Recent Advances in the Development of Novel Pharmacological Agents for the Treatment of Cognitive Impairments in Schizophrenia

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Wayne Fenton was a major driving force behind the establishment of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) project mechanisms. These projects were designed to facilitate the development of new drugs for the treatment of cognitive impairments in people with schizophrenia. The MATRICS project identified 3 drug mechanisms of particular interest: cholinergic, dopaminergic, and glutamatergic. The TURNS project is designed to select potential cognitive-enhancing agents and evaluate their potential efficacy in the context of proof of concept or clinical efficacy trials. This article reviews the rationale for these 3 approaches and provides an update on the development of therapeutic agents, which act through one of these 3 mechanisms.

Key words: cognitive impairments/nicotinic receptors/dopamine/glutamate

Introduction

People with schizophrenia are characterized by a broad range of cognitive impairments. Areas of impairment include attention/information processing, problem-solving, processing speed, verbal and visual learning and memory, and working memory.1 Despite appropriate treatment with either first-generation antipsychotics (FGAs) or second-generation antipsychotics (SGAs),2–4 people with schizophrenia continue to exhibit pronounced cognitive impairments. The lack of marked cognitive benefit of antipsychotics has led to the investigation of alternative agents and mechanisms for the treatment of these impairments.

In order to facilitate the development of new pharmacological approaches for the treatment of cognitive impairments in schizophrenia, Wayne Fenton, Ellen Stover and colleagues developed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS; PI: Stephen R. Marder, MD) and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS; PI: Stephen R. Marder, MD) project mechanisms. The MATRICS project (http://www.matrics.ucla.edu) was designed to identify core cognitive impairments in schizophrenia, identify promising targets for drug development, develop a battery to assess cognition in clinical trials, and develop study design guidelines for clinical trials of cognitive-enhancing agents. The TURNS project (http://www.turns.ucla.edu) is a network of academic sites charged with selecting potential cognitive-enhancing agents and evaluating their potential efficacy in the context of proof of concept or clinical efficacy trials.

In a 2-day conference, the MATRICS Neuropharmacology Committee identified leading targets for the treatment of cognitive impairments.5 The selection was based on consensus opinion of academic and industry experts. The top candidates were from the following 3 classes: (1) cholinergic agents, including β7-nicotinic agents; (2) dopaminergic agents, including D1 agonists; and (3) glutamatergic agents, including agents that act at either the ionotropic or metabotropic receptors. The current article provides an update on the current status of drug development in each of these classes.

Cholinergic Agents

Introduction

Acetylcholine acts at muscarinic and nicotinic cholinergic receptors. These receptors are broadly distributed throughout the brain, including the neocortex, hippocampus, thalamus, and basal ganglia.6 These regions are part of various neural circuits that subserve simple...
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and complex cognitive processes. The cholinergic system has been implicated in the regulation of attention, memory, processing speed, and sensory gating; processes that are impaired in schizophrenia. Several lines of evidence suggest that the cholinergic system may be disrupted in schizophrenia. Postmortem studies have demonstrated alterations in muscarinic receptor and nicotinic receptor availability or expression.\(^1\)\(^2\)\(^3\) In a recent single-photon emission computed tomography study, muscarinic receptors were significantly reduced in the cortex, thalamus, and basal ganglia of people with schizophrenia. Acute nicotine administration has been shown to improve attention, eye tracking, sensory gating, verbal and visual memory, and working memory in people with schizophrenia.\(^4\)\(^5\)\(^6\)

In combination, these studies suggest that people with schizophrenia may have multiple abnormalities of the cholinergic system and that agents, which enhance cholinergic function may act as cognitive enhancers.

\(\alpha7\)-Nicotinic Agents

A series of \(\alpha7\)-nicotinic cholinergic receptor agonists have been developed in an attempt to further characterize central nervous system (CNS) cholinergic function and as potential candidates for the treatment of schizophrenia. Pfizer has a drug development program concentrating on azabicyclic aryl amides.\(^2\) The \(\alpha7\)-selective agonist DMXB-A, 3-[(2,4-dimethoxy)benzylidene]-anabaseine, is one of a series of anabaseine compounds developed by William Kem’s laboratory at University of Florida.\(^3\)\(^4\)

Convergent neurobiological and genetic evidence has implicated the \(\alpha7\)-nicotinic receptor in the pathophysiology of schizophrenia and hence a potential therapeutic target. Nicotine is heavily abused by people with schizophrenia, an observation that has sometimes been explained as an attempt at self-medication. About 80\% of people with schizophrenia smoke, with a mean consumption of 30 cigarettes/d; per cigarette, they extract 50\% more nicotine than other smokers. Higher nicotine levels are consistent with activity at \(\alpha7\) receptors, which are less sensitive to nicotine than \(\alpha4\beta2\) nicotinic receptors, the other common neuronal nicotinic receptor that is found on presynaptic terminals of many different neuronal types. Nicotine has positive neurocognitive effects in schizophrenia, particularly on attention, which are consistent with the relationship between diminished sensory gating and attention dysfunction. However, these effects, which are also observed in healthy subjects, are severely limited by tachyphylaxis and are not clinically significant.\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\) Thus, although nicotine itself has no useful therapeutic effect, its actions prompt investigation of less toxic and more effective agonists.

DMXB-A is a derivative of the naturally occurring alkaloid anabaseine.\(^2\) DMXB-A is a partial agonist at human \(\alpha7\)-nicotinic receptors and at higher concentrations a weak \(\alpha4\beta2\) receptor and serotonin 5-HT3 receptor antagonist.\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) The partial agonist activity of DMXB-A may help to minimize the problem of tachyphylaxis observed with the full agonist nicotine. DMXB-A had a positive effect on neurocognition in an initial single-dose proof of concept test in 12 people with schizophrenia.\(^7\) The subjects were concurrently treated with antipsychotic drugs and were currently nonsmoking. Subjects who smoked were excluded to prevent interference with effects of DMXB-A by the effects of chronic exposure to nicotine. The effects for some subjects were sufficiently robust, ie, an 8- to 12-point increase in Repeatable Battery for the Assessment of Neuropsychological Status total scale score,\(^8\) to be suggestive of a meaningful clinical effect. There was an accompanying increase in the suppression of the P50 auditory evoked potential to repeated stimuli. Increased inhibition of the P50 response during DMXB-A supports the hypothesis of an agonist effect on \(\alpha7\)-receptors located on inhibitory interneurons. In animal models, stimulation of \(\alpha7\)-nicotinic receptors with DMXB-A selectively decreases the test response amplitude, as was found in this study.\(^9\) The study results suggest that inhibitory circuits, which are normally responsible for suppression of the test response and appear to be dysfunctional in schizophrenia, may remain susceptible to activation by nicotinic agonists, as well as other treatments.

Several compounds in current clinical use may also have direct or indirect effects on \(\alpha7\)-nicotinic receptors. Galantamine is discussed below. Tropisetron, a 5HT3 antagonist approved for use outside the United States as an antinausea drug, has nearly equal potency as an \(\alpha7\)-nicotinic receptor agonist. Tropisetron also improves the inhibition of P50 responses in schizophrenia, perhaps through \(\alpha7\)-nicotinic receptor agonism.\(^10\) The SGA clozapine is not a direct nicotinic agonist, but it indirectly increases release of acetylcholine in the hippocampus, a property not shared by FGAs and other SGAs.\(^11\) Clozapine increases P50 auditory response inhibition in schizophrenia, with animal models demonstrating that this effect is mediated by stimulation of \(\alpha7\)-nicotinic receptors.\(^12\)\(^13\) Clinical response to clozapine is greater in people with schizophrenia who smoke before the initiation of treatment, compared with those who do not, and also results in decreased smoking behavior during treatment, perhaps consistent with nicotinic cholinergic agonism as 1 mechanism of its antipsychotic effect.\(^14\)\(^15\)

Acetylcholinesterase Inhibitor Agents

Acetylcholinesterase inhibitors (AChEIs) act primarily through the inhibition of acetylcholinesterase, the enzyme primarily responsible for metabolizing acetylcholine in the synaptic cleft and terminating cholinergic transmission. Inhibition of the enzyme increases the
amount of acetylcholine at both the muscarinic and nicotine cholinergic receptors.

There have been a series of studies of AChEIs in schizophrenia.44 The most frequently tested agent has been donepezil. Although several open-label and small sample–controlled studies have suggested a beneficial effect on cognitive impairments,45–47 large controlled trials have failed to demonstrate a beneficial effect on cognition.48–51 In the largest study to date (121 subjects randomized to donepezil and 124 subjects randomized to placebo), donepezil did not differ from placebo on the global composite score or on any of the individual cognitive measures.51 Similarly, positive open-label reports of a beneficial effect of rivastigmine,52,53 have not been replicated in a double-blind, placebo-controlled study.54 There have been 2 published double-blind, placebo-controlled galantamine studies55,56 and 2 unpublished studies (http://clinicaltrials.gov; Buchanan et al57). In the small-sample size, double-blind, placebo-controlled studies (n = 14; 55, n = 24; 56), galantamine treatment was associated with selective benefits for attention and delayed memory55,56 and visual recognition.56 In a larger double-blind, placebo-controlled study (n = 73), Buchanan et al57 failed to find a significant galantamine/placebo difference for the global composite score. However, galantamine did exert a significant benefit for processing speed and verbal memory. Finally, in an industry-sponsored study, there was no significant difference between galantamine and placebo on a global measure of cognition (http://clinicaltrials.gov). The results for individual measures were not provided.

In general, the AChEI results have not been overly supportive of this approach. There is a suggestion that galantamine, in contrast to donepezil and rivastigmine, may have selected benefits for verbal memory and processing speed measures.55–57 If the galantamine results are valid, then the question arises, why does galantamine have a beneficial effect for cognition but donepezil and rivastigmine apparently do not? One possible explanation is that, in addition to its AChEI actions, galantamine is also a positive allosteric modulator of the \( \alpha_4 \beta_2 \) and \( \alpha_7 \)-nicotinic receptors.58–61 The allosteric properties of galantamine could directly lead to increased release of acetylcholine and sensitization of postsynaptic nicotinic receptors59 or indirectly effect cognition through its effects on the release of other neurotransmitters, especially glutamate and DA.61,62 Schilstrom et al61 have recently demonstrated that galantamine increases dopaminergic activity and release in the prefrontal cortex in a dose-dependent manner. Wang et al62 demonstrated that galantamine increased DA release in the hippocampus, through its allosteric mechanism, and that this effect of galantamine was related to its ability to improve cognitive impairments in a mouse model of Alzheimer disease.

**Summary**

There is an extensive literature supporting the beneficial effects of acute nicotine administration on cognitive impairments in people with schizophrenia. Whether this effect is mediated through the \( \alpha_4 \beta_2 \) or \( \alpha_7 \) or both nicotinic receptors has not been clearly established. The advent of selective agents for these receptors will enable the eventual delineation of their respective therapeutic roles. Initial studies with DMXB-A and galantamine suggest that agents that act as either partial agonists or allosteric modulators of the \( \alpha_4 \beta_2 \) or \( \alpha_7 \)-nicotinic receptors may be of particular interest.

**Dopaminergic Agents**

**Introduction**

The DA system has long been integral to our understanding of the pathophysiology of schizophrenia.63–66 Although, historically, DA was thought to be involved in positive symptom pathophysiology, more recently, it has also been implicated in the pathophysiology of negative symptoms and cognitive impairments.65,67–69 Specifically, it has been hypothesized that schizophrenia involves a biphasic dysregulation of DA signaling, in which subcortical mesolimbic DA pathways are disinhibited and overactive and mesocortical DA pathways are underactive; the combination of these effects results in decreased prefrontal DA signaling.70,71 This model is consistent with the pattern of cognitive impairments seen in schizophrenia, which includes functions mediated by frontal cortical structures such as working memory and executive functions.72 The model is also consistent with functional brain imaging studies in which people with schizophrenia demonstrated abnormal prefrontal activation associated with impaired performance of cognitive tasks (eg, working memory, executive functions).73,74

Although this model has been heuristic, it has presented significant challenges for the development of therapeutic agents. The use of DA antagonists to suppress overactivity, while therapeutic for positive symptoms, runs the risk of exacerbating negative symptoms and cognitive impairments by further decreasing DA signaling in the frontal cortex. At the same time, the use of indirect DA agonists, while proven to be effective in transiently reducing negative symptoms and improving cognition, risks exacerbating psychosis.75,76 Thus, more precise pharmacodynamic approaches are needed.

**D\(_1\) Agonists**

DA signaling is mediated by DA receptor subtypes that are members of the G protein–coupled receptor super-family.77–79 The receptors are categorized into 2 groups, D\(_1\) like and D\(_2\) like. D\(_2\) receptors are predominantly expressed in subcortical regions including the midbrain,
DA receptors are critical mediators of the direct and indirect modulatory effect of DA on pyramidal cell activity. Prior studies (postmortem and in vivo imaging) suggest that D1 receptors may be upregulated in schizophrenia; an effect presumably due to a chronic impairment in DA tone in the cortex.

The location and function of D1 receptors make them attractive targets for the treatment of negative symptoms and cognitive impairments. Although support for this strategy comes from the work of many investigators, the work of the late Patricia Goldman-Rakic was particularly influential. Preclinical studies from her laboratory showed that chronic blockade of DA D2 receptors by antipsychotic drugs down regulates D1 receptors in the prefrontal cortex and produces severe impairments in working memory. More specifically, studies in primates showed that the D1 agonist ABT-431 reversed working memory deficits associated with chronic antipsychotic therapy. Consequently, there is a strong rationale for evaluating the potential efficacy of DA D1 agonists in people with schizophrenia. The most promising compounds are DAR-0100 and its stereoisomer DAR-0100A.

DAR-0100 (published as dihydrexidine; (±)-trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine; see Table 1) is a potent, full-agonist D1 DA receptor agonist. DAR-0100 binds with high affinity to the D1 receptor (IC50 = 10 nM). Additionally, DAR-0100 has been screened for activity at 40 additional binding sites and found to be inactive (IC50 > 10 μM) at all except D2 DA receptors (IC50 = 130 nM) and α2 adrenergic receptors (IC50 = 230 nM). DAR-0100 is as efficacious as DA and approximately 70 times more potent in the stimulation of adenylate cyclase. This effect is blocked by the D2 antagonist SCH 23390 but not by D2, 5-HT2, muscarinic, or alpha- or beta-adrenergic receptor antagonists. Despite its D1 affinity, the functional effects of DAR-0100, both in situ and in vivo, are attributable almost entirely to interaction with the D1 receptor. Binding and functional activity are associated only with the dextrorotatory enantiomer, DAR-0100A.

While many have recognized the value of a full D1 agonist in the treatment of a variety of neurological and psychiatric disorders, the advancement of this type of drug has been hindered by a variety of factors. In the case of DAR-0100, the issues preventing the advancement to market had been (1) a lack of oral bioavailability, and (2) a short half-life that would require repeated daily dosing. With the patch or pump delivery devices now available for subcutaneous administration, as well as buccal administrations such as Zydis, these limited hindrances can be resolved. Compounds such as DAR-0100 can be formulated into viable treatment options, allowing the drug to be practically administered. The low dosing level required would limit the potential for hypotension, an unintended effect related to peripheral D1 receptors, seen with all DA agonists.

To date, DAR-0100 has been tested as a single 20-mg dose (15-minute subcutaneous infusion) in people with Parkinson disease and 20 people with schizophrenia with no significant blood pressure drop. In the latter study, the effects of DAR-0100 on the neural correlates of working memory (BOLD signal) were recently investigated using a 3T MRI scanner during a 2-back working memory task. Gadolinium perfusion sequences prior to and after DAR-0100 were also acquired.

### Summary

Although there is extensive data to support the utility of the D1 agonist strategy, practical issues have hindered the development of drugs to adequately evaluate this approach. However, if successful, then this approach would constitute yet another practical benefit from the durable DA hypothesis of schizophrenia.

### Glutamate

#### Introduction

Glutamate is the primary excitatory neurotransmitter in brain. It is contained as a neurotransmitter in approximately 60% of brain neurons, including almost all cortical pyramidal neurons. Further, virtually 100% of brain neurons contain some type of glutamate receptor. The role of glutamate as a transmitter was only discovered only about 25 years ago. To date, few medications are available that impact meaningfully on glutamatergic neurotransmission. Nevertheless, the last decade has seen

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**Table 1. Binding Affinities of DAR-0100 at Striatal D1 and D2 Receptors**

<table>
<thead>
<tr>
<th>Test Ligand</th>
<th>D1 Like</th>
<th>D2 Like</th>
</tr>
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<tbody>
<tr>
<td>Chlorpromazine</td>
<td>ND</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>SCH23390</td>
<td>0.69 ± 0.05</td>
<td>ND</td>
</tr>
<tr>
<td>Dopamine</td>
<td>500</td>
<td>70</td>
</tr>
<tr>
<td>DAR-0100</td>
<td>5.5 ± 0.9</td>
<td>61.0 ± 5.0</td>
</tr>
</tbody>
</table>

Note: ND = not determined.
a dramatic increase in interest in the glutamatergic system on the part of major pharmaceutical companies and a growing number of compounds targeting glutamate entering preclinical and clinical testing.

Glutamate mediates its CNS effects via both ionotropic and metabotropic receptors. Ionotropic receptors are differentiated based on sensitivity to the synthetic glutamate derivatives N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate. NMDA receptors are particularly linked to schizophrenia based upon the psychotomimetic actions of NMDA antagonists including phencyclidine and ketamine.

Metabotropic receptors are divided into several groups, which show differential effects on glutamatergic function. Group I receptors, consisting of mGluR1 and mGluR5, function predominantly to potentiate both presynaptic glutamate release and postsynaptic NMDA neurotransmission. Conversely, group II (mGluRs 2 and 3) and Group III (mGluRs 4, 6, 7, and 8) receptors serve to limit glutamate release, particularly during conditions of glutamate spillover from the synaptic cleft.

In general, based upon the action of NMDA antagonists, it is posited that schizophrenia is associated with reduced glutamatergic neurotransmission. Treatment strategies, therefore, have attempted to potentiate glutamatergic neurotransmission at either NMDA or non-NMDA receptors. It has also been proposed, however, that some symptoms of schizophrenia result from rebound hyperglutamatergic secondary to primary NMDA blockade. Such deficits may be reversed, particularly in frontal areas, by mGluR group II/III agonists, which may also reverse effects of ketamine in both rodent and human studies.

Specific Targets
There are 3 major classes of glutamatergic targets: NMDA, AMPA, and metabotropic receptors.

NMDA Receptors: Glycine Site Agents  NMDA receptors contain multiple binding sites, which may serve as targets for drug development. Target development to date has focused primarily on the glycine allosteric modulatory site. Proof of concept studies have been conducted using naturally occurring agonists of the glycine receptor as medical treatments. In general, the full agonists, such as glycine, have proven more effective than the partial agonist D-cycloserine. Further, effects have generally been more robust when these agents have been used in combination with antipsychotics other than clozapine, suggesting that clozapine’s unique therapeutic effects may be due, in part, to its ability to stimulate NMDA receptor–mediated neurotransmission.

To date, 7 small-scale studies have been published in which full agonists were combined with FGAs or SGAs other than clozapine. In these studies, glycine has been used at doses of 0.4–0.8 g/kg (approximately 30–60 g/d), d-serine at doses of 30 mg/kg (approximately. 2.1 g/d), and D-alanine at a dose of 100 mg/kg (approximately. 7 g/d). These studies have involved a total of approximately 200 subjects. Across all studies, a highly significant (P < .0001), roughly 20% improvement in negative symptoms was observed, along with improvement in the Positive and Negative Syndrome Scale (PANSS) “cognitive” symptom cluster. The PANSS “cognitive” symptom is comprised of symptoms, such as poor attention and disorientation, thought to be related to cognitive function, and is not a formal assessment of cognitive function.

Only 2 studies to date have reported neuropsychological test results. In the first study, there was a significant d-serine/placebo group difference in Wisconsin Card Sort Test categories completed, but perseverative error rate was not differentially affected. A large multicenter study of glycine (n = 37) versus d-cycloserine (n = 41) versus placebo (n = 37) did not find either cognitive improvement, as assessed using a MATRICS-like neuropsychological test battery, or overall therapeutic effectiveness of either glycine or D-cycloserine, leaving unresolved whether cognitive improvement would occur in the context of significant symptomatic change.

Because of the involvement of NMDA receptors in neurodevelopment, neuroplasticity, and trophic brain functions, an ideal use of the compounds may be in reversing symptoms and neurocognitive symptoms early in the schizophrenia prodrome, prior to any long-term, irreversible structural changes. One small-scale, (n = 10) open-label study of glycine in prodromal schizophrenia found large (d = 1.2) effect-size changes on prodromal symptoms, which were larger than those observed in a prior double-blind trial of olanzapine. However, double-blind findings with NMDA agonists in the schizophrenia prodrome are not yet available. In this study as well, no cognitive endpoints were included.

NMDA Receptors: Glycine Transport Inhibitors  A second approach to treatment has been use of glycine transport inhibitors (GTIs) to increase extracellular glycine levels by preventing neuronal and glial uptake. Although clinical data with GTIs remain limited, 2 small-scale studies have been performed with the naturally occurring compound sarcosine, given at a dose of approximately 2 g/d. In 1 study, sarcosine treatment produced a 17% reduction in PANSS negative symptoms, a 14% reduction in PANSS positive symptoms, and a 13% improvement in PANSS “cognitive” symptom cluster in people with chronic schizophrenia stabilized on FGAs or SGAs. More recently, similar effects were observed following addition of sarcosine to risperidone treatment for acutely decompensated subjects. As with direct glycine site
agonists, no beneficial effects of sarcosine were observed in clozapine-treated people with schizophrenia.123 Lead GLYT1 inhibitors currently entering clinical testing show approximately 1000-fold greater potency than sarcosine at the GLYT1 transporters, along with >1000-fold selectivity versus other CNS targets. Encouraging preclinical results have been observed with several prototypic GTIs, including glycyldodecylamide,124 N-[3-(4’-fluorophenyl)-3-(4’-phenylphenoxy)propyl]sarcosine (NFPS),125–128 Org24461,128 Org 24598,129 and SSR504734,130 in several preclinical assays thought to be relevant to neurocognition, including potentiation of NMDA receptor activity in vitro and in vivo, and reversal of schizophrenia-like prepulse inhibition abnormalities124,128,130–136 (Table 2). Nevertheless, clinical data remain lacking.

**AMPA Receptors** AMPA receptors mediate the bulk of fast glutamatergic neurotransmission in the brain. In addition, AMPA receptors work synergistically with NMDA receptors and are needed to maintain overall integrity of glutamate synapses. AMPA receptors desensitize quickly following agonist stimulation at the AMPA glutamate receptor site, which limits the utility of this approach. However, allosteric modulators, termed AMPAkines, may be able to stimulate AMPA receptors without causing desensitization. AMPAkines have been found to improve cognitive performance in animal models137,138 and to act synergistically with antipsychotics to reverse amphetamine-induced hyperactivity.139 To date, 2 clinical studies have been published with the AMPAkine CX-516. In a small n study (n = 19) of CX-516 added to clozapine, improvements in memory and attention were observed despite lack of symptomatic improvement.140 However, in a larger multicenter study (n = 95), CX-516 was not found to be effective when added to clozapine, olanzapine, or risperidone.141 CX-516 has also been studied as monotherapy, with no clear beneficial effects.142 Studies of other, high-affinity, more potent AMPAkines are ongoing, which may provide a more rigorous test of the utility of this approach.

### Metabotropic Receptors

As opposed to ionotrophic receptors, which are linked directly to ion channels, metabotropic receptors are linked to second messenger systems and affect neuronal metabolism, leading to alterations in glutamate release. Metabotropic receptors are divided into 3 groups based upon functional activity and structure.143 One agent in particular, LY354740, a group II agonist, has been found to reverse effects of NMDA antagonists in both rodents and humans,107,108 suggesting a potential role in treatment of schizophrenia. Recently, encouraging phase II results have been reported for the mGlu2/3 agonist LY2140023 (http://www.lillytrials.com/initiated/studies/initiated_9777.html), especially against positive symptoms. However, no neuropsychological battery was included in the study; thus, the effects of these agents on neurocognition remain lacking.

### Summary

Glutamatergic function remains an area of active drug development, with promising preclinical results having been reported for several classes of compound. Many compounds are only now entering early-stage clinical trials. Because of the NMDA effects on brain development and neuroplasticity, glutamatergic agents may be particularly appropriate for reversal of symptoms and emerging neurocognitive dysfunction in prodromal schizophrenia, although double-blind, randomized controlled clinical trials are required.

### Conclusion

The MATRICS and TURNS project mechanisms have stimulated considerable interest in the development of cognitive-enhancing agents. Multiple cholinergic, dopaminergic, and glutamatergic agents have been developed and are in the early stages of evaluation. Preliminary results with agents that modulate the α4β2 or α7-nicotinic receptors are supportive of this approach. For various reasons, the development of dopaminergic and glutamatergic

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**Table 2. Preclinical Paradigms of Relevance to Schizophrenia in Which Glycine Transport Inhibitors Have Been Shown to Potentially Have Beneficial Effects**

<table>
<thead>
<tr>
<th>Test Measure</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Inhibition of PCP-induced hyperactivity in vivo</td>
<td>Javitt et al,124 Harshing et al,128 Javitt et al131</td>
</tr>
<tr>
<td>Potentiation of hippocampal NMDA responses in vitro</td>
<td>Bergeron et al132</td>
</tr>
<tr>
<td>Potentiation of prefrontal/hippocampal NMDA responses in vivo</td>
<td>Depoortere et al,130 Chen et al,133 and Kinney et al134</td>
</tr>
<tr>
<td>Normalization of PPI deficits in rodents</td>
<td>Depoortere et al,130 Kinney et al,134 and Le Pen et al135</td>
</tr>
<tr>
<td>Normalization of PCP-induced increases in amphetamine-stimulated dopamine release</td>
<td>Javitt et al136</td>
</tr>
<tr>
<td>Reversal of locomotor hypersensitivity to amphetamine neonatally PCP-treated rats</td>
<td>Depoortere et al130</td>
</tr>
</tbody>
</table>

*Note: PCP, phencyclidine; NMDA, N-methyl-D-aspartate; PPI, prepulse inhibition.*
agents has lagged behind that of cholinergic agents and there is less clinical data to support these approaches, though the theoretical rationale for both is very strong. Despite these efforts, cognitive impairments remain one of the most important unmet therapeutic challenges in schizophrenia. The ultimate tribute to Wayne Fenton will be the successful development of an effective drug for this indication.

Acknowledgments

Dr Javitt holds intellectual property rights for use of glycine-site agonist and glycine transport inhibitors for treatment of schizophrenia and holds stock in Glytech, a company developing these compounds for clinical use.

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