Unmet Needs in the Treatment of Schizophrenia: New Targets to Help Different Symptom Domains

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Current treatments for schizophrenia, although effective for positive symptoms, have not proven as effective for negative symptoms and cognitive dysfunction. Additional strategies, such as combining antipsychotics or adding adjunctive agents to antipsychotics, have also yielded disappointing results in both negative and cognitive symptom domains. However, the *N*-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis, with its focus on the glutamate system's effect on dopamine, can explain the positive, negative, and cognitive symptoms in schizophrenia. Therapeutic targets are being explored that focus on NMDA receptors (eg, glycine, D-serine), glycine reuptake inhibition (such as sarcosine and bitopertin), and, through a different pathway, α-7 nicotinic acetylcholine receptor agonism (eg, encenicline).

(J Clin Psychiatry 2014;75[suppl 1]:21–26)

Schizophrenia consists of a set of symptom domains that respond differently to treatment. Positive symptoms such as suspiciousness, paranoia, grandiosity, delusions, unusual thought content, and hallucinations are often the target of attention and treatment. However, negative symptoms and cognitive symptoms are also distinct symptom domains. Negative symptoms, such as blunted affect, emotional withdrawal, social avoidance, lack of spontaneity, and poor rapport, and cognitive symptoms, like poor attention, conceptual disorganization, difficulty in abstract thinking, and disorientation, can adversely affect social and occupational functioning. Negative and cognitive symptoms may persist even when positive symptoms are successfully treated. Meta-analyses[1,2] have shown that first- and most second-generation antipsychotics have similar overall efficacy. In addition, many antipsychotics can cause troublesome side effects including weight gain, extrapyramidal symptoms, and sedation.[1,2] New therapeutic targets are needed to treat the full constellation of symptoms in persons with schizophrenia.

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This article is derived from the planning teleconference series "Measurement-Based Strategies to Assess and Manage Schizophrenia," which was held in August 2013 and supported by an educational grant from Genentech.

Dr Citrome is a consultant for Alexza, Alkermes, Bristol-Myers Squibb, Eli Lilly, Envivo, Forest, Genentech, Janssen, Lundbeck, Merck, Mylan, Novartis, Noven, Otsuka, Pfizer, Reviva, Reckitt Benckiser, Sunovion, and Takeda; is a member of the speakers/advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, Merck, Novartis, Otsuka, Pfizer, Sunovion, and Takeda; and is a stock shareholder of Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Pfizer.

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doi:10.4088/JCP.13049su1c.04

CURRENT TREATMENT STRATEGIES FOR NEGATIVE AND COGNITIVE SYMPTOMS

In addition to psychological and psychosocial treatment approaches, pharmacologic treatments are often used to try to address persistent symptoms of schizophrenia. However, no medications are currently approved by the US Food and Drug Administration (FDA) to treat persistent negative symptoms or cognitive dysfunction. Current FDA-approved pharmacologic options for schizophrenia focus on antagonism or partial agonism at the dopamine D_2 receptor and, in the case of second-generation antipsychotics, antagonism at the serotonin 5-HT_{2A} receptor.[3] While these medications may alleviate positive symptoms, several medication strategies, such as antipsychotic combinations and adjunctive use of nonantipsychotic agents, have been attempted to treat patients with persistent negative symptoms or cognitive impairment.

Antipsychotic Combinations

Antipsychotic combinations are usually given to patients with treatment-resistant schizophrenia or persistent negative or cognitive symptoms.[4] Some reasons for using this strategy include the potential for improved efficacy or speed of treatment response.[4] In general, combination studies include patients with persistent symptoms who have been taking clozapine with another second-generation antipsychotic.[5] A review[5] found that, of about 20 randomized controlled trials of antipsychotic combination therapy, only 5 supported a combination approach. A few studies demonstrated some modest or incremental improvement in both positive and negative symptoms.[5] Clinicians must weigh the potential benefits of combination therapy against the risks of increased side effects, medication costs, drug interactions, and adherence problems.[4]

Adjunctive Agents

Compared with the number of studies of antipsychotic combinations, more randomized controlled trials have

Clinical Points

- Antipsychotic combinations and adjunctive strategies have so far failed to effectively and consistently address negative and cognitive symptoms in schizophrenia.
- The rationale for the use of glutamatergic agents is the *N*-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis, which can explain positive, negative, and cognitive symptoms.
- New therapeutic agents in phase 3 of clinical development are medications that can impact the functioning of NMDA receptors. In parallel to this is the development of agents that can act on different pathways, such as α-7 nicotinic acetylcholine receptor agonists.

been conducted on adjunctive agents added to antipsychotic treatment (Table 1).[5] For example, many studies have examined adjunctive antidepressants with antipsychotics for the treatment of chronic schizophrenia.[5] In a meta-analysis[6] of 23 trials comparing the effect of add-on antidepressants versus placebo for negative symptoms in schizophrenia, the effect size was moderate (–0.48) for antidepressants. However, current evidence is insufficient to support any augmentation strategy as a standard treatment recommendation for negative symptoms.[7]

Similarly, no adjunctive agent currently has enough evidence to support its efficacy for treating cognitive impairments.[7] Overall, results have been negative for more than 50 randomized controlled trials that focused on augmenting medicines for cognitive dysfunction in chronic schizophrenia, including drugs traditionally used for Alzheimer's disease and agents prescribed for attention deficit/hyperactivity disorder (ADHD; eg, methylphenidate, atomoxetine) or for promoting wakefulness (such as modafinil).[5] Other adjunctive agents that require further investigation because studies have yielded ≥ 2 positive and ≤ 2 negative results include celecoxib, neurosteroids, hormones, purinergic agents, serotonin 5-HT_{1A} receptor agonists, and serotonin 5-HT_3 receptor antagonists.[5] Another promising intervention for negative and cognitive symptoms is to use adjunctive agents that act on glutamate receptors.[8]

GLUTAMATE SYSTEM

Research into the glutamate system has revealed connections between glutamate, dopamine, and the pathophysiology of schizophrenia.[8] Glutamate is a widely distributed excitatory neurotransmitter in the central nervous system and is involved in fast synaptic transmission, neuroplasticity, and higher cognitive functions such as memory.[9,10] Excessive glutamate can cause neurotoxicity. Evidence that implicated glutamate in schizophrenia came from pharmacologic studies[9] with glutamate receptor antagonists, such as phencyclidine (PCP) and ketamine, which can induce positive, negative, and cognitive symptoms in healthy individuals and worsen these symptoms in patients with schizophrenia.[10]

Types of Glutamate Receptors

There are 2 principal types of glutamate receptors: metabotropic and ionotropic.

Metabotropic glutamate receptors. Metabotropic glutamate receptors involve G-proteins, making them similar to most dopamine, serotonin, and norepinephrine receptors, and they activate phospholipase C or inhibit adenylate cyclase. Metabotropic receptors are divided into 3 subgroups[9]:

(1) type I (mGluR1 and 5)
(2) type II (mGluR2 and 3)
(3) type III (mGluR4, 6, 7, and 8).

Ionotropic glutamate receptors. Ionotropic glutamate receptors involve ion channels and include 3 main subtypes[9]:

(1) α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)
(2) kainate
(3) *N*-methyl-D-aspartate (NMDA).

AMPA and kainate receptors control sodium influx and potassium efflux across the cell membrane and exhibit rapid kinetics. AMPA receptors are primarily postsynaptic, while kainate receptors are primarily presynaptic. NMDA receptors, which are primarily postsynaptic, are considerably more complex than AMPA or kainate receptors, involve slower kinetics, and allow calcium to enter the neuron in addition to sodium influx and potassium efflux.[9]

Glutamate Receptor Relationships

Complex relationships exist between glutamate receptors, which are located in different areas of the synapse. Ionotropic and metabotropic glutamate receptors bind to different specific domains of synaptic proteins. They are also found on γ-aminobutyric acid (GABA) interneurons as well as on glial cells. Metabotropic glutamate receptors are located at the periphery of the synapse, whereas NMDA and AMPA receptors are located more centrally.

For the NMDA receptor to function, it must be activated by both glutamate and glycine (thus glycine is a coagonist).[11] Molecules that are similar to glycine can also bind at the glycine site on the NMDA receptor; these include D-serine and D-cycloserine.[11]

In addition to the simultaneous binding of glutamate and glycine that occurs, partial depolarization of the membrane must also be present for the NMDA receptor to be activated.[12] Thus, the NMDA receptor is colocalized with AMPA or kainate receptors in order for this partial membrane depolarization to happen.

NMDA Receptors and Cognitive Function

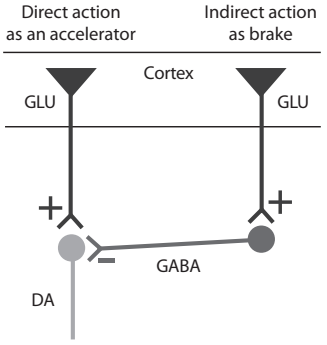
In the prefrontal cortex, NMDA receptors are involved in high-level processes such as executive processing, while NMDA receptors in the visual cortex are involved in magnocellular function and motion detection.[13] Impairment in these processes can lead to problems with executive function

Table 1. Agents Studied as Adjuncts to Antipsychotics for Negative Symptoms and/or Cognitive Impairment in Patients With Schizophrenia[a]

Acetylsalicylic acid and nonsteroidal anti-inflammatory agents	Anticonvulsants and lithium
Antidepressants	Antiglucocorticoids
Agents used to treat attention-deficit/hyperactivity disorder	β blockers
Cholinesterase inhibitors and other agents used to treat Alzheimer's disease	Experimental agents that act on glutamate receptors
$GABA_A$ receptor drugs	Neurosteroids and hormones
Omega-3 fatty acids	Opioid system agents
Peptides	Purinergic agents
Serotonin 5-HT_{1A} receptor agonists	Serotonin 5-HT_3 receptor antagonists
Wakefulness promoting agents	

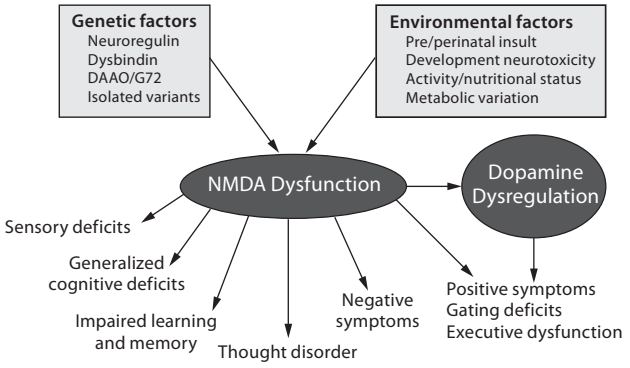
[a]Reprinted with permission from Citrome.[5]
Abbreviation: GABA = γ-aminobutyric acid.

Figure 1. Cortical Glutamate Regulates Brainstem Neurons in 2 Ways[a,b]



[a]Reprinted with permission from Citrome,[14] as adapted from Tsapakis and Travis.[9]
[b]Symbols: + = excitatory action, − = inhibitory action.
Abbreviations: DA = dopamine, GABA = γ-aminobutyric acid, GLU = glutamate.

Figure 2. NMDA Dysfunction and Dopamine Dysregulation in Schizophrenia[a]



[a]Reprinted with permission from Kantrowitz and Javitt.[16]
Abbreviations: DAAO = D-amino acid oxidase, NMDA = *N*-methyl-D-aspartate.

and visual function, such as are found in schizophrenia. Auditory sensory memory involves NMDA receptors in the auditory cortex, and NMDA dysfunction here affects processes such as discriminating among different tones.[13] Finally, in the hippocampus, NMDA receptors initiate processes that form the basis for learning and memory.[13] Patients with schizophrenia can show severe impairments in memory formation.[13]

GLUTAMATE AND DOPAMINE

Cortical glutamate neurons can regulate dopamine neurons either directly, acting as an accelerator, or indirectly, acting as a brake (Figure 1).[14] Glutamate will act as a direct accelerator by means of glutamatergic fibers projecting to brainstem neurons where glutamate will promote activity at the dopamine neuron, thus allowing additional dopamine to be released in areas such as the dorsolateral prefrontal cortex and the ventral medial prefrontal cortex. Glutamate can also act as an indirect brake on dopamine neurons through a GABA interneuron. Because excitation by glutamate of a GABA interneuron results in the release of GABA, an inhibitory neurotransmitter, this will inhibit the dopamine neuron down the chain, decreasing the release of dopamine. Thus, excitation of glutamate can produce 2 different outcomes: an increase or a decrease in the release of dopamine downstream. Feedback loops probably exist in these brain pathways, and dysfunction in these pathways can provide a possible model for schizophrenia.[9,15]

NMDA RECEPTOR HYPOFUNCTION AS A MODEL OF SCHIZOPHRENIA

One possible explanation regarding the pathophysiology of schizophrenia is the NMDA receptor hypofunction hypothesis, which can possibly explain the positive, negative, and cognitive symptoms experienced by patients (Figure 2).[15,16] When cortical glutamate neurons act to provide tonic excitation at the dopamine neuron (direct acceleration), more dopamine is provided to circuits going back to the cortex, particularly the dorsolateral and ventral medial prefrontal cortices. When a lack of tonic excitation occurs, such as with NMDA receptor hypofunctioning (no acceleration), insufficient dopamine reaches the cortex, resulting in the cognitive and negative symptoms of schizophrenia.[15]

With NMDA receptor hypofunction in cortical brainstem projections of patients with schizophrenia, hyperactivity of the mesolimbic dopamine pathway occurs. Under normal circumstances, glutamate neurons excite the GABA interneuron, thus acting as an indirect brake on dopamine release. With NMDA receptor hypofunctioning at the GABA interneuron, the GABA interneuron is unable to

release sufficient amounts of GABA, which results in excess dopamine being released in the mesolimbic pathway and thus producing the positive symptoms of schizophrenia.[15]

In summary, glutamate neurons are upstream of dopamine neurons and will excite dopamine neurons if connected directly to them. However, glutamate neurons can also inhibit dopamine function or activity by connecting through inhibitory GABA interneurons. Thus, the NMDA receptor hypofunction hypothesis can explain the positive, negative, and cognitive symptoms of schizophrenia.

GLUTAMATE-BASED TREATMENTS

Based on the connection between glutamate and dopamine in the brain, researchers are exploring glutamate-based treatments for schizophrenia that may alleviate more than just positive symptoms. While both metabotropic and ionotropic glutamate receptors have been explored, the majority of development has focused on NMDA receptors.

Metabotropic Glutamate Receptors as Treatment Targets

Metabotropic glutamate receptors, specifically mGlu2/3 receptors, have been considered as potential therapeutic targets in schizophrenia.[17] MGlu2/3 agonists have been tested in patients with schizophrenia.[18,19] Although an initial efficacy study[18] with a selective agonist for mGlu2/3 appeared promising, further results have failed to replicate the results, leading to the discontinuation of development of this agent.[19,20] Thus, more attention is now being placed on ionotropic glutamate receptors as a therapeutic target.

Ionotropic Glutamate Receptors as Treatment Targets

As mentioned, the 3 types of ionotropic glutamate receptors are AMPA, kainate, and NMDA. AMPA receptors have been tested as a therapeutic target; however, no advantage for cognition or other symptoms was evident in a randomized controlled trial[21] of ampakine CX516 as an adjunct to antipsychotics. Kainate receptors have also been a therapeutic target, as tested with topiramate as an adjunct to atypical antipsychotics. A randomized controlled study,[22] however, revealed cognitive dulling with adjunctive topiramate.

Glycine/D-serine/D-cycloserine. While randomized controlled trials have been scarce for AMPA and kainate receptors, NMDA receptors have been the subject of multiple randomized controlled trials with promising results.[13] Because NMDA receptors require both glutamate and glycine to be present, a possible method to increase NMDA receptor activity may be by increasing the availability of glycine. Compounds other than glycine, such as D-serine and D-cycloserine, can also bind to the glycine site on NMDA receptors.[11] Thus, therapeutic options involving NMDA receptor activity include administering glycine, D-serine, or D-cycloserine or increasing the availability of glycine in another way.[11,23]

A meta-analysis[24] showed that glycine and D-serine adjunctive to antipsychotics demonstrated improvements in multiple symptom domains in patients with schizophrenia, while D-cycloserine did not. In particular, adjunctive D-serine with risperidone or olanzapine was statistically superior to placebo for negative symptoms. Of note, those receiving clozapine did not improve with these adjunctive treatments.[24]

Sarcosine. Instead of providing exogenous glycine or an analog of glycine, an alternative therapeutic option is to increase the availability of endogenous glycine through glycine reuptake pump inhibition.[23] The glycine transporter type 1 (GLYT1) reuptake pump is the major root of inactivation of synaptic glycine. Several GLYT1 pump inhibitors exist, such as the natural agent *N*-methyl-glycine, also called sarcosine, as well as drugs in clinical development.[23] The action of GLYT1 inhibitors is analogous to that of drugs that inhibit reuptake of other neurotransmitters, such as selective serotonin reuptake inhibitors.[11] Glycine is not known to be synthesized by glutamate neurons, meaning that glutamate neurons must obtain glycine from glycine neurons or from glial cells.[11] When the reuptake pump on the glial cell is blocked, more glycine is available in the synapse, increasing the potential activity of the NMDA receptor.

Sarcosine, a GLYT1 inhibitor, has been tested as monotherapy in antipsychotic-naive patients with schizophrenia and appeared to reduce symptoms with minimal side effects.[25] In a meta-analysis,[24] sarcosine augmentation with antipsychotics improved multiple symptom domains compared with placebo, with the exception of patients who were receiving clozapine.

Clozapine. The atypical antipsychotic clozapine has been hypothesized to act, in part, by glycine transport inhibition, as demonstrated in a preclinical trial by Javitt et al.[26] Clozapine's differential clinical efficacy compared with other antipsychotics may be linked to its regulation of synaptic glycine levels.[26]

Bitopertin. Bitopertin (RG1678), a potent, noncompetitive inhibitor of GLYT1, is currently in phase 3 of clinical development.[27,28] An 8-week, phase 2, randomized controlled trial[27,29] examined 3 doses of bitopertin (10 mg, 30 mg, and 60 mg) or placebo once daily as adjunct to antipsychotic treatment in clinically stable schizophrenia patients (N = 323) with predominately negative symptoms. Responders were defined as patients showing ≥ 20% reduction in the Positive and Negative Syndrome Scale (PANSS) negative symptom factor score. Response rates were higher in the 10-mg/d and 30-mg/d bitopertin groups (65% and 60%, respectively) versus placebo (43%; $P = .013$ and $P = .088$, respectively) but not in the 60-mg/d bitopertin group (43%).[29,30] However, this has yet to be replicated, and initial results for 2 phase 3 trials of bitopertin have not demonstrated reductions in negative symptoms. A third phase 3 study evaluating bitopertin for persistent, predominant negative symptoms of schizophrenia is ongoing, and 3 phase 3 studies investigating bitopertin for suboptimally controlled symptoms of schizophrenia are in progress.[28]

In terms of safety, bitopertin was well tolerated with a favorable safety profile.[29] In a study[31] of the effects of

bitopertin in healthy male volunteers, no major safety or tolerability problems were found with either the 30-mg/d or 175-mg/d bitopertin dose. The 175-mg/d bitopertin group experienced more nausea, dizziness, and blurred vision compared with the 30-mg/d bitopertin or placebo groups.[31]

OTHER TREATMENT IN PHASE 3 OF CLINICAL DEVELOPMENT

Encenicline (EVP-6124) is hypothesized to work through a completely different mechanism of action than discussed here so far.[32] Encenicline is a selective α-7 nicotinic acetylcholine receptor (N-A7A) agonist. N-A7A receptors are located in several brain areas involved in cognitive domains including attention and long-term and working memory. The procognitive effects of encenicline (0.3 mg/d or 1 mg/d) were tested in an 84-day, phase 2 randomized controlled trial[32] in 319 patients with chronic stable schizophrenia taking antipsychotics other than clozapine. The 0.3-mg/d dose of EVP-6124 had a positive effect on global cognitive function and on functionality, as well as on the PANSS negative symptom subscale. EVP-6124 was well tolerated with no clinically significant findings on electrocardiograms, vital signs, hematology, and serum chemistry evaluations. The most commonly reported adverse events were headache, nausea, and nasopharyngitis.[32]

CONCLUSION

Efficacious treatments for negative and cognitive symptoms remain an unmet need in schizophrenia. So far, combining antipsychotics and adding adjunctive agents to antipsychotics have yielded disappointing results in treating both negative symptoms and cognitive impairments. However, the NMDA receptor hypofunction hypothesis, with its focus on the glutamate system's effect on dopamine, can explain the positive, negative, and cognitive symptoms in schizophrenia. With this model in mind, therapeutic targets are being explored to treat negative and cognitive symptoms, including testing adjunctive agents that bind to sites on NMDA receptors (eg, glycine, D-serine, D-cycloserine) and adjunctive glycine reuptake inhibitors (such as sarcosine and bitopertin). Also being tested are agents that work through different pathways, such as α-7 nicotinic acetylcholine receptor agonists (encenicline).

Drug names: atomoxetine (Strattera), clozapine (Clozaril, FazaClo, and others), ketamine (Ketalar and others), methylphenidate (Focalin, Daytrana, and others), modafinil (Provigil), topiramate (Topamax).
Disclosure of off-label usage: Dr Citrome has determined that, to the best of his knowledge, atomoxetine, bitopertin, CX516, encenicline, ketamine, methylphenidate, modafinil, and topiramate are not approved for the treatment of schizophrenia.

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