is 1–10 ng/mL.

Iloperidone is a new atypical antipsychotic drug. It is a more potent antagonist at α_1-adrenoceptors and serotonin 5-HT_{2A} receptors than at dopamine D_2 receptors. Its elimination half-life is 18–33 h. It is metabolized primarily by CYP2D6 with additional contribution of CYP3A4 isoenzymes. Combinations with inhibitors of CYP2D6 may enhance the risk of side effects. The therapeutically recommended plasma concentration of iloperidone is 5–10 ng/mL.

Levomepromazine antagonizes dopamine D_2 and D_3 receptors with low affinity and has high affinity to histamine H_1 and acetylcholine M_1 receptors. Due to high anticholinergic activity it should not be combined with drugs exhibiting anticholinergic properties such as biperiden or diphenhydramine. Due to the dose-dependent prolongation of the QTc interval, combinations with other QTc-lengthening medications such as quinidine, disopyramide, procainamide, amiodarone, or sotalol should be used with caution. The oral bioavailability of levomepromazine is about 50 % and its elimination half-life is about 24 h. It is metabolized by CYP1A2 and CYP2D6. It is an inhibitor of CYP2D6. In combinations (Table 2) TDM may be valuable. The therapeutically recommended plasma concentration of levomepromazine is 30–160 ng/mL.

Melperone antagonizes with moderate-affinity dopamine D_2, serotonin 5-HT_2, and α_2-adrenergic receptors. Due to the potential of QTc prolongation, combinations with other QTc-lengthening medications should be used under ECG control. The oral bioavailability is about 60 % and its elimination half-life is 4–6 h. Enzymes involved in its metabolism are unknown. It should be used with caution in combination with drugs that are preferred substrates of CYP2D6, since melperone is an inhibitor of CYP2D6. The therapeutically recommended plasma concentration of melperone is 30–100 ng/mL.

Olanzapine antagonizes all subtypes of dopamine receptors and also serotonin 5-HT_2, acetylcholine M_1 and M_2, histamine H_1, and α_1-adrenergic receptors. Combinations with tricyclic depot antipsychotics are contraindicated. Due to anticholinergic activity, caution is advised for combinations of drugs with similar properties. Metabolic disturbances (glucose, lipids) and weight gain are frequently induced by olanzapine. Therefore, combinations with drugs leading to metabolic abnormalities should be used with caution. The oral bioavailability of olanzapine is about 80 % and its elimination half-life is 30–60 h. It is metabolized primarily by CYP1A2 and *N*-glucuronidation. Therefore, TDM is recommended under combinations with inhibitors of CYP1A2 (Table 2) and when patients change their smoking habits because of the inducing effects of smoke on CYP1A2 (Table 3). The therapeutic reference range of olanzapine concentrations in plasma is 20–80 ng/mL.

Paliperidone is a high-affinity antagonist of serotonin 5-HT_{2A} receptors and to a lesser extent of dopamine D_2, serotonin 5-HT_{2C}, and α_1-adrenergic receptors. It has moderate antagonistic activity on histamine H_1 receptors. The bioavailability of paliperidone is 30–60 % and its elimination half-life is about 23 h. It undergoes only little phase 1 metabolism via CYP3A4. It is a substrate of P-gp. Since

carbamazepine and St. John's wort induce CYP3A4 and P-gp (Table 3), TDM-guided dose adaptation can be valuable under such combinations. The therapeutic reference range of paliperidone concentrations in plasma is 20–60 ng/mL.

Perazine is an antagonist of dopamine D_2, histamine H_1, acetylcholine M_1 receptors, and α_1-adrenoceptors. Due to anticholinergic and QTc prolongation activity, caution is advised for combinations with other drugs exhibiting these properties or affecting potassium blood levels. The oral bioavailability of perazine is about 3 % and its elimination half-life is 8–16 h. It is metabolized primarily by CYP2C19 and to a lesser extent by CYP1A2, CYP3A4, and a flavin monooxygenase. It is a potent inhibitor of CYP1A2 and possibly other CYP isoforms. Therefore TDM should be used for such combinations. The therapeutic reference range of perazine concentrations in plasma is 100–230 ng/mL.

Perphenazine is a high-affinity antagonist of dopamine D_2 and D_3 receptors and a low-affinity antagonist of histamine H_1, serotonin 5-HT_2, and α_1-adrenergic receptors. Due to QTc prolongation activity, caution is advised for combinations with other drugs exhibiting these properties or affecting potassium blood levels. The oral bioavailability of perphenazine is about 40 % and its elimination half-life is 8–12 h. It is metabolized almost exclusively by CYP2D6, and it inhibits this enzyme. Under combinations with other CYP2D6 inhibitors (Table 2) or substrates the use of TDM is advised. The therapeutic reference range of perphenazine concentrations in plasma is 0.4–2.4 ng/mL.

Pimozide is an antagonist of dopamine D_2 and serotonin 5-HT_7 receptors. Due to marked QTc prolongation activity, combinations with other drugs exhibiting these properties or affecting potassium blood levels should be avoided. The combination with sertraline is therefore contraindicated. The elimination half-life is 24–43 h. It is metabolized primarily by CYP3A4 and to some extent by CYP1A2. It should not be combined with inhibitors of CYP3A4 unless the dose is adapted under TDM control. Therapeutically recommended plasma concentrations of pimozide are 15–20 ng/mL.

Pipamperone is a moderate to weak antagonist of serotonin 5-HT_2, dopamine D_2 and D_4, and α_1-adrenergic receptors. Due to QTc prolongation activity, caution is advised for combinations with other drugs exhibiting these properties or affecting potassium blood levels. Its elimination half-life is 17–26 h. Enzymes involved in its metabolism are unknown. Therapeutically recommended plasma concentrations of pipamperone are 100–400 ng/mL.

Prothipendyl is a weak antagonist of dopamine D_2 and serotonin 5-HT_{2A} receptors and a high-affinity histamine H_1 receptor antagonist. Caution is advised for combinations with other sedating drugs. The oral bioavailability is 8–15 % and the elimination half-life is 2–3 h. Enzymes involved in its metabolism are unknown. Therapeutically recommended plasma concentrations of prothipendyl are 5–10 ng/mL.

Quetiapine is a low-affinity antagonist of dopamine D_1, D_2, and D_3 and serotonin 5-HT_1 and 5-HT_2 receptors and an affinity antagonist of histamine H_1 receptors. Its metabolite norquetiapine exhibits inhibitory activity on acetylcholine M_1 receptor and noradrenaline reuptake (Jensen et al. 2008). The use of quetiapine should be avoided in combination with drugs known to increase the QTc interval, and caution

should be exercised for combination with drugs known to cause electrolyte imbalance. Body weight may increase under medication with quetiapine. Therefore, combinations with drugs leading to metabolic abnormalities should be used with caution (Misawa et al. 2011). The oral bioavailability of quetiapine is almost 100 % and the elimination half-life is about 7 h. It is metabolized almost exclusively by CYP3A4 with some additional contribution of CYP2D6. For combinations with CYP3A4 inhibitors the dose should be adapted under TDM control. Due to the almost 90 % decrease of plasma concentrations quetiapine should not be combined with carbamazepine or other inducers of CYP3A4 (Table 3). The therapeutic reference range of quetiapine concentrations in plasma is 100–500 ng/mL.

Risperidone antagonizes dopamine D_2 and serotonin 5-HT_{2A} receptors and with highest affinity 5-HT_{2C} receptors. It has also antagonistic activity on α_1-adrenoceptors and histamine H_1 receptors. Risperidone may prolong the QTc interval. The combination with other drugs known to increase the QTc interval or cause electrolyte imbalance should be monitored. Body weight may increase under medication with risperidone. Therefore, combinations with drugs leading to metabolic abnormalities should be used with caution (Misawa et al. 2011). The oral bioavailability of risperidone is 66–80 %. Risperidone is metabolized primarily by CYP2D6 to its active metabolite 9-hydroxyrisperidone (paliperidone) and to a lesser extent by CYP3A4. The elimination half-life of risperidone is only about 3 h and 24 h for the metabolite. TDM is of value for combination therapies with inhibitors of CYP2D6 or CYP3A4 (Table 2) or inducers of CYP3A4 (Table 3). The therapeutic reference range of risperidone plus 9-hydroxyrisperidone concentrations in plasma (active moiety) is 20–60 ng/mL.

Sertindole is a long lasting antagonist of dopamine D_2, serotonin 5-HT_{2A} and 5-HT_{2C}, and α_2-adrenergic receptors. It prolongs the QTc interval. Therefore, the use of sertindole in combination with drugs known to increase QTc interval or cause electrolyte imbalance (e.g., amiodarone, erythromycin, or sotalol) is contraindicated. The oral bioavailability of sertindole is about 74 % and the elimination half-life is 55–90 h. It is metabolized by CYP2D6 and CYP3A4. Under combinations with interacting drugs (Tables 2 and 3) the dose should be adapted under TDM control. The therapeutic reference range of sertindole concentrations in plasma is 50–100 ng/mL

Sulpiride is an antagonist of dopamine D_2 and D_3 receptors. Due to the dose-dependent prolongation of the QTc interval, combinations with medications which can induce torsades de pointes, such as amiodarone, disopyramide, mefloquine, procainamide, quinidine, or sotalol, or drugs that cause electrolyte imbalance should be avoided. Since the convulsive threshold may be lowered by sulpiride, caution is advised for combinations with anticonvulsant drugs. Sulpiride has a bioavailability of 33–45 % after oral ingestion. The elimination half-life is 12–20 h. The drug undergoes little metabolism. Pharmacokinetic interactions are therefore unlikely to occur and have so far not been reported. The therapeutic reference range of sulpiride concentrations in plasma is 200–1,000 ng/mL.

Thioridazine and its active metabolites mesoridazine and sulforidazine antagonize dopamine D_1, D_2 and D_3, serotonin 5-HT_2, acetylcholine M_1, and α_2-adrenergic

receptors. The drug may cause serious cardiotoxicity including ventricular arrhythmias. QTc interval prolongation is more common with thioridazine than with other antipsychotics. The problem is dose-related but is apparent even at low doses. Combination with drugs known to increase QTc interval are contraindicated. Due to anticholinergic activity caution is advised for combinations with other drugs exhibiting anticholinergic properties such as atropine, amitriptyline, or diphenhydramine. The oral bioavailability is about 60 % and its elimination half-life is 12–16 h. It is metabolized primarily by CYP2D6 with additional contribution of CYP1A2 and CYP2C19. TDM is valuable to prevent intoxications. Combinations with CYP2D6 inhibitors like paroxetine are contraindicated (Table 2). The therapeutic reference range of thioridazine concentrations in plasma is 100–200 ng/mL.

Ziprasidone is an antagonist with moderate affinity at dopamine D_2/D_3, histamine H_1 and D_1/D_5 receptors and a high affinity antagonist at serotonin 5-HT_{2A} and 5-HT_{2C} receptors. Moreover, it inhibits noradrenaline and serotonin reuptake. Since it causes a mild to moderate dose-related prolongation of the QTc interval, ziprasidone should not be given together with medicinal products that are also known to prolong the QTc interval such as arsenic trioxide, cisapride, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, moxifloxacin, or sparfloxacin. The oral bioavailability of ziprasidone is about 60 % and can be enhanced to 100 % when administered with food. Its elimination half-life is 12–16 h. It is metabolized primarily by an aldehyde oxidase and to some extent by CYP3A4. In isolated cases there have been reports of serotonin syndrome temporally associated with the therapeutic use of ziprasidone in combination with other serotonergic compounds such as selective serotonin reuptake inhibitors. TDM is valuable for combinations with CYP3A4 inhibitors (Table 2) or inducers (Table 3). The therapeutic reference range of ziprasidone concentrations in plasma is 50–200 ng/mL.

Zotepine is an antagonist of dopamine D_1 and D_2, serotonin 5-HT_{2A} and 5-HT_{2C}, and histamine H_1 receptors, and it is an inhibitor of noradrenaline reuptake. Zotepine has a dose-related proconvulsive effect and should therefore not be prescribed for patients taking anticonvulsant drugs. The oral bioavailability of zotepine is 7–13 % and the elimination half-life is about 13–16 h. It is metabolized primarily by CYP3A4 with additional contribution of CYP1A2 and CYP2C9. TDM is valuable for combinations with CYP3A4 inhibitors (Table 2) or inducers (Table 3). Therapeutically recommended plasma concentrations of zotepine are 10–150 ng/mL.

Zuclopenthixol antagonizes with high-affinity dopamine D_2, serotonin 5-HT_{2A}, histamine H_1, and α_1-adrenergic receptors and has moderate affinity to dopamine D_1 receptors. It should not be combined with monoamine oxidase inhibitors. Due to prolongation of the QTc interval, combinations with medications which can induce torsades de pointes or drugs that cause electrolyte imbalance should be well controlled. The oral bioavailability of zuclopenthixol is about 45 % and its elimination half-life is 15–25 h. It is metabolized almost exclusively by CYP2D6. TDM is therefore valuable for combinations with CYP2D6 inhibitors (Table 2). Therapeutically recommended plasma concentrations of zuclopenthixol are 4–50 ng/mL.

5 Conclusions and Perspectives

Antipsychotic drugs may undergo multiple drug–drug interactions. Due to heterogeneous pharmacodynamic and pharmacokinetic properties the interaction profiles differ markedly between the available antipsychotic drugs. They all exhibit more or less potent antidopaminergic activity. Combinations of antidopaminergic drugs therefore always increase the risk for motor side effects, whereby the risk is the highest for typical antipsychotics. Pharmacodynamic actions that differ markedly between antipsychotics are anticholinergic effects, highest for clozapine and thioridazine but not relevant under therapeutic doses for aripiprazole, haloperidol, perphenazine, risperidone, or ziprasidone, metabolic disturbances, with the highest risk for clozapine and olanzapine and less relevant for aripiprazole or ziprasidone, and QTc-lengthening properties to be considered for many antipsychotics, especially for pimozide, sertindole, or thioridazine but also for haloperidol. Combination of drugs complicates the medication with antipsychotic drugs. It enhances, as any combination, the risk of adverse events and medication errors and it reduces drug adherence. Some drug interactions, however, can be used constructively to improve treatment effectiveness. Drug combinations that may lead to drug interactions which can be harmful should be known and avoided or at least be supervised appropriately. It is a general recommendation to keep the number of drugs to a minimum. Nevertheless, combination treatment is common and obviously required in clinical practice of antipsychotic pharmacotherapy for many patients. Due to the ever expanding knowledge base it is possible to understand most of the multiple pharmacokinetic and pharmacodynamic drug interactions. Clinicians are obligated to use the available knowledge to provide the highest possible safety for their patients under polypharmacy. TDM should be used more often than actually, since it is a valuable tool to guide the treatment under combinations with drugs that affect the pharmacokinetics of antipsychotic drugs.

The effectiveness and advantage of an antipsychotic drug combination is obvious in clinical practice for any individual patient who did not respond sufficiently under monotherapy but improved markedly after adding another drug. On the other hand, most clinical trials failed so far to give convincing evidence that combination therapies with antipsychotic drugs are superior to monotherapy. Further research should therefore focus on patients' characteristics to identify subgroups for whom a combination is potentially harmful or beneficial.

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Delivery Systems and Dosing for Antipsychotics

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Abstract Schizophrenia is a devastating illness, affecting approximately 1–2 % of the world population. Age of onset is generally between 20 and 30 years of age with a chronic, unremitting course for the duration of the patient's life. Although schizophrenia is among the most severe and debilitating illnesses known to medicine, its treatment has remained virtually unchanged for over 50 years. This chapter covers several major concepts in experimental drug development and delivery: (1) the concept of "typical" vs. "atypical" classifications for antipsychotic drugs as it relates to dosing; (2) the development of depot formulations for improved medication adherence; and (3) several promising areas for future therapeutic advances related to the methods and duration of drug administration. These areas include sublingual, injectable, and implantable drug delivery strategies that have the potential to effect rapid and dramatic improvements in schizophrenia outcomes.

Keywords Atypicality • Adherence • Depot formulation • Chlorpromazine equivalents • Dopamine hypothesis of schizophrenia • Dosing equivalents of antipsychotics • Release mechanisms • Implants for long-term delivery • Sublingual drug delivery • Transdermal delivery systems

1 Background

Schizophrenia is a devastating illness, affecting approximately 1–2 % of the world population. Age of onset is generally between 20 and 30 years of age with a chronic, unremitting course for the duration of the patient's life. Schizophrenia is characterized by positive and negative symptom clusters, as well as lasting cognitive and functional disability. Positive symptoms, so named for the disease's outward manifestations, include hallucinations, delusions, paranoia, and disorganized thinking. Negative symptoms include loss of interest and motivation, as well as loss of normal ability to both feel and express emotion. Lasting functional decline, a hallmark of the illness, leads to enormous personal, familial, and societal costs due to disability and lost productivity.

Although there have been effective medications for the positive symptoms of schizophrenia since the mid-1950s, there has been little success in treating the negative, cognitive, and functional domains. Recent large-scale multicenter studies and meta-analyses demonstrate that newer "second-generation" (formerly called atypical) medications have had little impact on improved efficacy, tolerability, or adherence with treatment (Jones et al. 2006; Keefe 2006; Lieberman et al. 2005). Additionally, non-adherence to existing medications significantly complicates treatment because the majority of patients do not take medication consistently (Ascher-Svanum et al. 2006; Valenstein et al. 2004). Future treatments will focus on both new mechanisms of action and improved delivery systems to target unmet needs in schizophrenia.

1.1 History

This chapter addresses briefly historical and current approaches to the treatment of schizophrenia. Although schizophrenia is among the most severe and debilitating

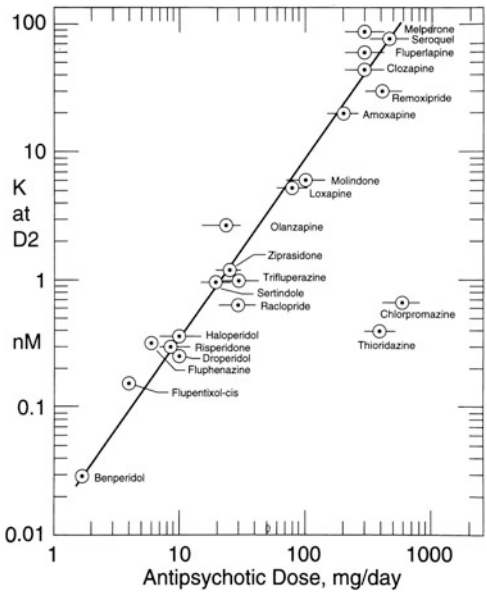

Fig. 1 Average clinical doses (in mg/day) for controlling schizophrenia correlate with the antipsychotic dissociation constants in vitro (from Seeman and Tallerico 1998)

illnesses known to medicine, its treatment has remained virtually unchanged for over 50 years due to a paucity of significant advances to our understanding of pharmacological targets (Siegel and Ralph 2009). This problem is due in part to a lack of adequate animal models and preclinical screening tools to identify biological, mechanistic, or molecular therapeutic targets that address the pathophysiology of negative symptoms and cognitive deficits (Amann et al. 2010). This chapter covers several major concepts in experimental drug development and delivery (1) the concept of "typical" vs. "atypical" classifications for antipsychotic drugs; (2) the development of depot formulations for improved medication adherence; and (3) several promising areas for future therapeutic advances. These concepts include sublingual, injectable, and implantable drug delivery strategies that have the potential to effect rapid and dramatic improvements in schizophrenia outcomes.

The use of medication in schizophrenia treatment dates back to 1952 with the serendipitous observation that chlorpromazine yielded symptomatic improvement when given as a preanesthetic agent (Delay et al. 1952a, b; Shen 1999). This observation was followed by the empiric discovery of other chemical entities with similar therapeutic effects. Approximately 10 years later, a seminal article by Seeman et al. documented that the clinically derived dose of all antipsychotic medications was highly correlated with the activity (IC_{50}) at striatal dopamine receptors (Fig. 1) (Seeman et al. 1975; Seeman and Lee 1975; Seemen and Tallerico 1998). A similarly important discovery resulted from complementary evidence that agents that improved psychosis in schizophrenia resulted in increased dopamine metabolites in brain and cerebrospinal fluid (Carlsson and Lindqvist 1963; Sedvall 1980).

1.2 Dopamine Hypothesis

These observations in total were the basis for the dopamine hypothesis of schizophrenia, which remains as valid today as it was then. The treatment of positive symptoms, the most obvious characteristic of schizophrenia, appears to be related to antagonism of the dopamine D_2-type receptor. When dopamine binds to this receptor subtype, it leads to a cascade of intracellular events that decrease adenylyl cyclase activity, which then decreases cyclic adenosine monophosphate (cAMP) formation and reduces activation of protein kinase A (PKA, cAMP dependent protein kinase). This in turn reduces phosphorylation of many intracellular substrates including ion channels and DNA-binding proteins. The presence of a D_2 receptor antagonist reduces this process and increases intracellular cAMP and its downstream effects. The D_2 mechanism of antipsychotic medication is discussed in more detail in this Handbook by Ginovart and Kapur (2012).

1.3 Clozapine and the Myth of "Atypicality"

The next major advance in the treatment of psychosis resulted from the observation by John Kane and colleagues that clozapine appeared to have superior efficacy as compared with other agents among a population of treatment resistant patients (Gründer et al. 2009; Kane et al. 1988; Vauquelin et al. 2012). Another notable feature of clozapine was that it appeared to achieve improvement without the typical motor side effects seen with most other agents (Agid et al. 2008). This lack of motor side effects (though other notable effects are present) at therapeutic doses led to the term "atypical antipsychotic" for clozapine. Unfortunately, the term "atypical" medication took on broader meanings as it was applied to newer medications over time. Similarly, the terms "first- and second-generation" medications were created to distinguish older and newer medications. Like its predecessor, however, it has no basis in enhanced clinical benefits, reduced side effects or mechanism of action. For example, many theories have been proposed to suggest why clozapine displays efficacy without the same degree of dopamine blockade as other drugs. These theories are based on positron emission tomography (PET) studies suggesting that effective doses of clozapine display lower levels of dopamine D_2 receptor binding (Nordstrom et al. 1995). Such studies suggest clozapine binds approximately 67 % of available D_2 receptors at clinically relevant doses. Alternatively, other antipsychotic agents were estimated to bind approximately 70–80 % of D_2 receptors, albeit at doses that likely exceed the appropriate equivalent clinically indicated amount. Additionally, a close inspection of the data presented in the landmark Seeman and Lee article clearly show that clozapine sits squarely on the same correlation line as all other drugs for dopamine blockade and dose (Seeman et al. 1997). Thus, the observation is more accurately stated that clozapine appears to have a lower degree of motor side effects despite the same

level of dopamine blockade as other medications. Much attention was then placed on decomposing the receptor-binding profile for clozapine to discover which receptor-binding properties might contribute to the relative lack of motor side effects. This finding led to initial hypotheses that the ratio of serotonin type 2 (5-HT) to dopamine type 2 (D_2) receptor binding was a key feature of atypicality (Ereshefsky et al. 1989; Nordstrom et al. 1993, 1995).

However, the aforementioned theory has failed to yield any medications that match clozapine in efficacy. Additionally, chlorpromazine (the first antipsychotic medication) actually meets this and many other definitions of "atypicality" since it has significant 5-HT_2 and D_2 receptor binding at clinical doses (Trichard et al. 1998). A number of other theories have been proposed in an attempt to retain the idea that newer medications are categorically, mechanistically, or clinically distinguished from older ones. For example, one theory poses that "atypical" agents have less prolactin elevation than typical ones (Rauser et al. 2001). However, risperidone, which is considered atypical, has among the highest prolactin elevation among all antipsychotic medications, and chlorpromazine, the original agent, has only moderate increases (Cheer and Wagstaff 2004; Gruen et al. 1978; Kinon et al. 2003; Langer et al. 1977). Similarly, many authors have hypothesized that "atypical" agents might improve cognition (Meltzer and McGurk 1999). However, several studies have not found cognitive benefits for newer agents over older ones and a recent large scale comparison of newer agents vs. the "typical" agent perphenazine showed that the older, typical agent resulted in a slight but significant advantage over newer drugs for cognitive improvement (Keefe 2006; Keefe et al. 2007; Siegel et al. 2006a). Other definitions have similarly failed to distinguish any class-like properties among older (pre-risperidone) and newer (risperidone and newer) agents. Table 1 lists a summary of antipsychotic agents available in the USA. Because there is no clinical or scientific basis to distinguish older from newer medication, this chapter will not use the terms typical, atypical, first generation, or second generation because we believe that these terms are largely misnomers or marketing terms.

2 Dosing

Dose conversion equivalents. The term "chlorpromazine equivalents" was used previously to indicate that doses of all antipsychotic medications could be normalized to a single reference agent based on potency. The scale is defined by how the clinically efficacious dose of each medication compares to the efficacious dose of all others. By convention, chlorpromazine is used as the standard because it was the first agent. For example, the system correctly notes that 100 mg of chlorpromazine is about as efficacious as 2 mg of haloperidol. Thus, haloperidol is 0.02 (2 %) chlorpromazine equivalents (e.g., 500 mg of chlorpromazine will work about as well as 10 mg of haloperidol). All antipsychotic medications can be described in this manner using the maximum or average doses. There is a very high correlation between chlorpromazine equivalents and binding affinity at the

Table 1 List of antipsychotic medications

Medication	Class	Prominent side effects	Daily dose (mg)	Frequency	Dosing equivalents (based on clinically indicated dose)
Aripiprazole	Quinolinone	Insomnia, agitation, anxiety	10–15	Daily	0.02
Asenapine	Dibenzo-oxepino pyrrole	Dysgeusia, hypoesthesia, akathisia	10	Twice daily	0.15
Chlorpromazine	Phenothiazine	Sedation, hypotension, shuffling gait	200–800	Three times daily	1.00
Clozapine	Dibenzodiazepine	Sedation, tachycardia, sialorrhea	300–600	Twice daily	0.75
Fluphenazine	Phenothiazine	Nausea, EPS	2.5–10	Daily	0.01
Fluphenazine decanoate	Phenothiazine with ten carbon ester linkage	Nausea, EPS	12.5–100/month	Monthly	0.00
Haloperidol	Butyrophenone	EPS, akathisia	1–15	Twice daily	0.02
Haloperidol decanoate	Butyrophenone with ten carbon ester linkage	EPS, akathisia	50–100 monthly	Monthly	0.005
Iloperidone	Piperidinyl-benzisoxazole	Dizziness, dry mouth, fatigue	12–24	Twice daily	0.03
Loxapine	Dibenzodiazepine	EPS, sedation	60–100	Twice daily	0.13
Molindone	Dihydroindolene	Sedation, EPS	50–200	Three times daily	0.25
Olanzapine	Thienobenzodiazepine	Weight gain, constipation	10–20	Daily	0.03
Olanzapine—rapidly dissolving	Thienobenzodiazepine	Weight gain, constipation	10–20	Daily	0.03
Perphenazine	Phenothiazine	EPS, sedation	8–64	Twice daily	0.08
Pimozide	Diphenylbutylpiperidine	Akethesia, EPS	2–10	Twice daily	0.01
Quetiapine	Dibenzothiazepine	Sedation	150–750	Twice to three times daily	0.94
Risperidone	Benzisoxazole	EPS, hypotension, hyperprolactinemia	1–4	Daily	0.01
Risperidone microspheres	Risperidone in PLGA microspheres	EPS, hypotension, hyperprolactinemia	25–50 every 2 weeks	Bimonthly	0.00
Thioridazine	Phenothiazine	Sedation, dry mouth, constipation	200–800	Twice to three times daily	1.00
Thiothixene	Thioxanthene	Akathisia, EPS	4–15	Twice daily	0.02
Trifluoperazine	Phenothiazine	Hypotension, EPS	4–10	Twice daily	0.01
Ziprasidone	Benzothiazolylpiperazine	Sedation, headache	80–160	Twice daily	0.20

Extrapyramidal side effects (EPS)

dopamine D_2 receptor because antipsychotic efficacy is essentially a function of D_2 antagonism. However, it is a misconception to think that equivalents are based on, or determined by, binding affinities instead of clinical, empirical data. This system allows clinicians to estimate the dose of a new medication based on the dose a patient took of a previous one. For example, a patient switching from 4 to 6 mg of risperidone would need 15–20 mg of olanzapine or 8–12 mg of haloperidol for equivalent effect.

Although there were some efforts to move away from using the term chlorpromazine equivalents for newer agents, there is no rationale to distinguish older or newer medications on this scale. The movement to create a new system was driven by several factors including the misconception that equivalents reflected something other than the empirical dose used in practice, a misconception that D_2 antagonism was less relevant in newer agents than older ones, and an agenda to support the illusion that new agents acted through a fundamentally different mechanism than older ones. Since there is now overwhelming data that newer and older antipsychotic medications are indistinguishable in efficacy or mechanism, the system of equivalents is just as valid today as it was 30 years ago (Geddes et al. 2000; Keefe 2006). Table 1 shows dosing equivalents for available antipsychotic medications.

Despite exploration into non-D_2 contributions to antipsychotic efficacy, the majority of emerging compounds appear to act through the familiar D_2 binding (Ginovart and Kapur 2012). Similarly, neither old nor newer compounds address current clinical needs for negative and cognitive symptom improvement and continuous medication delivery. Thus, while the field searches for improved drug targets and mechanisms, developments in techniques of medication release can provide a complementary avenue towards targeting incomplete adherence and other unmet needs in schizophrenia.

3 Adherence: Clinical Perspective

Non-adherence with medication remains the primary obstacle to better treatment outcomes in schizophrenia. Although the acceptance of a prescribed pharmacological regimen often dictates treatment outcome, more than 35 % of patients demonstrate adherence problems during the first 4–6 weeks of treatment and within 2 years, up to 74 % of patients are unable to adhere to their original prescribed treatment (Gilmer et al. 2004; Lieberman et al. 2005; Valenstein et al. 2004). The short and long-term consequences of non-adherence to pharmacological treatment include increased relapses, more frequent and longer hospitalizations, cumulative deteriorations in functioning, and a diminished capacity to maintain employment and relationships. The more relapses a patient has, the more difficult it is to achieve remission after the next episode, creating a positive feedback loop that severely hinders long-term functioning and quality of life (Turner and Stewart 2006)

Non-adherence to antipsychotic medication treatment leads to several clinically relevant outcomes, including psychotic relapse, increased clinic and emergency

department visits, rehospitalization, and deterioration in social function (Adams and Howe 1993; Bergen et al. 1998; Casper and Regan 1993; Cramer and Rosenheck 1998; Rittmannsberger et al. 2004; Valenstein et al. 2001; Viguera et al. 1997; Weiden and Olfson 1995). There is overwhelming evidence for an increased risk of recurrent psychotic episodes with interruptions in antipsychotic therapy, even in the early course of the disorder. Non-adherence to pharmacological intervention, then, leads to a fivefold chance of increased relapse. In a study performed by Johnson (1981), patients who suffered a relapse did not return to their prelapse level of social adjustment one year after recovery. This finding emphasizes that the clinical and societal costs of relapse is much greater than just the cost of rehospitalization (Marder 2003). Furthermore, the functional gap present between the adherent and non-adherent groups at baseline widens over time as a result of sustained improvements among adherent patients and decline among non-adherent patients. These differential outcome trajectories bode well for the adherent group, but signal alarm for non-adherent patients (Ascher-Svanum et al. 2006).

3.1 Causes of Poor Adherence

Although there are numerous factors underlying non-adherence in schizophrenia, the primary reasons that determine the degree to which a patient adheres to treatment include comorbid substance abuse, cognitive impairment and forgetfulness, and unclear understanding of one's illness associated with lack of insight (Nasrallah and Lasser 2006). Some studies suggest that up to 60 % of patients with schizophrenia have a comorbid substance abuse (Kane et al. 2003). Substance abuse is a significant factor precipitating psychotic episode relapse and is also positively correlated with poor treatment adherence (Castle and Pantelis 2003). Another considerable factor in the degree of patient adherence arises from inherent cognitive deficits and working memory impairment of patients with schizophrenia. As many as 75 % of schizophrenia patients demonstrate some form of deficiency on neuropsychological test batteries (Kasper 2006). Cognitive domains implicated in schizophrenia include working memory, attention, learning of new information, and cognitive flexibility, all of which may be barriers to adhering to a complicated oral antipsychotic regimen (Palmer and Jeste 2006). Comorbid substance abuse and cognitive impairment may impact a patient's ability to adhere to treatment, but many psychiatrists contend that lack of insight is the most salient factor in patient non-adherence (McEvoy et al. 1989a; Siegel and Ralph 2009). Recent studies suggest that poor insight is causally related to medication non-adherence, stressing the direct linear relationship between the two variables. Poor insight in psychosis is described as lacking awareness of the deficits, consequences of the disorder, and need for treatment (David 1990; McEvoy et al. 1989b). Essentially, the patient's acknowledgement of his illness is significantly associated with the level of medication adherence (McEvoy et al. 1989c). Although insight is the major determinant of adherence, other factors such as negative symptoms, cognitive deficits, and lack of

social supports may also contribute to patients' inability or ambivalence to take their medication as specified by their physician (Ascher-Svanum et al. 2006; Hudson et al. 2004).

3.2 Development of Depots

3.2.1 Clinical Studies

To address the sequelae of medication discontinuation, drug development began to focus not only on new molecules but also on new vehicles of drug delivery. Hence, researchers in the 1960s introduced monthly intramuscular depot antipsychotic drugs, consisting of an ester of antipsychotic agent in a fat-soluble solution (Adams et al. 2001). Because they provide lower steady-state therapeutic drug concentrations and more sustained release characteristics compared with oral medications, depot formulations are associated with a lower propensity to induce side effects (Keith 2006). Thus, depot formulations augment the impact of oral formulations by providing further reductions in morbidity and mortality (Kane et al. 2003). Because they bypass the gastrointestinal tract, depot treatments decrease the amount of medication needed and may minimize certain peripheral side effects including hepatotoxicity (Knox and Stimmel 2004). There are currently five long-acting depot formulations available in the USA. These include monthly formulations such as haloperidol (which is likely still the most effective), perphenazine, paliperidone, and olanzapine, as well as a 2-week formulation of rispridone. Interestingly, the older formulations (haloperidol and perphenazine) remain the most convenient (and therefore most effective) since they are packaged in premade solutions and can be administered in small volumes through smaller needles, enabling deltoid administration. Alternatively, newer agents all require lengthy procedures at the time of administration to reconstitute the drug in a larger volume for gluteal administration.

One such depot formulation, comprising a salt of pamoic acid and olanzapine, is suspended in an aqueous vehicle for intramuscular injection. In a randomized, 8 week, double-blind placebo-controlled international study of 404 adult patients with schizophrenia olanzapine long-acting injection (LAI) was shown to be significantly more effective than placebo based on deceases in total positive and negative syndrome scale (PANSS) scores (Lauriello et al. 2008). Study authors also noted that the early efficacy of injectable olanzapine without supplementation rivaled that of oral olanzapine. This finding suggests long-acting drugs may provide the adequate amount of medication release at the outset of treatment, rather than needing time to "build up" in the systems. One caveat to the study's conclusion is concerns regarding the potential for postinjection syndrome (delirium) following olanzapine LAI, suggesting additional safety considerations (Fleischhacker et al. 2009).

Risperidone depot (Consta) has been available for a significantly longer period of time than olanzapine LAI. Pharmacokinetic studies have found that risperidone depot produces total drug exposure (area under the time–plasma concentration curve) similar to that of oral risperidone, but with lower peak plasma concentration and less peak-to-trough variability in plasma drug concentration (Love 2002). The efficacy and safety of extended-release risperidone were examined in a large randomized double-blind placebo-controlled clinical trial (Kane et al. 2003). A total of 400 patients with schizophrenia were randomized to biweekly injections of either placebo or one of three doses of long-acting risperidone (25, 50, or 75 mg). Placebo-treated patients exhibited a slight worsening from baseline (an increase of 2.6 points) on the PANSS, the primary study endpoint. In contrast, patients in the three risperidone groups improved from baseline by an average of 6.2, 8.5, and 7.4 points for the 25, 50, and 75 mg dose groups, respectively. Treatment with long-acting risperidone was well tolerated by the patients, and local injection-site reactions were rarely rated as painful. Motor symptoms were no more common in the low-dose risperidone group (10 %) than with placebo (13 %). The incidence of motor side effects was greater in the two higher dose risperidone groups.

A recent meta-analysis of ten studies using rigorous selection criteria supports the contention that depot formulations provide improved medication adherence, and therefore improved clinical outcomes. This meta-analysis of 1,700 participants demonstrated that depot antipsychotics are significantly superior for relapse ($p < 0.0009$) relative to oral medication (Leucht et al. 2011). Additionally, the study found that depot medications were superior for dropouts due to lack of efficacy and close to significant superiority for all dropouts ($p = 0.06$). Although the meta-analysis found that rehospitalization was not different for depot compared to oral treatments, data as a whole suggest a significant benefit to long-acting formulations.

3.2.2 Barriers to Creating More Agents

Many depot formulations have limitations that restrict more significant improvements in adherence and efficacy. Decanoate treatment is limited by chemistry, as most compounds are unable to make the required ester linkages. Additionally, depot injections are irreversible and can result in prolonged pain at the injection site, which increases the likelihood that patients will discontinue treatment (Bloch et al. 2001; Kane et al. 1998). More currently, a new depot formulation seems to bypass the chemistry barrier faced by most antipsychotics. Paliperidone (Invega), the major active metabolite of risperidone, contains an available hydroxyl group for esterification. The creation of paliperidone represents a different strategy in drug development. Rather than fitting a delivery system to an existing drug, researchers developed a novel form of an older drug with the appropriate chemistry for long-term delivery. Invega Sustenna, the palmitate of paliperidone, is a

long-acting injectable formulation of paliperidone indicated for once-monthly injection after an initial titration period (Chwieduk and Keating 2010). A recent multicenter, randomized, double-blind, parallel group study of paliperidone palmitate vs. placebo in 518 adult patients with schizophrenia showed significant improvement for the drug vs. placebo in PANSS total score, Clinical Global Impression Severity scores, and PANSS negative and positive symptom factor scores (Nasrallah et al. 2010). However, as with all newer antipsychotics, chronic functional decline was not improved; there was no significant difference between groups on the Personal and Social Performance scale.

3.3 Potential Benefits of Continuous Infusion

Previous studies demonstrate that monthly depot formulations consistently yield superior efficacy as compared to oral administration. Although this superiority is generally attributed to reducing the incidence of discontinuation, we propose that continuous infusion from long-term delivery systems may also have superior biological benefits relative to even moderate adherence to medication without large gaps in treatment. Multiple studies indicate that intermittent adherence to antipsychotic medication leads to reduced efficacy (Keith and Kane 2003). Dosing an antipsychotic medication less frequently than its plasma half-life yields wide fluctuations in drug levels, with reduced efficacy (Borgman 1982; Ereshefsky and Mascarenas 2003). This problem is compounded by interindividual variation in plasma half-life for each drug, complicating the ability to achieve steady-state levels with a unitary dosing regimen (i.e., once a day or twice a day for every person). The average serum half-life for risperidone is approximately 14 h, suggesting that optimal dosing should occur approximately twice a day to maintain steady state (Borison et al. 1994). However, many patients choose to take their medication once a day, resulting in wider peaks and troughs than are ideal. Higher peak values result in excess side effects, and lower troughs lead to periods of unopposed disease process (i.e., increased dopamine availability at the D_2 receptor). Indeed, fluctuations in drug level may lead to a continuously dynamic state, with alternating periods of hyperdopaminergic tone at the receptor during drug level troughs and excessive D_2 blockade during drug level peaks. We propose that such fluctuations at the D_2 receptor impede the ability of the postsynaptic cell to arrive at a stable state of intracellular signal transduction. Variation in antipsychotic drug level from oral administration and resulting fluctuations in D_2 blockade impedes the ability of the postsynaptic cell to establish homeostasis with respect to dopamine tone. Alternatively, steady-state infusion of antipsychotic medication may provide constant modulation of dopaminergic tone, thereby allowing the brain to remodel in a stable therapeutic environment. For a more detailed mechanism of D_2 signaling, see Boyd and Mailman (2012).

3.4 Alternative Hypothesis

Although the authors propose that continuous administration of antipsychotic medication will have biological benefits relative to intermittent oral administration, the counterargument has been advocated by Kapur et al. (Kapur and Seeman 2001; Kapur et al. 2000; Samaha et al. 2008). According to this line of reasoning, chronic antipsychotic treatment leads to long-term upregulation of postsynaptic D_2 receptors, which results in both motor side effects and breakthrough psychosis. Ginovart et al. modeled clinically salient chronic administration of antipsychotics in cats through the continuous infusion of haloperidol at 0.25 mg/kg to produce high and stable (exceeding 78 %) levels of D_2 receptor occupancy. They observed that this dosing paradigm created a robust upregulation of striatal D_2 receptors and induced the development of behavioral tolerance to the effect of haloperidol on spontaneous locomotor activity (Ginovart et al. 2009). The authors postulated that continuously high levels of D_2 receptor occupancy result in D_2 receptor upregulation, which in turn is responsible for the development of drug tolerance, loss of antipsychotic efficacy, and the development of tardive dyskinesia. This argument reflects the widespread misconception that the incidence of tardive dyskinesia differs among older and newer medications. Rather, this claim has been made based on the inability to accurately assess tardive dyskinesia without total discontinuation of medication for weeks to months, and the comparison of older populations on one drug to younger populations on another (Glazer 2000a, b). It should however be noted that tardive dyskinesia is actually a primary manifestation of schizophrenia rather than a medication side effect and may therefore not be related to either continuous or intermittent medication exposure (Fenton 2000; Fenton et al. 1997, 1994). Additionally, Kapur et al. suggest that whereas tolerance develops following continuous administration, reverse tolerance, i.e., sensitization, follows intermittent antipsychotic administration because the drug is allowed to wear off between repeated administrations (Barnes et al. 1990; Csernansky et al. 1990; Ezrin-Waters and Seeman 1977; See and Ellison 1990). Future studies will examine these two opposing perspectives using animal models of antipsychotic efficacy and side effects, as well as molecular measures of drug response and PET imaging.

3.5 Beyond Depots: Sublingual and Transdermal Delivery Systems

Based on the premise that lapses in adherence may decrease medication efficacy, systems in addition to depot formulations have been developed to improve the efficiency of drug delivery and minimize toxic side effects (Johnson 1984; Lambert et al. 2003). Sublingual absorption of antipsychotics represents one such method. Asenapine (Saphris) is an Food and Drug Administration (FDA)-approved

antipsychotic as of 2009 indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and the acute treatment of schizophrenia in adults (Citrome 2009). It has a moderate (35 %) bioavailability when taken as a sublingual tablet compared to <2 % when taken orally. The sublingual tablet dissolves in saliva within seconds and is absorbed into oral mucosa with a time to maximum concentration (T_{max}) of 30–90 min (Gerrits et al. 2010). Steady-state concentrations are reached within 3 days of twice daily dosing. Unique drawbacks of sublingual systems include oral hypoesthesia (numbness) and dysgeusia (bad taste). Despite such side effects, asenapine sublingual tablets are a new option for the treatment of acute episodes of schizophrenia. While efficacious acute treatment is necessary, the chronicity of the illness necessitates continual medication delivery.

3.6 Transdermal Delivery Systems

3.6.1 Potential Benefits

Transdermal drug delivery systems, i.e., patches, deliver long-term medication to individuals with chronic conditions that optimizes dosing and convenience while minimizing side effects. The first transdermal patch for systemic delivery, a 3-day patch that delivers scopolamine to treat motion sickness, was FDA approved for use in 1979 (Prausnitz and Langer 2008). Today there are at least 19 such transdermal delivery systems available in the USA (Tanner and Marks 2008). Transdermal patches are designed to deliver therapeutically effective amounts of drug across a patient's skin to exert a systemic effect. The rationale behind patches echoes the reasoning behind both injectable and implantable delivery systems. Reasons include improved patient adherence; avoidance of first-pass metabolism, which can prematurely metabolize drugs; maintenance of sustained therapeutic plasma concentrations of drugs; and greater flexibility in dosage, such that dosing can be easily terminated by removal of the patch (Chan et al. 2008; Tandon et al. 2006).

3.6.2 Passive Systems

Patches are usually designed such that the drug is stored in a reservoir that is enclosed on one side with an impermeable backing and an adhesive in contact with skin on the other side (Venkatraman and Gale 1998). Some patches utilize drug dissolved in a liquid or gel-based reservoir. This design is composed of four layers: an impermeable membrane, a drug reservoir, a semi-permeable membrane, and an adhesive layer. Other transdermal patches incorporate the drug into a solid polymer matrix, which may simplify manufacturing (Prausnitz and Langer 2008). Patches may be designed to deliver medication for periods of a single day (e.g., methylphenidate), 1 week (e.g., clonidine), or even 4 weeks (e.g., ethinyl estradiol with norelgestromin) (Tanner and Marks 2008).

3.6.3 Limitations

The most significant barrier to the production of transdermal delivery systems is that only a limited number of drugs are amenable to administration via the skin. The criteria for transdermal delivery are a relatively low molecular mass, hydrophobicity, and dosages of a few milligrams per day or less (Prausnitz et al. 2004). Despite these challenges, it is likely that transdermal drug delivery will have an increasingly widespread impact on medicine in the future.

Microparticles

Biodegradable microparticles represent another method of continuous administration with the ability to administer a wider range of drugs than many other systems. The initial promise of microparticles for extended oral delivery was dampened by the fact that there was a size limit of less than 10 μm for the particles to cross the intestinal lumen into the lymphatic system (Lemoine and Preat 1998; Torche et al. 2000). However, there are several other routes through which microparticles are a useful drug delivery system. Subcutaneous or intramuscular administration of microparticles is less constrained in terms of the size limits than those required to be suitable for oral delivery or intravenous delivery of particles (Rafati et al. 1997). In these injectable depot formulations, one can take advantage of the sustained release from microparticles to release small molecular weight drugs, peptides, and proteins (Berkland et al. 2002; Oh et al. 2006). Drugs such as gentamicin and vaccines for mucosal immunity can be delivered intranasally (Lim et al. 2002; Spiers et al. 2000). Microparticles have also proven effective for pulmonary administration, albeit this method of administration is less relevant to antipsychotic medications (Sharma et al. 2001).

Microparticle technology has been applied with the antipsychotic medication risperidone in order to create a biweekly-dosing formulation. This extended-release risperidone formulation uses biodegradable drug-containing microspheres that are manufactured from poly-lactic-co-glycolic acid (PLGA). PLGA is a copolymer used for a wide variety of medical applications, due to its biocompatibility and nontoxicity. The US FDA approved this product for clinical use in late 2003.

3.7 Potential Extension to Implants

3.7.1 Nondegradable

As previously stated, one of the goals for the development of a long-term delivery system is to reduce the side effects associated with the peaks that result from conventional oral dosing (Siegel 2005; Siegel et al. 2002). For the antipsychotic

haloperidol, this is particularly important due to the emergence of motor side effects at higher plasma concentrations. Ideally, a continuous low concentration of haloperidol would decrease these side effects. In order to produce a long-term delivery system for psychoactive compounds, several nonbiodegradable polymer systems were previously developed. Although these systems have not yielded therapeutic products, some are worth mentioning in part due to their similarity to biodegradable delivery systems currently in development. Implants were made in a previous study using the nondegradable ethylene vinyl acetate (EVA) copolymer with 37.5 % haloperidol (wt/wt) (Kohler et al. 1994). After 3 weeks of in vivo studies in rats, similar dopamine supersensitivity was seen in the rats with haloperidol implants as well as the rats receiving daily doses of haloperidol. The major limitation to such nondegradable systems is the need for implant removal at the end of the delivery interval. Thus, biodegradable systems may offer more flexibility due to the ability to provide similar intervals of delivery without the need for eventual removal (Siegel et al. 2002).

3.7.2 Biodegradable Systems

Biodegradable polymers retain their properties for a limited period of time in vivo and then gradually degrade into materials that can become soluble or are metabolized and excreted from the body. Biodegradable polymers have some advantages for the purpose of drug delivery since there is no need for surgical removal of the exhausted polymer matrix. In order to be used for in vivo applications the polymers used for such systems must have favorable properties for biocompatibility, processability, sterilization, and shelf life.

4 Implants for Long-Term Delivery

4.1 Materials

4.1.1 PLGA/PLA

Many biodegradable systems rely on the polymers of PLGA or poly-lactic acid (PLA). These classes of polymers are highly biocompatible and have good mechanical properties for drug delivery applications (Kitchell and Wise 1985). The biomedical use of PLGA has been reported since the 1960s (Kulkarni et al. 1966). Numerous systems already utilize PLGA and PLA to successfully achieve long term delivery, including several microparticle and nanoparticle systems, as well as devices to control thyrotropin-releasing hormone in controlling metabolism (Okada and Toguchi 1995), L-DOPA to treat Parkinson's Disease (Sabel et al. 1990) and naltrexone in treating narcotic addiction (Sharon and Wise 1981). Several

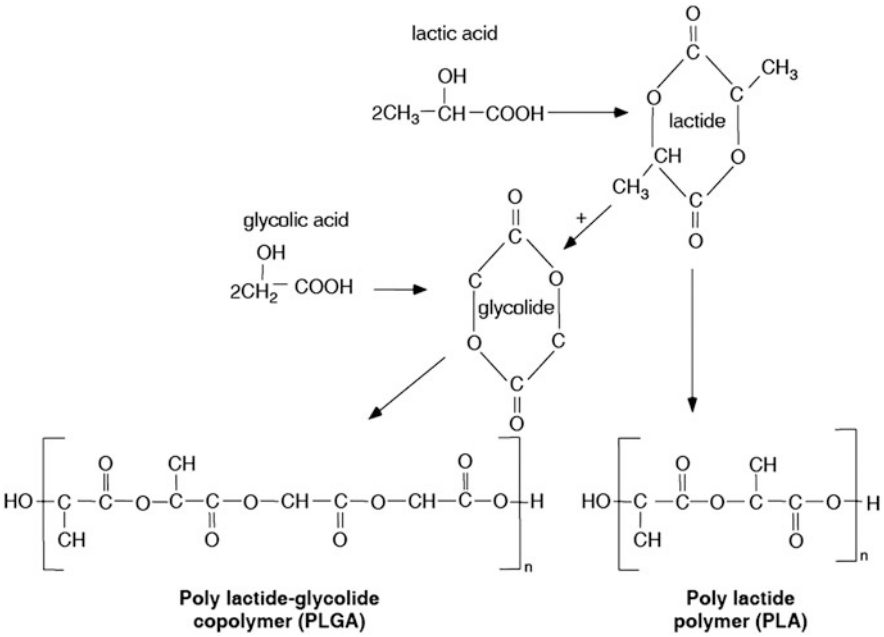

Fig. 2 Schematic representation of PLGA and PLA synthesis: Biodegradable polymers of poly-lactide-*co*-glycolide are formed from units of individual monomers of lactic and glycolic acids. The resulting polymer degrades by simple hydrolysis and the rate of degradation is proportional to the size of the polymer chain

intraocular systems, including Vitrasert® (Bausch and Lomb), offer biocompatible delivery systems with controlled-release drug therapy for periods ranging from several days up to 1 year. In addition, PLA and PLGA have been approved by the FDA for clinical applications, such as sutures, bone plates, and abdominal mesh. Indeed, the major rationale for using PLGA in a variety of existing products such as Risperdol Consta® as well as implants in development is that it is the only biodegradable polymer currently FDA approved for drug delivery. Having this material on the FDA inactive ingredient list dramatically reduces development costs. Because of this fact, some equally safe polymers with superior physical and chemical properties, such as polycaprolactone (PCL), cannot be used without very significant additional financial investment.

PLGA degrades chemically by hydrolytic cleavage of the ester bonds in the polymer backbone (Fig. 2). Its degradation products, lactic acid and glycolic acid, are water soluble, nontoxic products of normal metabolism that are either excreted or further metabolized to carbon dioxide and water in the Krebs cycle (Jain 2000; Okada and Toguchi 1995). Polymer molecular weight, while being an important determinant of mechanical strength, is also a key factor in determining the degradation rate of biodegradable polymers. Low molecular weight polymers degrade faster and lose their structural integrity more quickly than high molecular weight

polymers. As chain scission occurs over time, the small polymer chains that result become more soluble in the aqueous environment of the body. This phenomenon introduces "holes" into the polymer matrix. Consequently, lower molecular weight polymers release drug molecules more quickly (Blanco and Alonso 1998). This knowledge can be exploited to engineer a system to control the release rate. A combination of molecular weights might be used to tailor a system to meet the demands of specific release profiles (Metzger et al. 2007; Rabin et al. 2008).

4.1.2 Poly (ε-caprolactone)

As noted above, polycaprolactone (PCL) is biodegradable, nontoxic polymer that could be used for drug delivery. Advantages of PCL include extremely high durability and strength while remaining flexible. These materials are also very easily processed at low temperatures, facilitating the ability to incorporate a wide variety of drugs without degradation. Delivery interval, as well as physical properties such as flexibility and strength, is dictated by the molecular weight of the PCL chosen. These materials are also very hydrophobic and therefore do not allow a high degree of implant hydration. As such, this material is well suited for release of hydrophilic drugs that are less amenable to delivery by PLGA.

4.2 Drug Release Mechanisms

Biodegradable polymers release drug in one of two ways: erosion and diffusion. Drug release from biodegradable polymers in vivo is governed by a combination of both mechanisms, and therefore depends on the relative rates of erosion and diffusion. The specific drug used and concentration of that drug will affect the mechanism of release as well as polymer degradation (Siegel et al. 2006b). In short, hydrophobic drugs draw water into the polymeric delivery system and accelerate diffusion and degradation. Highly hydrophobic drugs retard hydration of the delivery material (implant or particle) and therefore reduce degradation of the polymer and diffusion of drug through the matrix. Thus, highly hydrophobic drugs such as risperidone and haloperidol are ideal for such delivery systems since higher drug loads cause longer delivery intervals and therefore can produce comparable release rates for longer periods of time as well as smaller systems. A third mechanism of release results from the fact that degradation of PLGA causes a reduction in pH within the polymeric matrix. This reduction can facilitate release of drugs with pH-dependent water solubility. For example, both haloperidol and risperidone are more water soluble at low pH. Thus, degradation of the polymer increases solubility, which increases diffusion of remaining drug. This feature allows for pH-dependent control of release as a third mechanism to control delivery (Rabin et al. 2008).

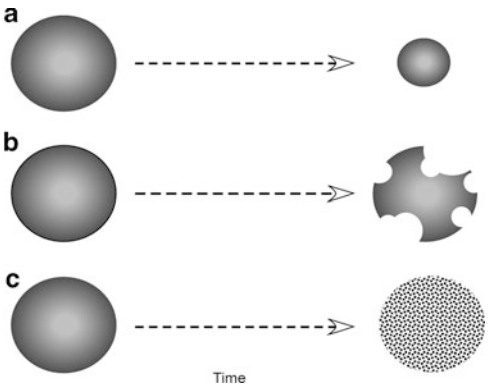

Fig. 3 Types of polymeric delivery system drug release: (**a**) Surface erosion of a homogeneous polymer matrix. Note that the matrix degrades and drug is released only from the surface, while the internal regions remain unchanged. (**b**) Heterogeneous surface erosion. Note that the matrix degrades and the drug is released from the surface, but since the polymer matrix is not homogeneous the surface degradation is not evenly distributed. (**c**) Bulk erosion of a polymer matrix. Note that the matrix is degraded and drug is released from the entire volume of the system. As the polymer matrix is eroded, drug molecules are free to be released via diffusion as well

4.2.1 Erosion

Erosion is defined as the physical dissolution of a polymer as a result of its degradation (Edlund and Albertsson 2003). Most biodegradable polymers used for drug delivery are degraded by hydrolysis. Hydrolysis is a reaction between water molecules and bonds in the polymer backbone, typically ester bonds, that repeatedly cuts the polymer chain until it is returned to smaller polymers and monomers (Fig. 3). There are two possible mechanisms of erosion. When water is confined to the surface of the matrix, as in the case of a hydrophobic polymers like PCL, polymer hydrolysis will occur only on the surface and drug will be released as the surface of the polymer matrix erodes (Fig. 3a), which is called surface erosion. If, however, water penetrates the polymer matrix faster than it hydrolyzes the bonds on the surface then erosion will occur throughout the entire material, which is also called bulk erosion (Fig. 3b, c). In many cases, the erosion of a polymer matrix in vivo is a combination of these mechanisms.

4.2.2 Diffusion

In the case of diffusion-controlled release, the drug's concentration gradient in the polymer matrix is the driving force for the molecules to diffuse into the surrounding medium. The diffusion of a drug molecule through the polymer matrix is dependent upon the solubility of the drug in the polymer matrix and the surrounding environment (subcutaneous space), its concentration throughout the polymer matrix, and

the distance necessary for diffusion. Thus, when a drug is dissolved in the matrix and the mechanism for delivery is diffusion, then the driving force for release is the concentration gradient.

Frequently, diffusion-controlled release is important in the early stages of drug release. For many of the polymeric delivery systems there is some concentration of drug molecules entrapped near and adsorbed onto the surface of the matrix. Upon immersion into a medium, the release of these drug molecules is controlled by the rate of diffusion of the drug into the surrounding environment. This process can cause a problem referred to as the "burst effect," that can potentially release a toxic amount of drug within the first 24 h (Huang and Brazel 2001). In many drug delivery applications, the burst effect must be overcome before the system is suitable for clinical trials.

The specific chemical and biological characteristics of the drug and the polymer are crucial in designing a polymeric delivery system. For example, drugs with greater hydrophilicity can increase the overall release rate by promoting polymer swelling and degradation, which in turn increases drug diffusion. Additionally, certain drug molecules may potentially react with the polymer matrix (Liu et al. 2003). The drug's molecular weight, solubility in biological fluids, and its miscibility in the polymer matrix also influence the drug's diffusivity from the system and the concentration profile of the drug throughout the matrix.

4.3 Advantages

4.3.1 Duration

Successes with depot technology in schizophrenia treatment indicate that the introduction of long-acting medications to prevent relapse could significantly improve the pharmacologic treatment of many psychiatric conditions. Despite the advent of newer antipsychotic medications with the promise of less severe and disabling side effects, there is little evidence that progress has been made in increasing adherence to these compounds (Zygmunt et al. 2002). For example, Conlon et al. (2002) switched patients from older depot antipsychotics to treatment with a newer oral medication. The acute study period was 6 months, with additional follow-up for as long as 2 years. Compared with baseline, the oral medication was associated with small improvements in symptoms and quality of life during the 6-month treatment phase. However, the rate of treatment discontinuation by the patients was very high during long-term follow-up; 40 % of orally-treated patients discontinued treatment over 2 years, whereas none of the patients who continued on depot antipsychotics discontinued treatment. These findings suggest that although some "atypical" antipsychotics may be more tolerable for patients than older antipsychotics, the marginal benefits of lower side effects were outweighed in long-term treatment by clinically significant advantages of a superior depot delivery method.

With an understanding of the benefits and limitations of depots, we introduced the idea of using implantable systems for long-term medication delivery to improve adherence in schizophrenia (Siegel et al. 2002). Such long-term drug delivery systems may complement the development of new molecules not yet available for clinical application or not yet demonstrating an impact on adherence rates. In this way, implants could provide a complementary approach for improved adherence while bypassing the limiting irreversibility of depot formulations.

Implants are reversible and adjustable to the dosing paradigm. The type and molar ratio of individual monomer components (lactide and glycolide) in the copolymer chain partially determines the implant's degradation rate. Polyglycolic acid (PGA) is more hydrophilic than polylactic acid (PLA) (Dorta et al. 2002). Subsequently, higher glycolic acid molar ratio polymers degrade more quickly through hydrolysis by allowing more biological fluids to penetrate and swell the polymer matrix (Mundargi et al. 2008). Essentially, the proportion of glycolide is a critical parameter to control the hydrophilicity of the polymer and thus the degradation and drug release rate. Geometry also affects implant degradation and drug delivery rates. Several geometries for implants are possible, including films, rods, disks, and gels. As in the case of microparticles, the surface area of the implant will affect release rate. Although previous studies indicate that the shape of an implant (i.e., rod vs. film) does not have a significant effect on release rate independent of surface area, it does affect the induction time for drug release (Witt and Kissel 2001; Witt et al. 2000). Various methods are available for implant fabrication, such as solvent casting, compression molding, and extrusion (Coombes and Heckman 1992; Siegel et al. 2002; Wang et al. 2010; Witt and Kissel 2001; Witt et al. 2000).

4.3.2 Reversibility

Implantable systems can be easily removed in case of adverse side effects, offering a degree of reversibility not available with depot injections. Specifically, in the case of an emergency, an overdose, or a change of consent, the remaining drug and matrix can be removed from the body. The reversibility of implants also means that patients maintain the ability to discontinue a specific treatment if they chose to stop or switch medications. However, this ability would be an active decision by the patients, as part of a process involving their physician, rather than a passive or unintentional act of not taking a daily pill.

Because medication adherence is poor across many persistent disorders, the implant approach has now been extended for the treatment of substance abuse using the opiate antagonist naltrexone. Long-term delivery of such agents is less dependent on patient participation to maintain efficacy, and is therefore more likely to ensure that patients continue to receive their medication even when confronted by cues that increase their risk of relapse. Additionally, evidence suggests that a more gradual delivery of naltrexone could improve substance abuse treatment.

A pilot study conducted in the UK found that naltrexone implants reduced the reinforcing properties of opiate drugs and reduced the incidence of early relapse in a supervised opiate detoxification program (Foster et al. 2003).

4.4 Limitations

4.4.1 Physical Drug Characteristics

Stability of the Molecule in a Physiological Environment

Long-term implantable delivery systems require pharmaceutical compounds that are chemically stable under physiological conditions for the entire delivery interval. This stability is important to ensure that the drug molecules that are released at the end of the intended interval remain bioactive and effective despite sequestration in a biological environment. Previous studies demonstrate that both haloperidol and risperidone remain stable in both physiologic and low pH environments, as may occur inside of biodegradable implants for greater than 12 months (Metzger et al. 2007; Rabin et al. 2008). Less is known about the stability of other agents in biodegradable polymeric systems.

Water Solubility

Hydrophobicity of a pharmaceutical agent has a large effect on how well it can be delivered from implantable long-term delivery systems. Ideal agents have very low water solubility as this retards hydration of the implant, which results in prolongation of both implant degradation and drug release.

4.4.2 Tolerability in the Subcutaneous Environment

A lack of local irritation with a resulting high degree of tolerability in the subcutaneous space is a key requirement for any implantable system. Several reports have shown that PLGA implants are well tolerated in the subcutaneous environment (Metzger et al. 2007; Okada and Toguchi 1995; Rabin et al. 2008; Siegel et al. 2002). However, the tolerability of any specific drug implant system will vary substantially based on the biocompatibility of the pharmaceutical compound in the subcutaneous environment. For example, studies in the authors' laboratory indicate that implants made with the atypical agent quetiapine result in local irritation and small cutaneous lesions, similar to but less severe than those caused by subcutaneous injection of the compound alone. Risperidone and haloperidol implants are well tolerated in the subcutaneous space in mice (Metzger et al. 2007; Rabin et al. 2008; Siegel et al. 2002). Similarly, risperidone is well tolerated in humans when injected

Table 2 Estimated implant mass for each antipsychotic medication

Agent	Daily oral dose (mg)	Daily parenteral dose (mg/kg/day)	Monthly parenteral dose (mg/kg/month)	Monthly parenteral dose (mg/month)	Semiannual implant dose (mg)
Asenapine[a]	10	0.02	0.6	30	180
Risperidone	4–8	0.03–0.06	1–2	50–100 (Consta)	300–600
Haloperidol	6–12	0.03–0.06	1–2	50–100 (Decanoate)	300–600
Iloperidone	12–24	0.06–0.12	2–4	100–200	600–1,200
Olanzapine	10–20	0.05–0.10	2–4	100–200	600–1,200
Aripiprazole	10–30	0.05–0.15	2–6	100–300	600–1,800
Ziprasidone	120–160	0.6–1.2	20–40	1,000–2,000	6,000–12,000
Quetiapine	400–600	3–6	100–200	5,000–10,000	30,000–60,000

[a]Estimate for asenapine based on 30 % bioavailability from oral administration

intramuscularly, supporting the hypothesis that risperidone implants would be well tolerated in rats and eventually humans. Additionally, ziprasidone is currently available in an acute injectable formulation, suggesting that it too would likely be well tolerated in the subcutaneous space. Although implants can be easily removed, they do require at least an initial implantation procedure that may be unfavorable to some patients. There is also a greater risk of local infection and immunogenic reaction at the implant site where there is a higher concentration of both released drug and degradation products.

4.4.3 Dose/Potency

The potency and resulting daily dose of each antipsychotic agent is an important characteristic when considering the feasibility of sequestering a 6-month supply in the subcutaneous space through long-term delivery implants. Specifically, lower dose requirements result in smaller and therefore more easily tolerated implants for any duration. For example, haloperidol decanoate is traditionally given at approximately 0.03 mg/kg/day (1 mg/kg/month = 50–100 mg/month). Similarly, the biweekly depot preparation of risperidone (Consta®, Janssen) requires about the same dose (25–50 mg/14 days = 50–100 mg/month). The feasibility for each of the newer antipsychotic agents can be assessed based on the comparable oral doses required to achieve symptom remission. Using these ratios, the required parenteral dose in a 6-month implant for each agent can be estimated based on package inserts (Table 2) from (Rabin et al. 2008). As shown, risperidone results in the lowest amount of drug required in an implantable system with resulting reduction in size of the proposed implants. For example, ziprasidone and quetiapine would require implants that are 20 and 100 times larger than those using risperidone. Alternatively, olanzapine and aripiprazole would require only a two to threefold increase in size relative to risperidone.

4.5 Ethical Considerations

Ethical considerations related to the use of implantable delivery systems in psychiatric populations may arise as the concept gains clinical momentum. Ethical factors include careful attention to protect patient autonomy; safeguards to ensure patients' ability to provide informed consent; and assessment of the patient's comprehension of the intervention and desire to continue or discontinue throughout the course of implantation. By allowing patients to make decisions regarding long-term treatment during periods of relative health, this method of delivery may minimize interruptions in antipsychotic medication. A series of recent studies indicates that the majority of psychiatric patients are able to comprehend the issues related to long-term drug delivery. Approximately 40 % of patients, 75 % of family members, and 85 % of health care providers would utilize this approach (Dankert et al. 2008, 2010; Irani et al. 2004). Furthermore, comprehension was highly correlated with the decision to endorse a long-term delivery system for schizophrenia medication (Dankert et al. 2008).

4.6 Extension to Other Areas

The widespread applicability of PLGA polymer implants is especially pertinent given the significant medication non-adherence among patients of chronic illnesses, such as acquired immunodeficiency syndrome (AIDS), asthma, diabetes, and hypertension. In studies of patients with diabetes and hypertension, the rates of medication adherence were only 25 % and 53 %, respectively (Hudson et al. 2004). Like these medical conditions, schizophrenia requires long-term medication management. Despite rapid advances in the development of antipsychotic drugs, non-adherence remains a pernicious block to long-term improvements in the quality of life of patients with schizophrenia. Furthermore, non-adherence does not appear to be significantly ameliorated by the advent of new agents in clinical trials (Jones et al. 2006). This finding was quantified in the NIH sponsored Clinical Antipsychotic Trials of Intervention Effectiveness, during which 74 % of patients discontinued their initial medication despite being enrolled in a clinical trial (Lieberman et al. 2005). In addition to the clinical consequences of non-adherence, researchers estimate the economic burden of healthcare costs for non-adherence in mental illness is at least $2.3 billion annually in the USA (Menzin et al. 2003). Implantable antipsychotic medication may complement future development of new molecules in the service of improved adherence and long term clinical improvement and cost effectiveness.

5 Barriers to Development of Novel Delivery Systems

There are several unique challenges to the clinical development of long-term delivery systems (Rabin and Siegel 2010). Specifically, there is little or no precedent for an antipsychotic medication product that could last 6 months or more. As such, pharmaceutical companies need to create clinical trial designs that allow the field to traverse additional barriers to bring forward this approach. Additionally, the length of a clinical trial for novel long-term delivery systems would need to exceed the intended interval for the system. For example, an implant that lasts 6 months would likely require a Phase I clinical trial lasting at least 6 month to demonstrate the full pharmacokinetic profile, stability, as well as reversibility over that time course. Because these systems would also need to be replaced at the end of each delivery interval in patients, a clinical trial would likely need to last twice the delivery interval to establish the optimal timing for repeated administration intervals. Inclusion of normal controls in Phase I trials would present another unique issue for very long-term trials of antipsychotic medication. Specifically, it may not be possible to expose nonpatients to antipsychotic medications for 6 months to examine the pharmacokinetic and safety profile of the delivery system. As such, phase I trials may need to be performed with patients that normally take antipsychotic medication. This approach would reduce the risks associated with long-term exposure to antipsychotic medications in nonpsychotic individuals. A similar approach was used in the testing of implants for prostate cancer and may provide precedence for antipsychotic medications (Blom et al. 1989; Fowler et al. 2000). The use of placebo arms in Phase III clinical trials always presents significant risk to patients. However, the FDA has traditionally insisted that a placebo arm is required in order to demonstrate antipsychotic efficacy for new chemical entities. However, new long-term delivery systems using existing medications may present unique challenges and solutions to this dilemma. One possible solution would be to have a traditional Phase III clinical trial design with active agent compared to placebo for a short initial period of 6–8 weeks, comparable to designs for oral medications. This trial could be followed by a longer trial of 6–12 months in which active implants could be compared to oral medication for noninferiority rather than compared to placebo. Regardless of interval, all patients in such trials would likely need to have both an implant and oral medication using a double dummy design in order to retain the blinded conditions. Participants on oral medication would need placebo implants (polymer without drug), and participants on implanted medication would need placebo pills. An alternative design could test novel delivery systems to active comparators only. This approach has been used for implants to treat prostate cancer (Astra Zeneca's Zoladex) (Adis R&D Profile 2005). Similarly, testing of antipsychotic implants for 6–12 months could incorporate both the ethical contraindication to lengthy placebo arms and the exceedingly high replace rates over that interval. Specifically, there is a substantial amount of data indicating that 60–80 % of patients would relapse with severe psychotic exacerbations if not treated for 12 months. Thus, it is possible that significantly reduced relapse rates over that interval could be shown without having to include a placebo group.

6 Summary and Conclusions

"Schizophrenia is a terrible illness. It most commonly strikes people at a young age. It severely limits their potential to work and support themselves, to marry, and to have healthy relationships (McEvoy 2004)." If left untreated or undertreated, schizophrenia marginalizes the individual, who continues to follow a deteriorating trajectory for the duration of their life. Despite recent efforts to create improved medications, antipsychotics have not changed in their basic mechanism, dopamine D_2 receptor antagonism, since the advent of chlorpromazine in 1952. Furthermore, discontinuation or irregular dosing of antipsychotic medication is correlated with worse long term functioning, diminished quality of life, and inability to maintain employment and relationships (Gilmer et al. 2004; Nasrallah 2008).

To ameliorate the problems associated with non-adherence, novel mechanisms of drug delivery have been developed that offer continuous infusion of antipsychotic medication. Depot, polymer-based microspheres, implantable, and transdermal systems are long-term methods of delivery that may have biological and psychological benefits compared to conventional dosing, leading to superior clinical outcomes. These methods can provide consistent, controlled delivery that avoids wide fluctuations in drug levels. Additionally, these novel delivery systems avoid first-pass metabolism and avoid the peaks and troughs of conventional oral delivery, which are potentially detrimental in psychiatric conditions.

Drug development for schizophrenia continues to focus on novel mechanisms of action including positive allosteric modulators at NMDA and metabotropic glutamate receptors, selective nicotine receptor agonists, and modulators of intracellular cAMP. As we wait for these new mechanisms of action to be validated, current and future advancements in long-term delivery provide a complementary approach to reduce morbidity and mortality from the consequences of untreated psychosis.

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Imaging as Tool to Investigate Psychoses and Antipsychotics

Jan Booij and Thérèse van Amelsvoort

Contents

Abstract The results of imaging studies have played an important role in the formulation of hypotheses regarding the etiology of psychosis and schizophrenia, as well as in our understanding of the mechanisms of action of antipsychotics. Since this volume is primarily directed to molecular aspects of psychosis and antipsychotics, only the results of molecular imaging techniques addressing these topics will be discussed here.

One of the most consistent findings of molecular imaging studies in schizophrenia is an increased uptake of DOPA in the striatum, which may be interpreted as an increased synthesis of L-DOPA. Also, several studies reported an increased release of dopamine induced by amphetamine in schizophrenia patients. These findings played an important role in reformulating the dopamine hypothesis of schizophrenia. To study the roles of the neurotransmitters γ-aminobutyric acid (GABA) and

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glutamate in schizophrenia, SPECT as well as MR spectroscopy have been used. The results of preliminary SPECT studies are consistent with the hypothesis of NMDA receptor dysfunction in schizophrenia. Regarding the GABA deficit hypothesis of schizophrenia, imaging results are inconsistent. No changes in serotonin transporters were demonstrated in imaging studies in schizophrenia, but studies of several serotonin receptors showed conflicting results. The lack of selective radiotracers for muscarinic receptors may have hampered examination of this system in schizophrenia as well as its role in the induction of side effects of antipsychotics. Interestingly, preliminary molecular imaging studies on the cannabinoid-1 receptor and on neuroinflammatory processes in schizophrenia have recently been published. Finally, a substantial number of PET/SPECT studies have examined the occupancy of receptors by antipsychotics and an increasing number of studies is now focusing on the effects of these drugs using techniques like spectroscopy and pharmacological MRI.

Keywords SPECT • PET • MRI • Spectroscopy • Neurotransmitters • Receptors • Psychosis • Schizophrenia • Neuroimaging • Antipsychotics

1 Introduction

The findings of imaging studies have played a major role in the development of hypotheses on the pathophysiology of schizophrenia (Howes and Kapur 2009). In the first part of this chapter, we will focus on the findings of neurochemical imaging (including receptor studies with PET and SPECT, phMRI, and spectroscopy) particularly in schizophrenia and groups of patients with an increased risk to develop psychosis. Because most molecular imaging studies focused on alterations of the dopaminergic system, we will start to describe the findings of imaging studies of the dopaminergic system in psychosis. Since this book is primarily directed to molecular aspects of psychosis and antipsychotics, the findings of functional MRI will not be highlighted exhaustively, and findings of structural imaging will not be described. In the second part, the role of neurochemical imaging in the mechanisms of action of antipsychotics will be discussed.

2 Part I. Imaging as a Tool to Investigate Psychosis

2.1 Imaging Studies on the Central Dopaminergic System

The hypothesis that disturbances of the central dopaminergic neurotransmission system are essential to the pathophysiology of schizophrenia has proven to be almost immune to spirits of the times [for a review see Howes and Kapur 2009; and the chapters of Ginovart and Kapur (2012) and Kuepper et al. (2012)].

Recently, Howes and Kapur provided a new version of the dopamine hypothesis of schizophrenia (version III, also called "the final common pathway") based on their comprehensive review of critical developments in research on the pathophysiology of schizophrenia: findings of neurochemical imaging studies, genetics, environmental risk factors, research into the extended phenotype, and studies in animals (Howes and Kapur 2009). Firstly, in this novel hypothesis it is postulated that multiple "hits" (e.g., stress or use of drugs of abuse such as the dopamine releasing amphetamines) may interact to result in dopamine dysregulation (the final common pathway to psychosis in schizophrenia). Moreover, this model does not rely only on the neurotransmitter dopamine alone. It postulates that dopaminergic dysregulation can result from dysfunctions of other neurotransmission systems as well (e.g., the glutamatergic system). Secondly, the locus of dopamine dysregulation moves from being primarily at the *postsynaptic* level to *presynaptic* dopaminergic activity (dopamine synthesis and release; vide infra; Fig. 1). Finally, dopamine dysregulation is linked to "psychosis" rather than schizophrenia, and perhaps even more to proneness to develop full-blown psychosis.

2.1.1 DOPA PET Imaging

Receptor imaging studies in psychosis have focused on different aspects of the central dopaminergic neurotransmission system. Techniques like positron emission tomography (PET) or single-photon emission computed tomography (SPECT) offer the unique possibility to assess in vivo the availability of dopamine receptors and transporters in living human brain (Fig. 1). Moreover, the DOPA PET technique provides a measure of structural and biochemical integrity, and function of presynaptic dopaminergic neurons. L-DOPA, the precursor of dopamine is commonly labeled with [^{18}F], in some clinical studies with [^{11}C]. After the radiotracer has passed the blood–brain barrier, it is taken up in dopaminergic neurons via the amine acid transporter (Fig. 1) and is then decarboxylated to fluorodopamine (by the enzyme aromatic amino acid decarboxylase) and temporarily stored in vesicles within the nerve terminals. Therefore, striatal DOPA uptake reflects predominantly a regulated aspect of presynaptic dopamine synthesis (Pavese et al. 2012). Since the enzyme aromatic amino acid decarboxylase also plays a role in the synthesis of serotonin and noradrenaline, extrastriatal DOPA uptake in the raphe nuclei complex and the locus coeruleus may reflect predominantly in vivo uptake in serotonergic and noradrenergic neurons, respectively (Moore et al. 2003; Pavese et al. 2012).

Eight out of ten DOPA PET studies (Table 1) in patients with schizophrenia reported significantly elevated presynaptic striatal dopamine synthesis capacity (i.e., influx constant; Ki) in schizophrenia (in the whole striatum or in parts of the striatum) (Meyer-Lindenberg et al. 2002; McGowan et al. 2004; Hietala et al. 1995, 1999; Howes et al. 2009; Lindström et al. 1999; Nozaki et al. 2009; Reith et al. 1994), with modest to large effect sizes (Howes et al. 2007). The other two studies, one in chronic and one in first episode drug-naïve patients, reported either a small nonsignificant elevation or a small nonsignificant reduction in striatal

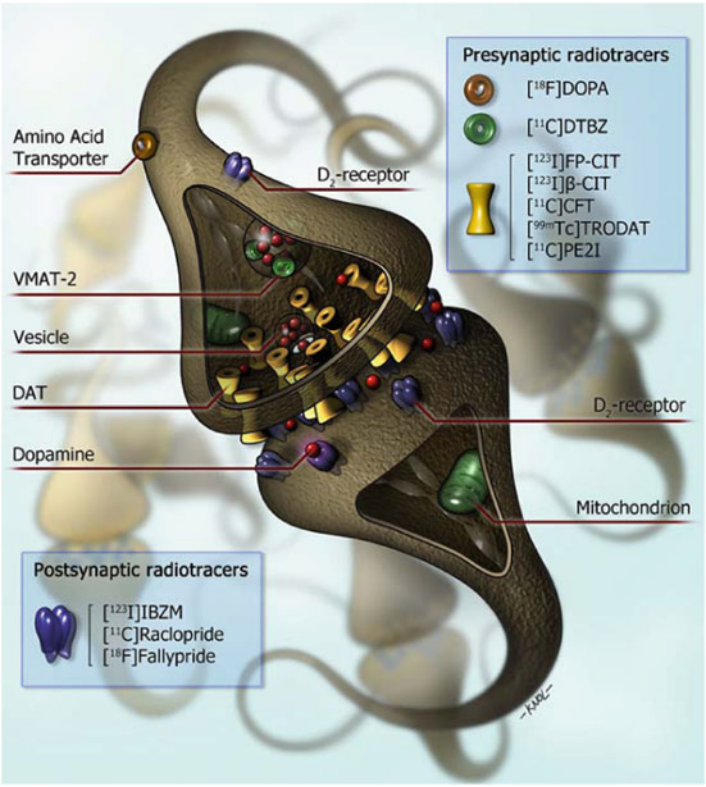

Fig. 1 Simplified diagram of a striatal dopaminergic synapse. On the presynaptic side, markers for imaging of dopaminergic neurons are shown. [^{18}F]DOPA PET provides a measure of the structural and biochemical integrity of the dopaminergic neurons. The radiotracer is taken up in the dopaminergic neuron via an amine acid transporter and is then decarboxylated to fluorodopamine and temporarily stored in vesicles within the nerve terminals. [^{11}C]DTBZ is a commonly used marker for the vesicular monoaminergic transporter (VMAT-2) in humans. Substituted (nor) phenyltropanes ([^{123}I]FP-CIT, [^{123}I]β-CIT, [^{11}C]PE2I, [^{11}C]CFT, and [^{99m}Tc]TRODAT) are frequently used PET and SPECT tracers for imaging of the dopamine transporter (DAT) in humans. Dopamine D_2 receptors are much more expressed on the postsynaptic side than on the presynaptic side of the dopaminergic synapse. Commonly used antagonist radiotracers for $D_{2/3}$ receptors are substituted benzamides ([^{123}I]IBZM, [^{11}C]raclopride, and [^{18}F]fallypride). For convenience, only D_2 receptors are shown on the postsynaptic cell, whereas other dopaminergic receptors (e.g., D_1 receptors) are also located on this side. (Reprinted from Booij and Kemp (2008) Eur J Nucl Med Mol Imaging 35(2): 424–438, with permission from Springer)

dopamine synthesis (Dao-Castellana et al. 1997; Elkashef et al. 2000). As recently reviewed by Howes and Kapur (2009), the studies that investigated acute psychotic patients reported elevated presynaptic striatal DOPA uptake (Hietala et al. 1995, 1999; Howes et al. 2009; Lindström et al. 1999). Thus, increased striatal DOPA uptake is a replicated finding of central dopaminergic abnormality in schizophrenia,

Table 1 Results of DOPA ([^{18}F] or [^{11}C] labeled) PET studies in patients with schizophrenia as compared to controls

Authors (year)	No. patients/ controls	Illness length	Antipsychotic treatment	Change DOPA uptake
Reith et al. (1994)	5/13	Chronic	4 naïve; 1 treated	27 % increase[a]
Hietala et al. (1995)	7/8	First-episode	All naïve	13 % increase[b]
Dao-Castellana et al. (1997)	6/7	Not listed	2 naïve; 4 AP-free	8 % increase (ns)[c]
Hietala et al. (1999)	10/13	First-episode	All naïve	13 % increase[d]
Lindström et al. (1999)	12/10	First-episode	10 naïve; 2 AP-free	13 % increase[e]
Elkashef et al. (2000)	19/13	Chronic	9 naïve; 10 treated	2 % decrease (ns)[f]
Meyer-Lindenberg et al. (2002)	6/6	Chronic	All drug-free	19 % increase
McGowan et al. (2004)	16/12	Chronic	All treated	12 % increase[g]
Howes et al. (2009)	7/12	First-episode/chr	3 naïve; 4 AP-free	11 % increase[h]
Nozaki et al. (2009)	20/18	First-episode/chr	14 naïve; 4 AP-free	2 % increase[i]

All studies have a cross-sectional design. The change in striatal uptake (uptake constant; K_i) is estimated from combined caudate nucleus and putamen values, when not reported for whole striatum, and compared to reported control data

[a]Statistically significant in the right and left caudate nucleus

[b]Statistically significant in the right putamen

[c]Statistically significant higher variability in patients than in controls

[d]Statistically significant in the putamen (bilaterally) and left caudate nucleus

[e]Statistically significant in the caudate nucleus and putamen

[f]Statistically significant reduction in the ventral striatum only in the AP-free subgroup

[g]Statistically significant in the ventral but not the dorsal striatum

[h]Statistically significant in the whole striatum, and the associative striatum

[i]Statistically significant only in the left caudate nucleus

and the evidence indicates that the effect size is moderate to large. In addition, using new methods for the quantification of [^{18}F]DOPA steady-state kinetics, Kumakura et al. (2007) showed that not only the synthesis but also the turnover of [^{18}F]DOPA was elevated almost twofold in the striatum of schizophrenia patients. Importantly, in most of the above-mentioned clinical DOPA PET studies, static striatal [^{18}F] DOPA uptake was assessed relative to tracer uptake in a reference tissue (reflecting nonspecific uptake) using linear graphical analysis, which is convenient for clinical studies in which arterial samples are not available (Kumakura and Cumming 2009). However, the kinetic properties of [^{18}F]DOPA are very complex due to the entry of a metabolite of DOPA into brain as well as due to the eventual washout of metabolites. Consequently, relatively long acquisitions of dynamic PET images and analysis relative to the metabolite-corrected arterial [^{18}F]DOPA input yield a more physiological index of [^{18}F]DOPA utilization, including the turnover of [^{18}F]DOPA (for a review see Kumakura and Cumming 2009). Importantly, in several studies striatal DOPA uptake showed significant correlations with symptom scores

(Meyer-Lindenberg et al. 2002; Hietala et al. 1999). All in all, these robust imaging findings have dramatically influenced the creation of the third version of the dopamine hypothesis, since it clearly demonstrates a dysregulation of the striatal dopaminergic system at the presynaptic level.

Schizophrenia is usually preceded by a prodromal period before the first psychotic episode, with mild, often transient, positive psychotic and negative symptoms, nonspecific symptoms, and/or a decline in psychosocial functioning. Researchers have developed instruments for the assessment of symptoms and signs in order to predict transition to psychosis prospectively (Klosterkötter et al. 2001; Miller et al. 2003; Yung et al. 2003). The transition rates vary from 10 to 40 % after a 2-year follow-up (Cannon et al. 2008; Ruhrmann et al. 2010; Yung et al. 2008). Patients in these studies were described to have an "at-risk mental state" (ARMS) or an "ultra-high risk" (UHR) to develop psychosis. Although an elevated striatal dopaminergic transmission is one of the most robust pathophysiological features of schizophrenia, a causal relationship remains to be established. In this regard, particularly neurochemical imaging studies in ARMS/UHR may be of relevance.

Recent studies showed that the [^{18}F]DOPA uptake in the associative part of the striatum was increased in the ARMS group (Howes et al. 2009; Fusar-Poli et al. 2010, 2011a), although this could not be reproduced in a more recent study of the same group (Allen et al. 2011). Interestingly, the degree of prefrontal activation (measured with functional MRI) during a working memory task was significantly and negatively correlated with the level of DOPA uptake in the associative striatum in the ARMS group (Fusar-Poli et al. 2010). Since the associative part of the striatum has a connection with the dorsolateral part of the prefrontal cortex, this finding supports the postulation that abnormal frontostriatal interactions may underlie cognitive impairments and psychotic symptoms in schizophrenia and may predate the onset of illness (Fusar-Poli et al. 2010). Also, recent PET studies showed that dopamine synthesis capacity was significantly greater in the ARMS group that subsequently developed a psychotic disorder than in the nontransition group (Howes et al. 2011a). The increased [^{18}F]DOPA uptake increases even further after transition to psychosis (Howes et al. 2011b).

Regarding the question whether striatal hyperactivity of dopaminergic neurons (as reflected by increased striatal DOPA uptake) may be a vulnerability marker for schizophrenia, studies on twins and first-degree family members of patients are relevant. A recent small study, however, failed to show increased striatal DOPA uptake in unaffected co-twins of patients with schizophrenia or in the twins with schizophrenia compared to the control twin pairs (Shotbolt et al. 2011). This finding suggests that striatal hyperdopaminergia is not a vulnerability marker for schizophrenia. On the other hand, however, Huttunen et al. (2008) showed that first-degree relatives of patients with schizophrenia had higher striatal [^{18}F]DOPA uptake values than unrelated controls.

2.1.2 Dopamine Transporter and VMAT Imaging

Dopamine transporters (DATs) are expressed exclusively in presynaptic terminals of dopaminergic neurons and are considered markers of dopamine terminal density. It has been proposed that, in psychosis, sustained hyperactivity of dopamine neurons might be associated with an altered expression of DATs, since the DAT is an important regulator of synaptic dopamine concentration. Alternatively, neurotoxic loss of dopamine neurons over the course of schizophrenia may occur (Lieberman et al. 1997). Therefore, several imaging studies (PET as well as SPECT) have evaluated the expression of DATs in schizophrenia (Tables 2 and 3 describe 12 respective studies and the radiotracers for the DAT used in these studies).

Eight out of twelve DAT imaging studies in patients with schizophrenia reported no statistically significant difference in in vivo DAT availability (i.e., DATs that are available to bind the radiotracer, and are thus not occupied by endogenous dopamine and/or drugs) as compared to data obtained in healthy controls. The other four studies, two in chronic and two in first episode drug-naïve patients, reported either a small but significant decrease or a large increase in striatal DAT availability. The only study that showed significantly increased striatal DAT availability was a small study in which the healthy controls were significantly older than the patients (Sjøholm et al. 2004).

The effect sizes of the studies, however, are ranging from low to large (Table 2). Nevertheless, also in studies that reported a significant change in DAT availability and assessed symptomatology as well, DAT availability was unrelated to symptomatology (Mateos et al. 2007; Laakso et al. 2001), and not affected by antipsychotics (Mateos et al. 2007). Regarding the studies that did not demonstrate a significant difference between patients suffering from schizophrenia and healthy controls, only two studies reported a significant correlation of DAT availability and symptomatology (Schmitt et al. 2006, 2008), while the other studies failed to find such correlations (Laruelle et al. 2000; Schmitt et al. 2005; Yang et al. 2004; Hsiao et al. 2003; Lavalaye et al. 2001a). In addition, although an association between duration of illness and DAT availability has been suggested (Laakso et al. 2000), other studies could not reproduce this finding (Laakso et al. 2001; Laruelle et al. 2000; Hsiao et al. 2003). Finally, in several studies no significant effects of antipsychotics on in vivo DAT availability could be demonstrated (Lavalaye et al. 2001a; Mateos et al. 2007; Booij and Kemp 2008), although animal studies did report that neuroleptics may decrease DAT availability in rats (blockage of presynaptic DA D_2-like receptors may enhance dopamine release and DAT expression might decrease as a compensatory mechanism; Nikolaus et al. 2009).

All in all, results of DAT imaging in schizophrenia are not consistent, but most studies did not show a correlation with symptomatology nor with duration of the illness. Therefore, even if a small decrease of DAT in schizophrenia may exist, it should at best be regarded as an illness trait, instead of an illness state (Mateos et al. 2007). In this regard, it is of interest that a PET study that examined the vesicular

Table 2 Results of dopamine transporter ([^{18}F]CFT, [^{123}I]β-CIT, [^{123}I]FP-CIT or [^{99m}Tc]TRODAT) imaging studies (PET/SPECT) in patients with schizophrenia as compared to controls

Authors (year)	No. patients/controls	Illness length	AP treatment	Change DAT uptake	Effect size
Laakso et al. (2000)	9/9	First episode	All AP-naïve	1 % increase caudate (ns)	0.11
Laruelle et al. (2000)	22/24	Chronic	8 AP-free	7 % decrease striatum (ns)	0.39
			16 on AP		
Laakso et al. (2001)	8/8	Chronic	All on AP	11 % decrease caudate	1.10
				12 % decrease putamen	1.11
Lavalaye et al. (2001a)	10/36	First episode/chronic	10 drug-naïve	1 % increase caudate (ns)	0.03
				4 % increase putamen (ns)	0.13
			3 drug-free; 23 AP	2 % decrease caudate (ns)	0.11
				1 % decrease putamen (ns)	0.18
Hsiao et al. (2003)	12/12	First episode	Drug-naïve	1 % decrease caudate (ns)	0.07
				3 % decrease putamen (ns)	0.17
Sjøholm et al. (2004)	5/5	Chronic	All on AP	51 % increase striatum	NA[a]
Yang et al. (2004)	11/12	First episode	All naïve	1 % increase striatum (ns)	0.04
Mateos et al. (2005)	20/10	First episode	All on AP	11 % decrease caudate	1.59
				12 % decrease putamen	1.76
Schmitt et al. (2005)	10/10	First episode	All naïve	2 % decrease striatum (ns)	0.14
Schmitt et al. (2006)	28/12	First episode	All naïve	2 % decrease striatum (ns)	0.08
Mateos et al. (2007)	20/15	First episode	All naïve	14 % decrease caudate	1.46
				15 % decrease putamen	1.85
Schmitt et al. (2008)	20/12	First episode	All naïve	5 % increase striatum (ns)	0.37

All studies have a cross-sectional design. The change in binding ratios is estimated from whole striatum data, or separately from caudate nucleus and putamen values as data are available (average of both sides), and compared to reported control data

ns difference is not statistically significant

[a]No individual data available to estimate the effect size

AP antipsychotic

Table 3 Radiopharmaceuticals used to assess dopamine transporters in humans in vivo

Name	SPECT/PET tracer	Selective for DAT
[^{18}F]CFT	PET	Yes[a]
[^{123}I]β-CIT	SPECT	No[b]
[^{123}I]FP-CIT	SPECT	No[c]
[^{99m}Tc]TRODAT-1	SPECT	No[d]

[a]See: Canfield et al. (1990)
[b]See: Laruelle et al. (1993); Neumeyer et al. (1991); de Win et al. (2005)
[c]See: Scheffel et al. (1997); Abi-Dargham et al. (1996); Booij et al. (2007)
[d]See: Dresel et al. (1999)

monoamine transporter (VMAT-2; Fig. 1) availability in the striatum did not show significant differences between schizophrenia patients and controls, and no correlations with duration of illness nor symptom severity (Taylor et al. 2000). VMAT is expressed in presynaptic dopaminergic neurons, but not exclusively in these neurons; in this particular study [^{11}C]dihydrotetrabenazine was used as a selective radiotracer for the VMAT-2.

2.1.3 PET Imaging of Dopamine D_1 Receptors

The dopamine D_1 receptor is the most prevalent dopamine receptor in the striatum and neocortex, and is located postsynaptically. Radiopharmaceuticals for this receptor have been developed successfully for PET imaging, and research in schizophrenia has focused on expression of this receptor type in the striatum and prefrontal cortex. The PET tracers [^{11}C]NNC 112 and [^{11}C]SCH 23390 have been used to assess dopamine D_1 receptor availability in schizophrenia. Both tracers bind in vivo also to serotonin 2A receptors (5-HT_{2A}), and it is assumed that approximately 25 % of cortical binding is due to binding to 5-HT_{2A} receptors (Ekelund et al. 2007). On the other hand, binding to dopamine D_2-like receptors is much lower (Andersen et al. 1992). However, these tracers may also bind to dopamine D_5 receptors (Chou et al. 2006; Sunahara et al. 1991). Until now, the development of SPECT tracers for the dopamine D_1 receptor has not been successful.

Four imaging studies measured D_1 receptor availability in drug-naïve or drug-free patients suffering from schizophrenia and consistently reported unchanged levels of D_1 receptors in the striatum (Abi-Dargham et al. 2002, 2012; Karlsson et al. 2002; Okubo et al. 1997). One recent small study in chronic, medicated patients showed however decreased striatal binding (Kosaka et al. 2010).

Furthermore, Okubo et al. (1997) demonstrated a decrease in D_1 receptor availability in the prefrontal cortex in schizophrenia, and significant associations with negative symptoms and cognitive symptomatology. This decrease was confirmed by a recent small study in chronic, medicated patients (Kosaka et al. 2010). A third study, however, using the same radiotracer for the D_1 receptor as used by Okubo et al. (i.e., [^{11}C]SCH23390), failed to observe significant differences in this

brain area between patients and controls (Karlsson et al. 2002). A fourth study (Abi-Dargham et al. 2002) used another radiotracer for the D_1 receptor (i.e., [^{11}C]NNC 112) and found significantly elevated D_1 receptor availability in the prefrontal cortex in patients. Furthermore, in vivo receptor availability was associated with poor working memory performance. Finally, a recent study showed elevated D_1 receptor availability in prefrontal cortex in drug-naïve but not in drug-free patients (Abi-Dargham et al. 2012), which suggest that upregulation of D_1 receptors in prefrontal cortex in schizophrenia may be related to the illness itself and may be normalized by chronic antipsychotic treatment.

Several factors may contribute to the discrepancies of these findings, including differences in clinical characteristics of the patients, differences in properties of the different radiotracers, and/or other aspects of PET methodology (for an extensive discussion, see Thompson et al. 2009). In addition, these discrepancies do not support consistently the proposed cortical hypodopaminergic state, as postulated in version II of the dopamine hypothesis. However, as discussed by Thompson et al., the fact that two studies (Okubo et al. 1997; Abi-Dargham et al. 2002) showed that alterations in dopamine D_1 receptor availability were associated with impairments of working memory in patients suggest that these alterations may reflect the same underlying dopaminergic deficit (Thompson et al. 2009). A recent study, however, did not show such an association (Abi-Dargham et al. 2012). All in all, it seems likely that cortical D_1 receptor availability in vivo is altered in schizophrenia patients.

Interestingly, Hirvonen et al. (2006) examined the genetic and nongenetic effects on D_1 receptor availability in schizophrenia by studying monozygotic and dizygotic twin pairs discordant for schizophrenia as well as healthy comparison twins. High D_1 receptor availability in the prefrontal cortex was associated with increasing genetic risk for schizophrenia. This observation further highlights a possible link between genetics, dopamine D_1 receptors, and schizophrenia.

2.1.4 PET and SPECT Imaging of Dopamine $D_{2/3}$ Receptors

The vast majority of striatal dopamine $D_{2/3}$ receptors are located postsynaptically (Fig. 1). Many molecular imaging studies examined striatal $D_{2/3}$ receptor availability in schizophrenia using antagonist radiotracers. Two meta-analyses of this literature reported a modest but statistically significant increase in in vivo striatal $D_{2/3}$ receptor availability in patients with schizophrenia (Laruelle 1998; Kestler et al. 2001).

In most SPECT studies that measured striatal $D_{2/3}$ receptors in schizophrenia, an antagonist radiotracer was used ([^{123}I]IBZM). The affinity of this tracer for both receptors is in the low nanomolar range (Videbaek et al. 2000). In most PET studies on schizophrenia, [^{11}C]raclopride was used as a radiotracer. Like IBZM, it has an affinity for these receptors in the low nanomolar range. Due to the higher sensitivity and resolution of clinical PET systems compared to SPECT, it is well accepted to

study subdivisions of the striatum as well as binding in extrastriatal areas expressing $D_{2/3}$ receptors like the thalamus with this PET tracer.

Recently, agonist radiotracers for the $D_{2/3}$ receptors have been developed successfully for PET imaging (for a review see Finnema et al. 2010a). Agonist radiopharmaceuticals are thought to bind preferentially to receptors in their high-affinity, or functional, state. Therefore, PET imaging with agonist radioligands may provide information on the existence of the high-affinity state in vivo, which may be relevant to study the presumed dopaminergic supersensitivity of schizophrenia (Seeman et al. 2005). However, until now, the existence of a high- and low-affinity state in vivo has not been conclusively confirmed (Finnema et al. 2010a), although in vitro studies extensively demonstrated the existence of the low- and high-affinity state for dopamine D_2 receptors. Indeed, initial PET findings using an agonist radiotracer in schizophrenia do not support the postulation that schizophrenia patients are characterized by a higher proportion of dopamine D_2 or D_3 receptors in the high-affinity state, although the possible role of increased endogenous dopamine in masking such alterations cannot be ruled out (Graff-Guerrero et al. 2009).

The development of radiopharmaceuticals with high affinity (picomolar range) for $D_{2/3}$ receptors (e.g., [^{123}I]epidepride and [^{18}F]fallypride) has offered the unique opportunity to image these receptors in brain regions expressing $D_{2/3}$ receptors in low densities such as the midbrain, thalamus, and cortical regions. The most consistent finding of studies using such radiotracers is a decrease of $D_{2/3}$ receptor availability in the thalamus of patients, although not all studies could reproduce this finding (Buchsbaum et al. 2006; Kessler et al. 2009; Talvik et al. 2003; Yasuno et al. 2004a; Glenthoj et al. 2006; Tuppurainen et al. 2006). Importantly, significant negative associations have been demonstrated between positive symptoms and $D_{2/3}$ receptor availability in the thalamus (Buchsbaum et al. 2006; Yasuno et al. 2004a). $D_{2/3}$ receptor availability has also been assessed in several cortical areas, as well as in the midbrain; however findings have not been consistent (Kessler et al. 2009; Kegeles et al. 2010b; Talvik et al. 2003; Tuppurainen et al. 2003; Suhara et al. 2002).

Regarding $D_{2/3}$ receptor imaging in subjects at genetic risk to develop schizophrenia, Hirvonen et al. (2005) showed that unaffected monozygotic co-twins of patients with schizophrenia had increased $D_{2/3}$ availability in the caudate nucleus compared with unaffected dizygotic co-twins and healthy control twins. In addition, this increase was associated with a poor performance on cognitive tasks related to schizophrenia vulnerability (Hirvonen et al. 2005). Furthermore, other studies focusing on the laterality of striatal $D_{2/3}$ receptors also suggested alterations in asymmetry in patients with schizophrenia (Farde et al. 1990; Acton et al. 1997; Pilowsky et al. 1994). Indeed, Lee et al. (2008) showed that in subjects with high genetic risk for schizophrenia, there was a loss of asymmetry of $D_{2/3}$ receptors in the putamen, whereas Brunelin et al. (2010) observed increased asymmetry in $D_{2/3}$ receptors in siblings of schizophrenia patients in response to acute metabolic stress.

All antagonist radiopharmaceuticals used to study $D_{2/3}$ receptor availability in clinical studies on psychosis or schizophrenia label both D_2 and D_3 receptors in vivo (Videbaek et al. 2000; Rabiner and Laruelle 2010). The agonist tracer [^{11}C]PHNO predominantly labels D_3 receptors in vivo, but also this tracer is not selective (Rabiner and Laruelle 2010). Taking into account the different roles of D_2 and D_3 receptors, there is a need for the development of radiotracers to selectively image D_2 and D_3 receptors.

The enzyme catechol-*O*-methyltransferase (COMT) plays an important role in the degradation of dopamine, particularly in the frontal cortex because of paucity of DAT in the frontal cortex. Indeed, a functional polymorphism of the COMT gene has been linked to functioning of the frontal cortex and consequently this gene has been suggested a susceptibility gene to develop psychosis, although this relationship might not be so straightforward (Williams et al. 2007). The COMT gene is located in a fragment of the chromosome 22q11. Interestingly, velo-cardio-facial syndrome or 22q11 deletion syndrome (22q11DS) is associated with chromosome 22q11 microdeletions and very high rates (30 %) of schizophrenia-like psychosis (Boot et al. 2008). Therefore, susceptibility for psychosis in 22q11DS may be partially explained by haploinsufficiency of COMT. Indeed, 22q11DS subjects had higher urine dopamine levels, lower plasma concentrations of the predominant dopamine metabolite homovanillic acid (HVA) (Boot et al. 2008), and reduced expression of the COMT gene (van Beveren et al. 2012). However, striatal $D_{2/3}$ receptor availability might be unchanged in this syndrome (Boot et al. 2010), which is in line with the argument that COMT is less important for degradation of dopamine in the striatum. However, a recent preliminary study showed that a functional polymorphism in the COMT gene (Val^{158}Met) influences striatal dopamine $D_{2/3}$ receptor binding ratios in 22q11DS (Boot et al. 2011). More specifically, Met hemizygotes, which have lower COMT activity, had significantly lower mean $D_{2/3}$ receptor availability than Val hemizygotes, which have higher COMT activity. These preliminary data suggest that low COMT activity may affect dopamine levels in striatum in humans and this may have implications for understanding the contribution of COMT activity to psychiatric disorders, and particularly psychosis.

All in all, recent studies suggest that dopamine dysregulation is present in subjects at high risk of psychosis and, thus, dopamine dysregulation may indeed be linked to proneness to develop full-blown psychosis.

2.1.5 Molecular Imaging of Dopamine Release and Depletion

Direct evidence for a subcortical hyperdopaminergic state in schizophrenia has emerged from molecular imaging studies. Five studies reported an increase in dopaminergic neurotransmission following acute amphetamine challenge (administration of amphetamine can induce a large release of endogenous dopamine) in patients with schizophrenia (for a schematic presentation of the study paradigm to measure dopamine release, see Fig. 2), thus further demonstrating a dysregulation

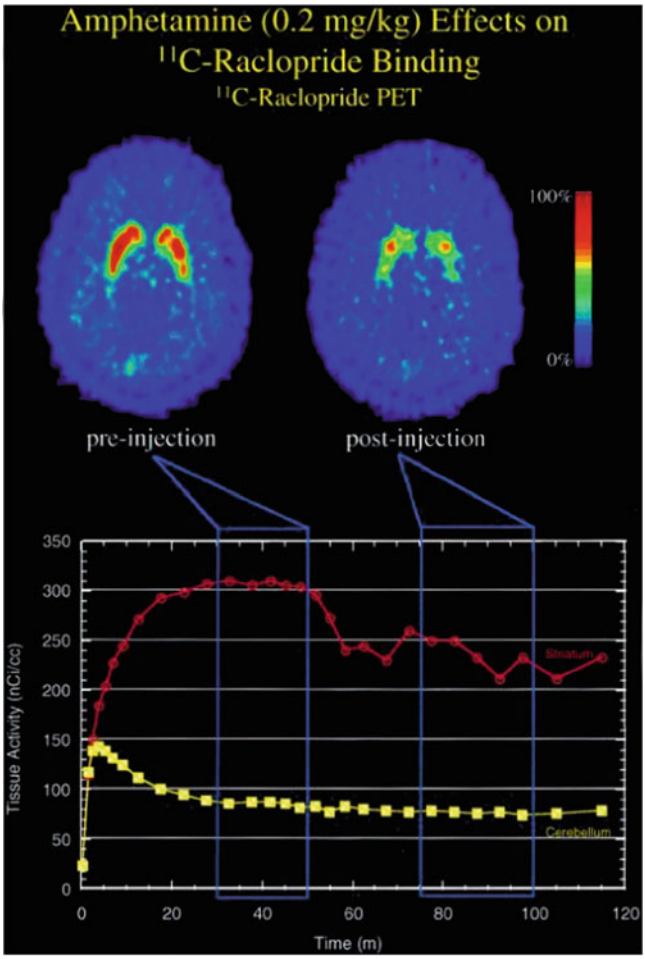

Fig. 2 The effects of amphetamine on [^{11}C]raclopride (antagonist radiotracer for $D_{2/3}$ receptors) binding in a patient with schizophrenia. Amphetamine was injected at 50 min. (*Upper panel*) "Sum" images of five [^{11}C]raclopride PET scans obtained before (*left*) and after (*right*) amphetamine administration. (*Lower panel*) Time–activity *curves* obtained in the striatum (*red*) and cerebellum (*yellow*), representing nonspecific binding with a bolus/constant infusion of [^{11}C] raclopride. Note the decrease of activity in the striatum, which reflects amphetamine-induced dopamine release. (Reprinted with permission from Breier et al. (1997) Proc Natl Acad Sci USA 94(6): 2569–2574; "Copyright (1997) National Academy of Sciences, USA")

of the central dopaminergic system in schizophrenia (Laruelle et al. 1996, 1999; Breier et al. 1997; Abi-Dargham et al. 1998, 2009). In this paradigm, the displacement of radiotracers that bind to postsynaptic dopamine $D_{2/3}$ receptor binding by administration of amphetamine is measured, and the displacement is an indirect measure of the amount of dopamine released by amphetamine.

Laruelle et al. (1999) demonstrated that a hyperdopaminergic state is present in schizophrenia during the initial episode and subsequent relapses, but not in periods of remission. Moreover, dopamine release induced by amphetamine (and measured as displaced striatal binding of an antagonist for dopamine $D_{2/3}$ receptors; Fig. 2) was positively related to increases of positive symptoms, but not with changes in negative symptoms (after removing two outliers; Laruelle et al. 1999). Interestingly, a recent study also showed that stress-induced dopamine release was larger in antipsychotic-naïve schizophrenia patients as compared to controls (Mizrahi et al. 2012). This study is also of interest because the agonist [^{11}C]PHNO was used and previous studies suggest that agonist radiotracers may be more sensitive to endogenous competition by dopamine than antagonist radiotracers (Narendran et al. 2010).

Another paradigm used in molecular imaging is also based on the principle of competition between radiopharmaceuticals and endogenous dopamine for binding to dopamine $D_{2/3}$ receptors at the synaptic level, but this paradigm involves acute depletion of dopamine (instead of stimulating release) to "unmask" dopamine $D_{2/3}$ receptors occupied by endogenous dopamine (for a schematic representation of the study design, see Kegeles et al. 2010a, and for a review see Thompson et al. 2009). The increase in radiotracer binding after acute dopamine depletion may reflect baseline occupancy of striatal $D_{2/3}$ receptors by endogenous, but nonstimulated, dopamine. This paradigm involves depleting dopamine acutely by, e.g., oral administration of the reversible tyrosine hydroxylase inhibitor α-methyl-para-tyrosine (AMPT) (for a review see Bloemen et al. 2008).

Using this paradigm and the SPECT tracer [^{123}I]IBZM for $D_{2/3}$ receptors, Abi-Dargham et al. (2000) demonstrated in a hallmark study a significantly increased $D_{2/3}$ receptor availability after AMPT depletion in schizophrenia patients, indicating increased occupancy of striatal $D_{2/3}$ receptors by dopamine (in the nonstimulated or baseline condition). All the patients participating in the study were experiencing an episode of exacerbation and AMPT exposure led to a significant reduction in severity of positive symptoms (Abi-Dargham et al. 2000).

As compared to SPECT, clinical PET systems have a higher sensitivity to detect photons (efficiency) and a better spatial resolution. This advantage offers the opportunity to assess accurately dopamine $D_{2/3}$ receptor binding in substriatal areas. Using PET and the antagonist [^{11}C]raclopride to label dopamine $D_{2/3}$ receptors, it was reported that patients with schizophrenia had a significantly increased receptor availability after dopamine depletion in the associative striatum, but not in other subregions of the striatum (Kegeles et al. 2010a). This finding is in agreement with the demonstration that amphetamine-induced dopamine release also takes place predominantly in this striatal subregion (Howes et al. 2009; Fusar-Poli et al. 2010, 2011a). As discussed earlier, this region has important connections with the dorsolateral prefrontal cortex, and therefore this finding may further support the hypothesis that abnormal frontostriatal interactions may be crucial in the pathophysiology of cognitive impairments and psychotic symptoms in schizophrenia.

Schizotypal personality disorder (SPD) is genetically related to schizophrenia. Abi-Dargham et al. (2004) showed an increased dopamine release (induced by amphetamine) in SPD patients. Interestingly, the amount of dopamine release was not associated with significant changes in positive or negative symptoms. Moreover, the dopamine release was similar in SPD to that observed in remitted schizophrenia patients, but significantly lower than that observed during illness exacerbation in schizophrenia. Abi-Dargham et al. (2004) concluded that this finding may suggest that dopamine dysregulation in SPD might have a trait component, present in remitted patients with schizophrenia and in SPD, and a state component, associated with psychotic exacerbations. This topic is addressed in the third version of the dopamine hypothesis, since it is postulated that a dysregulated dopaminergic system may reflect the proneness to develop full-blown psychosis. Finally, a first preliminary study failed to show increased dopamine $D_{2/3}$ receptor availability after AMPT in UHR subjects in vivo as compared to healthy controls (Bloemen et al. 2011), although like Abi-Dargham et al. (2000), they found that AMPT exposure led to a significant reduction in symptom severity.

2.1.6 Dopamine, Salience, and Schizophrenia

In general, receptor imaging studies do support the theory that dopaminergic neurotransmission is dysregulated in schizophrenia or related disorders, even in subjects at high risk to develop psychosis. Recently, it has been proposed that dysregulation of the central dopaminergic neurotransmitter system in schizophrenia may lead to aberrant attribution of incentive salience and contribute to the appearance of positive symptoms. The release of dopamine has been conceptualized to be linked to a prediction error that indicates the difference between received and predicted reward (Schultz et al. 1997). In addition, the incentive salience hypothesis states that dopamine mediates the attribution of "incentive salience" to conditioned cues that predict reward (Robinson and Berridge 1993). It was hypothesized that increased firing of dopaminergic neurons of patients with schizophrenia attributes incentive salience to otherwise irrelevant stimuli. Interestingly, a recent review directly addressed this hypothesis (Heinz and Schlagenhauf 2010). After reviewing the literature, the authors suggest that neuronal functions associated with dopaminergic signaling, such as the attribution of salience to reward-predicting stimuli and the computation of prediction errors, are indeed altered in schizophrenia patients and that this impairment appears to contribute to delusion formation. Importantly, apart from receptor imaging studies, functional brain activation with functional magnet resonance imaging (fMRI) studies performed in humans played an important role to come up with these important conclusions (Heinz and Schlagenhauf 2010).

2.2 *Imaging Studies of Nondopaminergic Systems*

2.2.1 Molecular Imaging of the Glutamatergic System

In recent years, scientific research has increasingly implicated dysfunction of glutamatergic neurotransmission in the pathophysiology of schizophrenia (for reviews see Goff and Coyle 2001; Stone 2009). The glutamatergic system represents the major excitatory pathways in the brain. The *N*-methyl-D-aspartate (NMDA) receptor is the most abundant receptor of the glutamatergic system and the involvement of glutamate in schizophrenia seems to be particularly related to NMDA receptor hypofunction. Evidence for the role of NMDA receptor hypofunction in schizophrenia comes from pharmacological studies of phencyclidine (PCP) and ketamine, and imaging studies in chronic ketamine users (Narendran et al. 2005).

Because of a lack of an adequate radiotracer to image NMDA receptors, neurochemical imaging studies, investigating the glutamatergic system involving the NMDA receptor, initially consisted of using ketamine challenge and selective dopamine $D_{2/3}$ tracers. In summary, these imaging studies have demonstrated that ketamine disrupts dopaminergic neurotransmission with acute ketamine challenge leading to increased dopaminergic sensitivity or dopamine release and chronic ketamine leading to reduced prefrontal dopaminergic neurotransmission (Narendran et al. 2005; van Berckel et al. 2006). Subsequently, the development of a SPECT tracer for the NMDA receptor, [^{123}I]CNS-1261, which binds to the ketamine/PCP/MK-801 binding site of activated NMDA receptors in vivo (Knol et al. 2009; Erlandsson et al. 2003) made it possible to investigate the glutamatergic system directly. A group of patients with schizophrenia treated with clozapine showed reduced NMDA receptor availability in all brain regions (Bressan et al. 2005), and a trend for reduced NMDA receptor availability was seen for typical antipsychotic drugs. In antipsychotic-free patients with schizophrenia loss of binding in the left hippocampus was reported that was less marked in the clozapine-treated group. Furthermore, a significant correlation was found between [^{123}I]CNS-1261 binding in the left hippocampus and negative symptoms in patients on typical antipsychotic drugs (Pilowsky et al. 2006). The results of these preliminary studies are consistent with the hypothesis of NMDA receptor dysfunction in schizophrenia.

2.2.2 Molecular Imaging of the GABAergic System

Because GABA has an inhibitory effect on dopamine release, it has been postulated that disinhibition of dopaminergic function in schizophrenia may be induced by a GABAergic deficit. This hypothesis has been supported by postmortem findings (Benes et al. 1992).

Until now, in vivo imaging studies investigated the benzodiazepine binding site of the $GABA_A$ receptor complex. Three SPECT studies using [^{123}I]iomazenil as a radiotracer have investigated benzodiazepine receptor availability in patients with schizophrenia, and two found no differences as compared to controls (Abi-Dargham et al. 1999; Busatto et al. 1997). Verhoeff et al. (1999) reported a significant decrease in benzodiazepine receptor availability in the left precentral gyrus of the frontal cortex in patients with schizophrenia. A PET study, using a radiotracer that has relatively high affinity for α5-containing $GABA_A$ receptors, did not find any significant differences in patients with schizophrenia and controls (Asai et al. 2008).

Although three studies reported significant associations between symptom severity and benzodiazepine receptor availability, in another study an association was not demonstrated (Abi-Dargham et al. 1999; Busatto et al. 1997; Schröder et al. 1997).

In postmortem studies, tracers were used to measure the GABA site of the $GABA_A$/benzodiazepine complex. Therefore, it would be of interest to study the GABA deficit hypothesis in vivo by using radiotracers that label the GABA site on the $GABA_A$/benzodiazepine complex, and/or to study GABA levels by spectroscopy (vide infra; Kegeles et al. 2012).

2.2.3 Molecular Imaging of the Serotonergic System

The Serotonin Transporter

The serotonin transporters (SERTs) are expressed exclusively in terminals of serotonergic neurons, play a role in the regulation of extracellular serotonin (5-HT) concentrations, and are considered markers of serotonin terminal density. Postmortem studies suggested altered expression of SERTs in cortex and subcortical brain areas in schizophrenia (Joyce et al. 1993). Therefore, molecular imaging studies have evaluated in vivo SERT availability in schizophrenia (for a review see Veltman et al. 2010).

Laruelle et al. (2000) found that patients with schizophrenia did not differ in midbrain SERT availability. A limitation of this study is that a nonselective SPECT tracer was used ([^{123}I]β-CIT; de Win et al. 2005), which did not allow for accurate assessment of SERTs outside the SERT-rich diencephalon and midbrain. However, Frankle et al. (2005) used a selective SERT tracer ([^{11}C]DASB) and PET and also found no significant differences in brain areas expressing high concentrations of SERTs in schizophrenia versus controls. As indicated by the authors, this study did not rule out the possibility that schizophrenia might be associated with alterations of SERTs in cortical regions, where specific binding of the radiotracer is too low for reliable quantification of SERTs (Frankle et al. 2005).

The 5-HT_{2A} Receptor

Interest in the role of the 5-HT_{2A} receptor in schizophrenia was stimulated by the introduction of the atypical antipsychotic clozapine. As well as acting on dopamine D_2 receptors, clozapine blocks the 5-HT_{2A} receptor. In fact, all atypical or second-generation antipsychotics show high affinity for 5-HT_{2A} receptors with only one exception: amisulpride (which has high dopamine D_3 and 5-HT_7 affinity). Also, the occupancy by atypical antipsychotics is usually higher for 5-HT_{2A} as compared to $D_{2/3}$ receptors (Zhang and Bymaster 1999).

Dopamine D_2, but not 5-HT_{2A} blockage, seems to be primarily responsible for the clinical antipsychotic effect of clozapine (Abbott 2010). Nevertheless, postmortem studies suggested a decrease of the 5-HT_{2A} receptor in schizophrenia. Four PET studies examined 5-HT_{2A} receptor availability in patients with schizophrenia and found no significant reductions in cortical 5-HT_{2A} density (Erritzoe et al. 2008; Lewis et al. 1999; Okubo et al. 2000; Trichard et al. 1998), suggesting that the cortical 5-HT_{2A} receptor alterations detected in postmortem studies may be caused by medication effects (Thompson et al. 2009). However, a small PET study reported a significant decrease in 5-HT_{2A} receptor availability in the frontal cortex (Ngan et al. 2000). Another study failed to replicate this finding, but reported increased 5-HT_{2A} receptors in patients in the caudate nucleus (Erritzoe et al. 2008). In these studies, antagonist radiotracers for the 5-HT_{2A} receptor were used, like [^{18}F]altanserin, [^{18}F]setoperone, or [^{11}C]*N*-methylspiperone. While the first two radiotracers are relatively selective for the 5-HT_{2A} receptor, the last one is not selective.

The 5-HT_{1A} Receptor

Postmortem studies showed an increase in 5-HT_{1A} receptors in the (pre)frontal cortex in schizophrenia (for a review see Abi-Dargham 2007). For PET imaging, radiotracers have been developed successfully to assess the availability of 5-HT_{1A} receptors in vivo in humans. With such techniques, it may be possible to differentiate autoreceptors in the dorsal raphe nucleus from heteroreceptors in living human brain (Sibon et al. 2008). Three PET studies examined this receptor in schizophrenia. In these studies, the same selective antagonist for the 5-HT_{1A} receptor, [^{11}C]WAY 100635, was used, but the results were conflicting. Tauscher et al. (2002a) reported increased 5-HT_{1A} receptor availability in the temporal, but not frontal, cortex. Yasuno et al. (2004b) reported a decrease of 5-HT_{1A} receptor availability in the amygdala of patients with schizophrenia and this decrease was positively associated with negative symptoms. Finally, Frankle et al. (2006) failed to detect any significant differences in 5-HT_{1A} receptor availability in schizophrenia.

Postmortem studies suggested more pronounced increases of 5-HT_{1A} receptors in schizophrenia in superficial cortical layers. Current PET technology, however, does not allow for the detection of receptors within specific cortical layers (for a review see Thompson et al. 2009). So, current molecular imaging modalities may

not have sufficient sensitivity and spatial resolution to detect alterations in 5-HT_{1A} receptors (Thompson et al. 2009). Finally, to test the serotonin hypothesis of schizophrenia, it may be of value to use in future studies radiotracers that are sensitive enough to detect changes in endogenous serotonin, e.g., radiotracers for the 5-HT_{1B} receptor (Finnema et al. 2010b).

2.2.4 Molecular Imaging of the Cannabinoid-1 Receptor

Multiple lines of evidence show that an altered cannabinoid system may play an important role in psychotic illnesses and particularly in schizophrenia (Giuffrida et al. 2004). Interestingly, using a novel PET tracer for the cannabinoid-1 (CB_1) receptor ([^{11}C]OMRA; a derivative of the CB1 antagonist/inverse agonist rimonabant), Wong et al. (2010) recently reported on an increased CB_1 receptor availability in the pons of patients with schizophrenia. Furthermore, receptor availability in certain brain regions correlated inversely with negative symptoms. Since the precise role of the endocannabinoid system in the pathophysiology of psychosis and schizophrenia is unclear, molecular imaging studies may play a major role in future studies to unravel this role.

2.2.5 Molecular Imaging of Muscarinic Receptors

It is increasingly evident that the pathology of schizophrenia also involves the muscarinic cholinergic system (for a review see Raedler et al. 2007). Interest in the role of muscarinic receptors in schizophrenia was strengthened after the introduction of the antipsychotics olanzapine and clozapine, as these drugs have relatively high affinities for the muscarinic receptors M_1–M_4 (see Lavalaye et al. 2001b; Raedler 2007). Muscarinic receptor availability has been studied with SPECT and a nonselective antagonist radiotracer for muscarinic receptors, [^{123}I]IQNB, which binds specifically and with subnanomolar affinity to all five muscarinic receptors (Raedler et al. 2003). In patients with schizophrenia, in vivo binding of the radiotracer was reduced in all studied regions of interest except the pons. Furthermore, positive symptoms of schizophrenia correlated negatively with muscarinic receptor availability in the striatum and the frontal cortex (Raedler et al. 2003).

2.2.6 Imaging of Neuroinflammation in Schizophrenia

Inflammatory/immunological processes are suggested to play a major role in the pathophysiology of schizophrenia. Activated microglia cells express intensively the peripheral benzodiazepine receptor/18 kDa translocator protein (TSPO). Interestingly, recent studies reported significantly higher binding of the selective TSPO PET tracer [^{11}C]PK11195 (for a review of available radiotracers see Dollé et al. 2009) in the hippocampus of schizophrenia patients in a psychotic phase (Doorduin et al.

2009) and in total gray matter in patients with a recent-onset schizophrenia (van Berckel et al. 2008). In chronic, medicated patients with schizophrenia no such significant difference was found (Takano et al. 2010). However, a positive correlation was demonstrated between cortical TSPO availability and severity of positive symptoms as well as with duration of illness (Takano et al. 2010). All in all, these novel data suggest that neuroinflammation may play an important role in schizophrenia during psychosis.

2.2.7 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a validated method for in vivo quantification of several neuronal metabolites. This noninvasive method can provide quantitative biochemical information about brain tissue. Using this method, regional concentrations of glutamate, GABA, *N*-acetyl aspartate (NAA), choline, myoinositol, and creatine can be assessed. Whereas SPECT/PET studies are able to detect changes in dopamine levels at the synaptic level in the nano- or picomolar range, due to the use of specific radioligands (Breier et al. 1997), MRS measures metabolites in a given voxel. For a brain metabolite to be reliably measured with MRS methods, currently available on clinical MRI systems, its concentration must be in the millimolar range and it must be in a freely mobile form (not anchored to a membrane or organelle). Molecules that are not free to rotate rapidly in solution generally do not generate a resonance detectable with clinical MRI systems. Therefore by using MRS it is not possible to differentiate whether the metabolites are produced in neurons, oligodendrocytes, or astrocytes in living human brain (Maddock and Buonocore 2012).

There have been several MRS studies in schizophrenia. A recent meta-analysis suggested reduced concentrations of NAA, a marker for viable neuronal tissue (Maddock and Buonocore 2012) in frontal lobe, hippocampus/temporal lobe, and thalamus in first episode and chronic schizophrenia (Brugger et al. 2011). In people at high risk of schizophrenia, NAA levels or ratios to creatine, a frequently used normalization in clinical MRS studies, were reduced in thalamus (Brugger et al. 2011; Yoo et al. 2009), in hippocampus (Callicott et al. 1998), and anterior cingulate (Keshavan et al. 1997).

Several studies on quantification of glutamate, glutamine, or the combined measure Glx using MRS in schizophrenia have been published over the last decade. One of the first of these reported elevation of glutamine in medial frontal cortex of 10 never-medicated patients with schizophrenia (Bartha et al. 1997) using a relatively low magnetic field (less than 3 T) MRI scanner. This finding was replicated using a 4 T MRI scanner in 21 never-medicated first episode schizophrenia patients (Théberge et al. 2002). In teenagers at genetic risk for schizophrenia increased Glx/Creatine (Cr) levels were found in medial prefrontal cortex (Tibbo et al. 2004) and decreased glutamate in several brain regions (Lutkenhoff et al. 2010). Different findings were reported in patients with chronic schizophrenia. Decreased glutamine levels were found in anterior cingulate, and increased levels in thalamus (Théberge

et al. 2003). Ohrmann et al. (2005) found reduced Glx in dorsolateral prefrontal cortex in patients with chronic schizophrenia, but no difference in patients with first episode psychosis compared to healthy controls. A recent study by Kegeles et al. (2012) compared unmedicated and medicated patients with schizophrenia to controls. They found an increased level of medial prefrontal cortex Glx in unmedicated patients compared to controls, whereas no differences were found in the medicated group compared to controls. In subjects with an at-risk mental state (ARMS) for psychosis, thalamic glutamate levels were lower in the ARMS group than in the control group. Within the ARMS group, thalamic glutamate levels were negatively associated with activation in the right dorsolateral prefrontal and left orbitofrontal cortex, but positively associated with activation in the right hippocampus and in the temporal cortex bilaterally (Fusar-Poli et al. 2011b). Bloemen et al. (2011) found decreased hippocampal glutamate in the ARMS group compared to healthy controls.

It is difficult to interpret the scarce literature on the effects of antipsychotic treatment on glutamatergic MRS outcome measures. Reduced glutamine in dorsolateral prefrontal cortex (Stanley et al. 1996) and more recently no change in Glx levels or ratios have been reported following antipsychotic treatment (Goff et al. 2002; Szulc et al. 2005). Reduced thalamic glutamine was correlated with parietal and gray matter loss (Théberge et al. 2007). A correlation between temporal Glx levels and negative symptoms has been described, whereas others found that improvement in negative symptoms was found in those patients with significant increases in cingulate Glx/Cr (Goff et al. 2002). Recently, da Silva Alves et al. (2011) found significantly increased concentrations of glutamate in the hippocampal region in patients with 22q11DS and schizophrenia compared to 22q11DS patients without schizophrenia.

The recent development of high magnetic field MRS techniques enables us to quantify GABA levels in specific brain regions. One recent study described decreased GABA in the basal ganglia of patients with schizophrenia, whereas no differences were found in parieto-occipital or frontal lobes (Goto et al. 2009). Another group reported reduced GABA levels in the visual (occipital) cortex in 13 patients with schizophrenia and this reduction was correlated with impaired cortical visual inhibition (Yoon et al. 2010). Tayoshi et al. (2010) did not find any difference in GABA concentration in left basal ganglia and anterior cingulate cortex between 38 patients with chronic schizophrenia and 29 controls. The recent finding by Kegeles et al. (2012) of elevated GABA in medial prefrontal cortex in unmedicated patients was unexpected and suggests possibly greater involvement of interneurons than previously thought. In summary, MRS allows quantification of additional metabolites and neurotransmitters, and as such might be of added value to the PET/SPECT techniques described above. Moreover, recent preliminary results of dynamic MRS studies that allow quantification of metabolite changes following intervention are promising developments.

2.2.8 Pharmacological MR Imaging

Functional MR imaging is playing an important role in the investigation of neurotransmission in schizophrenia. fMRI does not provide information at neurotransmitter receptor or transporter level, but measures hemodynamic changes induced by local alterations in neuronal activity. Therefore, fMRI investigations coupled with pharmacological manipulation can provide information on physiological effects of neurotransmitters beyond its primary site of action. This innovative approach in imaging, also called pharmacological MR imaging (phMRI), has been employed increasingly over the last few years to investigate the effects of neurotransmission on, e.g., cognitive tasks or clinical symptoms in schizophrenia.

PhMRI studies using dopaminergic drugs in schizophrenia have been limited to the use of antipsychotic drugs. Enhancement of prefrontal activity associated with alleviation of negative and cognitive symptoms following treatment with atypical antipsychotics has been described by several authors (for a review see da Silva-Alves et al. 2008). More recently, increased activity in the anterior cingulate cortex during a working memory task was observed following switching from conventional antipsychotics to the partial agonist aripiprazole in schizophrenia patients (Schlagenhauf et al. 2010). Also, using phMRI, Aasen et al. (2005) administered rivastigmine, a cholinesterase inhibitor, as an add-on therapy to antipsychotic treatment in patients with schizophrenia. Rivastigmine increased cerebellar activity (cerebellum contains both nicotinic and muscarinic receptors, and receives cholinergic innervations) and influenced attentional processes. The authors suggest that cholinesterase inhibitors potentially have a role in restoring the abnormal cerebellar functioning observed in schizophrenia. The same group later reported enhanced neuronal activity in the middle occipital gyrus following rivastigmine treatment, a region associated with visual and spatial attention and known to receive cholinergic innervations (Kumari et al. 2006). A partial α7-nicotinic receptor agonist (DMXB-A) influenced hippocampal inhibitory interneurons in patients with schizophrenia (Tregellas et al. 2011) while performing a smooth pursuit eye movement task. Most phMRI studies have been done in healthy volunteers, as investigators are cautious employing pharmacological challenges in patients with schizophrenia.

3 Part II. Receptor Imaging as a Tool to Investigate Antipsychotics

3.1 In Vivo Occupancy of Receptors by Antipsychotics

Molecular imaging can be used as a means to assess the in vivo occupancy of receptors by antipsychotics over time, and to study the relationship between occupancy, plasma concentrations, and clinical efficacy or side effects (Tauscher

et al. 2002b). So, molecular imaging techniques are of potential value to evaluate quantitative aspects of the mechanism of action of antipsychotics.

Since the 1980s, the occupancy of striatal dopamine D_2-like receptors by antipsychotics has been assessed in vivo with molecular imaging techniques (Farde et al. 1986; Wolkin et al. 1989a, b). Also the concept of a "therapeutic window" for antipsychotics emerged (Bollini et al. 1994). It has been suggested that receptor occupancy in the range of 60–70 % is needed for a satisfactory response to a classic antipsychotic (Kapur et al. 1996; Nordström et al. 1993; Nyberg et al. 1995). For the classic antagonist haloperidol, a stepped increase in response was found beyond 65 % occupancy, while extrapyramidal side effects were evident beyond 78 % (Kapur et al. 2000). It was also found that exceeding the threshold dose of haloperidol resulted in more extrapyramidal side effects but not in better clinical efficacy (McEvoy et al. 1991). Finally, receptor imaging studies demonstrated that dopamine striatal D_2-like occupancy by antipsychotics was virtually identical in responders and nonresponders (Wolkin et al. 1989b).

Since the year 2000, several studies reported on the relationship between occupancy of dopamine D_2-like receptors (striatal as well as extrastriatal) and subjective well-being of patients with schizophrenia (de Haan et al. 2000, 2003, 2005; Mizrahi et al. 2007). It appeared that higher D_2 receptor occupancy is associated with negative subjective experience in patients taking risperidone or olanzapine (Mizrahi et al. 2007). Furthermore, the degree of D_2 receptor occupancy between 60 and 70 % by the antagonists haloperidol or olanzapine may be optimal for subjective experience of patients with recent-onset schizophrenia (de Haan et al. 2003).

The antipsychotic aripripazole is a partial agonist with high affinity for dopamine D_2 and D_3 receptors. Interestingly, Yokoi et al. (2002) showed in a study performed in healthy volunteers that even at striatal $D_{2/3}$ receptor occupancy values above 90 %, extrapyramidal side effects were not observed. In addition, Mizrahi et al. (2009) recently demonstrated that patients who were switched to aripiprazole showed improvement in their subjective well-being. This improvement was observed despite a very high degree of $D_{2/3}$ occupancy (82–99 %), which is in contrast to the effects of antagonist antipsychotics on subjective well-being.

A recent PET study assessed the occupancy of striatal as well as extrastriatal $D_{2/3}$ receptors by aripiprazole. Occupancy was high, ranging from 72 % (at 2 mg/day) to 97 % (at 40 mg/day). In addition, occupancy was higher in extrastriatal brain regions, i.e., insula, thalamus, midbrain, temporal cortex, amygdala, hippocampus, entorhinal cortex, than in the striatum. Positive symptom improvement correlated with striatal but not extrastriatal occupancies. As concluded by the authors, these intriguing findings suggest that aripiprazole most directly affects positive symptoms through its modulation of striatal rather than extrastriatal dopaminergic activity, which may be also true for antagonist antipsychotics (Kegeles et al. 2008).

A recent PET study measured the occupancy of $D_{2/3}$ receptors (using [^{11}C] raclopride) by the antipsychotic risperidone, but also the effects on presynaptic dopamine synthesis (L-DOPA uptake). A significant negative correlation was reported between the baseline dopamine synthesis capacity and the changes in

dopamine synthesis capacity induced by the drug, indicating that this antipsychotic can be assumed to stabilize the presynaptic dopamine synthesis (Ito et al. 2009). Indeed, antipsychotics do not only block postsynaptic striatal dopamine $D_{2/3}$ receptors, but also terminal autoreceptors and presynaptic $D_{2/3}$ autoreceptors in the midbrain. These autoreceptors play a major role in the synthesis and release of endogenous dopamine (Mercuri et al. 1997). The finding by Ito et al. is also of interest in that within the third version of the dopamine hypothesis the locus of dopamine dysregulation moves from being primarily at the postsynaptic site to the presynaptic dopaminergic level (Howes and Kapur 2009). Finally, with high-affinity antagonist radiotracers for the dopamine $D_{2/3}$ receptors, e.g., [^{18}F] fallypride, it may be possible to measure dopamine $D_{2/3}$ receptor availability and the occupancy by antipsychotics in the midbrain in the near future (Buckholtz et al. 2010). Such studies may shed more light on the role of antipsychotics in the release of dopamine in living human brain.

Receptor imaging studies did not only investigate the relationship between D_2-like receptor occupancy by antipsychotics and extrapyramidal side effects, but also its relationship with addictive behavior. Based on the earlier mentioned salience theory, it has been suggested that a low availability of these receptors (e.g., by blockage by antipsychotics) may increase the risk for addictive behavior. Indeed, a recent SPECT study showed that the frequency of cigarette smoking in schizophrenia patients treated with antipsychotic medication is significantly and negatively related to the availability of striatal $D_{2/3}$ receptors (de Haan et al. 2006). Also, occupancy of D_2-like receptors by antipsychotics will influence emotions. A recent study investigated the differential effects of relatively tightly (risperidone, haloperidol) versus loosely (olanzapine) binding antipsychotics on the experience of emotions in the realm of daily life by using the experience sampling method (Lataster et al. 2011). Interestingly, for the tight-binding-agent users, but not for olanzapine, increasing levels of estimated D_2 receptor occupancy were associated with decreased feelings of positive affect and increased feelings of negative affect, in the flow of daily life.

All currently used antipsychotics are antagonists (or partial agonists) at dopamine D_2-like receptors, but most of them have effects on a variety of other G protein-coupled receptors, e.g., D_1, 5-HT_2 or muscarinic receptors. Consequently, to increase insights into the mechanism of action of antipsychotics, receptor imaging studies did not only investigate the occupancy of dopamine $D_{2/3}$ receptors by antipsychotics but also evaluated the differences in occupancy of receptors by different antipsychotics. Hallmark PET studies showed a relatively low occupancy of D_2 receptors at therapeutic dosages of the atypical antipsychotic clozapine in comparison to most other antipsychotics (Farde et al. 1992; Nordström et al. 1995). On the other hand, occupancy of D_1 receptors by clozapine was relatively high and 5-HT_2 receptor occupancy was very high. The results of this PET study also revealed that D_2 receptor occupancy was not described by a curvilinear relationship between serum drug concentration and receptor occupancy, which has been demonstrated for other antipsychotics. This finding may explain the lack of extrapyramidal side effects. Additionally, clozapine serum concentrations

did not predict the degree of occupancy in brain and have not been shown to predict clinical effects. Thus, the authors concluded that a careful clinical titration cannot be replaced by monitoring of drug concentrations for optimization of clozapine treatment in individual patients (Nordström et al. 1995). In addition, a more recent PET study in nonhuman primates, using [^{11}C]NNC112, showed that clozapine occupies more cortical dopamine D_1-like receptors than striatal D_1-like receptors, which may reflect a different affinity of clozapine for D_1 and D_5 receptors (Chou et al. 2006), and consequently might explain clozapine's atypical actions.

SPECT studies showed higher in vivo occupancy of muscarinic receptors in striatum and cortical brain areas by the antipsychotic olanzapine than risperidone in patients with schizophrenia. This substantial occupancy of muscarinic receptors may contribute to low incidence and severity of extrapyramidal side effects of olanzapine (Lavalaye et al. 2001b). Also, Raedler (2007) compared moderate-dose clozapine with high-dose olanzapine, and showed significantly lower muscarinic receptor availability for clozapine in cortical brain regions of interest. This finding suggests that treatment with clozapine results in a stronger blockade of the muscarinic receptors than with olanzapine, in line with the high rate of peripheral anticholinergic side effects seen with clozapine in clinical practice (Raedler 2007). However, in these studies nonselective radiotracers for muscarinic receptors were used. As the results of preclinical studies suggest that different subtypes of muscarinic receptors may be involved in various side effects of atypical antipsychotics (and not exclusively anticholinergic side effects; but also side effects such as diabetes mellitus; Nasrallah 2008), there is a need for selective radiotracers that bind in vivo to different muscarinic receptor subtypes to get a better insight into the role of the muscarinic system (both central as well as peripheral) in the mechanisms of action of antipsychotics in the future.

3.2 Developments in the Field of Novel Antipsychotics

The efficacy of an agonist for metabotropic glutamate 2/3 receptors (mGluR2/3), LY2140023, which is an oral prodrug of LY404039, has recently been evaluated in clinical studies in patients with schizophrenia (Patil et al. 2007; Kinon et al. 2011). Since presynaptic mGluR2/3 modulate glutamatergic activity in brain synapses (Fell et al. 2012), and considering the involvement of glutamatergic abnormalities in schizophrenia, it may be of interest to study the effects of such novel drugs using neuroimaging techniques. Although there are at present two validated imaging methods available to assess glutamatergic neurotransmission in living humans: [^{123}I]CNS-1261 SPECT to measure NMDA receptor availability, and proton MRS to measure glutamate and glutamine concentrations (for a review see Stone 2009), promising novel radiotracers for mGluRs are now being evaluated in humans (Burger et al. 2010; Deschwanden et al. 2011; Kimura et al. 2010). Although selective radiotracers for mGluR2/3 are still lacking, selective PET tracers for mGluR1 and GluR5 are on their way (Burger et al. 2010; Kimura et al.

2010; Yamasaki et al. 2012). Also, imaging may be used to assess the effects of glutamatergic drugs on the dopaminergic system (van Berckel et al. 2006), which will increase our understanding of novel antipsychotics.

Small molecules that enhance the NMDA neurotransmission (e.g., the glycine transporter-I inhibitor sarcosin) have recently shown efficacy, particularly against negative symptoms, as adjuvant therapy for schizophrenia in preliminary studies (Lane et al. 2008, 2010). Indeed, several companies are developing glycine transporter-1 inhibitors (for a review see Hashimoto 2010). The development of selective ^{11}C-labeled PET tracers for the type 1 glycine transporter is on its way (Passchier et al. 2010). Also, promising ^{18}F-labeled PET tracers (e.g., [^{18}F]MK-6577) for this type of transporter were recently synthesized and evaluated in nonhuman primates (Sanabria-Bohórquez et al. 2012). An ^{18}F-labeled tracer has a longer half-life than a ^{11}C-labeled tracer (110 versus 20 min, respectively), which offers the opportunity to use this kind of tracers also in hospitals/research centers without an cyclotron.

Finally, phosphodiesterases are enzymes that inactivate intracellular second messengers. Phosphodiesterase is highly expressed in medium spiny neurons in the striatum, and plays a role in motor as well as cognitive processing (Celen et al. 2010). Inhibition of phosphodiesterase 10A has recently shown promise for the treatment of schizophrenia (for a review see Bray et al. 2010). Also, the evaluation of PET tracers for imaging of this enzyme is going on (Celen et al. 2010). More specifically, the PET tracer [^{18}F]JNJ41510417 labels selectively phosphodiesterase 10A (Celen et al. 2010). This development offers the unique opportunity to assess in the future the role of this enzyme in the pathophysiology of schizophrenia as well as the occupancy of this enzyme by novel phosphodiesterase inhibitors as potential antipsychotics.

4 Conclusions

Imaging has shown to be an important means to study the pathophysiology of psychosis, as well as mechanism of action of antipsychotics, on a molecular level. Results from molecular imaging studies of the dopaminergic system, for instance, played a critical role in the creation of the third version of the dopamine hypothesis of schizophrenia (Howes and Kapur 2009). However, to get a better insight into the mechanism of action of antipsychotics and the pathophysiology of psychosis in schizophrenia, it would be helpful to develop selective radiotracers for dopamine, muscarinic, and $mGlu_{2/3}$ receptor subtypes, as well as radiotracers that label the GABA site on the $GABA_A$/benzodiazepine complex. Finally, proton MR spectroscopy and phMRI studies are more and more used in clinical studies on psychosis and the mechanism of action of antipsychotics. Although this is an important development, the interpretations of findings are not always straightforward.

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Biomarkers for Antipsychotic Therapies

Emilio Merlo Pich, Gabriel Vargas, and Enrico Domenici

Contents

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Abstract Molecular biomarkers for antipsychotic treatments have been conceptually linked to the measurements of dopamine functions, mostly D_2 receptor occupancy, either by imaging using selective PET/SPECT radioactive tracers or by assessing plasma prolactin levels. A quest for novel biomarkers was recently proposed by various academic, health service, and industrial institutions driven by the need for better treatments of psychoses. In this review we conceptualize biomarkers within the Translational Medicine paradigm whose goal was to provide support to critical decision-making in drug discovery. At first we focused on biomarkers as outcome measure of clinical studies by searching into the database clinicaltrial.gov. The results were somewhat disappointing, showing that out of 1,659 antipsychotic trials only 18 used a biomarker as an outcome measure. Several of these trials targeted plasma lipids as sentinel marker for metabolic adverse effects associated with the use of atypical antipsychotics, while only few studies were aimed to new disease specific biological markers. As an example of a mechanistic biomarker, we described the work done to progress the novel class of glycine transporter inhibitors as putative treatment for negative symptoms of schizophrenia. We also review how large-scale multiplex biological assays were applied to samples from tissues of psychiatric patients, so to learn from changes of numerous analytes (metabolic products, lipids, proteins, RNA transcripts) about the substrates involved in the disease. We concluded that a stringent implementation of these techniques could contribute to the endophenotypic characterization of patients, helping in the identification of key biomarkers to drive personalized medicine and new treatment development.

Keywords Biomarkers • Fluids • Schizophrenia • Psychoses • Endophenotypes • Drug discovery • Neuroleptics • Metabolomics • Proteomics • Transcriptomics • Glycine transporter • Dopamine • Translational medicine • Personalized medicine

1 Introduction

This article is focused on molecular biomarkers and their role in the assessment of novel antipsychotic therapies based on drug treatments. Psychosis can be loosely defined as a condition in which loss of contact with reality, impaired insight, thought disorder, change of personality, hallucinations, and delusions occur in various modalities and intensities. The most common psychotic disorder is schizophrenia, but psychotic episodes are also observed in other psychiatric disorders or as "organic psychoses", e.g., in dementia, poisoning, encephalitis, and end-stage of several systemic disorders (diabetes, brain tumors, etc.). The wide range of causative conditions suggest that there is more than one form of "psychosis" with different underlying pathogenetic mechanisms and hence the complexity of identifying molecular biomarkers.

Since the advent of chlorpromazine, a prevalent dopamine D_2 antagonist originally developed as a major tranquilizer for postsurgical patients in the early 1950s (Barondes 1999), a series of "atypical" antipsychotic medications with improved

tolerability have been developed, mostly blocking D_2 receptors and 5-HT_2 receptors of the Central Nervous System (CNS). These treatments are generally effective on positive symptoms (hallucination and delusion), but not on negative symptoms and cognitive impairment, which are critical components of the schizophrenic psychosis (Seeman 2002). In addition, while atypical antipsychotics have been rationally designed to reduce the motor extrapyramidal symptoms that characterized the first generation antipsychotics, a series of subtle metabolic adverse effects were observed, leading to obesity and diabetes (Newcomer 2005). In spite of dynamic research activities, to date, no molecular biomarkers for selecting treatments or for monitoring the therapeutic effects of antipsychotic medications are recognized neither by regulatory agencies nor by the scientific clinical community. An exception is molecular imaging targeting receptor occupancy using positron emission tomography (PET) or single-photon emission computed tomography (SPECT), useful for assessing the engagement of the antipsychotic with their molecular targets in the brain (Nyberg et al. 1999; Kapur et al. 2000; Catafau et al. 2008), but these approaches are beyond the scope of this review and they are the focus of another chapter in the present volume. Therefore, the current use of molecular biomarkers in blood, serum, or cerebrospinal fluid (CSF) for antipsychotic therapies is mostly for monitoring side effects (i.e., increase of plasma glucose or prolactin) and less for making therapeutic decisions or for the development of novel antipsychotic treatments.

The challenge to enhance the efficacy of antipsychotic therapies and at the same time to reduce further the burden of adverse effects has been engaging the medical community and the pharmaceutical industry since the 1990s, initially with disappointing results. This disappointment was partially related to the reduced efficiency of the pharmaceutical industry to deliver effective treatments to patients, mostly due to an inefficient drug discovery process that, according to FDA, "...does not keep pace with the tremendous advances in the basic sciences" (US Food and Drug Administration 2004). Several pharmaceutical industries, academic centers, the NIH, and the EC Framework funding agencies took seriously the challenge and engaged in R&D reorganization and precompetitive initiatives [e.g., for MATRICS/TURNS see Harvey (2006)] by implementing cutting-edge biomarker technologies. This engagement is only now beginning to deliver. For example, converging preclinical and clinical biological findings pointed to the critical role of glutamate neurotransmission in psychotic negative symptoms, and biomarkers were developed and used to progress novel antipsychotics aimed to glutamate-related targets. However, these are exceptions. We are still at the very beginning of proper biomarker implementation of novel antipsychotic discovery.

In this review we will briefly define the concept of biomarker and cover some historical attempts to find biomarkers for schizophrenia and its treatments. A survey of the present state of implementation of biomarkers in drug discovery for antipsychotic therapies in schizophrenia will be given by reviewing the official database "clinicaltrial.gov", where most of the trials that investigate novel compounds are recorded. Some examples of biomarker implementation, in particular those integrating biomarkers in the context of the Translational Medicine, will be provided. Finally, the potential for multi-marker large-scale biology approaches

(microarray, proteomics, multiplex assays, etc.) to generate disease-related biomarkers in the near future, in particular for applications to "personalized medicine", will be briefly discussed.

2 Biomarkers: Historical Perspective

The quest for peripheral biomarkers reflecting the severity of psychiatric disorders was probably started more than two centuries ago, with the serological investigations by William Lauder Lindsay and his attempts to correlate structural elements in the blood to the level of "insanity" of psychiatric patients (Lauder Lindsay 1855). This pioneering work led back in the nineteenth century to the development of the "corpuscular richness paradigm," a theory claiming a "close connection" between "improvement in the quality of the blood and mental recovery" based on the difference in the relative proportion of red and white cells in different stages of madness (MacPhail 1892). Other serological paradigms, the metabolic paradigm and the immuno-serodiagnostic paradigm, have been subsequently developed during the following decades thanks to advances in endocrinology and immunology, as elegantly discussed by Richard Noll in a recent review (Noll 2006). Since then a number of studies in schizophrenia patients have shown evidence of changes in peripheral serological markers, setting the ground for the possible identification of disease biomarkers. Most of the investigations were stimulated by emerging hypotheses around the pathophysiology of schizophrenia, e.g., focusing on the immune system, the phospholipid metabolism, and, more recently, the neurotrophin pathway [for a review of disease hypothesis-based biomarkers see Domenici and Muglia (2007) and Mikkelsen et al. (2010)]. Another productive line of research with relevance to drug discovery stemmed from the identification of central monoaminergic neural systems as main substrates of the activity of antipsychotic drugs. Supported by the evidence of commonalities between central neurochemical mechanisms and peripheral neuroendocrine systems (Gladkevich et al. 2004) the neurotransmitter metabolism and monoamine receptor expression have been investigated as potential markers for schizophrenia and antipsychotic treatment, not only in central but also in peripheral tissues. Much attention was focused on the leading hypothesis of dopaminergic pathway dysfunction, whose metabolite levels, radioligand receptor binding, and expression studies have produced variable results. Dopamine receptors have been deeply investigated in schizophrenia, and whilst studies in the CNS had some degree of success [as an example, PET and SPECT receptor occupancy has proven to be effective in informing on dose selection in clinical studies (Nord and Farde 2011; Catafau et al. 2011)], the results from peripheral lymphocyte investigations were inconsistent. For example, in 2001, two independent studies reported an increased D_3 expression, in lymphocytes from schizophrenia patients (Ilani et al. 2001; Kwak et al. 2001). In one of the studies, drug medicated patients were found to display lower expression with respect to drug-free or drug-naïve patients. A subsequent study reported a reduction of D_3

expression in schizophrenia patients (and bipolar patients) that was normalized upon therapy (Vogel et al. 2004). Interestingly, in bipolar patients, D_3 receptor mRNA expression levels were found to correlate with personality traits, smoking habit, and addiction (Czermak et al. 2004a, b; Godarzi et al. 2009), supporting a lack of specificity as biomarker. More recently dopamine receptors in peripheral blood mononuclear cells from schizophrenia patients on therapy with haloperidol and olanzapine were investigated, showing some degree of correlation between changes in D_2 and D_4 gene expression and improvement in the Clinical Global Impressions score (Shariati et al. 2009). Finally, peripheral expression of dopamine receptors was investigated as a potential predictor of central response to dopamine receptor agonists, showing a correlation between peripheral D_3 receptor mRNA levels and cognitive improvement following treatment (Ersche et al. 2011).

Dopamine-related plasma metabolites have been more successfully used as mechanistic biomarkers, exploiting the increase in dopamine turnover and metabolism produced by the dopamine receptors blockade by antipsychotics. For example, plasma and cerebrospinal fluid (CSF) concentrations of the dopamine metabolite homovanillic acid (HVA) were found correlated with the clinical outcome for positive symptoms, while inconsistent results have been produced when attempting to correlate with negative symptoms (Beuger et al. 1996; Davila et al. 2007). However, the most reliable circulating biomarker for those antipsychotics that bind to dopamine receptor targets is the pituitary hormone prolactin, useful in predicting both beneficial and adverse clinical effects given its dynamic range (Kapur et al. 2000; DeVissier et al. 2001). Prolactin is released from the pituitary gland and is normally inhibited by endogenous dopamine via D_2 receptors. Interestingly, increasing plasma levels of prolactin produced by escalating doses of antipsychotics correlate with increasing levels of striatal D_2 receptor occupancy using imaging technologies (Kapur et al. 2000; Tomasson-Perret et al. 2008) as well as with extrapyramidal symptoms (EPS) at high doses [for a recent review see Nord and Farde (2011)].

3 Biomarkers for Antipsychotic Therapies: Current Clinical Applications

The role of biomarkers in the discovery process for novel antipsychotics can be schematically divided into diagnostic, prognostic, and surrogate markers. However, for the purpose of this review we prefer an operational definition based on the use that a biomarker can have by answering questions that are critical for drug discovery. In Fig.1 we summarize where and how biomarkers can be used within the framework of the drug discovery process. Here are the proposed definitions:

1. Endophenotypic Biomarker (at baseline) to identify subclasses of the disease. According to their levels, biomarkers can be used to identify if a given patient is part of a subgroup of the disease whose specific endophenotypes (Allen et al. 2009) indicate a particular pathogenetic mechanism that responds differently to

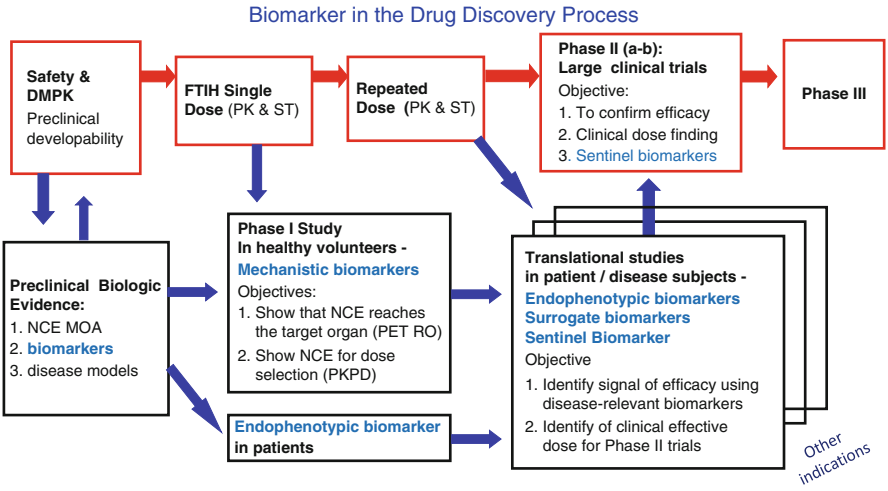

Fig. 1 Schematic diagram of the proposed role of biomarkers in the context of the drug discovery process. Red boxes indicate the trials required by the conventional regulatory path leading to the late stage development of Phase III. Black boxes indicate the science-driven studies necessary to build a proper Translational Medicine approach based on biomarkers that will reduce the risk of failure in Phase III. Activities related to biomarkers are marked in blue. FTIH: first trial in human; DMPK: drug metabolism and pharmacokinetics; NCE: novel chemical entity; MOA: mechanism of action; PET RO: receptor occupancy calculated using the neuroimaging technique of positron emission tomography; PK: pharmacokinetics; PKPD: pharmacokinetics-pharmacodynamic models; ST: safety and tolerability

a given treatment. In clinical trials these biomarkers are useful to aid diagnosis and to allow stratification. For example, stratification of schizophrenia subjects was made using their response to the niacin test (Tavares et al. 2003), or more recently, amyloid peptides (Frisoni et al. 2011). All these studies are small in size and need replication before being properly applied for diagnosis or drug discovery.

2. Mechanistic Biomarker (during treatment) as indicator of molecular target engagement. It is not necessary that the biomarker level is modified by the disease state; what counts is the capacity to measure the pharmacodynamic effects produced by certain concentrations of the antipsychotic in a given tissue. In some cases these data can be obtained also in healthy volunteers. This analysis requires the integration of most information regarding the antipsychotic agent cumulated during its discovery (Bieck and Potter 2005). In clinical trials these biomarkers provide information about target occupancy and related functional effects, indicating that the antipsychotic compound is actually reaching its molecular target. This is the case of D_2 or 5-HT_2 receptor occupancy in striatum or cortex as measured using PET or SPECT, currently considered the most reliable biomarker of target engagements for current antipsychotics (Catafau et al. 2008, 2011; Nord and Farde 2011; Uchida et al. 2011). Other markers of drug actions are plasma prolactin levels, electrophysiological signatures,

impairments in cognitive tests, and, at higher doses, extrapyramidal signs and sedation (de Visser et al. 2001). CSF, plasma, and urine levels of dopamine metabolites may also be considered, the most reliable being the CSF values (Beuger et al. 1996).

3. Surrogate Biomarker of the disease state/severity used to monitor the effect of a treatment. For example, a given analyte is found high just before and during the symptomatic state of the disease and its elevation predicts the occurrence of exacerbation. Effective treatments would re-normalize its levels and predict a reduction of symptoms and exacerbations, acting as a surrogate marker. To our knowledge no convincing example of such a biomarker related to antipsychotic treatment has been published.
4. Sentinel (safety) Biomarkers can inform about the occurrence of adverse events during treatment. For example, increased blood glucose levels and lipids were consistently observed in chronic treatment with atypical antipsychotic (Newcomer 2005). In clinical trials these biomarkers are included to inform about a potential liability regarding safety or tolerability.

The way biomarkers are implemented in clinical trials should be different according to the different goals, but also optimized to give maximal information. For example, dynamic range, sensitivity, and specificity of a given test should be built into the design and statistical consideration of the trial, requiring a clinical trial simulation test before implementation for drug discovery. From an clinical operation standpoint, it is preferable to run a "feasibility trial" before the proper biomarker study. The feasibility trial allows a proper assessment of the various factors affecting the variability of the measurements, often resulting in changes of the study protocol that will be critical for the success of the following Phase Ib-II trials. Recently, a correlational approach was proposed by Kalos (2010), suggesting to measure the same biomarkers in every trial of the drug discovery process, resulting in a cumulative gain of information. In particular, it is believed that well-designed and performed early stage correlative studies have the potential to strongly influence further clinical development. According to this view, the collection of biomarkers would start in Phase I and continue in Phase II–III of the development of a novel therapeutic product and should be able to generate a series of progressively more informative correlative analysis between exposure, effect, and tolerability signals. While in principle attractive, this approach requires a biomarker with sufficient validation and a consistent and stable investment in logistics (e.g., a central reference laboratory, an annotated database, a central storage facility) not always easily achievable in both academic and industrial research centers.

Ideally, once a biomarker is identified in preclinical discovery and it is related to the mechanism of action of a novel compound, the next step is translation into humans, rationally supporting the process of drug discovery. Unfortunately this is not always the case, in particular regarding the limited predictive validity of some animal models with respect to clinical efficacy. The implementation of modern experimental medicine technology to bridge the preclinical information into clinically relevant data is a recent achievement, and is often identified with the paradigm

of Translational Medicine (Marincola 2003). There is a common view that biomarkers will become relevant in drug discovery only if implemented within Translational Medicine paradigms. The culture of Translational Medicine is evolving and progressing. In 2006 the NIH launched the Clinical and Translational Science Awards (CTSA) Consortium with the establishment of 12 centers, increased recently to 46, with the goal to accelerate clinical research for new therapeutics. In Scotland a Translational Medicine consortium, working with the pharmaceutical industry, proposed a definition of the role of translational medicine, which is "to provide biomarkers that support decision making at critical milestones of the drug discovery process". In this view a biomarker is a quantifiable biological variable that characterizes cellular, organ, physiological, pathological, or clinical conditions. In our review we consider as translationally relevant data obtained in psychotic patients, while data obtained in healthy volunteers were considered relevant only to provide estimate of clinical dose before Phase II (e.g., PET receptor occupancy data). Biomarkers for novel antipsychotic therapies can be obtained in two ways: exploring the molecular underpinnings of the diseases, e.g., schizophrenia; or focusing on the mechanism of action of a given compound, including its off-target effects.

What is the actual implementation of biomarkers in the search for novel antipsychotics? An interesting representation of current biomarkers in translational investigation for drug discovery can be obtained by looking into the "clinicaltrial.gov" database, a registry of clinical trials conducted in the United States and around the world. Most drug companies and NIH-sponsored research institutions are voluntarily loading information on studies they are conducting for drug development. In September 2011 the database reported 105,590 trials. Using the key word search "antipsychotics" and "schizophrenia" we found 1,659 and 1,528 trials, respectively. When the Boolean crossing was used with "biomarkers" as outcome, the search gave 18 and 21 results, respectively. Only seven of them were overlapping, probably due to insufficient key word labeling. In fact, nine biomarker studies that did not appear on the list of "antipsychotics" did indeed have reported therapeutic interventions. Two studies on antipsychotics in schizophrenia did not show up in the other list, two studies were in healthy volunteers, and one misplaced (in alcoholism). Interestingly, antipsychotic biomarkers were also investigated in depression (three studies), inflammatory bowel diseases (three studies), neurodegenerative disorders (two studies) and delirium in critical illness (two studies), suggesting the trend for exploring biomarkers and efficacy of antipsychotics in other kinds of psychoses. Overall 18 biomarker studies of antipsychotic intervention in schizophrenia were found, with 8 active, 8 completed and 2 of unknown status trials. The term biomarker was used loosely in five trials aimed to assess cognitive performance of novel interventions using computer-based test batteries rather than molecular bioassays. In eight trials blood test biomarkers were used as "sentinel" to profile the metabolic effects of atypical antipsychotics or their remedies. Blood profiling of other molecular biomarkers was performed in five trials, three of them exploring lipids and only one cytokines. Only two of these studies included genotyping and one study neuroimaging. An additional search was

made using "cerebrospinal fluid" and "biomarkers", resulting in 40 studies, the crossing with "schizophrenia" and "antipsychotics" producing five and eight studies, respectively, two of them overlapping. Both these studies were exploring the effects of glycine and D-cycloserine measuring metabolites of monoamines. One study including novel compounds was aimed to assess "-omics" profile and endocannabinoids, but it was in healthy volunteers (NCT00916201). Interestingly, five trials with biomarker endpoints for antipsychotic therapy were under study for neurodegenerative disorders. In summary, the number of trials engaging molecular biomarkers for antipsychotic therapies was just below 2 % of the total trials with antipsychotic interventions present in the clinicaltrial.gov database. At least one third of these biomarker trials were targeting the metabolic syndrome associated with the long term treatment of atypical antipsychotics, almost all sponsored by the pharmaceutical industry. Investigations of the effects of antipsychotic medications on other molecular biomarkers engaged in the disease are still relatively uncommon, with less than ten studies, mostly sponsored by NIH or academic institutions. This result, within the limitation of the search engine and completeness of the clinicaltrial.gov database, indicates that the use of molecular biomarkers for the discovery of novel antipsychotic therapeutics is still at its infancy.

How many of these trials were fitting the concept of Translational Medicine? In other words, were molecular biomarkers properly used to investigate novel compounds? Indeed very few. The best example is the recent biomarker-driven progress in antipsychotic drug discovery of the inhibitor of the glycine transporter type 1 (GlyT1), RG1678, which is described in the next section. Another potentially interesting example is from an academic center, not included in clinicaltrial.gov, that consist of the composite outcome of two clinical trials and some preclinical preparatory studies regarding the use of cannabinoids, recently communicated at a conference (Leweke et al. 2011). More is coming. Information from recent scientific conventions and proposed grant applications are suggestive of an imminent delivery of a series of Translational Medicine studies that fit the proper definition of this paradigm (i.e., need of convergent findings and replications for supporting conclusion).

4 Hypothesis-Driven Biomarker Approach: Translational Investigation for a Novel Glycine Transporter Type 1 Inhibitor

Converging findings support the hypothesis that psychotic symptoms in schizophrenia are secondary to hypofunction in the glutamate neurotransmitter pathway resulting, among other effects, in a defective activation of the *N*-methyl-D-aspartic acid (NMDA) receptors (Coyle and Tsai 2004; see also Coyle et al. 2012). Treatment of normal healthy subjects with an NMDA receptor blocker, e.g., ketamine or phencyclidine, recapitulates a clinical phenotype similar to psychoses and thus

strengthen the glutamate hypothesis. The observation that several genes implicated in schizophrenia susceptibility are associated with glutamatergic signaling is also indirectly supportive of this idea (Greenwood et al. 2011). Therefore, after a series of failures in the 1990s, a new generation of drugs is currently under development aimed at facilitating NMDA receptor transmission. For example, one way to facilitate NMDA receptor transmission is to increase the extrasynaptic levels of glycine, an obligatory channel opening modulator. Inhibitors of the glycine transporter prevent the reuptake of glycine from the synapse into the neighboring glial cell and terminals and thus increase concentrations of this amino acid, which putatively leads to better NMDA receptor function (Javitt 2010; see also Javitt 2012). We briefly review how biomarkers were implemented during drug discovery to assess the engagement of the molecular target and the functional effects produced by the novel compounds that is predictive of a clinically relevant effect.

Hoffmann-La Roche recently completed a positive Phase II proof-of-concept clinical trial in schizophrenia using RG1678, a potent and selective noncompetitive inhibitor of the glycine transporter type 1 (GlyT1). The data from this trial suggest that this compound is effective in the negative symptoms of schizophrenia (Umbricht et al. 2011). This clinical trial was an 8 week multicenter, randomized, double-blind, parallel group study, which compared RG1678 to placebo in patients who had been selected to have predominantly negative symptoms of schizophrenia with stable positive symptoms. The primary endpoint was efficacy as measured by change from baseline in the Positive and Negative Syndrome Scale (PANSS) negative symptom factor score (Marder et al. 1997) and secondary endpoints included clinical global impression improvement (CGI-I) ratings in negative symptoms. Four parallel arms utilizing three dose regimens of RG1678 (10, 30, and 60 mg) and placebo were assessed as add-on to standard antipsychotic treatment in stable patients. The study demonstrated a statistically significant improvement in negative symptoms in patients taking RG1678 compared to placebo as shown by both changes in PANSS negative symptom factor score and CGI improvement. This is the first major trial showing positive effects in the treatment of negative symptoms of schizophrenia and holds promise for the development of a new class of non-dopaminergic agents. The success of this trial was partly dependent on the appropriate use of biomarkers prior to the start of the patient study. In particular, data from measurements of glycine levels in the CSF in normal healthy volunteers coupled with PET studies enabled accurate dose decisions for the Phase II study.

(a) Biomarker data measuring CSF glycine levels. The evidence that RG1678 was reaching its target was achieved by measuring the concentration of glycine in the CSF, a biomarker selected on the basis of biologic evidence of RG1678 mechanism of action. A small proof-of-mechanism study in healthy volunteers was performed to test this hypothesis. This study investigated whether increasing doses of the GlyT1 inhibitor compound would lead to increases in glycine levels in the samples of CSF collected using an indwelling lumbar catheter at baseline and after 10 days of treatment in human volunteers (Hofmann et al. 2011). A dose-dependent increase in the CSF glycine concentration was observed

after RG1678 treatment by comparing the area under the curve (AUC) measured at baseline to the AUC measured 10 days after. This glycine increase was not observed in plasma, suggesting that such measurements were not useful to assess GlyT1 inhibitor treatments. Conversely, measurement of CSF glycine levels in healthy volunteers can be used as a pharmacodynamic biomarker to demonstrate the engagement of the target by the candidate compound (i.e., GlyT1 inhibition). Similar effects were measured also in rodents, showing two-to threefold increases in glycine levels vs. basal in rats as well as in humans at maximal tolerated doses, indicating that the biomarker enables translation. These data were used in the preclinical development of other GlyT1 inhibitors and allowed the calculation of the potential efficacious dose in humans by measuring glycine concentrations in CSF fluid in rodents. The importance of having a biomarker which can help in dose selection cannot be overestimated. Coupled with additional preclinical data and PET data (see below) this biomarker approach enabled the correct dosing decisions for the schizophrenia Phase II proof-of-concept clinical trial with RG1678. Interestingly the dose which proved to be most effective in this Phase II study was 10 mg with the 60 mg dose being least effective suggestive of an inverted U-shaped dose-response curve. A potential explanation for this observation comes from preclinical data from rat hippocampal CA1 neurons suggesting that glycine primes the receptors for clathrin-dependent endocytosis (Nong et al. 2003). It may be that at higher doses of the GlyT1 inhibitor there is increased NMDA receptor internalization leading to a decreased clinical efficacy.

(b) Biomarker data using PET tracer. Preclinical PET data obtained using the GlyT1 ligand [^{3}H] RO5013853 in rats demonstrated that approximately 50 % occupancy of the GlyT1 target by RG1678 is sufficient to show efficacy in preclinical models of antipsychotic effects (Alberati et al. 2011). Studies using the same radiotracer in monkeys show similar results, with significant effect in the delayed-match-to-sample cognitive task at approximately 40 % occupancy of the GlyT1 target (Borroni et al. 2011). These preclinical data were further supported by similar studies in humans showing comparable amount of GlyT1 occupancy under basal conditions (Umbricht et al. 2011). Since the relationship between target occupancy and pharmacologic effect was known in the preclinical models, the knowledge of the RG1678 dose at which the target occupancy in human was similar to that of the preclinical models informed about the expected effective dose in psychotic patients. Therefore the use of PET as an imaging biomarker can enable dose decision-making for human studies. In the case of RG1678 the use of PET, preclinical efficacy data, and human glycine CSF measurements enabled the selection of doses for the proof-of-concept Phase II study, which delivered a signal of effect on negative symptoms in patients. Again the possibility to use biomarkers to predict the proper clinical effective dose is of importance as it is well recognized that the failure of novel compounds in drug development is often due to incorrect dose selection.

5 Hypothesis-Free Biomarker Approaches: The Engine for Novel Biomarker Discovery for Antipsychotic Treatment?

In addition to mechanistic biomarkers and to pathway dysfunction-related biomarkers based on existing hypotheses of the disease mechanisms, great hopes currently lie in the application of large-scale, -omic based, approaches for the identification of biomarkers, which would give the advantages to explore untapped pathways in an unbiased fashion. Since psychiatric disorders are complex and heterogeneous and show high degree of comorbidities that might involve multiple biological mechanisms, single biomarkers based on stand-alone mechanisms will hardly prove to be specific and applicable on a wide scale or for a wide range of patients. In the last five years the potential offered by large-scale genomic, proteomic, and metabolomic profiling in psychiatry has been increasingly documented, suggesting that blood-derived disease signatures for CNS disease can be derived, but direct clinical applications are still limited to a few examples.

5.1 Genomic Signatures for Psychosis

The first claim for a blood genomic signature for psychotic patients is coming from the work by Tsuang et al. (2005) who compared gene expression profiles from schizophrenic patients, bipolar patients, and healthy controls, resulting in the identification of a specific set of transcripts enabling one to distinguish the different disease groups from controls. This exciting finding has stimulated the search for blood signatures for schizophrenia and other psychiatry disorders based on the disease collections (Domenici and Muglia 2007). New candidate biomarkers for schizophrenia classification have been described based on subsequent blood gene expression profiling investigations (Kuzman et al. 2009). Recently, a new blood-based gene expression signature derived from supervised classifier analysis of data from 52 antipsychotics-free schizophrenia patients and 49 normal controls was proposed as a diagnostic tool for schizophrenia (Takahashi et al. 2010). An interesting line of research is based on the combination of gene expression data from patients with data from preclinical models and from genetic investigations, for the identification of disease biomarkers based on convergent functional genomics (Le-Niculescu et al. 2009). Based on the above gene or pathway-centric approach, a consensus article recently proposed putative blood biomarkers for core psychotic symptoms, such as sensory (hallucinations) and cognitive (delusions) symptoms (Kurian et al. 2011). Less attention has been paid to investigate the effects of antipsychotic treatments on a genome-wide scale in peripheral blood, and the potential application of gene expression profiling as surrogate or prognostic biomarkers. For example, the effects of fluvoxamine in combination with antipsychotics on gene expression profile in peripheral mononuclear cells were studied by Chertkow et al. (2007). In their study, gene expression changes

associated to augmentation therapy were identified, which occurred in parallel to clinical improvement in negative symptoms. In spite of the small sample size, a significant relationship between gene expression and clinical improvement was determined, suggesting potential biomarkers.

Overall, the relevance of gene expression profiling in providing biomarkers to support the development of new antipsychotic therapies has still to be proven. Nevertheless, a putative application was recently proposed by a UK-based company (Curidium Medica plc), who claimed to have identified a blood diagnostic tool based on gene expression signatures (PsychINDx™). This gene profiling diagnostic classifies schizophrenia/bipolar disorder patients into four subgroups with distinct underlying pathophysiology that was proposed amenable for the development of personalized approaches [reported by Caffo (2008)].

5.2 *Application of Metabolomic Profiling*

Metabolomics (or metabonomics) is a rapidly expanding technology, based on either NMR or LC/GC-based mass spectrometry, which now allows for the identification of complex metabolite profiles in tissues or biofluids and establish their correlation with disease (German et al. 2005). Some applications have been described for the identification of dysregulated metabolic pathways in schizophrenia patients by looking into peripheral samples, i.e., in plasma [see for example Tsang et al. (2006)]. A recent application of metabolomic profiling in the clinics as sentinel biomarker exemplified the feasibility of identifying patterns of lipid changes in schizophrenia patients specifically related to metabolic side effects or to therapeutic efficacy of atypical antipsychotics (Kaddurah-Daouk et al. 2007). The authors adopted a "lipomic" platform to quantify over 300 polar and nonpolar lipid metabolites in patients treated with three common atypical antipsychotic drugs, and identified baseline lipid alterations correlated with acute treatment response. Despite this very encouraging preliminary data, no subsequent global lipidomic or metabolomic study showing an association of metabolic profile with antipsychotic treatment outcome has been reported yet.

5.3 *Proteomic Profiling of Psychotic Patients*

Work by many groups over the last 10 years has provided data suggesting that large-scale measurements of a panel of proteins also indicated as "proteomic" when performed in serum provide useful information to aid in disease understanding, biomarker identification, and diagnostic discovery (Huijbers et al. 2010). Most of this work has been done in oncology, but it is believed that hypothesis-free proteomic approaches may have a place in modern drug discovery for novel CNS treatments.

Progression towards the identification of a schizophrenia serum proteomic signature was started from the use of surface-enhanced laser desorption ionization mass spectrometry in CSF samples of 58 first-onset, drug-naïve, paranoid schizophrenia patients and of 90 demographically matched controls schizophrenic patients vs. healthy volunteers (Huang et al. 2006). The most striking changes were the upregulation of a 40-amino acid VGF peptide and the downregulation of transthyretin. The advantage this study had over many others is the access to CSF from drug-naïve schizophrenia patients. In fact, in some countries CSF is collected in patients as part of the clinical work-up in those presenting with symptoms of first-onset psychosis. The interpretation of these data is not affected by the confounding factor of concomitant medications, as in most of the other studies. However, in other countries CSF sampling is not a common procedure for non-neurological conditions and the availability of these samples for biomarker exploration could be a limiting factor for the general application of the biomarker as diagnostic, prognostic, or surrogate marker.

The measurements of serum proteins using multi-analyte and/or array profiling techniques provide the simultaneous detection of hundreds of proteins with high sensitivity and accuracy and can be successfully applied to identify biomarkers (or clusters of biomarkers) that correlate with disease. This approach was used initially in cancer and recently applied also for other diseases (Bertenshaw et al. 2008; Duan et al. 2008; Visvanathan et al. 2010). In psychiatric disorders there have been several attempts to correlate specific serum biomarkers with the illness, mostly limited to a few analytes such as BDNF or cytokines. A handful of multi-analyte/array studies regarding psychotic disorders have been published so far, showing the promise of this approach (Domenici et al. 2010; Schwarz et al. 2010). In particular, Domenici et al. have profiled plasma samples from 750 subjects including schizophrenia patients, depressed, and healthy control subjects by adopting a multiple analyte profiling platform, which includes series of cytokines, chemokines, and neurotrophins previously suggested to be involved in the pathophysiology of schizophrenia and depression. The study was able to separate the cluster of schizophrenia patients vs. depressive patients and healthy controls and to associate certain upregulated proteins to a specific disease, with some overlapping markers (Fig. 2a, b). In particular, this investigation illustrated the potential of plasma biomarker profiling for psychiatric disorders, when conducted in large collections, to identify biomarker signatures for depression and schizophrenia as well as for pharmacologic treatment.

More recently a serum proteomic signature to classify schizophrenia vs. other disorders or healthy volunteers was proposed using an extended Rules-Based Medicine panel (RBM; DiscoveryMAP assay) comprising 181 analytes, which culminated in a laboratory-based diagnostic for schizophrenia (Schwarz et al. 2011). Two-hundred-fifty samples derived from first- and recent-onset schizophrenia patients and 230 control subjects collected from four different sites in Germany and the Netherlands were used, resulting in the identification of a 51-analyte signature which separated schizophrenia from controls (Schwarz et al. 2010). In the validation phase a new panel devised by RBM and containing these 51 immunoassays was used

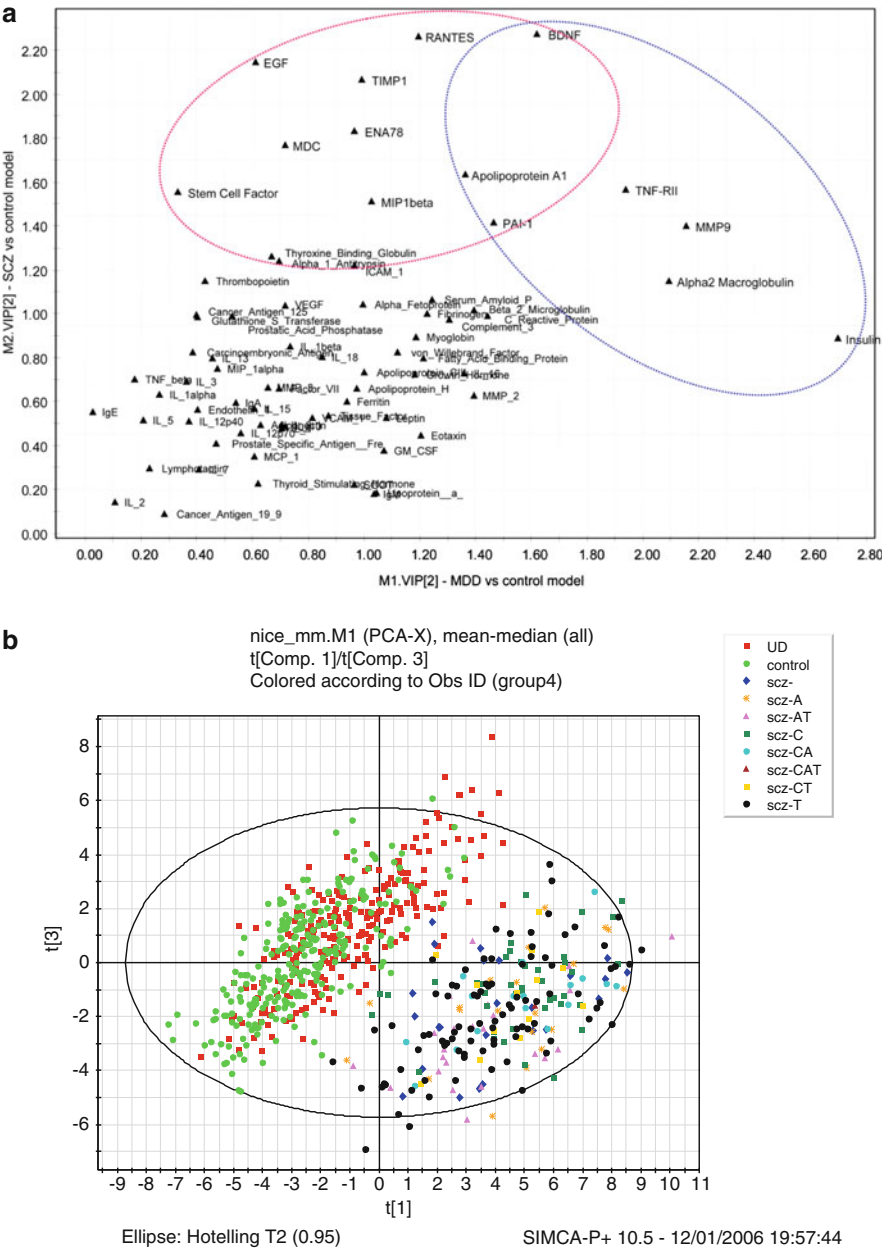

Fig. 2 Multiple analytes that contribute to the separation of control-depression and control-schizophrenia samples (Domenici et al. 2010). On the Y- and X-axis the Variable Importance of Information (VIP) which ranks markers for their contribution to case–control separation from PLS discrimination analysis (M2). Analytes were measured using the multiplex platform of Ruled-Base Medicine. Analytes within the blue contour are prevalent in Major Depressive Disorders while

to classify schizophrenia patients vs. control in a new cohort of 577 schizophrenia patients and 229 control subjects. Data were entered into a linear support vector machine (SVM) algorithm for classification. The sensitivity and specificity using this algorithm applied to the 51 immunoassay measurement were 83 % with a receiver operating characteristic (ROC) area under the curve of 89 %. These data led to the production of a marketed diagnostic in the USA known as VeriPsych™.

This diagnostic is not unique in using multi-analyte proteomic profiling together with an algorithm. The OVA1 (Vermillion) test for ovarian cancer assays five biomarkers (transthyretin, apolipoprotein A-1, beta2-microglobulin, transferrin, and cancer antigen 125) and uses a proprietary algorithm to determine the likelihood of malignancy (Fung 2010; Albrethsen 2011). VeriPsych™ is the first proteomic-based blood test marketed for a psychiatric condition. It is important to note that this is not an in vitro diagnostic (IVD) and does not have Food and Drug Administration (FDA) approval. Instead, it relies on the fact that the test is performed in Clinical Laboratory Improvement Amendments (CLIA) certified laboratories. Furthermore, it is not a diagnostic which will replace the psychiatric interview and it is intended to be an aid to diagnosis for research purposes, with potential issues associated with the risk of false positives. It remains unclear how well it will do in regards to other psychoses, such as delusional disorder, head trauma, drug induced psychosis, etc.

There are limitations in the application of proteomic multi-analyte approaches to clinical trials that need to be mentioned. Some are related to the technology used to measure the analytes, e.g., if based on antibody-mediated detection one cannot measure all the analytes together since the detecting antibodies can interfere with one another. In addition some analytes are naturally expressed at low levels while others at high levels, requiring scaling approaches based on sample dilutions (when possible) so to be able to provide all measures within a proper dynamic range. Another problem is the false discovery rate of the multiplex large-scale assay, which is a real issue when the number of analytes exceeds the number of patients. The Alzheimer's disease field exemplifies these difficulties even when using a relatively small panel: a biomarker signature of 18 analytes was identified in well-executed studies, but these findings have never been replicated in full (Ray et al. 2007).

Fig. 2 (continued) analytes within the red contour are prevalent in schizophrenia. MDD = Major Depressive Disorder; SCZ = schizophrenia; control = healthy subjects matched by age. (**b**) Principal Component Analysis plot showing the separation of both untreated and treated schizophrenics (scz) from Unipolar Depression (UD) cases and healthy (control) individuals. PCA plot was obtained by multivariate analysis of the multiple analyte profiling data using SIMCA (from Domenici et al. 2010). Data are the same represented in Fig. 2a. Schizophrenics are coded according to the different medications: "C" indicates treatment with clozapine, "A" treatment with other atypical antipsychotics, "T" indicates treatment with typical antipsychotics, "-"indicates untreated subjects. Note that the dark blue schizophrenic group (untreated, diamond) does not separate out from the whole schizophrenic group under treatment

Multi-analyte serum profiling could be included in clinical trials aimed to assess novel treatment for psychoses (Visvanathan et al. 2010). Unfortunately most of the clinical trials implementing peripheral biomarkers suffer from relevant limitations: they were based on small numbers of subjects, on different assays and different pre-analytical procedures, often in patients whose characteristics and comorbidities differed and rarely included a placebo arm or properly dosed antipsychotic treatments. Given the relevance of these limitations we chose not to review these studies here, waiting for larger and better designed sets of trials.

6 Future Perspectives: Biomarkers for Targeted Drugs and Personalized Medicine?

Biomarkers can contribute to tailored treatments for groups of individuals that share similar endophenotypic features, i.e., a particular subclass of psychoses, becoming a critical component of the Personalized Medicine approach. This approach is currently operationalized in oncology but it is perceived as difficult to apply (Chin et al. 2011), facing not only the scientific problem of reliability for the biomarker methodology but also an economic problem related to the reimbursement for a novel expensive treatment. While there is a general interest in progressing Personalized Medicine or biomarker-driven approaches in the treatment of cancer or neurological disorders, in psychiatry this is not happening. This fact may be attributable to the intrinsic difficulty in the diagnosis of these disorders and in its stability, and to the limited understanding of their biology and the lack of validated biomarkers. However, despite this gap, several academic laboratories, precompetitive consortia, and industrial partners are attempting this paradigm shift (Gerretsen et al. 2009; Glick et al. 2011, NEWMEDS). This trend is supported by recent activities of the USA Food and Drug Administration regarding the implementation of personalized medicine via the Critical Path Initiative and of the European Medicines Agency that support a stratified medicine approach driven by biomarkers.

7 Conclusions

We have provided some examples of successful applications of mechanistic and sentinel biomarkers in assisting antipsychotic drug development. In particular, studies implementing biomarker pharmacodynamic endpoints together with pharmacokinetic data were used to predict the clinical effective dose for a GlyT1 inhibitor, facilitating the translation of preclinical findings into clinical trial. Sentinel biomarkers were successfully used to map the metabolic risks of long term treatment with atypical antipsychotics. Conversely no progress was made in identifying predictive biomarkers or biomarker of severity of the disease.

However, the advent of "-omic" and neuroimaging approaches has opened up unprecedented opportunities for the unbiased search of new disease markers for psychosis and schizophrenia. Widespread efforts in the area of molecular biomarkers have undoubtedly resulted in an increased understanding of the pathophysiological mechanisms underlying psychiatry disorders (even though not necessarily their etiology), suggesting new areas for research and potentially for new target investigations.

Unfortunately, a real impact in drug development and in the clinical practice of biomarkers has yet to be demonstrated, likely because most investigations have focused so far on the search for markers which differentiate subjects affected by psychosis from controls, instead of characterizing them into different subclasses or predicting treatment effects.

Overall, if only one goal should be set for the next decade regarding biomarkers for antipsychotic treatment, this goal would be the identification of biomarkers for "personalized medicine", i.e., biomarkers that classify patients affected by psychotic disorders into subtypes, based on their endophenotypes. In theory, such biomarkers could be the basis for a different "molecular taxonomy" of the disorder suggesting subtypes independent from clinical symptom dimensions. These biological markers or signatures could complement clinical observations and be of help in reducing the heterogeneity of disorders, with a foreseeable impact for therapy and its economic counterpart.

Note At the time of the manuscript editing in February 2012 the number of trials with "antipsychotic" in the database clinicaltrial.gov was 1883, and those with "biomarkers" as outcome were 24. These numbers indicate that trials with biomarkers as outcome constituted 1.3 % of the antipsychotic trials, still lower than the average biomarkers use in all clinical trials of the database (4 %). Note that when a simple Boolean "and" was used to connect "antipsychotics" and "biomarker" the number jumped to 57, indicating a wider use of biomarkers as secondary endpoint (rather than outcome measure).

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Behavioral Animal Models of Antipsychotic Drug Actions

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Contents

Abstract Basic research in animals represents a fruitful approach to study the neurobiological basis of brain and behavioral disturbances relevant to neuropsychiatric disease and to establish and evaluate novel pharmacological therapies for their treatment. In the context of schizophrenia, there are models employing specific experimental manipulations developed according to specific pathophysiological or etiological hypotheses. The use of selective lesions in adult animals and

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the acute administration of psychotomimetic agents are indispensable tools in the elucidation of the contribution of specific brain regions or neurotransmitters to the genesis of a specific symptom or collection of symptoms and enjoy some degrees of predictive validity. However, they may be inaccurate, if not inadequate, in capturing the etiological mechanisms or ontology of the disease needed for a complete understanding of the disease and may be limited in the discovery of novel compounds for the treatment of negative and cognitive symptoms of schizophrenia. Under the prevailing consensus of schizophrenia as a disease of neurodevelopmental origin, we have seen the establishment of neurodevelopmental animal models which aim to identify the etiological processes whereby the brain, following specific triggering events, develops into a "schizophrenia-like brain" over time. Many neurodevelopmental models such as the neonatal ventral hippocampus (vHPC) lesion, methylazoxymethanol (MAM), and prenatal immune activation models can mimic a broad spectrum of behavioral, cognitive, and pharmacological abnormalities directly implicated in schizophrenic disease. These models allow pharmacological screens against multiple and coexisting schizophrenia-related dysfunctions while incorporating the disease-relevant concept of abnormal brain development. The multiplicity of existing models is testimonial to the multifactorial nature of schizophrenia, and there are ample opportunities for their integration. Indeed, one ultimate goal must be to incorporate the successes of distinct models into one unitary account of the complex disorder of schizophrenia and to use such unitary approaches in the further development and evaluation of novel antipsychotic treatment strategies.

Keywords Animal model • Antipsychotic drugs • Cognition • Negative symptoms • Positive symptoms • Psychosis • Schizophrenia

1 Introduction

Despite the growing consensus that schizophrenia is a brain disorder, a comprehensive neurobiological account of the disease (including the etiology, neuropathology, pathophysiology, psychopharmacology, and genetics) remains a considerable challenge to clinicians and scientists alike. Besides a direct exploration of these issues in human subjects, basic research in animals represents a fruitful approach to study the neurobiological basis of brain and behavioral disturbances relevant to schizophrenia and to establish and evaluate novel pharmacological therapies for their treatment. Indeed, the use of animal models allows a stringent experimental control of subjects in genetically homogeneous populations and facilitates the identification of neurobiological factors contributing to distinct forms of schizophrenia-related brain and behavioral abnormalities. Animal models also provide indispensable tools to test hypotheses which cannot be directly addressed in human subjects for technical and ethical reasons, including the verification of causal relationships in epidemiological studies.

One main goal of modeling a disease is to achieve a more profound understanding of its biology and thereby to identify possible targets for its treatment. It still appears that one of the major difficulties in the pharmacotherapy of schizophrenia is the limited clinical efficacy of antipsychotic drugs (APDs). Treatment with currently available APDs can only partially normalize psychopathological symptoms and are particularly poor in mitigating negative and cognitive symptoms (Buchanan et al. 2007; Nelson and Winslow 2009; Tandon et al. 2010). Discovery strategies for novel APDs for the past 30 years have been dominated by efforts to reproduce the advantages of the reference atypical APD clozapine, while at the same time circumventing the drugs' numerous side effects such as agranulocytosis, hypotension, weight gain, and diabetes (Tandon et al. 2010; Rummel-Kluge et al. 2012). Even though several second-generation APDs such as olanzapine, risperidone, amisulpride, or sertindole have been labeled as "atypical antipsychotics," none of these drugs has yet approached clozapine with respect to its clinical efficacy (Hill et al. 2010). Given this, it appears that there is still a strong need for the development and evaluation of novel compounds with antipsychotic properties, which are effective in normalizing especially the negative and cognitive aspects of the disorder, and which are accompanied by minimal side effects. Preclinical research in animals is an indispensable step towards this goal because it allows a direct evaluation of possible beneficial versus harmful side effects of novel compounds with potential antipsychotic properties.

In this chapter, we discuss current attempts to model schizophrenia-relevant abnormalities in animals. Thereby, we focus on the two most widely used species, namely rats and mice. We would like to point out that in addition to these rodent species, several other species have been proven highly valuable in the experimental study of schizophrenia-relevant dysfunctions. One example is the use of (nonhuman) primate models, which may enjoy some essential advantages over rodent models in the study of cognitive processes pertinent to schizophrenic disease. An excellent discussion of this issue can be found in several recent reviews (Castner et al. 2004; Nelson and Winslow 2009; Simen et al. 2009).

In the present chapter, we first summarize the general validity criteria of animal models and outline distinct behavioral read-outs that can be used to experimentally approximate distinct symptom classes of the disorders. We then go on to describe the principal experimental methods, by which schizophrenia-relevant behaviors can be induced in animals. We attempt to provide a synthesis of different experimental approaches, thereby discussing the advantages and limitations of existing behavioral procedures and models in preclinical schizophrenia research.

2 Modeling Schizophrenia in Animals

The attempt to model any human psychiatric condition in animals has always been met with some skepticism, and schizophrenia is a particularly illustrative case (Boksa 2007; Low and Hardy 2007). The obvious reason for this is that the

clinical manifestation of schizophrenia in humans includes symptoms such as hallucinations, delusions, major thought disorders, and alogia, which are specific to humans and impossible to ascertain without structured interviews (Ellenbroek and Cools 2000a). Hence, it seems impossible to utterly mimic a complex human brain disorder such as schizophrenia in animals. Over the last three decades, however, there have been tremendous efforts to develop animal procedures that allow translations of the symptomatology observed under clinical conditions (Arguello and Gogos 2006; Lipska and Weinberger 2000; Meyer and Feldon 2010; Tarantino and Bucan 2000). These efforts are aimed at increasing the relevance of animal procedures for predicting the therapeutic efficacy of a novel substance (Markou et al. 2009; Nestler and Hyman 2010). The requirement for such efforts has also been highlighted by three recent research initiatives, namely the National Institute of Mental Health (NIMH)-funded (Measurement and Treatment Research to Improve Cognition in Schizophrenia) (Green et al. 2004; Marder 2006; Young et al. 2009), the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) (Barch et al. 2009a, b; Nuechterlein et al. 2009), and the European Commission initiative NEWMEDS (Novel Methods Leading to New Medications in Depression and Schizophrenia) (Hughes 2009). As exemplified by the latter, these initiatives aim to "... generate translational technology that could help provide early indicators of efficacy [...] and [...] to develop tools to improve patient stratification to focus on the complexity and heterogeneity of the disease." One consensus of these research initiatives is that in the view of the complexity and "human nature" of schizophrenia, one fruitful experimental approach is to focus on individual behavioral, physiological, and neuroanatomical phenotypes of the disorder rather than to model the entire syndrome (Arguello and Gogos 2006; Barch et al. 2009a, b; Floresco et al. 2005; Geyer 2008; Hughes 2009; Lipska and Weinberger 2000; Meyer and Feldon 2010; Tarantino and Bucan 2000). In parallel with similar efforts in humans, behavioral neuroscience and related research fields have established a wide variety of behavioral paradigms pertinent to the assessment of schizophrenia-related traits in experimental models. Such cross-species translational paradigms have been developed for the identification and characterization of neuropsychological, cognitive, and psychopharmacological core dysfunctions implicated in human psychotic disorders. Table 1 provides a sample of the most commonly used paradigms for the phenotypic characterization of schizophrenia-related neuropsychological, cognitive, and psychopharmacological core dysfunctions in rats and mice. These paradigms have been proven valuable and informative experimental tools to assess psychosis-like traits in a variety of lesion-based, genetic, neurodevelopmental, or psychopharmacological rodent models (Arguello and Gogos 2006; Barak and Weiner 2011; Castner et al. 2004; Meyer and Feldon 2010; Meyer et al. 2005; Moser et al. 2000; Swerdlow and Geyer 1998; Weiner 2003). It should be emphasized that the collection of the paradigms summarized in Table 1 is far from exhaustive. Theoretically, they are also not mutually exclusive of each other, even though they have been developed as tests of schizophrenia-related dysfunction largely independently of each other. Conversely, the neural substrate underlying

Table 1 A sample of experimental tests used for evaluating schizophrenia-related behavioral, cognitive, and pharmacological abnormalities in rodents

Neuropsychological, cognitive, and chemical domains	Experimental paradigm	Symptoms in schizophrenia	References
Sensorimotor gating[a]	Prepulse inhibition of the acoustic startle reflex	Impaired	Braff et al. (2001), Swerdlow and Geyer (1998), Yee and Feldon (2009)
Attentional control of selective associative learning[b]	Latent inhibition	Impaired in patients with acute positive symptoms; abnormally enhanced in patients with marked negative symptoms	Feldon and Weiner (1992), Lubow (2005), Moser et al. (2000), Weiner (2003)
	Kamin blocking	Reduced especially in acutely ill patients	Jones et al. (1992), Moran et al. (2003, 2008)
Sustained attention and vigilance[c]	5-choice serial reaction time test	Impaired in patients with schizophrenia and their nonpsychotic first-degree relatives	Birkett et al. (2007), Elvevag et al. (2000), Laurent et al. (2000, 1999)
Working memory[d]	Delayed non-match to sample/position Radial arm maze Morris water maze Y-maze	Impaired	Castner et al. (2004), Goldman-Rakic (1994), Kellendonk et al. (2009)
Executive functions[e]	Intradimensional/extradimensional shift	Impaired at impaired set-shifting and concept formation	Barch et al. (2009a, b, Brown and Bowman (2002), Ceaser et al. (2008), Dalley et al. (2004), Garner et al. (2006)
	Discrimination reversal learning	Abnormally enhanced behavioral/cognitive flexibility in patients with marked positive symptoms (switching behavior); behavioral and/or cognitive inflexibility in patients with marked negative symptoms	Brown and Bowman (2002), Crider (1997), Murray et al. (2008), Yogev et al. (2003)
Social behavior[f]	Social interaction and recognition tests	Reduced especially in patients with negative symptoms	Crawley (2008), McGlashan and Fenton (1992)
Stereotypy[g]	Open field exploration test Holeboard exploration test	Presence of stereotypic behavior	Crawley (2008), Morrens et al. (2006), Ridley (1994)

(continued)

Table 1 (continued)

Neuropsychological, cognitive, and chemical domains	Experimental paradigm	Symptoms in schizophrenia	References
Dopamine-associated neurotransmission[h]	Behavioral reaction to amphetamine In vivo microdialysis following systemic amphetamine challenge to assess the (striatal) release of dopamine and other neurotransmitters	Increased sensitivity to dopamine-stimulating drugs; enhanced striatal dopamine release	Laruelle et al. (1996, 2003), Lieberman et al. (1987)
Glutamate-associated neurotransmission[i]	Behavioral reaction to ketamine, dizocilpine and phencyclidine In vivo microdialysis following systemic treatment with ketamine, dizocilpine and phencyclidine to assess the (striatal) release of dopamine and other neurotransmitters	Increased sensitivity to NMDA-receptor-blocking drugs; reduced glutamatergic signaling at NMDA receptors	Carlsson et al. (2001), Laruelle et al. (2003)

The table summarizes the most commonly used cross-species translational experimental paradigms used to assess schizophrenia-related functional brain abnormalities and outlines the corresponding psychopathological symptoms in the human clinical condition

[a]Prepulse inhibition (PPI) of the acoustic startle reflex refers to the reduction of startle reaction to a startle-eliciting stimulus (pulse) when it is shortly preceded by a weak stimulus (prepulse). It is an operational measure of sensorimotor gating which reflects the ability to filter or gate intrusive sensorimotor information

[b]Latent inhibition (LI) and Kamin blocking (KB) are forms of selective associative learning considered to indicate an organism's capacity to ignore irrelevant stimuli. LI is usually described as the retardation in learning about the significance of a stimulus as a result of its prior non-reinforced (nonconsequential) repeated pre-exposures. In associative conditioning, pre-exposure of the to-be-conditioned stimulus (CS) impedes the subsequent development of the conditioned response (CR) following pairings between the same CS and a significant event, the unconditioned stimulus (US). KB refers to the impediment of the development and/or expression of a CR when a target conditioned stimulus (CS2) is presented as part of a compound that includes another CS (CS1) that had been used previously to establish a CR

[c]Sustained attention and vigilance can be assessed using the 5-choice serial reaction time test (5-CSRTT), which tests the ability of a subject to sustain spatial attention divided among a number of locations over a large number of trials. This capacity is measured by the subject's accuracy of reporting the correct stimuli

[d]Working memory is a special short-term memory buffer with a limited temporal capacity and is used to hold relevant information active in order to guide ongoing behavior, including comprehension, reasoning, and problem solving. Numerous experimental paradigms can be used for the assessment of working memory in experimental animals, including the delayed non-match to sample/position (DNMTS/P) task, the radial arm maze, the Morris watermaze, and the

Y-maze. An important component of working memory as assessed in these paradigms is the short-term storage of trial-unique information, whereby unique information about specific stimuli (e.g., spatial location and object information) is retained briefly in a short-term memory buffer and discarded after an appropriate response is executed

[e]Executive functions are commonly referred to as a collection of brain processes which are crucial for planning, problem solving, maintenance of goal-directed behavior, and behavioral/cognitive flexibility. Two effective experimental procedures to study executive functions in rodents are the paradigms of intradimensional/extradimensional shifts and discrimination reversal learning. An intradimensional shift occurs when the subject is required to cease responding to one feature of a particular perceptual dimension (e.g., "red" for the dimension color) and begins responding to a new feature of the same dimension (e.g., "blue"). On the other hand, an extradimensional shift occurs when the subject is required to switch responding to a novel feature of a previously irrelevant perceptual dimension (e.g., from the color "blue" to "circles" from the dimension "shape"). In reversal learning, subjects first learn to respond differentially (typically approaching or avoiding) to two stimuli of opposing valence (S1+ vs. S2−), and are then confronted with the same two stimuli but with the reversed valence (S1− vs. S2+). The ability to recognize an unexpected consequence from a previously established associative learning rule and then to switch the response contingency accordingly is crucial to reversal learning

[f]Social behavior is commonly referred to behavior that takes place in a social context and results from the interaction between and among individuals (of the same species). Since most of the commonly used experimental animals, including rats and mice, are highly social animals, social interaction and recognition tests can be efficiently used to study social behavior under experimental conditions

[g]Stereotypy is defined as uniform, repetitive, and compulsive actions within a restricted pattern which often have no obvious goals or end-points. Stereotype behavior can be assessed using open field or holeboard exploration tests, in which persistent repetitions of particular actions can be measured by observing the animal's behavior over a certain period of time

[h,i]One effective and informative way to assess the functional consequences of altered dopamine- and/or glutamate-associated neurotransmission is to measure a subject's behavioral sensitivity to acute treatment with dopamine receptor agonists such as amphetamine or NMDA-receptor antagonists such as ketamine, dizocilpine (MK-801), and phencyclidine (PCP). This can be coupled with in vivo microdialysis in order to have a parallel measure of extracellular neurotransmitter release before, during, and after the drug challenge. Adapted from Meyer and Feldon (2010)

performances on each of these behavioral, cognitive, and psychopharmacological tests share considerable common elements, and their identification is particularly crucial to the disease process of schizophrenia. Hence, the power of validation is magnified many folds when these tests are applied as a battery of tests for the phenotypic characterization of functional abnormalities relevant to complex neuropsychiatric disorders such as schizophrenia, especially when the experimental model system does not rely on any specific presumption of the disorder's neuronal substrates.

2.1 General Validity Criteria of Animal Models

The extent to which it is possible to extrapolate from animal model systems to the clinical condition in humans, and consequently the value of the information that may be derived from animal models depends on several validity criteria of the model. In general, there are three main criteria which ascertain the validity of an animal model, namely face, construct, and predictive validity (van der Staay et al. 2009; Willner 1984, 1986). It should be emphasized that no animal model is likely to fulfill all validity criteria at the same time. In fact, validity criteria are often restricted to the specific purpose of the model, and there is no general consensus about how to weigh the different categories of validity in the model evaluation process [for a detailed discussion, see van der Staay et al. (2009)]. Besides the distinct validity criteria, another major requirement of an animal model is reliability, i.e., the readiness with which the model or animal procedure data can be reproduced satisfactorily (Floresco et al. 2005).

2.1.1 Face Validity

This refers to phenomenological and symptomatological similarities between the features of the model and the clinical condition. For example, face validity reflects the degree of descriptive similarity between the behavioral abnormalities seen in the model system and the human psychopathological condition. Face validity also includes the etiological and/or epidemiological significance of the experimental manipulation used for the induction of a particular phenotype which aims at mimicking the human condition.

2.1.2 Construct Validity

According to early definitions by Cronbach and Meehl (1955), "construct validity is involved whenever a test is to be interpreted as a measure of some attribute or quality which is not operationally defined." A narrower concept of construct validity is used to describe the degree of similarity between the mechanisms

underlying the particular phenotype in the model and that underlying the phenotype in the condition which is being modeled (van der Staay et al. 2009; Willner 1984, 1986). Construct validity thus accounts for mechanistic similarities between the model and the clinical condition. In the context of animal models of human brain disorders, construct validity is a theory-driven, experimental substantiation of the behavioral, pathophysiological, and/or neuronal elements of the model. Hence, it reflects the degree of fitting of the theoretical rationale and of modeling the true nature of the symptoms to be mimicked by the animal model.

2.1.3 Predictive Validity

Predictive validity of an animal model implies that the model allows extrapolation of the effect of a particular experimental manipulation from one species to another (e.g., from rodents to humans), and from one condition to another (e.g., from the preclinical model in animals to the clinical condition in humans). A narrower concept of predictive validity is used in psychopharmacological contexts. Here, predictive validity usually implies that pharmacological compounds that are known to influence a clinical state in humans should have a similar effect in the animal model. Hence, this validity criterion refers to the sensitivity of the model system to clinically effective drugs. As a consequence, pharmacological treatments that precipitate or exacerbate a human pathological condition should exert a similar effect on the model, whereas those pharmacological treatments relieving the human pathological condition should have a similar beneficial effect on behavioral and/or cognitive abnormalities modeled in animals.

2.2 Behavioral Read-Outs in Relation to Distinct Symptom Classes

Schizophrenia is a multisymptomatic disorder that includes distinct but often coexisting symptom classes. These are commonly referred to as positive, negative, and cognitive symptoms (Tandon et al. 2009). Positive symptoms are features that are normally not present in healthy individuals but appear as a result of the disease. These include visual and/or auditory hallucinations, delusions, paranoia, major thought disorders, and psychomotor agitation. Negative symptoms refer to features that are normally present but are reduced or absent as a result of the disease process, including social withdrawal, apathy, anhedonia, alogia, and behavioral perseveration. Cognitive symptoms of schizophrenia typically involve disturbances in executive functions, working memory impairment, and inability to sustain attention. Taken together, schizophrenia is characterized by a wide spectrum of behavioral and cognitive dysfunctions that can readily undermine basic human processes of perception and judgment.

There is increasing recognition of the importance of negative and cognitive symptoms in schizophrenia, partly because currently available APDs show a limited clinical efficacy in improving these dysfunctions (Buchanan et al. 2007; Nelson and Winslow 2009; Tandon et al. 2010). Negative symptoms are typically classified as primary or secondary, with primary negative symptoms representing a core feature intrinsic to the disorder, whilst secondary negative symptoms are temporary and often attributable to effects imposed by acute psychotic episodes and/or APD treatment (Möller 2004). Similar to the primary negative symptoms, cognitive symptoms of schizophrenia appear to be a core feature of the disorder and represent a major contributor to functional disability (Bowie and Harvey 2006; Elvevag et al. 2000). Both primary negative as well as cognitive symptoms often precede the onset of full-blown psychotic episodes and persist subsequent to the pharmacologically controlled resolution of acute psychotic phases (Möller 2004; Reichenberg 2005).

Given the heterogeneous nature of symptoms in schizophrenia, basic researchers who aim to develop heuristic animal models of the disorder are left with the challenge to establish and implement a set of behavioral procedures that can be used to indicate clinical features of the positive, negative, and cognitive symptoms. As reviewed in detail elsewhere [(Castagne et al. 2009; Ellenbroek and Cools 2000a; van den Buuse 2010); Table 1], the most commonly used and likely also the most reliable behavioral indices of positive symptoms in animal models are hyperlocomotor activity and behavioral stereotypies, which are taken to indicate psychomotor agitation and presence of stereotyped behavior in acutely psychotic patients. The rationale of using tests for locomotor hyperactivity and behavioral stereotypies as indices for positive symptoms is based upon the principle that enhanced dopaminergic activity in mesolimbic and nigrostriatal dopamine systems leads to enhanced locomotor activity and (in the event of pronounced hyperdopaminergia) stereotyped behaviors (Castagne et al. 2009; Ellenbroek and Cools 2000a; van den Buuse 2010). This fits well with the clinical condition showing that enhanced subcortical dopamine activity is essential in precipitating positive symptoms of schizophrenia (Laruelle 2000), but on the other hand, contrasts somewhat with the empirical evidence showing that schizophrenic patients do not display locomotor hyperactivity (Perry et al. 2009). Related to this, enhanced behavioral and/or neurochemical sensitivity to acute dopaminergic and/or glutamatergic drug challenge such as amphetamine or phencyclidine (PCP) exposure is another widely acknowledged index for approximating positive symptoms in animal models (Jentsch and Roth 1999; Robinson and Becker 1986; Steinpreis 1996). Besides spontaneous and drug-induced changes in locomotor activity and stereotyped behaviors, loss of selective associative learning in the form of disruption of latent inhibition (LI) is another cross-species translational index relevant to positive symptoms of schizophrenia (Feldon and Weiner 1992; Weiner 2003; Weiner and Arad 2009; Table 1). Indeed, consistent with the aforementioned contribution of enhanced subcritical dopaminergic activity to positive symptoms of schizophrenia, LI is readily disrupted by experimental manipulations that induce subcortical hyperdopaminergia, and attenuated LI is also found in acutely ill schizophrenic patients with marked positive symptoms (Weiner 2003; Weiner and

Arad 2009). Some researchers further suggest that disruption of prepulse inhibition (PPI) may be relevant for probing positive symptoms in animal models (van den Buuse 2010), even though it should not be considered as a straightforward model of positive symptoms as such but is more likely to represent the "interface of psychosis and cognition" (Desbonnet et al. 2009; van den Buuse 2010). In fact, since sensorimotor gating in the form of PPI involves pre-attentional/-cognitive processes preventing sensory overload and cognitive fragmentation, it may be used as a predictive index of cognitive dysfunctions relevant to schizophrenia (Geyer 2006).

Even though several cardinal aspects of the negative symptoms of schizophrenia are only hardly amenable to direct investigations in animal models, including poverty of speech and affective flattening, several behavioral procedures can readily serve to experimentally study behavioral abnormalities relevant for negative symptoms. For example, since rodents are highly social animals, social interaction can be efficiently studied under experimental conditions (Crawley 2007) and can therefore be used to probe deficient social interaction as one of the hallmark negative symptoms in schizophrenia (Foussias and Remington 2010; Table 1). Likewise, anhedonia is another hallmark of negative symptoms in schizophrenia, and anhedonic behavior can be assessed relatively easily in rodents using specific tests such as the sucrose preference test (Table 1). There are also several behavioral/cognitive tests that can be used to approximate the presence of behavioral/cognitive perseveration, which is commonly observed in schizophrenia patients with marked negative/cognitive symptoms (Crider 1997; Murray et al. 2008; Yogev et al. 2003). As outlined in Table 1, such tests include spatial and nonspatial forms of reversal learning as well as tests allowing the assessment of LI perseveration.

Within recent years, translational approaches have largely concentrated on the cognitive aspects of schizophrenia, primarily because of two reason: Firstly, cognitive symptoms of schizophrenia appear to be a core feature of the disorder and a major contributor to functional disability (Bowie and Harvey 2006; Elvevag et al. 2000). Secondly, cognitive aspects of schizophrenia may be more amendable to experimental investigations compared to the more florid psychotic manifestations, and therefore, they can be investigated in a relatively correspondent manner both in humans and in animals. The recent MATRICS and CNTRICS initiatives have identified separate core domains of cognition, all of which are (to a certain extent) affected in schizophrenia and which have to be treated to meet therapeutic needs (Green et al. 2004; Marder 2006; Young et al. 2009). These include working memory, attention/vigilance, reasoning and problem solving, processing speed, visual learning and memory, verbal learning and memory and social cognition (Green et al. 2004; Marder 2006; Young et al. 2009). As shown in Table 1, most of these cognitive domains can be experimentally addressed in animal models by the use of specific test batteries that characterize these domains. Hence, implementation of tests in existing or prospective animal models (see Sect. 3) is expected to significantly advance our understanding of the nature and possibly also the treatment of cognitive symptoms of schizophrenia.

3 Experimental Manipulations to Induce Schizophrenia-Relevant Brain Disease

In principal, most of the available rodent models of schizophrenia fit into four different induction categories, namely (1) pharmacological, (2) genetic, (3) lesion, and (4) neurodevelopmental manipulations. Notably, some of the currently used models fit into more than one category, and different induction methods can be combined so as to take into account multiple pathophysiological and/or genetic aspect of the disorder. The four cardinal induction categories are discussed in the succeeding sections.

3.1 Pharmacological Models

Pharmacological models of schizophrenia are driven by known or presumed neurochemical imbalances pertinent to the disorder's pathophysiology. Alterations in the central dopamine (DA) system have been discussed for decades, originally based on evidence that the therapeutically effective APDs act, at least in part, by blocking DA receptors, especially the DA D_2 receptor subclass (Seeman 1987) and that DA-stimulating drugs can induce psychosis-like behavior in nonpsychotic human subjects and exacerbate (positive) symptoms in schizophrenic patients (Carlsson et al. 2001; Howes and Kapur 2009). Subsequently, the putative impact of a hypofunctioning cortical DA system has been incorporated into the theories of altered DA functions in schizophrenia (Carlsson et al. 2001; Howes and Kapur 2009). In addition to these cortical-subcortical DA imbalances, functional changes in serotonergic and glutamatergic transmission seem highly relevant for the disorder (Abi-Dargham et al. 1997; Carlsson et al. 2001; Coyle et al. 2003; Javitt 2007). The current consensus is that alterations of these neurotransmitter systems either lead to a functional imbalance of DA transmission via interaction with the DA system, and/or contribute pathophysiologically to schizophrenia by direct non-dopaminergic actions. Finally, alterations in the central γ-aminobutyric acid (GABA) (Benes and Berretta 2001; Lewis et al. 2005) and cholinergic (Martin and Freedman 2007) systems have also been in the focus of attention by virtue of their modulatory functions at the relevant synapses and their impact on cognitive functions known to be impaired in schizophrenia.

Pharmacological models using acute and/or chronic administration of dopamine-releasing agents such as amphetamine or preferential dopamine receptor agonists such as apomorphine were among the first manipulations used to experimentally induce psychosis-related abnormalities in both animal models and humans [for a historical account, see Baumeister and Francis (2002)]. Indeed, behavioral changes induced by dopamine-stimulating drugs have been widely employed as screening procedures for the detection of compounds with potential antipsychotic properties (Table 2). However, even though such models may be relevant to

Table 2 Summary of schizophrenia-relevant abnormalities as identified in various pharmacological models (rats/mice)

	Behavioral, cognitive, and pharmacological functions						
Experimental manipulation	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	References
Acute amphetamine treatment	$\downarrow^{a,b}$	$\downarrow^{a,b}$	ND	ND	ND	$\uparrow^{a,b}$	Mansbach et al. (1988), Swerdlow et al. (1986), Warburton et al. (1994), Weiner et al. (1997a, b)
Chronic amphetamine treatment						$\uparrow$	Kokkinidis and Anisman (1981), Robinson and Becker (1986)
Withdrawal from amphetamine	$\downarrow^{a,b}$	$\downarrow$	$\downarrow/=$	$\downarrow$	ND	$\uparrow$	Featherstone et al. (2007a, b), Featherstone et al. (2008), Fletcher et al. (2005, 2007), Murphy et al. (2001), Peleg-Raibstein et al. (2008, 2006a, b, c, 2009), Russig et al. (2002, 2005), Tenn et al. (2005a, b)
Acute NMDA antagonists	$\downarrow^{b}$	$\downarrow^{b}$	$\downarrow^{b}$	$\downarrow^{a,b}$	$\downarrow^{b}$	$\uparrow^{b}$	Amitai et al. (2007), Chatterjee et al. (2011), Egerton et al. (2005), Geyer et al. (2001), Jentsch and Roth (1999), Mansbach and Geyer (1989), Mouri et al. (2007), Nabeshima et al. (1986), Paine and Carlezon (2009), Sams-Dodd (1995, 1996)
Chronic NMDA receptor antagonist	$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow^{b}$	$\uparrow^{a,b}$	Amitai et al. (2007, Becker and Grecksch (2004), Becker et al. (2003), Enomoto and Floresco (2009), Jentsch and Roth (1999), Lee et al. (2005), Mouri et al. (2007), Sams-Dodd (1999)
Withdrawal from NMDA antagonists	$\downarrow/=$	$=$	$\downarrow$	$\downarrow^{a,b\ NR}$	$\downarrow$	$\uparrow$	Amitai and Markou (2010), Becker and Grecksch (2004), Becker et al. (2003), Chatterjee et al. (2011), Paine and Carlezon (2009), Seillier and Giuffrida (2009), Tenn et al. (2005b)

(continued)

Table 2 (continued)

Experimental manipulation	Behavioral, cognitive, and pharmacological functions						References
	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	
Postnatal PCP treatment	ND	↓	↓	ND	ND	↑	Andersen and Pouzet (2004), Depoortere et al. (2005), Mouri et al. (2007), Sircar (2003), Tenn et al. (2005a), Wang and Johnson (2007)
Postnatal blockade of NMDA receptors	ND	↓[b]	↓	ND	ND	↑	Wedzony et al. (2008a, b)
Pretnatal MK-801 treatment						↑	Abekawa et al. (2007)
Postnatal MK-801 treatment	ND	↓	↓	ND	ND	ND	Baier et al. (2009), Stefani and Moghaddam (2005), Uehara et al. (2009)

Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively; the hyphens indicate that no changes were detected relative to the corresponding control manipulation (vehicle treatment)

ND not determined, *NR* no response to: APD treatment

[a]Normalization by typical (first-generation) APDs

[b]Normalization by atypical (second-generation APDs)

the study of neurochemical processes underlying the precipitation of positive symptoms, they readily fall short in capturing cardinal aspects of negative and cognitive symptoms of schizophrenia (Table 2). A clear refinement of acute and/or chronic administration of dopamine-stimulating drugs is the amphetamine withdrawal model (Featherstone et al. 2007a, b; Peleg-Raibstein et al. 2008, 2006a, b; Russig et al. 2002), which has been developed in the context of the endogenous dopamine sensitization theory of schizophrenia (Laurent et al. 2000; Lieberman et al. 1997). In contrast to acute amphetamine administration models, amphetamine withdrawal models have been shown to mimic at least certain aspects of cognitive dysfunctions relevant for schizophrenia (Featherstone et al. 2008; Fletcher et al. 2007).

The initial observation that administration of NMDA receptor antagonists such as ketamine or phencyclidine (PCP) disrupt various cognitive process and induce psychosis-like states in humans have led to the establishment of glutamatergic pharmacological models of schizophrenia (Kantrowitz and Javitt 2010). In essence, these models are based on acute or chronic treatment with NMDA receptor antagonists, including ketamine, PCP, and dizocilpine (MK-801), and more recently, such pharmacological agents have also been used to study the effects of withdrawal from NMDA antagonist exposure (Castner et al. 2004; Mouri et al. 2007; Nabeshima et al. 2006). Compared to dopamine-related pharmacological models, it appears that pharmacological NMDA receptor blockade models can capture a broader spectrum of schizophrenia-related dysfunctions, and notably, they may be more adequate in capturing positive, negative, and cognitive symptoms of schizophrenia (Table 2).

Hallucinogens acting on serotonin (5-HT) receptors, including lysergic acid diethylamide (LSD), psilocybin and mescaline, induce visual hallucinations in humans and cause characteristic behavioral signs in animals (Vollenweider and Kometer 2010). In rodents, acute or chronic treatments with such hallucinogenic drugs induce a set of measurable behavioral abnormalities such as paroxysmic scratching, forepaw treading, head twitches, and lower lip retraction (Cook et al. 1992; Vanover et al. 2006). Antagonism of the behavioral effects of serotonergic hallucinogens in animals would thus appear to provide a possible behavioral model for assessing antipsychotic activity, especially in relation to the suggested role of 5-HT receptor abnormalities in schizophrenia (Abi-Dargham et al. 1997). Similarly, based on the suggested role of cholinergic changes in the pathophysiology of schizophrenia (Barak 2009; Martin and Freedman 2007) acute or chronic administration of a cholinergic receptor antagonist, including scopolamine, dihydro-β-erythroidine (DHBE), or trihexyphenidyl, have been shown to robustly disrupt schizophrenia-relevant cognitive functions and to further induce other hallmark behavioral abnormalities such as disruption of LI and PPI (reviewed in Barak 2009; Barak and Weiner 2011). However, the full potential of cholinergic manipulations in preclinical research of schizophrenia still awaits further validation (Barak 2009).

3.2 Genetic Models

It has long been recognized that schizophrenia is a heritable disorder that probably involves multiple genetic abnormalities with relatively modest effects across large populations (Sullivan 2005). There have been tremendous efforts to identify potential schizophrenia susceptibility genes using single nucleotide polymorphisms (SNPs) approaches, and such investigations have put forward a number of genes that may be relevant for the genetic etiology of this disorder, including neuregulin-1 (NRG-1), catechol-*O*-methyltransferase (COMT), and disrupted in schizophrenia-1 (DISC-1) (Gogos and Gerber 2006; Harrison and Weinberger 2005). However, many of these genes have been identified and portrayed in relatively small populations, and recent research suggests that several of the presumed candidate genetic factors do not reach significance in association studies conducted in larger populations (Nieratschker et al. 2010; Sanders et al. 2008). Yet, discrete genetic abnormalities may contribute to distinct forms of behavior and cognition, so that individual schizophrenia susceptibility genes may be closely linked to a particular endophenotype of the disorder (Gottesman and Gould 2003; Gould and Gottesman 2006). For example, sensorimotor-gating deficiency in the form of PPI disruption appears to be a relatively robust endophenotype of schizophrenia which has a clear genetic contribution (Quednow et al. 2011, 2009; Roussos et al. 2011). Therefore, it may not be surprising that significant alterations in PPI are also reported in numerous genetic models which have been designed in relation to specific schizophrenia susceptibility genes (Table 3).

As a manipulative tool, the genetic approach to neuropsychiatric research has been a relatively recent event (Tarantino and Bucan 2000). Despite this, there is a rapidly increasing number of genetic mouse models that report behavioral, cognitive, and/or pharmacological alterations reminiscent of schizophrenic disease, so that the collection of genetic models presented in Table 3 is far from exhaustive. Further refinement based on temporal, regional, and cell-type specific transgenic technology will add considerable power to current genetic approaches (Abazyan et al. 2010; Ayhan et al. 2011; Kellendonk et al. 2009), and in overcoming interpretative issues concerning developmental compensation. It is expected that the genetic approach will be instrumental in the identification of the roles of specific candidate genes in the disease process of schizophrenia, and the interaction between genetic and environmental factors associated with the etiopathology of schizophrenia (Abazyan et al. 2010; Ayhan et al. 2011; Laviola et al. 2009), perhaps even paving the way to possible genetic interventions in the future (Lesch 1999).

3.3 Lesion Models

Although it has been known since Bleuler's and Kraepelin's early investigations (Bleuler 1911; Kraepelin 1919) that schizophrenia is not associated with gross brain degeneration or lesions, postmortem and imaging studies have been consistent in

Table 3 Summary of schizophrenia-relevant abnormalities as identified in various genetic models (rats/mice)

	Behavioral, cognitive, and pharmacological functions						
Experimental manipulation	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	References
$NR1^{-/-}$	ND	$\downarrow^{a,b}$	ND	ND	$\downarrow^{b}$	$\uparrow$	Duncan et al. (2006), Mohn et al. (1999), Moy et al. (2006)
mGluR5 KO	$\downarrow$	$\downarrow^{b}$	$\downarrow^{b,NR}$	ND	ND	$\uparrow^{b}$	Brody et al. (2004), Gray et al. (2009), Lipina et al. (2007)
$AKT1^{-/-}$	ND	ND	$\downarrow$	ND	ND	$\uparrow$	Eastwood et al. (2007)
$Nurr1^{+/-}$	ND	$\downarrow$	ND	BD	ND	$\uparrow$	Eells et al. (2006), Rojas et al. (2007)
$COMT^{+/-}$	ND	=	$\uparrow$/=	ND	=	ND	Babovic et al. (2008), Gogos et al. (1998), Papaleo et al. (2008)
$COMT^{-/-}$	ND	=	$\uparrow$	ND	ND	$\downarrow$	Babovic et al. (2008, 2007), Gogos et al. (1998), Huotari et al. (2002), Papaleo et al. (2008)
COMT–Val Tg	ND	=	$\downarrow$	ND	ND	$\uparrow$	Papaleo et al. (2008)
$Grin1^{D481N/K483Q}$	$\uparrow^{b}$	=	$\downarrow^{b}$	ND	$\downarrow$	$\downarrow$	Ballard et al. (2002), Labrie et al. (2008)
DAT KO	ND	$\downarrow^{b}$	$\downarrow$	ND	ND	$\downarrow^{a,b}$	Barr et al. (2004), Gainetdinov et al. (1999), Giros et al. (1996), Powell et al. (2008), Spielewoy et al. (2001)
$SynGAP^{+/-}$		$\downarrow$	$\downarrow$		=	$\downarrow^{b}$	Guo et al. (2009)
Alpha5 $GABA_A$ in hippocampus	$\downarrow$	$\downarrow$	$\downarrow$	ND	ND	ND	Gerdjikov et al. (2008), Hauser et al. (2005), Yee et al. (2004)
GLAST KO	ND	=	ND	ND	=	$\uparrow^{a}$	Karlsson et al. (2008, 2009)
DISC1 deletion	ND	ND	$\downarrow$	ND	ND	ND	Koike et al. (2006), Kvajo et al. (2008)
DISC1 Q31 L	$\downarrow^{b,NR}$	$\downarrow^{a,b,NR}$	$\downarrow$	ND	$\downarrow$	ND	Clapcote et al. (2007)
DISC1 L100P	$\downarrow^{b}$	$\downarrow^{a,b}$	$\downarrow$	$\downarrow$	=	ND	Clapcote et al. (2007)
DISC1-C Tg	ND	ND	$\downarrow$	ND	$\downarrow$	ND	Li et al. (2007)
DISC1-DN	ND	$\downarrow$	ND	ND	ND	ND	Hikida et al. (2007)

(continued)

Table 3 (continued)

Experimental manipulation	Behavioral, cognitive, and pharmacological functions						References
	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	
DISC1-hu Tg	ND	=	↓	ND	↓	ND	Pletnikov et al. (2008)
D2R tg	ND	=	↓	ND	ND	ND	Kellendonk et al. (2009, 2006)
Reeler$^{+/-}$	ND	↓	=	=	ND	↑	Krueger et al. (2006), Tueting et al. (2006)

Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively; the hyphens indicate that no changes were detected relative to the corresponding control genetic background

ND not determined, *NR* no effects of APD treatment

[a]Normalization by typical (first-generation) APDs

[b]Normalization by atypical (second-generation APDs)

showing structural as well as functional alteration in selective brain regions, including the prefrontal cortex, temporal regions, and ventral striatum as critical components in schizophrenia (Deakin and Simpson 1997; Harrison 1999, 2004; Laruelle and Abi-Dargham 1999; Lewis et al. 1999; Weinberger et al. 2001; Weinberger and Lipska 1995). The use of selective brain lesions in adult animals has been instrumental in providing a first approximation to the functional importance of such identified structures in relation to schizophrenia. For example, selective lesions of the entorhinal cortex can disrupt selective attention, enhance reaction to low doses of systemic amphetamine, and impair reversal learning (Table 4). It appears, however, that similar lesions fail to affect spatial as well as nonspatial working memory performance [(Marighetto et al. 1998; Pouzet et al. 1999; Yee and Rawlins 1998); Table 4].

Admittedly, whilst selective experimental lesions are indispensable in animal neuropsychological research, their utility as a model of schizophrenia seems limited in comparison to models of neurological disorders with more discrete or localized neuropathology such as the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of Parkinson's disease (Dauer and Przedborski 2003; Langston and Ballard 1984). Moreover, selective lesions introduced into adult animals also bear little resemblance to the subtle and developmental neuropathology observed in schizophrenia (Benes 2000; Harrison 1999). One promising approach, however, has been to incorporate the selective lesion approach within the context of neurodevelopment. Lipska et al. (1993) pioneered the neonatal ventral hippocampal (nVHP) lesion model in rats based on the neurodevelopmental hypothesis of schizophrenia (Weinberger 1987). This model has been shown to mimic the postpubertal onset of behavioral abnormalities, congenital hippocampal area damage, or dysfunction of the limbic dopaminergic system [reviewed in (Lillrank et al. 1995; Lipska and Weinberger 2000); Table 4]. More recent attempts have also focused on neonatal lesions of the entorhinal cortex (Schmadel et al. 2004), medial prefrontal cortex (Bennay et al. 2004; Schwabe et al. 2004), as well as the amygdala (Daenen et al. 2001, 2003; Hanlon and Sutherland 2000), which have thus far yielded mixed results, however (Table 4).

3.4 Neurodevelopmental Models

Over the last two decades, the neurodevelopmental hypothesis of schizophrenia (Weinberger 1987) has been highly influential in shaping our current thinking about modeling the disease in animals (Ellenbroek and Cools 2000b; Lillrank et al. 1995; Lipska and Weinberger 2000; Meyer and Feldon 2010; Weiss and Feldon 2001; Piontkewitz et al. 2012). One aim common to the neurodevelopmental approaches is to identify the etiological processes whereby the brain, following specific triggering events, develops into a "schizophrenia brain" over time.

One important feature of neurodevelopmental animal models is that the early cerebral insult does not necessarily induce static effects on brain and behavioral functions. Rather, the structural and functional effects of early brain lesions are

Table 4 Summary of schizophrenia-relevant abnormalities as identified in various neuropathological models (rats/mice)

	Behavioral, cognitive, and pharmacological functions						
Experimental manipulation	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	References
Entorhinal cortex lesions	↓[a]	ND	–	ND	ND	↑	Oswald et al. (2002), Pouzet et al. (1999), Yee et al. 1995)
Neonatal entorhinal cortex	ND	–	↓	ND	ND	↑	Schmadel et al. (2004)
Amygdala lesions	↑[a,NR,b]	↓[b]	ND	ND	ND	ND	Schiller et al. (2006), Shoemaker et al. (2003), Weiner (2003), Weiner and Feldon 1997)
Prefrontal cortex lesions	↑[a,NR,b]/=	↑/↓/–	↓/–	ND	ND	↑	Joel et al. (1997), Lacroix et al. (1998, 2000), Schiller et al. (2006), Schwabe et al. (2004), Yee (2000)
Neonatal prefrontal cortex lesions	ND	↑/↓	↓	ND	↓	↑	Brake et al. (2000), Lipska et al. (1998), Schneider and Koch (2005), Schwabe et al. (2004, 2006)
Neonatal ventral hippocampal lesions	↓	↓[a,NR,b]	↓	↓	↓[b,NR]	↑[a,b]	Al-Amin et al. (2001), Becker et al. (1999), Brady et al. (2010), Grecksch et al. (1999), Le Pen et al. (2003), Le Pen and Moreau (2002), Lipska (2004), Lipska et al. (2002, 1993, 1995), Lipska and Weinberger (1994, 2002), Sams-Dodd et al. 1997)
Nucleus accumbens shell lesions	↓[a]	↓	↓	ND	ND	↑	Gal et al. (1997), Kodsi and Swerdlow (1994), Weiner (2003), Weiner and Feldon (1997), Weiner et al. (1996)

Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively; the hyphens indicate that no changes were detected relative to the corresponding control manipulation (sham lesions)

ND not determined, *NR* no effects of APD treatment

[a]Normalization by typical (first-generation) APDs

[b]Normalization by atypical (second-generation APDs)

progressive in nature and are therefore often dependent on postnatal maturational processes (Meyer and Feldon 2010). This developmental component is particularly relevant to schizophrenia because the disorder's pathophysiological and neuropathological mechanisms are assumed to be progressive in nature (Borgwardt et al. 2009; Rapoport et al. 2005; Wood et al. 2008). Hence, neurodevelopmental animal models of schizophrenia allow a multifaceted, longitudinal monitoring of the disease process as it unfolds during the course of neurodevelopment from juvenile to adult stages of life and the concomitant evaluation of the influence of external environmental factors.

One class of developmental models in rodents makes use of environmental manipulations during postnatal brain development and maturation (Cirulli et al. 2003; Lehmann et al. 2000; Pryce and Feldon 2003; Pryce et al. 2002; Weiss and Feldon 2001). This class of models comprises early handling, maternal separation, and isolation rearing (Table 5). It is hypothesized that deviations from the "normal" maturation processes of the nervous system can be triggered by such manipulations, giving rise to an aberrant brain prone to the emergence of psychotic-like behavior. One difficulty of this approach is however the lack of a clear definition of a normal early-life environment in laboratory animals, and therefore the precise nature of the environmental manipulations remains somewhat ill-defined.

An alternative approach thus makes use of specific chemical agents to interfere with early (prenatal and perinatal) development of the CNS, such as methylazoxymethanol acetate (MAM), nitric oxide synthase (NOS) inhibitors, or cytosine arabinoside (Ara-C) to disrupt maturation of neurons and/or synaptogenesis during distinct periods of fetal brain development (reviewed in Lodge and Grace (2009); Table 5). Attempts in this direction have, however, yielded inconsistent results [e.g., see Jongen-Rêlo et al. (2004)]. Moreover, while these models may be instrumental in shedding light on the critical developmental processes involved, these toxic agents themselves have not been implicated in causing schizophrenia.

Another class of animal models is based on epidemiological evidence, including prenatal malnutrition (Brown and Susser 2008), obstetric complications (Cannon et al. 2002), prenatal stress (Selten et al. 1999; van Os and Selten 1998), and prenatal or perinatal exposure to bacterial or viral infections (Brown 2006, 2008; Brown and Derkits 2010). In contrast to experimental models in which the critical manipulations are conducted in adulthood, epidemiology-driven models of schizophrenia are based on interference with early brain development resulting from exposure to prenatal and/or perinatal environmental insults. One immediate consequence of such early brain disruption is that it leads to wide-ranging neurodevelopmental sequelae, eventually leading to multiple neuroanatomical and neurochemical abnormalities in adult life [reviewed in Meyer and Feldon (2010)]. Indeed, the emergence of wide-ranging neurodevelopmental sequelae and induction of a wide spectrum of schizophrenia-relevant behavioral, cognitive, and pharmacological abnormalities is a common feature of most epidemiology-driven models of schizophrenia and related disorders [Meyer and Feldon (2010); Table 5]. This offers an excellent opportunity to study the relationship between multiple structural and functional brain abnormalities with relevance to schizophrenia and to identify possible causal links between distinct brain and behavioral dysfunctions.

Table 5 Summary of schizophrenia-relevant abnormalities as identified in various neurodevelopmental models (rats/mice)

	Behavioral, cognitive, and pharmacological functions						
Experimental manipulation	Latent inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	References
Prenatal exposure to repeated restraint stress	↑/–	–	↓	ND	↓	↑	Bethus et al. (2005), Burton et al. (2006), Deminiere et al. (1992), Gue et al. (2004), Henry et al. (1995), Lee et al. (2007), Lehmann et al. (2000), Meunier et al. (2004), Shalev and Weiner (2001)
Prenatal exposure to variable stress	ND	↓	↓	ND	↓	↑	Koenig et al. (2005), Markham et al. (2010)
Prenatal corticosterone or dexamethasone treatment	↓/–	↓/–	ND	ND	↓	↑	Diaz et al. (1997, 1995), Hauser et al. (2006, 2009), Shalev and Weiner (2001)
Prenatal influenza exposure	ND	↓[a]	ND	ND	↓	↑	Moreno et al. (2011), Shi et al. (2003)
Prenatal poly(I:C) exposure	↓[a,b]	↓[a,b]	↓[b]	ND	↓	↑[a,b]	Bitanihirwe et al. (2010), Cardon et al. (2010), Li et al. (2009), Makinodan et al. (2008), Meyer et al. (2008a, 2005, 2006a, b, 2008b, c, 2006c), Ozawa et al. (2006), Piontkewitz et al. (2011, 2009), Shi et al. (2003), Smith et al. (2007), Vuillermot et al. (2011, 2010), Wolff and Bilkey (2008), Zuckerman et al. (2003a, b), Zuckerman and Weiner (2005)
Prenatal LPS exposure	ND	↓[a,b]	↓	ND	↓	↑	Basta-Kaim et al. (2011), Borrell et al. (2002), Coyle et al. (2009), Fortier et al. (2004, 2007), Golan et al. (2005), Romero et al. (2007, 2010)

Prenatal IL-6 exposure	↓	↓	ND	ND	↓	↑	Smith et al. (2007)
Prenatal turpentine exposure	ND	↓	↓	ND	ND	↑	Aguilar-Valles et al. (2010), Aguilar-Valles and Luheshi (2011), Fortier et al. (2007)
Prenatal MAM treatment	↓	↓	↓	↓	↓	↑	Featherstone et al. (2007b), Flagstad et al. (2005, 2004), Hazane et al. (2009), Le Pen et al. (2006), Leng et al. (2005), Lodge and Grace (2009), Moore et al. (2006), Penschuck et al. (2006), Phillips et al. (2012)
Developmental vitamin D deficiency	↓	–	ND	ND	ND	↑[a]	Becker et al. (2005), Burne et al. (2004, 2006), Eyles et al. (2006), Kesby et al. (2006), O'Loan et al. (2007)
Prenatal protein deprivation	↓	↓	ND	↓	ND	↑	Brioni et al. (1986), Palmer et al. (2008, 2004), Ranade et al. (2008), Tonkiss et al. (1998)
Cesarean section	ND	–	–	ND	↓	↑	Boksa et al. (1995), El-Khodor and Boksa (1998), Vaillancourt and Boksa (1998), Venerosi et al. (2004)

Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively; the hyphens indicate that no changes were detected relative to the corresponding control treatment

ND not determined, *IL*, interleukin, *LPS* lipopolysaccharide, *poly(I:C)* polyriboinosinic-polyribocytidilic acid

[a]Normalization by typical (first-generation) APDs

[b]Normalization by atypical (second-generation APDs)

4 Selecting the Right Model for Assessing Antipsychotic Drug Actions

Even though a plethora of schizophrenia-relevant animal behavioral/cognitive paradigms exist (Table 1), it is a challenging task to pick the right one(s) in attempts to assess APD actions. Indeed, there is no gold standard test or test battery for this purpose. The obvious reason for this is that performance in distinct behavioral/cognitive tests is, at in least part, determined by functions governed by specific neural networks and neurotransmitter systems. For example, experimentally induced hyperlocomotor activity typically seen following systemic amphetamine treatment is mainly driven by increased dopaminergic signaling in striatal structures (Creese and Iversen 1975). It is therefore not surprising that major dopamine receptor blockers such as the typical APD haloperidol are highly efficient in mitigating amphetamine-induced hyperactivity, whereas pharmacological compounds with minimal dopamine receptor blockade potential are much less so (Castagne et al. 2009; Ellenbroek and Cools 2000a; van den Buuse 2010). For this reason, it may be more fruitful to evaluate the effects of APDs against psychotomimetic agents that are known to modulate multiple neurotransmitter systems concomitantly. One class of psychotomimetic compounds that has received increasing appreciation in this context are NMDA receptor antagonist such PCP or MK-801, which have appreciable and simultaneous effects on the glutamatergic, dopaminergic, and serotonergic systems (Abi-Dargham et al. 1997; Carlsson et al. 2001; Coyle et al. 2003; Javitt 2007) and which are capable of inducing behavioral/cognitive abnormalities pertinent to positive, negative, and cognitive symptoms of schizophrenia (Table 2). Compared to primary dopaminergic psychotomimetic drugs such as amphetamine, the use of NMDA receptor antagonists can thus be expected to provide a broader spectrum of disturbances, against which potential APD activity can be assessed more thoroughly.

It is also important to realize that the eventual effects of APDs can be critically influenced by pre-existing neuronal and/or neurochemical state parameters. For example, whilst many atypical APDs such as clozapine are capable of normalizing cognitive impairments induced by specific pharmacological (Table 2), genetic (Table 3), neuropathological (Table 4), or neurodevelopmental (Table 5) manipulations, the same compounds can impair cognitive performance in non-manipulated control animals (Arguello and Gogos 2006; Barak and Weiner 2011; Castner et al. 2004; Meyer and Feldon 2010; Meyer et al. 2005, 2010; Moser et al. 2000; Swerdlow and Geyer 1998; Weiner 2003). Hence, the direction of effects (i.e., beneficial vs. detrimental) associated with APD activity can be critically influenced by the "pathophysiological background" of the animals. One implication is that non-manipulated "control" animals may not be ideally suited for screening APD activity in behavioral and cognitive tests because they are unlikely to reveal the drugs' anticipated beneficial effects on behavioral and cognition.

Assessing APD activity in non-manipulated animals may further obscure the expected outcomes because of ceiling or floor effects. For instance, PPI of the acoustic startle reflex has become one of the most widely used behavioral

paradigms to study schizophrenia-relevant functions, and as such, it has proven to be successful in detecting beneficial effects of APDs against experimentally induced sensorimotor-gating deficiency (Swerdlow and Geyer 1998; Swerdlow et al. 2008). The PPI paradigm can also be used to detect APD activity per se, that is, to identify PPI-potentiating effects of APDs in otherwise non-manipulated animals (Swerdlow and Geyer 1998; Swerdlow et al. 2008). In these attempts, however, one needs to carefully consider the fact that some mouse and rat species show relatively high levels of PPI under basal (non-manipulated) conditions, and this can readily preclude the anticipated PPI potentiation by APDs (Depoortere et al. 1997; Ouagazzal et al. 2001). One possible way to circumvent this problem is to adjust the parametric conditions of the PPI procedure such as that the level of PPI is minimal under basal (non-manipulated) conditions, so that potential PPI-potentiating effects of APDs are not masked by ceiling effects. A similar rationale would also apply to the behavioral/cognitive paradigms, including the LI procedure. Indeed, the latter has been shown to reliably detect APD actions even in otherwise non-manipulated animals, especially when the amount of LI in non-manipulated control animals is kept at minimum using specific parametric conditions such as low number of CS pre-exposure and/or conditioning trials (Arguello and Gogos 2006; Barak and Weiner 2011; Castner et al. 2004; Meyer and Feldon 2010; Meyer et al. 2005; Moser et al. 2000; Swerdlow and Geyer 1998; Weiner 2003).

Basic researchers aiming to explore APD activity in animals are also facing the challenge of selecting the appropriate experimental manipulation. As mentioned before, there are models of schizophrenia employing specific experimental manipulations developed according to specific pathophysiological or etiological hypotheses. The use of selective lesions in adult animals and the acute administration of psychotomimetic agents are indispensable tools in the elucidation of the contribution of specific brain regions or neurotransmitters to the genesis of a specific symptom or collection of symptoms, and enjoy some degrees of predictive validity. However, they may be inaccurate, if not inadequate, in capturing the etiological mechanisms or ontology of the disease needed for a complete understanding of the disease and may be limited in the discovery of novel compounds for the treatment of negative and cognitive symptoms of schizophrenia (see Sect. 5).

Under the prevailing consensus of schizophrenia as a disease of neurodevelopmental origin, we have seen the establishment of neurodevelopmental animal models which aim to identify the etiological processes whereby the brain, following specific triggering events, develops into a "schizophrenia-like brain" over time. This approach is not only wider in its scope than conventional lesion and pharmacological models, but it also readily lends itself to address data and hypotheses concerning the subtle histopathological findings revealed in postmortem and imaging studies (Harrison 2004; Laruelle and Abi-Dargham 1999; Shenton et al. 2001), as well as the genetic (Harrison and Weinberger 2005; Kim et al. 2011; Sullivan 2005) and environmental (Brown 2011; McDonald and Murray 2000) risk factors.

The heuristic value of the neurodevelopmental models for preclinical schizophrenia research is that they can successfully account for several aspects of the disorder's epidemiology, pathophysiology, symptomatology, and treatment:

1. Many neurodevelopmental models such as the vHPC lesion, MAM, and prenatal immune activation models can mimic a broad spectrum of behavioral, cognitive, and pharmacological abnormalities directly implicated in schizophrenic disease. These models allow pharmacological screens against multiple and coexisting schizophrenia-related dysfunctions, which together may critically help to reduce potential confounds of "false-positive" outcomes in preclinical behavioral tests of compounds against negative and cognitive symptoms of schizophrenia.
2. In many neurodevelopmental models (e.g., vHPC lesion, MAM, and prenatal immune activation models), the full spectrum of behavioral, cognitive, and pharmacological abnormalities is dependent on postpubertal maturational processes and thus only emerges in adult but not prepubertal subjects (Meyer and Feldon 2010). This maturational dependency offers the opportunity to evaluate the efficacy of early preventive interventions based on "prodromal-like signs" of schizophrenia and to identify progressive brain changes of the course of time.
3. By adjusting dosage and/or timing of the experimental manipulation, many neurodevelopmental models can be modified in such a way that the experimental manipulation only leads to a restricted pathological phenotype in the offspring. This feature strongly facilitates the identifications of possible synergistic interactions between the experimental manipulation of interest and other genetic or other environmental risk factors implicated in schizophrenia etiology.
4. Because they are often based on epidemiological findings, many neurodevelopmental models (e.g., prenatal immune activation and obstetric complication models) have intrinsic etiological significance to schizophrenia.

5 Can Behavioral Models Predict Therapeutic Efficacy of Novel Compounds?

In most cases, an animal model of a particular disease is initially established based on what is known about a disease so that the critical anchor between the animal model and the human disease is what is already known about the latter (Feifel and Shilling 2010). Driven by the rapidly growing literature implicating specific genetic, epigenetic, and environmental abnormalities in the etiopathogenesis and pathophysiology of schizophrenia (Brown 2011; Kim et al. 2011; Meyer and Feldon 2010), a great deal of current interest in preclinical schizophrenia research has focused on the characterization of their effects on distinct neurobiological phenotypes pertinent to schizophrenic disease. Indeed, such "neuroscience- or genetics-driven experimental approaches" seem to increase our capability to identify novel neural mechanisms that may be involved in the pathogenesis of schizophrenia psychopathology and neuropathology (Kvajo et al. 2012; Meyer and

Feldon 2010; O'Connell et al. 2011). Unfortunately, these laudable research efforts are often undermined by incomplete ascertainment of the predictive validity, so that many experimental models lack clear information about whether or not the modeled behavioral/cognitive traits respond selectively to APDs (Tables 2, 3, 4, and 5). Therefore, it may not be surprising that basic schizophrenia research has provided only incremental advances with respect to predicting the therapeutic efficacy of novel compounds against schizophrenia-relevant symptoms (Barak and Weiner 2011; Feifel and Shilling 2010; Moore 2010).

In view of the limited efficacy of APDs to normalize negative and cognitive symptoms, there is increasing recognition of the importance to develop novel pharmacotherapeutic approaches against these symptoms (Buchanan et al. 2007; Nelson and Winslow 2009; Tandon et al. 2010). With respect to the negative symptoms, animal models are readily capable of mimicking some associated core features such as deficits in social interaction, avolition, and anhedonia (Table 1), and several experimental models established in the context of schizophrenia have shown deficits in these domains following specific pharmacological, genetic, or environmental manipulations (Tables 2, 3, 4, and 5). However, anhedonia and other abnormalities related to the negative symptoms of schizophrenia are also prominent features of major depression and thus are by no means specific to schizophrenia (Treadway and Zald 2011). It therefore seems difficult, if not inappropriate, to assign strong validity for schizophrenia to an animal model that only displayed negative features in the absence of other co-expressed features that might link it more specifically to schizophrenia. As a consequence, the relative power of such approaches to predict therapeutic efficacy of novel compounds in the treatment of negative symptoms may be severely compromised and may lead to "false-positive" outcomes, i.e., to drugs that have shown promise in animal models but not in clinical trials (Moore 2010). The rate of such "false-positive" outcomes seems especially high for traditional back-translational psychopharmacological approaches such as acute or chronic treatment with PCP or other psychotomimetics: In such approaches, a number of drugs have been shown to mitigate or reverse negative psychopathological features, but only the minority of the tested compounds seem viable treatment options in the treatment of schizophrenia (Moore 2010). In spite of this criticism, it needs to be pointed out that there is thus far no in-depth analysis of the rate of such "false-positive" outcomes provided by traditional back-translational psychopharmacological approaches in animals. It also needs to be acknowledged that a number of factors can readily affect the outcome of clinical studies, including placebo effect rates or target biology differences between rodents and humans. Therefore, it would appear premature at this point of time to fully discard the validity of conventional psychopharmacological models in the preclinical schizophrenia research.

As recently discussed in detail elsewhere (Barak and Weiner 2011), there is also still a gap between the initial recommendations provided by MATRICS, CNTRICS, and other initiatives and the implementation of animal behavioral/cognitive strategies that might truly lead to the discovery of novel compounds with therapeutic efficacy against the cognitive symptoms of schizophrenia. Again, traditional back-translational psychopharmacological approaches have tested a number of

putative "cognitive enhancers" for potential application in the treatment of cognitive symptoms in schizophrenia, but it still appears that such compounds are not superior to atypical APDs in the normalization of experimentally induced cognitive abnormalities in animal models of schizophrenia (Barak and Weiner 2011). In other words: Most of the available models lack the capacity to differentiate between the potentially beneficial effects of "cognitive enhancers" and APDs in basic schizophrenia research. This lack of distinction is particularly unsatisfactory in view of the fact that currently available APDs show a limited therapeutic efficacy in improving cognitive symptoms of schizophrenia (Buchanan et al. 2007; Nelson and Winslow 2009; Tandon et al. 2010) so that there is a clear discrepancy between the experimental data derived from animal models and the human clinical condition. It thus seems highly warranted to develop and implement novel models in which the experimental manipulations lead to schizophrenia-relevant cognitive dysfunctions that are resistant to APDs but selectively sensitive to "cognitive enhancers" (Barak and Weiner 2011).

6 Concluding Remarks

There has been a great deal of efforts to establish behavioral and cognitive tests that allow translation of schizophrenia-relevant human symptomatology to experimental conditions in animal models (Arguello and Gogos 2006; Lipska and Weinberger 2000; Meyer and Feldon 2010; Tarantino and Bucan 2000). Parallel to these efforts, a wide variety of experimental manipulations exist and are currently being used to induce schizophrenia-relevant brain and behavioral pathology. Whilst traditional pharmacological models may be useful as quick screening tool for detecting at least some predictable APD activities, they seem inappropriate in the development and evaluation of novel compounds with potential antipsychotic and/or pro-cognitive properties. Neurodevelopmental animals may be more adequate for the latter goal because they can mimic multiple schizophrenia-relevant brain and behavioral pathologies and incorporate the developmental component of the disorder. Yet, the multiplicity of existing models is testimonial to the multi-factorial nature of schizophrenia, and there are ample opportunities for their integration. Indeed, one ultimate goal must be to incorporate the successes of distinct models into one unitary account of the complex disorder of schizophrenia and to use such unitary approaches in the further development and evaluation of novel antipsychotic treatment strategies.

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