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FEATURE REVIEW

Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs

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The treatment of schizophrenia has evolved over the past half century primarily in the context of antipsychotic drug development. Although there has been significant progress resulting in the availability and use of numerous medications, these reflect three basic classes of medications (conventional (typical), atypical and dopamine partial agonist antipsychotics) all of which, despite working by varying mechanisms of actions, act principally on dopamine systems. Many of the second-generation (atypical and dopamine partial agonist) antipsychotics are believed to offer advantages over first-generation agents in the treatment for schizophrenia. However, the pharmacological properties that confer the different therapeutic effects of the new generation of antipsychotic drugs have remained elusive, and certain side effects can still impact patient health and quality of life. Moreover, the efficacy of antipsychotic drugs is limited prompting the clinical use of adjunctive pharmacy to augment the effects of treatment. In addition, the search for novel and nondopaminergic antipsychotic drugs has not been successful to date, though numerous development strategies continue to be pursued, guided by various pathophysiologic hypotheses. This article provides a brief review and critique of the current therapeutic armamentarium for treating schizophrenia and drug development strategies and theories of mechanisms of action of antipsychotics, and focuses on novel targets for therapeutic agents for future drug development.
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The therapeutic armamentarium for the treatment of schizophrenia has grown and diversified in the half century since the advent of chlorpromazine and the beginning of the pharmacologic era in psychiatry. Over the past decade, much of our attention regarding the treatment for schizophrenia and related psychotic disorders has focused on a new class of antipsychotic medications. The reintroduction of clozapine represented a major step forward, and led to the proliferation of 'atypical' or second-generation antipsychotics (SGAs), including risperidone, olanzapine, quetiapine, ziprasidone, sertindole and zotepine. In fact, there is growing evidence that most of the new medications can offer some advantages over 'typical' or first-generation antipsychotics (FGAs) such as greater improvement in negative symptoms, cognitive impairment, relapse prevention, functional capacity, and quality of life with fewer extrapyramidal symptoms (EPS), and less tardive dyskinesia (TD) (for a review, see Miyamoto *et al*[1]). Accordingly, many clinicians are prescribing these new antipsychotics as first-line agents for acute and maintenance therapy for schizophrenia.[2–5] However, these advantages, thus far, have been regarded as incremental and not necessarily substantial. In addition, concerns about side effects such as EPS have been replaced by other distressing side effects, including weight gain, hyperglycemia and dyslipidemia. At present, we are still in the process of defining fully the clinical profiles of new agents in terms of the extent of their therapeutic efficacy and adverse effects, on a variety of other outcomes including cognition, affect, suicide, subjective response, social and vocational function, cost effectiveness, etc.[6]

Although intensive research on the new antipsychotic drugs has led to a greater understanding of the biochemical effects of these drugs, the pharmacological mechanisms underlying their various therapeutic properties remain to be identified. Moreover, an agent

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like clozapine that was clinically superior to other highly selective dopamine D_2 antagonists demanded reconsideration of the principal mechanisms of action of antipsychotics as well as the pathophysiological mechanisms in schizophrenia.[6,7] In addition, the limitations of existing antipsychotic drugs to alleviate all of the pathologic dimensions of the illness (ie negative symptoms, cognitive deficits and social disabilities) have produced an awareness that no single treatment may be sufficient and prompted the search for compounds that can be used adjunctively with antipsychotic drugs. Various adjunctive treatments, including benzodiazepines, lithium, anticonvulsants, antidepressants, beta-blockers and dopamine agonists, have been used to enhance the response to antipsychotic medications or to treat residual symptoms of chronic schizophrenia and comorbid conditions with schizophrenia (for reviews, see Miyamoto *et al*[5,8]). However, despite the prevalence of the use of adjunctive therapies in clinical practice, there are very few empirical data and theoretical rationale to support this practice. The development of additional novel strategies to obtain potentially new antipsychotic compounds and their adjuncts possessing unique pharmacological profiles with few side effects is being pursued based on specific hypotheses, and actually more agents with antipsychotic efficacy are being developed. (for reviews, see Miyamoto *et al*[5,9]). This article provides a brief review and critique of the current theory of mechanisms of action of antipsychotic drugs, and focuses on novel targets for therapeutic intervention and potential strategies for future drug development.

Current forms of treatment: first-generation antipsychotics and second-generation antipsychotics

The strategies and forms of treatment for schizophrenia vary according to the phase and severity of the illness. Pharmacologic treatment is the cornerstone and essential component of treatment for schizophrenia and its clinical management through the different stages of the illness. Although various psychosocial therapies, such as cognitive behavior therapy, psychoeducation and supported employment, are useful adjuncts to drug treatment,[8,10,11] they all require pharmacologic treatment to be maximally effective. In particular, adequate pharmacotherapy during the acute stage of the illness could set the stage for subsequent long-term treatment. Although all available pharmacological treatments have limitations in their effectiveness and are associated with uncomfortable side effects, it is an established fact that antipsychotics can improve the psychotic symptoms of schizophrenia and prevent their recurrence.[10,11] At present, a total of 11 different classes of antipsychotic medications are available in the US. Among them are the currently available FGAs (phenothiazines, butyrophenones and thioxanthenes) which, although effective, are far from being optimal treatments. Between 30 and 60% of patients with acutely exacerbated psychotic symptoms either fail to respond to these drugs or respond inadequately or partially.[12] In addition, they cause significant rates of undesirable acute and chronic adverse effects (for a review, see Miyamoto *et al*[9]). At this time, the only groups of patients in which the FGAs are clearly preferable are those for whom there is a clear indication for short- or long-acting injectable preparations (this will quickly change as injectable SGAs become more available), or who have a history of excellent response to a FGA with minimal side effects.[13,14]

Despite the superior clinical effectiveness and EPS profile of clozapine, its clinical utility is restricted by the propensity to cause agranulocytosis and mandatory hematological monitoring of patients. Newly developed SGAs in addition to the benzamide antipsychotic drugs (sulpirides and amisulprides) and aripiprazole, appear to provide important advances in side effect profile and efficacy for this drug class. However, a variety of side effects associated with individual SGAs and the substituted benzamides still affect patient health and quality of life in addition to their limitations in efficacy. Consequently, there is a continuing need for new and better drugs.

Over the last few years, new routes of administration for SGAs have been developed. As of December 2003, besides oral tablet form of medication, risperidone is available in a liquid form and long-acting microsphere preparations in the US and some European countries. Olanzapine is available as a rapidly disintegrating tablet (zydis) form and an intramuscular form in some countries. A short-acting intramuscular parenteral form of ziprasidone is available in the US and many European countries.[15] These newly available routes of administration could enhance the usefulness of the SGAs significantly (for a review, see Fleischacker[16]).

Theories of mechanisms of action of antipsychotic drugs

First-generation antipsychotic agents

The effect that is common to all FGAs is a high affinity for dopamine D_2 receptors,[17] and there is a strong correlation between the therapeutic doses of these drugs and their binding affinity for the D_2 receptor.[18–21] *In vitro* data show that FGAs such as haloperidol bind 'tightly' to the D_2 receptor and dissociate slowly.[22] *In vivo* positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have further demonstrated the importance of dopamine receptor occupancy as a predictor of antipsychotic response and adverse effects (for a review, see Remignton and Kapur[23]). Such studies have demonstrated that antipsychotic effects are associated with a striatal D_2 receptor occupancy of 65–70%,[24–27] and D_2 occupancy greater than 80% significantly increases the risk of EPS.[24] Recent imaging studies have also shown that therapeutic doses of FGAs produce high blockade of D_2-like receptors equally in limbic cortical areas

and the striatum.[28,29] Thus, a threshold between 65 and 80% D_2 occupancy appears to represent the therapeutic window to minimize the risk of EPS for FGAs.[23,27,30] However, this is not absolute as some patients can respond below this threshold, and nonresponders can be seen in spite of adequate D_2 receptor blockade reflecting the limitations of the receptor occupancy model.[27,31] Interestingly, low doses of haloperidol (2–5 mg/day) would be expected to induce 60–80% dopamine D_2 receptor occupancy,[25,32] while dosages five to 20 times as high are often prescribed in current clinical practice.[33] This may be partly accounted for by the fact that long-term treatment with FGAs induces upregulation in D_2 receptors in both animals[34,35] and humans,[36,37] which appears to be associated with dopamine D_2-mediated supersensitivity,[38,39] thus theoretically, increments in dose may be needed to produce the same effect on dopaminergic transmission for chronic patients.[27,31]

It is important to acknowledge that the gradual and time-dependant onset of therapeutic efficacy is not consistent with the rapid striatal D_2 receptor blockade induced by antipsychotics. Preclinical studies demonstrating that chronic treatment of rodents with FGAs can decrease the number of spontaneously active dopamine neurons in both the substantia nigra pars compacta (A9) and the ventral tegmental area (A10) have given rise to the 'depolarization inactivation (or block) hypothesis'.[40–42] Mereu *et al*,[43–45] however, have suggested that the depolarization inactivation of dopamine neurons may be an artifact produced by the use of general anesthetics, and thereby questioned the validity of this phenomenon and whether it would occur in the intact nonanesthetized unrestrained animals.[43–45] Nevertheless, a number of studies have demonstrated that FGA-induced dopamine cell depolarization block does occur in nonanesthetized animals[40,41,46,47] (for a review, see Grace *et al*[48]).

Benzamides

Amisulpride, a substituted benzamide analogue of sulpiride, is a highly selective anatagonist of D_2 and D_3 receptors with little affinity for D_1-like or nondopaminergic receptors (Table 1).[49,50] Its congener, sulpiride, demonstrates a generally similar pharmacological profile. Preclinical studies suggest that low doses of amisulpride (and probably sulpiride) preferentially block presynaptic D_2-like autoreceptors, and thus lead to an increase in dopaminergic release and neurotransmission, while higher doses reduce certain postsynaptic dopamine receptor-mediated behaviors that predict antipsychotic efficacy, but with little or no induction of catalepsy that predicts low EPS liability.[31,50,51] Several PET and SPECT studies in schizophrenia demonstrated that amisulpride selectively binds to temporal cortical D_2/D_3 receptors in a dose-dependent fashion, but this extra-striatal selectivity is lost at higher doses as striatal D_2/D_3 receptor occupancy increases.[52–54] Another PET study found no significant binding to 5-HT_{2A} receptors in amisulpride-treated patients.[55] It is also characterized by the rapid dissociation from the D_2 receptor similar to clozapine.[56] Amisulpride is essentially devoid of 5-HT_{2A} antagonism, thus its moderate affinity for striatal D_2 receptors and preferential occupancy of

Table 1 Relative neurotransmitter receptor affinities for antipsychotics at therapeutic doses (adapted from Miyamoto *et al*[1] and modified)

Receptor	*Clozapine*	*Risperidone*	*Olanzapine*	*Quetiapine*	*Ziprasidone*	*Sertindole*	*Sulpiride*	*Amisulpride*	*Zotepine*	*Aripiprazole*	*Haloperidol*
D_1	+	+	++	−	+	++	−	−	+	−	+
D_2	+	+++	++	+	+++	+++	++++	++++	++	++++	++++
D_3	+	++	+	−	++	++	++	++	++	++	+++
D_4	++	−	++	−	++	+	−	−	+	+	+++
5-HT_{1A}	−	−	−	−	+++				++	++	−
5-HT_{1D}	−	+	−	−	+++					+	−
5-HT_{2A}	+++	++++	+++	++	++++	++++	−	−	+++	+++	+
5-HT_{2C}	++	++	++	−	++++	++	−	−	++	+	−
5-HT_6	++	−	++	−	+				++	+	−
5-HT_7	++	+++	−	−	++				++	++	−
α_1	+++	+++	++	+++	++	++	−	−	++	+	+++
α_2	+	++	+	−	−	+	−	−	++	+	−
H_1	+++	−	+++	++	−	+	−	−	++	+	−
m_1	++++	−	+++	++	−	−	−	−	+	−	−
DA transporter	++		++							−	
NA transporter	+		++		++				++	−	
5-HT transporter					++					−	

− = minimal to none; + = low; ++ = moderate; +++ = high; ++++ = very high.

limbic cortical D_2/D_3 receptors may be reasons for its therapeutic efficacy and low liability to induce EPS.[54]

Second-generation antipsychotic agents

The serotonin–dopamine antagonism theory The 'serotonin–dopamine (S_2/D_2) antagonism theory' promulgated by Meltzer *et al*[57] suggests that a higher ratio of a drug's affinity for serotonin 5-HT_{2A} receptor relative to dopamine D_2 receptor affinity can predict 'atypicality' and will explain the enhanced efficacy and reduced EPS liability of SGAs (for reviews, see Miyamato *et al*,[1] Lieberman,[58] Duncan *et al*[59]).

PET studies showing that therapeutic doses of risperidone, olanzapine and ziprasidone produce greater than 70% occupancy of D_2 receptors suggest that a specific threshold of D_2 receptor antagonism could be important in producing antipsychotic effects of these drugs.[60,61,391] Clozapine and quetiapine, however, exhibit lower levels of D_2 receptor occupancy (less than 70%) at therapeutically effective doses (Table 1),[24,61–63] suggesting that a threshold level of D_2 receptor occupancy (and possibly antagonism) alone cannot fully explain the greater therapeutic efficacy of clozapine[59] or for that matter serve as a model to predict antipsychotic efficacy. The low occupancy of striatal D_2 receptors by clozapine and quetiapine could account for its low EPS liability.[30,62–64] Interestingly, ziprasidone exhibits high levels of D_2 occupancy at doses of 20–40 mg,[65,66] doses that are substantially below the therapeutically effective dose range (120–200 mg/day).[67,68] Thus, pharmacological properties other than a threshold level of D_2 receptor antagonism (at least as reflected by receptor occupancy levels) may account for the clinical efficacy of ziprasidone.

Clozapine, risperidone, olanzapine and ziprasidone occupy more than 80% of cortical 5-HT_{2A} receptors in the therapeutic dose range in humans (Table 1).[24,60,61,63,69,70] Although 5-HT_{2A} receptor antagonism is likely to be associated with the low EPS liability of SGAs, risperidone at higher doses produces EPS,[71] indicating that high levels of D_2. antagonism cannot be completely ameliorated by even maximal 5-HT_{2A} receptor antagonism. Moreover, at this point, it is unclear what clinical effects 5-HT_{2A} antagonism confers, beyond mitigating the adverse effect of striatal D_2 antagonism, and propensity to cause EPS.[72] In particular, the role of 5-HT_{2A} antagonism in the superior therapeutic responses to clozapine awaits further clarification.[59] The apparent lack of efficacy of monotherapy with the selective potential role of the 5-HT_{2A} receptor antagonist M-100907[73] indicates that $5HT_{2A}$ antagonism alone cannot explain the efficacy of SGAs. Further studies examining combination therapy with D_2 antagonist and M-100907 are necessary to evaluate the potential role of $5HT_{2A}$ antagonism.

The 'fast-off-D_2' theory To date, there is no evidence showing that an agent without some degree of D_2 binding can act as an effective antipsychotic.[6] The question has been do pharmacologic effects on dopamine-mediated pathways account for all of the clinical therapeutic effects of antipsychotic drugs. Recent *in vitro* studies have demonstrated that antipsychotics dissociate from the D_2 receptor at very different rates, expressed as a k_{off} value.[22,74] The SGAs have higher k_{off} values as a group, that is faster dissociation rates, than the FGAs, but they differ among themselves on this dimension as well (e.g., quetiapine > clozapine > olanzapine > ziprasidone > risperidone).[6,56,75] Kapur and Seeman hypothesized that dissociation from the D_2 receptor quickly makes an antipsychotic agent more accommodating of physiological dopamine transmission, permitting an antipsychotic effect without EPS, hyperprolactinemia, as well as conferring benefits along a variety of clinical dimensions such as cognitive, affective and secondary negative symptoms.[74] Accordingly, they suggest that sustained D_2 occupancy is not necessary for antipsychotic action. However, this theory cannot explain the greater therapeutic efficacy of clozapine compared with other SGAs, particularly in the management of treatment-resistant schizophrenia. The rapid dissociation of clozapine and quetiapine from D_2 receptors by endogenous dopamine may lead to more rapid clinical relapse after discontinuation of these medications.[75] At present, it remains unclear how long an antipsychotic agent must bind to the D_2 receptor to maximize therapeutic efficacy while minimizing the risk of D_2-related side effects.[31] Another limitation of this model is that all antipsychotics have not been studied with it, including the benzamides, low-potency FGAs and partial dopamine agonists (e.g. aripiprazole).

Potential therapeutic significance of targeting other neuroreceptors The SGAs, particularly clozapine, have multiple sites of action other than dopamine D_2 receptors, including dopamine (D_1, D_3, D_4), serotonin (5-HT_{1A}, 5-HT_{2C}, 5-HT_6, 5-HT_7), muscarinic cholinergic and histamine receptor (Table 1). Among them, it has been hypothesized that the partial agonist activity of clozapine at serotonin 5-HT_{1A} receptors may contribute to its efficacy against anxiety, depression, cognitive and negative symptoms of schizophrenia (Table 2).[76–79] Preclinical studies have also suggested that 5-HT_{1A} agonists may potentiate the antipsychotic activity of dopaminergic antagonists,[80] and activation of inhibitory 5-HT_{1A} autoreceptors may counteract the induction of EPS due to striatal D_2 receptor blockade.[81] Furthermore, 5-HT_{1A} agonism has been suggested to contribute to enhancement of prefrontal dopamine release.[82] Indeed, clozapine, and olanzapine and ziprasidone, but not haloperidol or risperidone, can preferentially augment dopamine and norepinephrine release in the prefrontal cortex relative to the subcortical areas, which may be related to their potential efficacy for negative symptoms and cognitive dysfunction of schizophrenia.[83] The

Table 2 Potential clinical efficacy and benefits related to the mechanisms of action of antipsychotics (adapted from Richelson[6] in part and modified)

Mechanisms	*Potential clinical efficacy*	*Potential consequences*
D_2R antagonism	↓ positive symptoms	EPS ↑Negative symptoms ↑Cognitive symptoms
D_2R partial agonism	↓ positive symptoms ↓ negative symptoms ↓ cognitive symptoms	Little or no EPS Behavioral activation
↑DA and NE release in the PFC	↓ negative symptoms ↓ cognitive symptoms ↓ depressive symptoms	Behavioral activation
ACh release in the PFC	↓ cognitive symptoms	
5-HT_{2A} antagonism	↓ negative symptoms	↓ EPS
5-HT_{1A} partial agonism	↓ negative symptoms ↓ cognitive symptoms ↓ anxiety symptoms ↓ depressive symptoms	
Muscarinic R antagonism	↓ EPS	↑ Anticholinergic symptoms e.g. dry mouth, constipation tachycardia
Muscarinic R agonism	↓ psychotic symptoms ↓ cognitive symptoms	
Glutamate modulation	↓ positive symptoms ↓ negative symptoms ↓ cognitive symptoms ↓ illness progression	

NE, norepinephrine; Ach, acetylcholine; PFC, prefrontal cortex; EPS, extrapyramidal symptoms.

prefrontal cortex contains high densities of 5-HT_{1A} and 5-HT_{2A} receptors located on affrents to and on pyramidal neurons.[84] It has been suggested that activation of 5-HT_{2A} receptors increases the release of glutamate onto pyramidal cells,[85] whereas serotonin, possibly via activation of 5-HT_{1A} receptors, inhibits the release of glutamate.[86] Thus, compounds with 5-HT_{2A} antagonism and/or 5-HT_{1A} agonism like clozapine could regulate the physiological balance between excitatory and inhibitory inputs onto prefrontal pyramidal neurons.[78,84] Some SGAs, particularly ziprasidone, can also increase serotonin activity in the frontal cortex by virtue of their affinity for the serotonin transporter.[87,88] In addition, some of the SGAs, but not FGAs, can increase the release of acetylcholine in the prefrontal cortex, which could be a possible factor contributing to improve cognition in schizophrenia.[89]

Antipsychotic interactions with the glutamate system The ability of noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP) and ketamine, to induce a spectrum of positive, negative and cognitive schizophrenia-like symptoms has led to the hypothesis that hypofunction of NMDA receptors is involved in the pathophysiology of schizophrenia.[90–95] In a wide range of preclinical paradigms, some of the SGAs, but not the FGAs, selectively antagonize the effects of experimentally induced NMDA receptor hypofunction at the cellular and behavioral levels,[96–100] which provides support for the NMDA receptor hypofunction hypothesis. For example, clozapine and olanzapine, but not haloperidol or raclopride, inhibit the electrophysiological effects of PCP in brain slices,[99,101,102] and attenuate NMDA antagonist-induced deficits in prepulse inhibition (PPI)[96,103] and social behavior.[97] In addition, ketamine-induced brain metabolic activation is blocked by acute administration of clozapine and olanzapine, but not haloperidol in rats.[98,100] The well-documented effects of the SGAs on responses to NMDA antagonists raise the possibility that the therapeutic mechanisms of action of these agents may be associated with counteracting the effects of NMDA receptor hypofunction.[104] However, since none of the SGAs have direct affinity for any of the glutamate receptors including the NMDA receptor, the mechanism by which these effects are mediated is poorly understood. A recent report by Sur *et al*.[105] could help to elucidate this question. They have shown that clozapine's biologically active metabolite, *N*-desmethylclozapine, which is a potent, allosteric agonist at muscarinic M_1 receptors, can potentiate hippocampal NMDA receptor currents through M_1 receptor activation.[105] Thus, clozapine's unique therapeutic profile may be, at least in part, attributed to *N*-desmethylclozapine through potentiation of NMDA

receptor function mediated by M_1 receptors. Further studies are needed to determine whether the inhibition of the effects of NMDA antagonists by the SGAs involves molecular modifications in glutamate receptors or altered other neurotransmitter–glutamate interactions.

In contrast to the acute effects, chronic administration of haloperidol can block not only PCP-induced deficits in PPI,[106,107] but also ketamine-induced brain metabolic activation.[108] Thus, adaptive changes elicited by chronic treatment with both the FGAs and the SGAs appear to attenuate the effects of NMDA antagonists.[108] To date, numerous animal studies have reported increases, decreases, or no change in binding sites of glutamate receptors in various brain regions after chronic administration of antipsychotics[109–115] (Table 3). At the molecular level, inconsistent and often opposite findings have also been reported in the gene expression of subunits composing different glutamate receptors following long-term treatment with both the FGAs and SGAs.[116–123] These discrepancies appear to be due to different treatment regimens, brain regions examined and the method of assessment. Thus, it is unclear whether such changes reflect increased or decreased function of different glutamate receptors after chronic antipsychotic treatments.

Microarray analysis of gene expression induced by antipsychotic drug treatment Microarray expression profiling appears to be a useful strategy to identify candidate target genes that may be relevant to the mechanisms of action of antipsychotic drugs. Kontkanen *et al*[124] have found that acute clozapine treatment induces the gene expression of chromogranin A and calcineurin A, and decreases synaptotagmin V mRNA in the rat frontal cortex. In addition, chronic administration of clozapine induced the differential mRNA expression patterns of chromogranin A, son of sevenless, and Sec-1 in the cortex. In contrast, chronic exposure to haloperidol regulated the gene expression of inhibitor of DNA-binding

Table 3 Major findings in studies examining effects of chronic antipsychotics treatment on glutamate receptor binding and mRNA expression (adapted from[109–123])

Antipsychotics	*NMDA-R*	*AMPA-R*	*KA-R*	*Metabotropic-R*
Haloperidol	MK-801binding → ↓ ↑ (cortex) ^{3}H-CGP-39653 binding ↑ (striatum, cortex) MK-801binding → ↑ (striatum, hippocampus) MK-801binding ↑ (Acb)	AMPA binding → ↑ (cortex) AMPA mRNA ↑ (GluB & GluC) (hippocampus) Subunits mRNA → (Acb, striatum) GluR1 protein ↑(cortex) GluR2 mRNA ↑ ↓ (cortex, striatum) GluR4 mRNA ↓ (cortex, striatum)	KA binding → (cortex) KA2 mRNA ↑ (cortex, striatum, hippocampus)	Group II mRNA → (cortex)
	NR1 protein ↑ (striatum) NR1 mRNA ↑ ↓ (striatum, cortex) NR1 mRNA ↑ (hippocampus) NR2A-C mRNA ↑ (striatum) NR2A mRNA ↓ (cortex, hippocampus)			
Clozapine	MK-801binding → ↓ (cortex) ^{3}H-CGP-39653 binding ↑ (cortex) MK-801binding ↓ (striatum) MK-801binding ↑ (Acb)	AMPA binding → (cortex) AMPA mRNA ↑ (GluB & GluC) (hippocampus) GluC mRNA ↓ (Acb) GluR1 protein ↑ (cortex) GluR2 mRNA → (striatum) GluR3 mRNA ↓ (cortex, striatum) GluR4 mRNA ↓ (striatum)	KA binding → (cortex) GluR7 mRNA ↑ (cortex, striatum) KA2 mRNA ↑ (striatum)	Group II mRNA ↑ (cortex)
	NR1 mRNA ↑ ↓ (Acb) NR1 mRNA → (cortex, striatum, hippocampus) NR1 protein → (striatum) NR2A mRNA ↓ (cortex, hippocampus) NR2C mRNA ↓ (cortex, Acb)			
Olanzapine	MK-801binding → (cortex)	AMPA mRNA ↑ (GluB & GluC) (hippocampus) AMPA binding ↑ Subunits mRNA → (cortex, striatum)	KA binding → (cortex)	Subunits mRNA → (striatum, hippocampus)
	MK-801binding ↓ Subunits mRNA → (cortex, striatum, hippocampus)			

Acb, nucleus accumbens.

2 (ID-2) and Rab-12. Moreover, the expression of visinin-like proteins was regulated by chronic treatments with both agents in various brain regions. Chromogranin A and synaptotagmin V have been suggested to play roles in presynaptic vesicle formation and secretion.[125,126] Calcineurin A, a Ca^{2+}/calmodulin-dependent protein phosphatase, and visinin-like proteins are involved in the regulation of intracellular Ca^{2+} metabolism (for reviews, see Bultynck *et al*[127] and Braunewell and Gundefinger[128]). Thus, it is possible that both antipsychotics may modulate neurotransmitter vesicle release and presynaptic organization as well as the regulation of intracellular Ca^{2+} in the cortex.[124] Interestingly, altered expression of genes involved in presynaptic function has been observed in the prefrontal cortex of the postmortem brains of schizophrenics.[129] However, Bauer *et al*.[130] failed to detect any significant changes in cortical synaptic protein levels or their encoding mRNAs after chronic haloperidol administration in rats. Furthermore, several genes involved in the presynaptic function were not altered after chronic haloperidol treatment in the prefrontal cortex of monkeys.[129] The effects of chronic antipsychotic administration on presynaptic function at the molecular and cellular levels require further study.

Partial dopamine agonists

Aripiprazole (OPC-14597), approved for clinical use in the US and more recently in Europe, is the first of a possible 'next- generation antipsychotics' with a mechanism of action that differs from currently marketed FGAs and SGAs.[79] It is a partial dopamine agonist with a high affinity for D_2 and D_3 receptors,[131–133] and demonstrates properties of a functional agonist and antagonist in animal models of dopaminergic hypoactivity and hyperactivity, respectively.[131,134] Aripiprazole acts on both postsynaptic D_2 receptors and presynaptic autoreceptors. Partial agonist activity at D_2 receptors could stabilize the dopamine system while avoiding the hypodopaminergia that may limit the efficacy and tolerability of FGAs.[135] In addition, aripiprazole displays 5-HT_{1A} partial agonism and 5-HT_{2A} antagonism.[136] The distinction, pharmacologically, between aripiprazole and the SGAs in this regard is that aripiprazole's affinity for the D_2 receptors exceeds that for serotonin by an order of magnitude.[6,137] It also has very modest affinity for alpha$_1$-adrenergic, histamine (H_1), 5-HT_6, and 5-HT_7 receptors, and no appreciable affinity for D_1, histaminergic or cholinergic muscarinic receptors (Table 1).[132,137] The clinical significance of these *in vitro* receptor-binding affinities as well as its partial 5-HT_{1A} agonism has not been determined apart from their obvious association with side effects.[138] It has also been proposed that aripiprazole induces 'functionally selective' activation of D_2 receptors coupled to diverse G proteins (and hence different functions), thereby explaining its unique clinical effects.[132,137]

Aripiprazole neither conforms to the standard 5-HT_{2A}/D_2 antagonist nor the fast dissociation theories of atypicality. It has a very high affinity for the D_2 receptor (greater than its 5-HT_{2A} affinity) and this is unlikely to have a fast k_{off}. Similarly, the compound has a long half-life and is therefore unlikely to show transient receptor occupancy. PET studies in normal humans indicate that although aripiprazole occupies up to 90% of striatal D_2-like dopamine receptors at clinical doses, it does not cause EPS, suggesting that its inherent agonism may provide a mechanism that protects against excessive blockade of the D_2 system.[139] This underlines aripiprazole's unique mechanism of action as a partial dopamine receptor agonist,[79,134] and possibly a novel form of treatment for schizophrenia.

Clinical pharmacological profiles of antipsychotic drugs

First-generation antipsychotic agents

Although the FGAs (eg, chlorpromazine and haloperidol) vary in potency, their pharmacological properties, and their propensity to induce side effects, they are equally effective in the treatment of positive symptoms of schizophrenia and in preventing their recurrence (for reviews, see Miyamoto *et al*[8,9], Davis *et al*[140] and American Psychiatric Assocoation[141]). However, approximately 30% of patients with acutely exacerbated psychotic symptoms, however, have little or no response to FGAs, and up to 60% of patients have only a partial response to medication.[12,142] FGAs are generally less effective against negative than positive symptoms of schizophrenia (for a review, see Miyamoto *et al*[8]). They also produce small and inconsistent effects on cognitive functioning.[143–145] Some studies report worsening, improvement, or no change in cognitive function with FGAs treatment.[144] The discrepancies may be due, in part, to differences in patient populations, specific tests used, and the differential response of psychopathology to antipsychotics.[144] Cognitive impairment may also be worsened by adjunctive anticholinergic medications, which are frequently required to treat EPS caused by FGAs.[146]

In addition, the prophylactic efficacy of FGAs for relapse prevention is limited by poor treatment compliance and the fact that even with full compliance approximately 20% of patients may relapse.[147,148] Other dimensions of treatment limitations are functional capacity, quality of life, prevention of illness progression and improvement of long-term outcome.

In terms of adverse effects, all of the FGAs can produce EPS at therapeutic doses, including parkinsonism, dystonia, akathisia and tardive dyskinesia to a varying degree, and increase serum prolactin concentration in the usual clinical dose range.[149] When present, these EPS side efffects can be unpleasant for the patient and frequently an important reason for noncompliance with medication.[150]

Benzamides

A meta-analysis of 11 randomized controlled trials of acutely ill schizophrenic patients comparing amisulpride with FGAs or placebo found amisulpride to be consistently more effective than FGAs for global schizophrenic symptoms and negative symptoms.[151] However, the mean effect size of amisulpride for change in the Brief Psychiatric Rating Scale (BPRS) score was relatively small (0.11). In four studies of patients with primary or predominantly negative symptoms, amisulpride was more effective than placebo, but not more effective than FGAs.[151] The agent also demonstrated its therapeutic benefit with little or no EPS, lower use of antiparkinsonian medication and fewer dropout rates due to adverse effects than FGAs.[151] Its main side effect is substantial elevations of prolactin. Additional research is necessary for clarifying whether amisulpride is really more effective for primary negative symptoms.

Second-generation antipsychotic agents

Efficacy There have been numerous double-blind studies comparing the efficacy and tolerability of SGAs with FGAs for acute and maintenance therapy for schizophrenia. Such an expansive review is, however, beyond the scope of this paper; thus, the reader is referred to other sources.[1,5,152] In general, although the proportion of patients who improve and the magnitude of therapeutic effects vary greatly, SGAs appear to be at least as effective for psychotic symptoms as FGAs (for reviews, see Markowitz *et al*[153] and Remington and Kapur[154]). However, there has been considerable debate with regard to the clinical superiority of SGAs over FGAs.

Geddes *et al* conducted a systematic review and meta-analyses of 52 randomized trials comparing new antipsychotics (clozapine, olanzapine, risperidone, quetiapine, sertindole and amisulpride) with FGAs (haloperidol or chlorpromazine).[155] There was no difference in efficacy between FGAs and SGAs, in trials that used a dose of an SGA in haloperidol equivalents of 12 mg/day or less. For example, the advantages of SGAs in terms of efficacy and dropout rates were not seen if haloperidol is used at doses of 12 mg/day or less, although SGAs still caused fewer EPS.[155] They concluded that the observed superior efficacy of some SGAs may be due to the negative effects on efficacy of the excessively high dose of the FGA comparator.

Leucht *et al*[156] also performed a meta-analysis and concluded that SGAs have efficacy and tolerability advantages over FGAs, although the benefits of new agents in terms of total, positive and negative symptoms are modest at best. However, they did not attempt to address dose in the same fashion as Geddes *et al*.[155]

A third meta-analysis was performed by Davis *et al*[157] on 124 randomized controlled studies with efficacy data on 10 SGAs vs FGAs, and 18 trials of comparisons between SGAs. The effect sizes of clozapine, risperidone, and olanzapine were 0.49, 0.25 and 0.21, respectively, and each was significantly greater than those of FGAs. Importantly, there was no evidence that the FGA dose affected the results. With respect to comparisons of efficacy among SGAs, Geddes *et al*[155] asserted that the SGAs are equally efficacious as a homogeneous group, but Davis *et al*[157] concluded that some SGAs (clozapine, risperidone and olanzapine) are superior to other SGAs (sertindole, quetiapine, ziprasidone and remoxipride). It should be noted that these three meta-analyses did not include data currently available to evaluate the other clinical dimensions (eg, cognition, affect, quality of life) now receiving more attention.[6] Moreover, the fact that most studies included in these reviews were pharmaceutical industry-sponsored trials,[158] used limited types of assessment measures and methods of data analysis (eg, last-observation-carried-forward analyses)[155] and were relatively short in duration could limit the ability to fully evaluate the comparative effects of the two drug classes.[158] Investigations of SGAs in very large samples and with head-to-head comparisons to each other, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), could provide adequate information regarding the role of SGAs in efficacy and effectiveness.[158]

Efficacy on negative symptoms Although SGAs have been shown to be more effective than FGAs in treating negative symptoms, there is a continuing debate as to whether these ostensible therapeutic effects are secondary to a reduction in EPS or other symptoms, or to a direct effect on primary negative symptoms.[71,154,159–162] Secondary negative symptoms may be associated with positive symptoms, EPS, depression and environmental deprivation,[163,164] but most clinical studies of SGAs do not distinguish between primary and secondary negative symptoms and generally involve acutely symptomatic patients undergoing treatment for their psychosis.[165] Moreover, the effect sizes of improvement on negative symptoms for SGAs are usually moderate to small in comparison with placebo or FGAs.[156,166,167] Path analyses, however, have suggested that both risperidone and olanzapine exert direct effects on (primary) negative symptoms independent of differences in psychotic, depressive or extrapyramidal symptoms.[168,169] Nevertheless, these path analytical statistical approaches were performed *post hoc*, and only the most effective doses of the SGAs were chosen. Thus, prospective studies on stable patients with predominant primary negative symptoms are necessary to draw conclusions on this issue.[170] A collaborative working group concluded that SGAs are superior in terms of the 'totality' of negative symptoms, but their impact on specific components is still under investigation.[164]

Efficacy on cognition Studies of the effect of SGAs on cognition have been limited, and the findings have

been inconsistent.[171–173] It is unclear whether this effect is dependent on or independent of treatment effects on psychotic symptoms.[2] Anticholinergic and sedative effects as well as the propensity to induce EPS associated with antipsychotic medications may have detrimental effects on some (but not all) areas of cognition.[174–176] Improvement in global cognitive functioning with SGAs may be secondary to less EPS liability and greater efficacy in the treatment of negative symptoms.[173] In general, the SGAs have demonstrated superior efficacy compared to FGAs on tests of verbal fluency, digit-symbol substitution, fine motor function, and executive function.[171,172,177] Measures of learning and memory were least affected by SGAs.[171] Because these tests all measure performance during a timed trial, enhanced performance with SGAs could result, in part, from reduced parkinsonian side effects 171. In a double-blind trial in the treatment of cognitive impairment in early-phase schizophrenia, risperidone (mean dose 6 mg/day) and olanzapine (mean dose 11 mg/day) produced significantly greater improvement in verbal fluency compared to haloperidol (mean dose 10 mg/day), and olanzapine was superior to both haloperidol and risperidone in effects on motor skills, nonverbal fluency and immediate recall.[178] This finding is, however, complicated by the high incidence of anticholinergic administration prior to the final cognitive assessment, and other problems in methodology.[179,180] In a recent double-blind 14-week trial in chronic schizophrenia,[181] olanzapine and risperidone were superior to haloperidol on global cognitive function, but not different from each other or from clozapine. Average effect sizes for improvement with the SGAs were in the small to medium range. Importantly, their results did not appear to be mediated by changes in symptoms, side effects, or blood levels of medications. In contrast, Green *et al*[182] have found no cognitive advantage for risperidone (mean dose 6 mg/day) over low doses of haloperidol (mean dose 5 mg/day) in stable schizophrenic outpatients over a 2-year period.[182] There is continued debate as to whether SGAs have pro-cognitive efficacy or have reduced cognitive liability.[183,184] As in efficacy studies for negative symptoms, dose equivalence is an important factor in trials comparing cognitive effects of SGAs, particularly since excessive doses can impair performance on time-sensitive tasks and can increase anticholinergic exposure. Keefe *et al*[171] reported a meta-analysis which found a significant advantage for SGAs on cognitive test performance.

Efficacy for treatment-resistant schizophrenia
Clozapine has been consistently shown to have efficacy against psychotic symptoms in well-defined treatment refractory patients over FGAs and as compared to other SGAs.[185–187] Chakos *et al*,[188] in a review and meta-analysis of seven controlled trials comparing clozapine to FGAs in treatment-resistant schizophrenia, found that clozapine is superior to FGAs in terms of overall psychopathology, EPS, and compliance rate. There are several controlled, double-blind trials comparing SGAs with FGAs in treatment-refractory schizophrenia, but the relative efficacy of other new agents is modest or less clear (for a review, see Miyamoto *et al*[1]). Volavka *et al*[389] in a double-blind PET found clozapine and olanzapine but not risperidone superior to haloperidol. Sequential controlled trials of the newer agents in treatment-resistant patients will be necessary to fully examine this issue.

Safety The major difference of the SGAs compared to the FGAs is their lower incidence of EPS and TD. Most of the SGAs have little or no EPS, while risperidone has less at low doses but at higher doses can cause EPS comparable to that of FGAs.[189] However, the individual SGAs have unique adverse effects that were less of an issue with FGAs, are of potential concern and undermine claims of safety advantages for the SGAs. There is mounting evidence of the increased risk of weight gain, diabetes mellitus, prolonged QTc interval and possible secondary cardiovascular complications.[6] These side effects are associated with potential long-term health risks of patients as well as decreased adherence to treatment regimens, and eventually may lead to relapse.[189]

Among SGAs, clozapine and quetiapine have been shown to carry minimal to no risk for EPS or hyperprolactinemia within the therapeutic dosage range.[185,190,191] Risperidone, however, can produce dose-related EPS ($\geq$6 mg/day).[192,193] With the exception of akathisia,[194] the incidence of EPS or hyperprolactinemia with olanzapine and ziprasidone is not significantly different from that with placebo.[195,196] The relative liability of the individual SGAs to produce EPS will become apparent only when they have been directly compared with each other in prospective clinical trials such as the NIMH = CATIE trials.[390]

Marked differences in liability for weight gain, diabetes, or hyperlipidemia are seen between the different SGAs. Analyses consistently report the largest increases in weight gain with clozapine and olanzapine, intermediate increases with risperidone and quetiapine, and minimal weight gain with ziprasidone.[197–199]

Aripiprazole: efficacy and safety
Several short-term double-blind, placebo-controlled trials of aripiprazole (2–30 mg/day) demonstrated efficacy greater than placebo, and similar to haloperidol (10 mg/day) and risperidone (6 mg/day) against positive and negative symptoms in patients with acute exacerbations of schizophrenia or schizoaffective disorder[200,201] (for a review, see Bowles and Levin[138]). These studies suggest that aripiprazole doses in the range of 15–30 mg/day are effective. It can be started at a full dose without an initial titration period. Two long-term double-blind studies showed that aripiprazole (15 or 30 mg/day) is superior to

placebo, and comparable or superior to haloperidol (10 mg/day) in maintaining antipsychotic response and relapse prevention.[202,203] All of the short- and long-term studies have shown that aripiprazole has a favorable safety and tolerability profile, with low liability for EPS, TD, weight gain, sedation, hyperprolactinemia, or QTc prolongation, and a lack of adverse effects on glucose and lipid metabolism.[204] However, it should be noted that the agent exhibits a lack of a predictable dose–response relationship for efficacy and adverse events.[201,204] Further clinical studies are needed to determine the efficacy and safety in special populations, including suicidal and treatment-resistant patients with schizophrenia, elderly and children, dementia, agitation, autism and other disease status in which antipsychotic use is helpful.[138] Long-term effectiveness studies are also necessary, particularly those examining the relative effects of aripiprazole and different SGAs on negative symptoms, cognitive function, relapse prevention, treatment adherence, disease progression, function, quality of life and use of health services.[205]

Future strategies of drug development

Dopaminergic agents

Dopamine D_1 receptor antagonist or agonist Evidence suggests an important role for D_1-like dopamine receptors in the pathophysiology of schizophrenia.[206,207] Earlier preclinical studies demonstrated that selective D_1-like antagonists were active in most traditional functional models held to predict antipsychotic activity (for a review, see Waddington[208]). A clinical trial of the selective D_1-like antagonist SCH39166,[209,210] and NNC 01-0687,[211] however, demonstrated no antipsychotic activity, and instead may have aggravated psychoses in some patients.[209]

In contrast to the ineffectiveness of D_1-like antagonists in the treatment of schizophrenia, low doses of selective full D_1-like receptor agonists, such as dihydrexidine, A77636 and SKF81297, have been reported to have cognitive-enhancing actions in nonhuman primates.[212–214] In drug-naïve schizophrenics, Okubo *et al*[215] found decreased D_1-like receptor binding using PET in the frontal cortex and basal ganglia, and correlation between the reduction in prefrontal D_1-like receptors and the severity of negative symptoms and cognitive disturbance. Such data are consistent with the fact that pyramidal neurons in the prefrontal cortex postulated to be involved in working memory express a high degree of D_1-like dopamine receptors.[207,216] It is postulated that either insufficient or excessive D_1-like receptor stimulation is deleterious to cognitive function of the prefrontal cortex, thus an 'optimal' level of D_1-like receptor activation is necessary for normal cognitive function.[216,217] The finding that full D_1-like receptor agonists can improve working memory suggests that such class of drugs might be novel potential treatments for negative and cognitive symptoms of schizophrenia.[9,21,218–221]

Dopamine D_4 receptor antagonist There are several lines of evidence suggesting that selective dopamine D_4 receptor antagonists may be potential novel antipsychotic drugs. For example, not only clozapine but also a number of clinically efficacious antipsychotics have a relatively high affinity for the D_4 receptors[222] (Table 1). In addition, an increase in D_4 receptors has been reported in the schizophrenic brains.[223,224] The selective D_4 antagonist, sonepiprazole (U-101387 or PNU-101387G) attenuates apomorphine-induced impairment of prepulse inhibition,[225] and antagonizes the decrease in *c-fos* expression in the medial prefrontal cortex and neurotensin mRNA in the nucleus accumbens produced by repetitive amphetamine administration in rats.[226] However, most of the *in vivo* pharmacological studies of sonepiprazole indicates the lack of effects in at least traditional preclinical models of antipsychotic activity.[227,228] Nevertheless, it entered Phase II clinical trials in patients with schizophrenia, but no further data are currently available.[228]

An initial clinical trial with another highly selective D_4 antagonist, L-745,870 failed to demonstrate any antipsychotic activity in the treatment of schizophrenia.[229,230] While the single dose tested and the small number of patients make it difficult to draw firm conclusions regarding the potential efficacy of D_4 antagonists as antipsychotic agents,[231] this drug seemed to cause a worsening of symptoms.[230] Similarly, NGD-94-1 and the D_4/5-HT_{2A} antagonist finanserin (RP62203) also did not show clinical efficacy in limited trials in schizophrenics.[228,232] Therefore, these data cast doubt as to whether D_4 antagonism alone is responsible for the antipsychotic efficacy of clozapine, and that selective D_4 antagonists could indeed have therapeutic potential in schizophrenia (for reviews, see Miyamoto *et al*[5], Waddington *et al*[31] and Rowley *et al*[233]).

Dopamine D_3 antagonist or partial agonist Dopamine D_3 receptor is a D_2-like dopamine receptor that is localized in the mesolimbic areas of the brain, and for which most antipsychotics have relatively high affinity (for a review, see Schwartz *et al*[234]). In addition, a post-mortem study demonstrated elevation of D_3 receptor levels in the limbic striatum of drug-free patients with schizophrenia, whereas D_3 receptor expression was normal in subjects treated with antipsychotic drugs.[235] These findings have prompted much interest in the D_3 receptor as a potential novel therapeutic target for antipsychotic activity.[31] A dopamine D3 receptor agonist, (+)-PD 128,907, can block stereotypy produced by NMDA antagonists in mice, suggesting its antipsychotic profile.[236] So far, partial agonists at D_3 receptors are, however, supposed to be beneficial only when administered to drug abusers or in Parkinson's

disease (for review, see Hacking and Stark[237]). The novel selective dopamine D_3 antagonists such as S33084, SB-277011-A, and AVE5997 have been developed for the treatment of psychosis like schizophrenia. While S33084 was not active in traditional models of antipsychotic activity in the manner of D_2 antagonists,[238] SB-277011-A can produce an increase in extracellular levels of dopamine, norepinephrine and acetylcholine in the rat anterior cingulate cortex, similar to the effects of SGAs, clozapine and olanzapine, but not haloperidol.[239] At present, the role of D_3 antagonism in antipsychotic activity remains unclear, and only controlled clinical trials with selective D_3 antagonists in schizophrenia will eventually clarify this issue.[31]

Glutamatergic agents

NMDA receptor positive allosteric modulators If reduced NMDA receptor function is involved in the pathophysiology of schizophrenia, then drugs that enhance NMDA receptor function could be therapeutic agents and potentially improve upon, or supplement, current antipsychotic treatments (for reviews, see Miyamoto *et al*[8], Duncan *et al*[59], Abi-Saab *et al*[240] and Goff and Coyle[241]). Direct agonists of the NMDA receptor, however, may not be feasible candidates in this regard, because of the propensity of such drugs to produce excessive excitation and seizures.

Glycine is a positive allosteric modulator and obligatory co-agonist at the NMDA receptor.[242] This allosteric regulatory site represents a potential target for drugs to augment NMDA-mediated neurotransmission. The glycine site agonists, including glycine, D-cycloserine and D-serine, appear to be effective in reducing negative symptoms and cognitive impairment in patients with schizophrenia when they are added to ongoing antipsychotic treatment, with the exception of clozapine.[243–249] Their beneficial effects on positive and depressive symptoms are less robust. The poor penetration of the blood–brain barrier by glycine, and the partial agonistic properties of D-cycloserine, appear to make these agents less than optimal for providing pharmacological agonism of the glycine regulatory site on the NMDA receptor.[59] Of these glycine agonists, D-serine appears to be the most promising agent. It is a full agonist on the strychnine-insensitive glycine site of NMDA receptor[250] and is more permeable than glycine at the blood–brain barrier, thus requiring a lower dosage. In an 8-week clinical trial, D-serine added to neuroleptic treatment in treatment-resistant patients with schizophrenia demonstrated significant improvements not only in negative and cognitive symptoms but also an in positive symptoms, which is different from glycine.[251]

Glycine reuptake inhibitors Glycine transporters, GLYT-1 and GLYT-2, have been identified on both neuronal and glial cells in the central nervous system. A function of these transporters has been suggested to control the extracellular glycine concentration.[252] Thus, blockade of the GLYT-1 transporter would increase NMDA receptor-mediated transmission. Although there is some controversy as to whether the glycine regulatory site on the NMDA receptor is saturated under physiological conditions, preclinical data demonstrate that *N*-(3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl) sarcosine, a selective and potent GLYT-1 reuptake inhibitor, can potentiate electrophysiological effects of NMDA.[252,253] Furthermore, the glycine reuptake inhibitor glycyldodecylamide attenuated PCP-induced hyperactivity more potently than glycine.[254,255] These preclinical data suggest that inhibition of glycine reuptake could represent a feasible approach to potentiate NMDA receptor-mediated neurotransmission and, possibly, treat schizophrenic patients.

Glutamate reuptake inhibitors Glutamate transporters (excitatory amino-acid transporters (EAATs)), normally expressed in both glia (EAAT1 and EAAT2) and neurons (EAAT3 and EAAT4), can control glutamatergic neurotransmission by removal of glutamate from the synaptic cleft (for a review, see Danbolt[256]). EAAT3 (called EAAC1 in the rodent) is predominantly expressed in the cerebral cortex, basal ganglia and hippocampus.[257] Post-mortem studies in schizophrenic patients revealed alterations in gene expression of glutamate transporters.[258,259] In addition, preclinical studies demonstrated that chronic treatment with clozapine or haloperidol can downregulate EAAT3 in the infralimbic cortex and hippocampal CA2.[260] Thus, glutamate reuptake inhibitors such as EAAT3 antagonists could increase the synaptic availability of glutamate, and increase glutamatergic action at the postsynaptic neuron, and thereby might produce therapeutic effects on some symptom dimensions following the model of diminished glutamate activity in schizophrenia.

Metabotropic glutamate receptors agonists Metabotropic glutamate (mGlu) receptors (mGluR), of which there are eight subtypes (mGluR1–8), are categorized into three groups according to their agonist pharmacology, sequence similarity and signal transduction pathways (for a review, see Rowley *et al*[233]). NMDA antagonists induce hyperlocomotion and stereotypy, accompanied by an increase in glutamate release in several brain regions of rats,[261] suggesting that pharmacological agents that decrease glutamate release should block the effects of the drugs. Group II mGluR (mGluR2/3) are located presynaptically on glutamate terminals where they may act as autoreceptors regulating glutamate release *in vivo* (for reviews, see Rowley *et al*[233] and Chavez-Noriega *et al*[262]). Administration of a group II mGluR agonist, LY-354740, blocks both behavioral activation and increased glutamate (but not dopamine) release provoked by PCP in rats.[263] Thus, group II mGluR agonists could be beneficial in the treatment of schizophrenia, although LY-354740 cannot attenuate

PCP-induced disruptions in prepulse inhibition (PPI) of acoustic startle responses. On the other hand, one of the effects induced by activation of group I mGluR (mGluR1/5), particularly of mGluR5, is a significant potentiation of NMDA receptor function, suggesting that mGluR5 agonists may display antipsychotic activity (for review, see Chavez-Noriega *et al*[262]).

AMPA/kainate receptor antagonists The increased release of glutamate observed in response to NMDA antagonists could mediate some of the behavioral actions of the drugs by activation of non-NMDA receptors, including α-amino-3-hydroxy-5-methy-isoxazole-4-propionic acid (AMPA) and kainate receptors.[261] In support of the hypothesis that behavioral effects of NMDA antagonists relate to increased glutamate release, administration of an AMPA/kainate receptor antagonist, LY-293558, partially reversed impairment of working memory induced by subanesthetic doses of ketamine in rats.[261] Furthermore, AMPA/kainate receptor antagonists reduce NMDA antagonist-induced hyperlocomotion[264–266] and neurodegeneration.[267] Systemic administration of other AMPA receptor antagonists GYKI52466 and LY-326325 can suppress conditioned avoidance response in rats.[268] These data suggest that AMPA/kainate receptor antagonists may possess an antipsychotic effect, and have utility for treatment of cognitive deficits in which NMDA receptor hypofunction is suspected.[261]

Ampakines (CX-516) In apparent contrast to the postulated utility of AMPA/kainate receptor antagonists as antipsychotics, ampakines, a class of compounds that allosterically enhance AMPA receptor function, have also been suggested to represent potential adjunctive treatments for schizophrenia. Ampakines and AMPA potentiators enhance excitatory (glutamatergic) transmission, facilitate long-term potentiation, learning and memory in rodents,[269,270] and have synergistic effects with FGAs and SGAs on blocking behavioral effects of methamphetamine.[271] In addition, preliminary results suggest that chronic administration of an ampakine (CX-516) can improve negative and cognitive symptoms in schizophrenia patients that also receive clozapine.[272] Thus, such findings are paradoxical with regard to the hypothesis that excessive glutamate release may be involved in behavioral effects of reduced NMDA receptor function. In a recent double-blind placebo-controlled small study of patients with schizophrenia who were partially refractory to treatment with the FGAs, CX516 as a sole agent did not produce dramatic effects on positive symptoms and cognitive impairment.[273] In the case of AMPA ligands, it seems at present unclear if agonists, antagonists or partial agonists/modulators have potential therapeutic application.

Glutathione prodrugs Glutathione is the principal nonenzymatic endogenous antioxidant, and plays a critical role in protecting cells from damage by reactive oxygen species generated by dopamine metabolism.[274,275] A glutathione deficit can leave the brain susceptible to oxidation, and oxidative stress-mediated cell damage has been considered in one of the pathophysiologies of schizophrenia. Indeed, a decrease of glutathione levels was observed in the cerebrospinal fluid and the medial prefrontal cortex in drug-naïve schizophrenic patients.[274] Its deficit would lead to degenerative processes in the surrounding of dopaminergic terminals, resulting in loss of connectivity.[274] Glutathione also potentiates the NMDA receptor response to glutamate via its redox modulatory site.[276] Taken together, although speculative, glutathione supplementation by glutathione prodrugs could be an interesting treatment strategy for schizophrenia in terms of preventing oxidative stress and enhancing neurotransmission at NMDA receptors in the brain.

Noradrenergic agents

Alpha-2 adrenergic receptor agonist or antagonist Norepinephrine plays an important role in cognitive function of the prefrontal cortex (PFC) by its actions at alpha-2 adrenergic receptors (Ars) located in the principal sulcus of the PFC (for reviews, see Goldman-Rakic *et al*[277], Arnsten *et al*[278] and Friedman *et al*[279,280]). Indeed, the alpha-2 agonist clonidine has been shown to improve performance on working memory tasks in young monkeys with noradrenergic depleting lesions of the PFC, presumably through its drug actions at post-synaptic alpha-2 Ars in the PFC.[281] In schizophrenia, clonidine also improves PFC-mediated cognitive dysfunction.[282] In addition, guanfacine, a selective alpha-2A agonist,[283] improves PFC-mediated working memory in aged non-human primates, but without the significant adverse effects associated with clonidine (eg, sedation, hypotension).[284] A 4-week, placebo-controlled, double-blind study demonstrated the efficacy and safety of guanfacine as adjunctive treatment of cognitive impairment in schizophrenia.[285] Those patients receiving guanfacine plus risperidone showed significant improvement on tasks of working memory and attention compared with patients receiving FGAs plus guanfacine.[285] The potential ability of alpha-2 agonists to improve cognitive performance on tasks dependent on PFC function appears to be of great importance in the search for a new pharmacologic approach for schizophrenia.

Clozapine and risperidone have potent antagonist properties at alpha-2 Ars. Millan *et al*[286] have postulated the significance of the alpha-2 Ars antagonistic activity for the antipsychotic effects of neuroleptics. Blockade of inhibitory alpha-2-AR heteroceptors on terminals of dopaminergic fibers can enhance frontocortical dopaminergic transmission compared with subcortical dopaminergic pathways.[287] Litman

et al[288] reported that combined treatment with idazoxan, a highly selective alpha-2-AR antagonist, and the FGA fluphenazine can produce a 'clozapine-like' profile of antipsychotic activity. Antagonist properties of alpha-2-Ars appear to be implicated in the functional actions of clozapine in humans,[289] and contribute to an improvement in mood.[286]

COMT inhibitors Considerable data suggest that catechol-*O*-methyl transferase (COMT), a postsynaptic methylation enzyme that metabolizes released dopamine, is primarily responsible for synaptic dopamine inactivation in the prefrontal cortex, and that variation in COMT activity may affect prefrontal cortical activity, especially during working memory tasks.[290,291] Interestingly, studies of COMT-deficient mice have demonstrated that dopamine levels are increased in the prefrontal cortex but not in the striatum, and that memory performance is enhanced.[292] Abnormalities of prefrontal dopamine function associated with working memory appear to be prominent features of schizophrenia, and certain alleles of the COMT gene run in families with a high incidence of the illness.[293] Tolcapone, a reversible, selective inhibitor of COMT has been reported to improve working memory in rodents,[294] and tolcapone as adjunct to L-dopa therapy has been shown to improve cognitive dysfunction in patients with advanced Parkinson's disease.[295] At present, Egan and Weinberger are conducting a trial of COMT inhibitors in schizophrenia and healthy controls with and without the high-risk combination of COMT alleles.[296] However, tolcapone was withdrawn from the market in Europe and Canada due to the risk of serious hepatic dysfunction,[297] and in the US restrictive liver enzyme monitoring measures are necessary, which severely limits the use of the agent.[298]

Cholinergic agents

Alpha-7 nicotinic receptor agonist Cognitive impairments are cardinal features of schizophrenia. Nicotinic acetylcholine receptors (nAChRs) have been implicated in cognitive function and formation of sensory processing (for a review, see Rezvani and Levin[299]). In particular, auditory gating is modulated by the alpha-7 nAChR subtype, which is a rapidly desensitizing low-affinity nAChR (for a review, see Simosky *et al*[300]). Genetic studies linking the alpha-7 nAChR gene to sensory processing deficits in schizophrenia, together with reductions of this receptor in discrete regions of the brains of schizophrenia patients, suggest that the alpha-7 nAChR may be a relevant therapeutic target in schizophrenia (for review, see Adler *et al*[301]). Interestingly, clozapine, but not haloperidol, can improve deficient inhibitory auditory processing through stimulation of alpha-7 nAChRs in mice.[302] Agonists at alpha-7 nAChRs such as 3-2,4-dimethoxybenzylidene anabaseine (DMXB-A or GTS-21) can normalize the auditory gating deficits in rodents.[303] Alpha-7 nAChR agonists are currently under development for clinical trial in schizophrenia, although it is unclear whether such agonists have beneficial effects on symptoms other than the auditory gating deficit. Moreover, long-term use of such agents might induce desensitization of nAChRs, leading to tolerance and therefore limiting the duration of efficacy.

Alpha4–beta2 nicotinic receptor agonist It has been suggested that alpha4–beta2 nAChRs affect auditory sensorimotor gating.[304] They are considered to represent more than 90% of the high-affinity nicotine-binding sites in rat brain,[305] and appear to play an important role in many of the behavioral actions of nicotine. SIB-1553A, an alpha4–beta2 subtype-selective nicotinic receptor agonist, appears to produce enhanced performance in a variety of models of cognitive impairment in areas such as spatial and nonspatial working and reference memory in aged rodents and monkeys.[306,307] Interestingly, SIB-1553A has also been shown to stimulate the release of dopamine, norepinephrine and acetylcholine in the frontal cortex and hippocampus in rats.[306] These data suggest that the use of alpha4–beta2 nicotinic receptor agonists could produce therapeutic benefit for the treatment of cognitive deficits in schizophrenia.

Allosteric modulators of nicotinic receptor and acetylcholinesterase inhibitor Galantamine is a positive allosteric modulator of nAChRs and an inhibitor of acetylcholinesterase (AchE), the enzyme responsible for catabolizing acetylcholine (Ach) (for a review, see Maelicke *et al*[308]). The allosteric interaction amplifies the actions of Ach at pre- and postsynaptic nAChR.[309] Presynaptic nAChRs are capable of modulating the release of Ach, and other neurotransmitters, such as glutamate, serotonin, and GABA, which may contribute to the symptoms of schizophrenia.[310] Galantamine has been shown to improve cognitive and global function in placebo-controlled trials in Alzheimer's disease patients (for a review, see Coyle and Kershaw[311]). Results from case reports suggest that adjuvant galantamine administration improves negative symptoms in patients with treatment-refractory schizophrenia.[312,313] The extent to which the clinical benefits of galantamine are attributable specifically to its nicotinic effects is unclear, and prospective double-blind data are required.

Several case studies and an open-label trial of adjunctive donepezil, a reversible AchE inhibitor, demonstrate some of its beneficial effects on cognitive impairment in schizophrenia.[314–316] However, a recent double-blind controlled trial of donepezil added to risperidone did not show any positive effects on cognitive deficit associated with schizophrenia.[317]

Muscarinic receptor agonist There is a large body of anatomical and pharmacological evidence for potential modulation of dopamine and glutamatergic neurons by cholinergic muscarinic receptors (for a review, see Bymaster[318]). Recent findings that partial agonists of muscarinic receptors are active in animal models are predictive of antipsychotic activity, and the SGAs clozapine and olanzapine are partial agonists for cholinergic M_1, M_2 and M_4 receptors. Recently, the *N*-desmethyl metabolite of clozapine was reported to preferentially bind to M1 muscarinic receptors with an IC_{50} of 55 nM, and was a more potent partial agonist (EC_{50}, 115 nM and 50% of acetylcholine response) at this receptor than clozapine.[105] Furthermore, pharmacological and site-directed mutagenesis studies suggested that *N*-desmethylclozapine preferentially activated M1 receptors by interacting with a site that does not fully overlap with the acetylcholine orthosteric site. Moreover, *N*-desmethylclozapine is able to potentiate hippocampal NMDA receptor currents through M1 receptor activation. In addition, muscarinic agonists have activity in animal models of negative symptoms, cognitive dysfunction and affective disorders, suggesting the potential usefulness of muscarinic agonists in the treatment of schizophrenia (for reviews, see Rowly *et al*[233] and Bymaster *et al*[319]). Examples of these agents are the muscarinic M_1/M_4 agonist xanomeline, and the muscarinic M_2/M_4 agonists PTAC, and BuTAC (for a review, see Bymaster[318]). Xanomeline has been demonstrated to have positive effects on cognitive and psychotic-like symptoms (eg, hallucinations and delusions) in Alzheimer's disease.[320] Accumulating data suggest that muscarinic partial agonists might be efficacious in treating not only positive, but also negative and cognitive symptoms in schizophrenia.[319,321,322]

Other agents

Cannabinoid CB_1 antagonist Acute cannabis intoxication can produce schizophrenia-like symptoms, including hallucinations, altered judgment, false beliefs and cognitive dysfunction,[323] and long-term cannabis use often induces negative schizophrenia-like symptoms.[324] In addition, cannabis can precipitate psychotic symptoms in schizophrenia, and may increase the risk of developing the illness.[325] Several reports also demonstrated elevated levels of the endogenous cannabinoids (anandamide and palmitylethanolamide) in both the cerebrospinal fluid and the blood of schizophrenic patients when compared to normal controls.[326,327] These accumulating evidences have led to 'a cannabinoid hypothesis of schizophrenia' in which cannabinoid receptors, the pharmacological target of cannabis-derived drugs, and their accompanying system of endogenous activators may be dysregulated in schizophrenia.[328] The endogenous cannabinoid system comprises at least two cannabinoid receptors, the CB_1 and CB_2 receptors. A selective CB_1 receptor antagonist, SR141716, can reduce hyperactivity induced in gerbils by various stimulant drugs, including cocaine, D-amphetamine, morphine and Win 55212-2, known to produce or exacerbate schizophrenic symptoms.[329] In addition, SR141716 dose-dependently alters Fos protein and neurotensin expression in a manner comparable to that observed with the SGAs.[330] These findings suggest that selective CB_1 receptor antagonists may be effective in the pharmacological treatment of schizophrenia.

Neurokinin 3 antagonist Neurokinin 3 (NK_3) tachykinin receptors appear to regulate midbrain dopamine neuronal activity.[331] Preclinical studies have shown that a potent and selective nonpeptide NK_3 antagonist, osanetant (SR-142801), selectively inhibits dopamine release in certain brain regions (for a review, see Kamali[332]). Several NK_3 compounds are currently in development (eg, osanetant (Sanofi-Synthélabo) and talnetant (Glaxo Smith Kline)) as potential treatments for schizophrenia. Preliminary clinical trials have demonstrated that osanetant is superior to placebo on global assessment of efficacy and measures of positive symptoms in schizophrenia.[333] Whether NK_3 antagonist administration in schizophrenia may serve as novel antipsychotics merits further investigation.

Neurotensin agonist Neurotensin (NT) is a neuropeptide that regulates the function of mesolimbic dopamine neurons,[334] and has been implicated in the pathophysiology of schizophrenia (for a review, see Binder *et al*[335]). The central administration of NT induces behavioral and biochemical effects that are very similar to the effects of antipsychotic drugs.[336] Thus, there is much interest in the potential use of NT agonists as novel antipsychotics. *In vitro* studies indicate that NT behaves as an agonist at NT_1 receptors and as an antagonist at NT_2 receptors.[337] Systematic administration of metabolically stable NT analogues such as PD-149163 and NT69L can attenuate amphetamine- or NMDA antagonist-induced hyperactivity and PPI without inducing catalepsy or affecting baseline startle responses.[338,339] NT_1 receptor agonists, however, may have problems in clinical use, since NT can produce autonomic adverse effects. Chronic administration of SR-48692, which is a nonpeptide and a high-affinity NT_1 receptor antagonist with agonist activity at NT_2 receptors, can decrease methamphetamine-induced dopamine release in the nucleus accumbens,[340] suggesting this compound could also have antipsychotic-like effects.

MAO B inhibitors It has been suggested that negative symptoms of schizophrenia may be manifestations of regionally deficient dopaminergic activity in the brain, thus augmentation of dopaminergic neurotransmission could be a beneficial treatment strategy. Selegiline (deprenyl) is a monoamine oxidase (MAO)-B inhibitor that selectively enhances

dopaminergic activity. Selectivity for inhibition of MAO-B without inhibition of MAO-A is clinically important, since MAO-A inhibition is responsible for most of the side effects of MAO inhibitors.[341] Although several case series reported the beneficial effects of selegiline on negative symptoms of schizophrenia,[342–344] one double-blind, controlled study of the agent as adjunct to antipsychotic treatment failed to offer therapeutic benefit.[345] The selective irreversible MAO-B inhibitors, selegiline and rasagiline, have been shown to possess neuroprotective activities in cell culture and *in vivo* models of Parkinson's disease (for a review, see Maruyama *et al*[346]). For example, these agents can prevent experimentally induced apoptotoic DNA damage, and induce pro-survival genes.[347] Thus, the MAO-B inhibitors may rescue degenerating dopamine neurons through inhibiting death signal transduction, but clinical trials failed to confirm it.[346] So far, no solid conclusions could be drawn from the data regarding the effects of the MAO-B inhibitors on schizophrenia.

PDE10 inhibitors PDE10A is a recently identified cyclic nucleotide phosphodiesterase expressed at high levels in the brain and more specifically in the medium spiny neurons of the striatum and associated nucleus accumbens and olfactory tubercle.[348] Papaverine, a potent and selective PDE10A inhibitor, can dose-dependently attenuate hyperactivity induced by both amphetamine and PCP in rats.[349] The agent does not affect extracellular dopamine in the striatum nor alter PCP-induced dopamine release in the nucleus accumbens. Papaverine can also produce a dose-dependent reduction in conditioned avoidance responding in rodents. These data suggest the possibility that selective inhibitors of PDE10 may provide a target for the development of a new class of antipsychotic drugs.[349]

NNOS inhibitor Nitric oxide (NO) is a diffusible gas and an important inter- and intracellular messenger in the central nervous system. NO activates guanylyl cyclase and increases the synthesis of cyclic GMP. Nitric oxide synthase (NOS) converts arginine into NO and citrulline in response to increased intracellular calcium levels (for a review, see Rowley *et al*[233]). Preclinical studies demonstrated that inhibition of NOS activity with methylene blue, L-NOARG, L-NAME, or 7-nitroindazole can attenuate hyperactivity and disruption of PPI produced by NMDA antagonists but not amphetamine.[350–354] In treatment-refractory schizophrenia, methylene blue moderately improved symptoms.[355] However, it should be noted that all available NOS inhibitors can produce serious side effects including hypertension and cognitive dysfunction, which may be due to poor selectivity for different NOS isoforms.[233]

Neurosteroids Dehydroepiandrosterone: Dehydroepiandrosterone (DHEA) and its sulfate derivative (DHEA-S) are neuroactive neurosteroids that represent steroid hormones synthesized *de novo* in the brain and acting locally on nerve cells.[356] Although DHEA and DHEA-S are the most abundant circulating steroid hormones in humans, their precise physiological roles remain uncertain. *In vitro* data suggest that DHEA and DHEA-S enhance neuronal and glial survival and differentiation.[357–359] In addition, DHEA-S shows marked neuroprotective ability against the glutamate-induced toxicity[360] and oxidative stress.[361] Interestingly, DHEA has been demonstrated to potentiate neuronal responses at the NMDA receptor.[359,362,363] The enhancement of physiological response to NMDA by DHEA has also been suggested to result from agonistic actions at ó$_1$ receptors in the brain.[363] Consistent with a positive modulatory action of DHEA at the NMDA receptor, the neurosteroid enhances memory,[364–367] and DHEA-S attenuates NMDA receptor antagonist MK-801-induced learning impairment in mice.[368] In chronic schizophrenics, significantly lower morning levels of plasma DHEA were observed.[369] Further, there are a number of earlier case reports suggesting that DHEA may be useful in the treatment of schizophrenia, especially for negative symptoms.[370–372] A recent double-blind study of DHEA as adjunct to antipsychotic treatment in chronic schizophrenic patients with prominent negative symptoms suggests that it can improve negative, depressive and anxiety symptoms of the illness, especially in women.[373] Although the mechanism of action of DHEA and DHEA-S has still to be further characterized, the possibility that these compounds may have efficiency in schizophrenia should be further investigated.

Pregnenolone: Intensive studies in animals established that neuroactive steroids such as pregnenolone (PREG) and pregnenolone sulfate (PREGS) display neuronal actions and influence behavioral functions.[374] For example, PREG and PREGS exhibit memory-enhancing properties in aged rodents (for a review, see Vallee *et al*[375]). It has also been suggested that PREGS can ameliorate MK-801-induced memory impairment by acting as ó$_1$ receptor agonists.[376] In addition, PREGS can attenuate the conditioned fear stress response via ó$_1$ receptors.[377] Albeit speculative, these findings suggest that PREG and PREGS may have therapeutic potential for improving cognitive deficit observed in schizophrenia.

Neurotrophic factors The role of neurotrophic factors in the pathophysiology of schizophrenia is rapidly becoming an important and exciting focus of investigation. A more recent pathophysiologic theory of schizophrenia suggests that it involves a limited neurodegenerative process reflected by the progressive and deteriorating clinical course of the illness.[378] Recent longitudinal neuroimaging studies of first-episode schizophrenia have demonstrated morphological changes in cortical gray matter and

ventricular volumes that have been suggested to reflect pathological processes of developmental maturation and/or illness progression.[379–381] The neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin (NT)-3/4/5 play a decisive role in a neurodevelopmental process, including neuronal and glial differentiation, migration, proliferation and regeneration.[382] They are not only active during embryo- and organogenesis but also influence the synaptic organization and the synthesis of neurotransmitters in the adult brain, and are therefore involved in the maintenance of neural plasticity.[382] Thus, pathological alterations of the neurotrophic factor system may lead to neural maldevelopment, migration deficits and dysconnections, which are proposed to be the characteristic pathogenetic features of the neurodevelopmental hypothesis of schizophrenia.[382,383] If neurotrophic factors salvage degenerating cells, facilitate desirable synaptic connections, and hence, halt the progression of neurodegenerative process of schizophrenia, drugs that selectively stimulate the production of neurotrophic factors could represent a new approach to forestall the progression of schizophrenia and prevent morbidity from increasing.[384] Although neurotrophic factors are unable to cross the blood–brain barrier, potential strategies for the administration of these factors are transplantation of neurotrophic factor-producing cells, direct transfection of neurotrophic factor gene and development of compounds which modulate endogenous neurotrophic factor homeostasis and/or the influence their signal transduction mechanisms.[382] The augmentation therapy with neurotrophic factors suggests novel and innovative pharmacotherapeutic, but as yet unproven, strategies for schizophrenia.

Future directions

Although a recent meta-analysis suggests that some SGAs are more efficacious than FGAs,[157] one cannot reliably predict which patient will respond best to a particular antipsychotic medication.[205] Significant differences between the new antipsychotics are emerging so that drug choice needs to be tailored for individual patients.[152] Recent developments in simultaneous profiling of gene transcripts (gene chips) and gene products (proteomics) will allow definition of the genes and proteins that are affected by antipsychotic medication. It is very likely that individual genetic differences are important determining factors in the efficacy and side effect profiles of antipsychotic medication.[385] Therefore, it is possible to improve drug response at the level of the individual patient by detecting single-nucleotide polymorphism in patients' DNA.[386,387] Knowledge of the relationship between specific genetic polymorphisms of genes involved in a drug's pharmacokinetics and pharmacodynamics may lead to better drug design and to individualized pharmacotherapy (for reviews, see Basile *et al*[385] and Arranz and Kerwin[388]). In addition, a more long-term approach may be to take advantage of information from clinical imaging (sMRI, structural magnetic resonance imaging; MRS, magnetic resonance spectroscopy; fMRI, functional MRI) and electrophysiologic (ERP, event-related potential) studies that are becoming increasingly sophisticated, providing more detailed information of the individual brain morphologic changes, pathways and circuits involved in various aspects and stages of schizophrenia.[233] These measures can also serve to define bio or surrogate markers of treatment effects.

As yet no drug that did not have some affinity for and activity at the dopamine D_2 receptor has been proven to have antipsychotic efficacy. Thus, the development of novel compounds targeting other systems than dopamine will likely be employed as adjunctive or combined treatments in addition to whatever monotherapeutic applications they may have.

With the improvements in pharmacological treatment seen over the last decade, the focus of therapy for schizophrenia has shifted from the relief of psychotic symptoms to other pathological domains including negative and mood symptoms, cognitive deficits and the functional impairment that undermines patients' capacities for daily functioning, reintegration into society, and recovery. At present, much remains to be done in terms of developing treatment strategies and the determination of its optimal use in conjunction with psychosocial and adjunctive therapies.

Conclusion

Psychopharmacological research efforts have focused on developing compounds with unique combinations of effects at different perisynaptic neurotransmitter sites as described above.[189] Future efforts must move beyond strategies that develop drugs which solely target the modulation of chemical neurotransmission at synapses to the development of agents that can affect other cellular functions including signal transduction, signaling pathways and gene expression, and that underlie mechanisms of cell development, plasticity and resilience. In addition, efforts to identify genetic mechanisms that underlie mental illnesses will reveal new targets for drug development. Such efforts could offer a more powerful method for identifying the neural and molecular mechanisms causing schizophrenia, and for developing animal models and novel therapeutic approaches. One of the important goals of pharmacological research should be to develop new ideal antipsychotic drugs with low associated risk, rapid onset of action, a more effective treatment for negative, cognitive and affective symptoms, in better efficacy against positive symptoms, and improved relapse rates and reduction or even reversal of cumulative morbidity.[189] The hope for further progress relies upon development of a number of different basic and

clinical neuroscience strategies, but with these innovations it is likely that future progress will be relatively quick to come.

Competing interests

The following financial interests by coauthors include consultant fees, honoraria and/or research funds.

Seiya Miyamoto: Eli Lilly Japan
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Christine E Marx: Eli Lilly
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