



# GLUTAMATE: New hope for SCHIZOPHRENIA treatment

Research on glutamatergic dysfunction may lead to therapies targeting negative and cognitive symptoms

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In patients with schizophrenia, positive symptoms typically respond to treatment, while negative and cognitive symptoms often persist and contribute to chronic disability.<sup>1</sup> Schizophrenia also is associated with widespread neurocognitive deficits—including impairments in executive functioning, learning, memory, and processing speed—that are a core feature of the disorder and may precede illness onset.<sup>2</sup>

Current treatment is based on the dopamine model of schizophrenia, which proposes that dopaminergic dysfunction is the basis for symptoms and cognitive deficits.<sup>3</sup> Although this model is effective in guiding treatment for some patients, most show persistent disability despite receiving the best available treatment. Over the last 2 decades, researchers have developed alternative conceptual models of schizophrenia based on the psychotomimetic effects of compounds such as phencyclidine (PCP) and ketamine.<sup>4</sup> These compounds function primarily by blocking *N*-methyl-D-aspartate (NMDA)-type glutamate receptors (NMDARs), which has lead researchers to focus on glutamatergic neurotransmission and NMDARs as a basis for new drug development. This article describes the glutamatergic model of schizophrenia and its implications for future treatments.

## Dopaminergic models

Since the discovery of chlorpromazine almost 60 years ago, the dopamine model of schizophrenia has been widely accepted. It has gone through several iterations but in general suggests that schizophrenia is caused





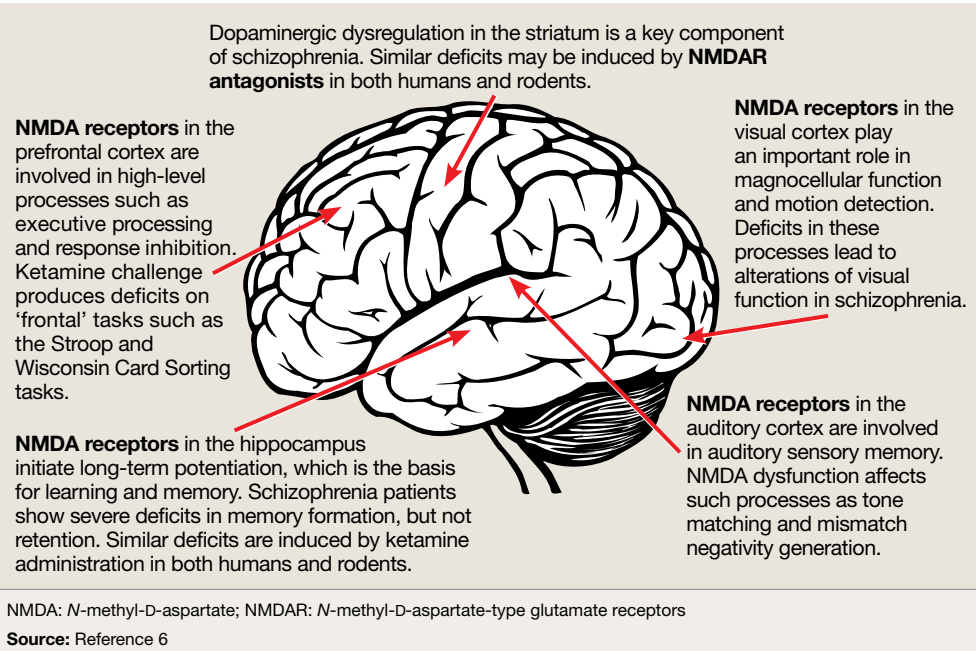
## Glutamate and schizophrenia

### Clinical Point

Dopaminergic dysfunction appears to account for only part of schizophrenia's symptoms and neurocognitive profile

### Figure

## The wide reach of glutamatergic dysfunction



by dopaminergic system dysfunction, particularly increased dopamine within subcortical brain regions such as the striatum or nucleus accumbens.<sup>3</sup> The ability of amphetamine or other dopaminergic agents to induce symptoms closely resembling positive symptoms supports this model, as do genetic studies that show dopamine-related genes are associated with schizophrenia.<sup>5</sup> In addition, all antipsychotics block dopamine type 2 receptors.

Unfortunately, limitations of this model continue to limit treatment:

- Dopaminergic compounds such as amphetamine do not induce negative symptoms or cognitive deficits similar to those observed in schizophrenia.
- Dopamine receptor blockers do not reverse cognitive dysfunction or negative symptoms.
- Dopaminergic instability observed during acute decompensation appears to resolve after stabilization even without symptom remission.
- Although dopaminergic systems preferentially innervate frontal brain regions, cognitive deficits in schizophrenia appear to be widespread, involving sensory as well as frontal brain systems.

Thus, dopaminergic dysfunction appears to account for only a part of schizophrenia's symptomatic and neurocognitive profile.

### Glutamatergic model

Approximately 20 years ago, researchers proposed an alternate schizophrenia model based on the observed clinical actions of "dissociative anesthetics," including PCP and ketamine. PCP was patented in 1953 as a surgical anesthetic, but serious side effects, such as hallucinations, agitation, and catatonic-like reactions, soon curtailed its clinical use. As early as 1959, some researchers noted similarities between PCP psychosis and schizophrenia.<sup>4,6</sup>

The binding site for PCP and other dissociative anesthetics ("PCP receptor") was first described in 1979 and subsequently localized within the ion channel formed by the NMDAR. Glutamate is the primary excitatory neurotransmitter in the brain, and binds to NMDA and non-NMDA (eg, metabotropic or alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) receptors. Binding of PCP prevents glutamate from activating

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NMDARs, which suggests that the pathogenesis of schizophrenia may be caused by dysfunction of NMDARs in particular or of the glutamatergic system in general. Unlike dopamine, the glutamatergic system is distributed throughout the brain and plays a prominent role in sensory processing and higher-level functions such as memory and executive functioning (Figure).<sup>6</sup> Therefore, glutamatergic theories open new approaches for potential schizophrenia treatments, most of which are now entering clinical evaluation.

### Effects of NMDAR antagonists

In initial studies with PCP and ketamine in the early 1960s, researchers noted that these agents produced psychotic effects similar to schizophrenia symptoms.<sup>6</sup> Further confirmation was obtained from retrospective studies of PCP abusers.<sup>6</sup> It was not until the 1990s, however, that studies using modern operationalized symptom and neuropsychological rating scales were conducted. In those studies, healthy participants developed positive symptoms, negative symptoms, and cognitive dysfunction after receiving ketamine.<sup>7,8</sup> Moreover, in these studies the balance between negative and positive symptoms was similar to that typically observed in schizophrenia, as was the pattern of cognitive dysfunction. Therefore, unlike dopaminergic agents, NMDAR antagonists appear to be able to produce the full constellation of symptoms and cognitive deficits associated with schizophrenia.

Similarly, ketamine worsened positive and negative symptoms in patients diagnosed with schizophrenia.<sup>9</sup> Although acute challenge with NMDAR antagonists does not produce schizophrenia-like auditory hallucinations in healthy controls, it does induce sensory distortions similar to those seen in individuals with early schizophrenia and does exacerbate pre-existing hallucinations in schizophrenia patients.<sup>10</sup> Thus, acute challenge with NMDAR antagonists appears to re-create a state similar to the earliest stages of schizophrenia.<sup>6</sup>

NMDAR antagonists also reproduce the widespread neuropsychological abnormalities of schizophrenia (Figure).<sup>6</sup> Ketamine

infusion results in the severity and type of disorganized thinking seen in schizophrenia. Given the importance of neurocognitive dysfunction to the conceptualization of schizophrenia, these findings further support a glutamatergic model.

### Sensory processing deficits

A key difference between dopaminergic and glutamatergic models is prediction of sensory processing deficits. Traditionally, dopaminergic models have viewed cognitive deficits of schizophrenia as being driven “top down” from higher order brain regions such as the prefrontal cortex, or from local dysfunction within regions such as the striatum.<sup>11</sup> In contrast, glutamatergic models predict that deficits also should be observed within sensory brain regions, such as the primary auditory and visual cortex.

Because of the focus on higher-level brain dysfunction, little research on sensory processing deficits was performed until recently. It has become increasingly clear that:

- patients with schizophrenia show severe deficits in early auditory and visual processing
- these deficits significantly contribute to patterns of cognitive dysfunction and psychosocial impairment.<sup>12,13</sup>

In the auditory system, patients show deficits in pitch perception and, specifically, the ability to match tones after a brief delay. Schizophrenia patients show dysfunction in a specific part of the visual system called the magnocellular visual system. Deficits in these regions lead to impaired ability to detect emotion based on vocal intonation or facial expression, among other deficits.

In addition, reading ability—which was once thought to be normal in patients with schizophrenia—has been found to be severely disturbed.<sup>14</sup> As in developmental dyslexia, impairments relate to dysfunction of underlying auditory and visual brain regions. Administering NMDAR antagonists to humans or animals causes deficits in the auditory and visual system similar to those seen in schizophrenia, which confirms the importance of NMDA dysfunction.

### Clinical Point

The pathogenesis of schizophrenia may be caused by dysfunction of NMDARs or of the glutamatergic system in general

continued



## Glutamate and schizophrenia

### Clinical Point

One new approach to schizophrenia treatment is to develop compounds that stimulate glutamate or NMDAR function

Table

## Glutamatergic drugs in development

Target	Proposed mechanism	Proposed agents	Phase of development
Glycine/D-serine receptor	Allosteric modulator of the NMDA receptor	Glycine, D-serine, D-alanine, D-cycloserine	Phase II
Glycine-type I transport inhibitor	Blocks the reuptake of glycine, akin to SSRIs' action on serotonin	Sarcosine, RG1678	Phase II/III
Metabotropic glutamate type 2/3 (mGluR2/3)	Blocks presynaptic glutamate release	LY-2140023	Phase II
Redox sensitive site	Allosteric modulator of the NMDA receptor	N-acetylcysteine	Phase II
D-amino acid oxidase (DAAO) inhibitors	Inhibits the enzyme that metabolizes D-serine	Remains in preclinical stage	
Tetrahydrobiopterin (BH <sub>4</sub> )	Indirectly modulates glutamatergic system	Remains in preclinical stage	

NMDA: N-methyl-D-aspartate; SSRIs: selective serotonin reuptake inhibitors

### Glutamate-based treatments

Because NMDAR antagonists can induce schizophrenia symptoms, the most straightforward approach for treatment is to develop compounds that stimulate glutamate or NMDAR function (Table). The NMDAR contains modulatory sites that may be appropriate targets for drug development, including one that binds the amino acids glycine and D-serine and a redox site that is sensitive to brain glutathione levels. Reductions in brain D-serine and glutathione levels have been reported in schizophrenia, which suggests that impaired NMDAR regulation may contribute directly to brain dysfunction.<sup>15</sup> Other treatment approaches being developed include targeting glycine transporters, which indirectly regulate brain levels of glycine, or metabotropic glutamate receptors, which modulate both pre-synaptic glutamate release and post-synaptic NMDAR function.

**Glycine/D-serine site agonists.** To date, most studies have used glutamatergic drugs adjunctive to antipsychotics and targeted the glycine/D-serine modulatory site, in part because glycine and D-serine are natural compounds and therefore FDA approval for their use could be obtained without the extensive preclinical development usually required for new chemical entities.<sup>16</sup> Unfortunately, these agents are less potent than traditional pharmaceuti-

cals, and delivering optimal doses may be impossible. Nevertheless, positive studies with these compounds have provided proof-of-concept for development of agents with higher affinity and specificity.

Studies have used glycine administered at doses up to 60 g/d, D-serine up to 8 g/d, or D-alanine approximately 6 g/d. For glycine, 60 g/d is the highest dose that can be given because of concerns about tolerability and replacement of other essential amino acids. D-serine originally was tested at approximately 2 g/d with promising results, but a recent open-label trial suggested that higher doses may be more efficacious.<sup>17</sup> D-serine doses are limited by potential renal toxicity, as demonstrated in rodents studies.

Although not all studies of glycine/D-serine site agonists have been positive, a recent meta-analysis suggests significant improvement in negative symptoms across studies.<sup>18</sup> Variability in statistical results across studies is related primarily to degree of placebo effect within individual trials, with a mean improvement in negative symptoms of approximately 15%. Glycine/D-serine site agonists seem to be less effective when combined with clozapine, possibly because clozapine may already enhance the glutamatergic system and increase synaptic glycine levels.<sup>6</sup>

One study that evaluated effects of open-label glycine in individuals with

schizophrenia symptoms observed a large effect-size improvement, including early remission in 3 of 10 patients.<sup>19</sup> These data—if confirmed by double-blind trials—would indicate that glycine/*D*-serine site agonists might have utility in treating the schizophrenia prodrome.

**Glycine transport inhibitors.** A potential indirect approach to raising glycine levels in the brain is using GlyT1-type glycine transport inhibitors (GTIs). GlyT1 transporters are co-localized in brain with NMDARs and modulate local glycine levels. Rather than binding directly to the NMDAR glycine binding site, GTIs increase glycine levels in the synapse by preventing its removal by GlyT1 transporters. Their function is analogous to using selective serotonin reuptake inhibitors to increase serotonin levels in patients with depression.<sup>6</sup>

Sarcosine (*N*-methylglycine) is a naturally occurring GlyT1 inhibitor that has been used in early clinical trials in Taiwan. Initial studies with sarcosine showed efficacy similar to—and in some cases better than—that of direct glycine/*D*-serine site agonists when added to first-generation or non-clozapine second-generation antipsychotics.<sup>18</sup> Sarcosine also has been found to be effective for acute treatment of schizophrenia.<sup>20</sup> At present, however, sarcosine is not available for experimental use in the United States because of toxicity considerations.

Using high-affinity GTIs for schizophrenia was first proposed in the mid-1990s,<sup>6</sup> but such compounds are only now entering clinical efficacy studies. Most recently, phase II results were presented for RG1678, a compound developed by Hoffman LaRoche.<sup>21</sup> The study targeted persistent negative symptoms in patients receiving chronic antipsychotic treatment. Adding RG1678, 10 mg and 30 mg, to antipsychotics led to significant improvement in persistent negative symptoms vs placebo. These promising results are being followed up in phase III studies.

**Other glutamatergic options.** Few compounds are available to modulate NMDARs at sites other than the glycine/*D*-serine site. One study administered *N*-acetylcysteine, a

glutathione precursor, as a potential treatment for persistent negative symptoms.<sup>22</sup> Encouraging clinical results were observed in this double-blind study, along with improvement in electrophysiologic measures, negative symptoms, and overall functioning, but the study was limited by relatively high rates of noncompletion. Preclinical studies have combined *D*-serine with an inhibitor of *D*-amino acid oxidase to prevent *D*-serine breakdown.<sup>23</sup> In rodents, this approach produces a 30-fold increase in *D*-serine potency.

Tetrahydrobiopterin (BH<sub>4</sub>) is a cofactor for enzymes responsible for the synthesis of dopamine and other monoamines, and presynaptic release of dopamine and glutamate. Reductions in BH<sub>4</sub> levels have been reported in schizophrenia, which suggests that this compound may be etiologically important.<sup>24</sup> Researchers have initiated a study of this compound in schizophrenia.

Other schizophrenia models propose that the crucial issue is not NMDA blockade but subsequent dysregulation of presynaptic glutamate release. Type 2/3 metabotropic glutamate receptors (mGluR2/3) are located on presynaptic glutamate terminals and inhibit presynaptic glutamate release. mGluR2/3 agonists have been shown to reverse ketamine's effects in humans and in animal models,<sup>25,26</sup> which suggests a potential role in schizophrenia treatment.

The first mGluR2/3 agonist entered into monotherapy clinical efficacy trials for schizophrenia was LY-2140023. In an initial trial, this compound showed significant efficacy in improving positive and negative symptoms, comparable to that of olanzapine.<sup>27</sup> However, a follow-up study failed because of a large placebo effect,<sup>28</sup> which leaves the efficacy question unresolved.

In contrast to mGluR2/3, type 5 metabotropic receptors (mGluR5) are co-localized with NMDA receptors and potentiate activation. Thus, mGluR5 agonists also may be effective for treating schizophrenia. These compounds remain in preclinical development. Other approaches, such as stimulating specific types of GABA receptors to overcome glutamatergic deficits, remain promising but have not been tested in definitive clinical trials.

## Clinical Point

**A meta-analysis suggests that glycine/*D*-serine site antagonists can significantly improve negative symptoms**





## Glutamate and schizophrenia

### Clinical Point

GlyT1-type transport inhibitors increase glycine levels by preventing glycine's removal by GlyT1 transporters

### Related Resources

- Kantrowitz JT, Javitt DC. N-methyl-D-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? *Brain Res Bull.* 2010;83(3-4):108-121.
- Kantrowitz JT, Javitt DC. Glutamatergic approaches to the conceptualization and treatment of schizophrenia. In: Kantrowitz JT, Javitt DC, eds. *Handbook of neurochemistry and molecular neurobiology: schizophrenia.* 3rd ed. New York, NY: Springer; 2009.

#### Drug Brand Names

Chlorpromazine • Thorazine      Ketamine • Ketalar  
Clozapine • Clozaril              Olanzapine • Zyprexa

#### Disclosures

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## Bottom Line

Glutamate models better account for persistent negative symptoms and cognitive and sensory dysfunction in schizophrenia than does the dopamine model, and offer new hope for treatment development in schizophrenia.