

Investigational Treatments



for

Cognitive Impairment in Schizophrenia

The authors examine the landscape of drug and nondrug therapies under active investigation for cognitive impairment in schizophrenia

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Available treatments for schizophrenia (eg, antipsychotics) are primarily effective on positive symptoms (hallucinations, delusions, etc.). It is, however, increasingly clear that schizophrenia also is a severe neuropsychiatric illness associated with deficits in cognitive function. These deficits represent a core feature of the disorder, and are a major determinant of long-term disability.¹ Cognitive dysfunction is among the earliest signs of illness that, typically, presents in the prodromal phase.

Since the formulation of the dopaminergic model of schizophrenia, cognitive studies of the disease primarily have examined dysfunction in dopaminergic-rich regions of the brain, such as the prefrontal cortex, and, therefore, have focused largely on executive functioning. But neurocognitive deficits in schizophrenia are not limited to executive functioning; comparable deficits have been observed across multiple areas of cognition.²

More recent formulations of cognitive dysfunction in schizophrenia divide deficits into multiple domains. These include verbal, visual, and working memory; attention and vigilance; speed of processing, reasoning, and problem solving; and social cognition (see the *Table* at Current Psychiatry.com). Neurocognitive impairments often are closely associated with deficits in early sensory processing and basic neurophysiology.³

The prevalence of cognitive dysfunction also can be estimated using baseline data from the large-scale Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial.⁴ Although cognitive dysfunction was not one of the inclusion criteria in CATIE, most patients who were enrolled had profound cognitive deficits.⁵ Furthermore, meta-analyses⁶ suggest that composite neurocognitive measures can explain as much as 60% of the variance of overall functioning in schizophrenia.

continued



Cognitive impairment

Clinical Point

Strong anatomic links also exist between muscarinic acetylcholine receptors and the brain dopaminergic system

See this article at

CurrentPsychiatry.com
for a table listing cognitive domains compromised in schizophrenia

Antipsychotics aren't the answer

The cognitive-enhancing benefits of antipsychotic medications are minimal.⁷ As evidence of a direct relationship between cognitive dysfunction and long-term functional outcome in schizophrenia becomes established, the need for safe and effective treatment for these symptoms becomes more urgent. Given the mechanistic complexity of the potential cause of poor cognitive performance, the search for an effective treatment is ongoing—but that search has not been successful.

Despite mixed results for recent novel mechanism trials (<http://newsroom.lilly.com/releasedetail.cfm?releaseid=703018>) and a number of companies ceasing drug development, the work to develop safe and effective treatments for cognitive dysfunction in schizophrenia continues, as exemplified by National Institute of Mental Health-initiated programs to spur development of drugs that work by a novel mechanism. Rather than simply assessing novel compounds with paper-and-pencil cognitive scales, such programs seek to assess the ability of the compound to engage with the intended receptor (target),⁹ using imaging or electrophysiological tools. Without utilization of a target engagement biomarker, there is no way to know whether 1) the drug simply does not get into the brain in sufficient concentration to be effective in humans or 2) the overall mechanism is wrong.

In this article, we review several promising targets and techniques that are the subject of active research on the treatment of cognitive disorders in schizophrenia. This list isn't exhaustive; our aim is to highlight a few of the promising treatments now being studied in clinical trials.

Acetylcholine receptors

Acetylcholine receptors comprise two major families, nicotinic and muscarinic receptors; evidence implicates deficits of both families in schizophrenia.¹⁰ Following up on epidemiological studies¹¹ of the high percentage of schizophrenia patients who smoke tobacco (60% to 90%), the role of alpha-7 nicotinic acetylcholine receptors ($\alpha 7$ nAChR) has been explored. Nicotine itself might normalize some disrupted auditory processes, as measured

by electroencephalography.¹²

Several clinical trials of partial $\alpha 7$ nAChR agonists have been conducted, with EVP-6124 and TC-5619 furthest along in development.

EVP-6124. Information is unavailable publicly on EVP-6124, except for an abstract presented in 2011 at the 51st Annual Meeting of the American College of Neuropsychopharmacology.¹³ In that study, 319 patients with schizophrenia were randomized to EVP-6124 (0.3 mg/d or 1 mg/d [n = 213]) or placebo (n = 106) adjunctive to at least 4 weeks of non-clozapine antipsychotics. Efficacy was shown up to 1 mg, in a dose-responsive manner. Modest, but significant, improvements in cognition, clinical function, and negative symptoms were seen. The most commonly reported side effects were headache (3.8%), nausea (3.2%), and nasopharyngitis (2.5%). Phase III studies are underway.

TC-5619. This partial $\alpha 7$ nAChR also showed positive results recently in a Phase II trial. Significant ($P < .05$) improvement was demonstrated in executive function in the Groton Maze Learning Task of the CogState Schizophrenia Battery and the Scale for Assessment of Negative Symptoms.¹⁴

Strong anatomic links also exist between muscarinic acetylcholine receptors and the brain dopaminergic system, especially muscarinic type-1 and type-4 (M1 and M4) receptors. The potential utility of an M1, M4, or combined M/M4 agonist is also supported by studies of M1 and M4 knockout mice, with particular evidence of cognitive enhancement with the use of M1 agonists.¹⁵

GSK1034702. Administration of the M1 allosteric agonist GSK1034702 to healthy human smokers, using the nicotine abstinence model of cognitive dysfunction, resulted in improvements in immediate recall.¹⁶

Xanomeline. In a small pilot study of 20 schizophrenia patients, xanomeline, a mixed M1/M4 agonist, demonstrated significant improvements in verbal learning, short-term memory, and overall symptoms.¹⁷

Dopamine receptors

All marketed antipsychotics block the dopamine type-2 (D2) receptor¹⁸; they are primarily effective on positive symptoms.⁴ In contrast, a role for the dopamine type-1 (D1) receptor in cognition is suggested by studies that demonstrate reduced D1 and *N*-methyl-D-aspartate (NMDA) glutamate receptor function in the prefrontal cortex.¹⁹⁻²²

In a model of cognitive impairment in non-human primates, low-dose intermittent dosing of D1-receptor agonists produced improvements in cognitive function.²³ This strategy aims to sensitize, rather than induce tolerance, to the effects of the D1-receptor agonist. Benefits were primarily seen in working memory. Phase II trials of a potent D1-receptor agonist, DAR-100A, the active enantiomer of dihydrexidine²⁴ are ongoing (www.clinicaltrials.gov/ct2/show/NCT01519557).

Glutamatergic receptors

Intoxication with NMDA antagonists (such as phencyclidine and ketamine) yields a phenotype with similarity to schizophrenia.²⁵ More than 20 years of research has provided evidence for the role of glutamatergic NMDA receptors in the pathophysiology of schizophrenia.^{26,27}

NMDA receptors are distributed widely in the brain, but specific glutamatergic processes are localized to areas that are associated with cognition. This relative distribution provides a convenient framework from which to view the pattern of cognitive dysfunction associated with schizophrenia:

- NMDA receptors in the prefrontal cortex contribute to development of executive processing
- NMDA receptors in the hippocampus are involved in learning and memory acquisition
- NMDA receptors in the visual cortex and auditory cortex are fundamental for auditory and visual sensory memory.

Previous reviews of ketamine administration have described cognitive deficits in healthy control subjects, comparable to what is seen in schizophrenia.²⁸ The deficits are noted primarily in measures of executive functioning, attention/vigilance, ver-

bal fluency, and visual and verbal working memory.

Most treatment studies of glutamatergic-based drugs have focused on positive and negative symptoms. Two recent comprehensive meta-analyses^{29,30} of NMDA-based treatments support small-to-moderate effect size improvement in total symptoms and in negative symptoms, in patients with chronic schizophrenia, when the drugs are used in combination with non-clozapine antipsychotics.

Bitopertin. A novel glycine-transport inhibitor, bitopertin, showed significant improvement in negative symptoms as an adjunctive treatment in a large Phase II trial.^{31,32} In the “per protocol” population (ie, patients who completed 8 weeks of treatment without any major protocol violations [$n = 231$]), negative symptoms diminished to a significantly ($P < .05$) greater degree from baseline in the 10 mg/d and 30 mg/d dosage groups, compared with placebo. Phase III studies of bitopertin are ongoing (www.clinicaltrials.gov/ct2/show/NCT01192906).

Direct evidence of a cognitive benefit of glutamatergic-based drugs is limited. In a recent large, multicenter study, low dosage D-serine (~30 mg/kg/d) did not separate from placebo,³³ but an open-label study suggests increased efficacy with dosages >30 mg/kg/d.³⁴ In addition to symptomatic improvements, a highly significant, large effect-size improvement was seen for overall cognition for dosages ≥ 60 mg/kg/d, leading to a significant dose-by-time interaction ($P < .01$).

Combination approaches. The value of combining glutamatergic medication and a cognitive training program is supported by the role of NMDA receptors in learning. For example, D-cycloserine, a glycine-site partial agonist, has been shown in several studies to enhance learning and behavioral therapies in anxiety disorders.³⁵ Although an initial study in schizophrenia was negative for the effectiveness of D-serine (a glycine-site full agonist) and combined cognitive training,³⁶ further research is ongoing to evaluate a role for such combined therapy.^{37,38}

Clinical Point

More than 20 years of research has provided evidence for the role of glutamatergic NMDA receptors in the pathophysiology of schizophrenia



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Cognitive impairment

Clinical Point

Applying rTMS over the left dorsolateral prefrontal cortex has led to improvement in verbal learning and visuomotor tracking

Brain stimulation

Two nonpharmacotherapeutic brain stimulation techniques, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have been applied in the study of schizophrenia symptoms, particularly for enhancing cognition.³⁹ Both techniques use electric stimulation to influence activity of underlying brain regions: rTMS utilizes a magnetic coil and electromagnetic induction; tDCS, in contrast, utilizes constant low (<2 mA) direct current to specific regions of the scalp.

Cortical neuronal excitability is increased by anodal tDCS and high-frequency rTMS and reduced by cathodal tDCS and low-frequency rTMS. Both tDCS and rTMS appear to be NMDA receptor-dependent. tDCS is relatively inexpensive and requires less expertise to administer than rTMS does.

Both techniques might be efficacious for treating resistant auditory hallucinations.^{40,41} Applying rTMS over the left dorsolateral prefrontal cortex has led to improvement in verbal learning and visuomotor tracking in patients with schizophrenia.³⁹ Stimulation of both sides of the prefrontal cortex with rTMS has brought improvement in visual memory, executive function, spatial working memory, and attention. Few papers have been published so far regarding enhancement of cognition with tDCS in schizophrenia,⁴² but beneficial effects of this technique have been seen across several disorders.⁴³

Cognitive remediation techniques

A fundamental starting point for cognitive remediation is the idea that there is plasticity in the brain and that repetitive practice can lead to cognitive improvement. Cognitive remediation therapy often adopts computerized programs and exercises that attempt to improve psychosocial function by targeting structures of the brain that are involved in cognitive function, such as attention, working memory, executive functioning, planning, and cognitive flexibility.

In schizophrenia, cognitive remediation studies have traditionally targeted higher-order processes, such as attention and higher level processes, that might lead to improvement in overall cognition and function.⁴⁴

Cognitive remediation typically is utilized complementary to pharmacotherapy, with some studies supporting the use of combined use of cognition-enhancing drugs and remediation programs.

A 2007 meta-analysis showed a medium-size but significant improvement in cognition through the use of cognitive remediation therapy⁴⁵—especially when it is combined with psychiatric rehabilitation. More recent studies utilizing techniques that focus on bottom-up (auditory and visual processing) techniques has shown significant improvements.⁴⁶⁻⁴⁸ Several multicenter studies utilizing Posit Science programs combined with antipsychotic medication are ongoing (www.clinicaltrials.gov/ct2/show/NCT01173874 and www.clinicaltrials.gov/ct2/show/NCT01422902).

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Related Resources

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Drug Brand Names

D-cycloserine	• Seromycin	Xanomeline	• Lumeron,
Ketamine	• Ketalar	Memcor	

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Clinical Point

Cognitive remediation is typically utilized complementary to pharmacotherapy

Bottom Line

Although cognitive dysfunction is a leading cause of disability in schizophrenia, no treatments are approved for this condition. Numerous novel-mechanism and nonpharmaceutical modalities are actively being studied for this difficult-to-treat problem, however—offering hope to patients.

A range of cognitive domains can be compromised in schizophrenia

Cognitive domain	Functions
Processing speed	The ability to automatically perform known and learned tasks
Attention	The ability to focus on a specific stimulus, when presented with several stimuli, in order to process information
Working memory	A system which transforms sensory information into permanent information retained on an enduring basis
Verbal learning	The acquisition and retention of verbal information
Visual learning	The acquisition and retention of visual information
Reasoning and problem solving	Foresight and planning applied in a condition with exposure to a problem
Social cognition	Encoding, retrieving, and processing information in a social context