Behavioral and Emerging Pharmacologic Treatment Options for Cognitive Impairment in Schizophrenia

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In recent years, the goal of treatment for individuals with schizophrenia has shifted from symptom control to functional recovery. For recovery to occur, the substantial cognitive impairments associated with this disorder must be addressed. Advances in neuroscience have paved the way for the development of more effective behavioral and pharmacologic treatments. Behavioral interventions such as cognitive training are tapping into the innate plasticity and adaptive qualities of the brain. Emerging pharmacologic treatments are targeting new neurotransmitters and systems, such as the glutamatergic system and the nicotinic-cholinergic system, which are involved in the cognitive and sensory deficits that lead to impairment. The best chances for recovery will most likely occur by combining behavioral and pharmacologic interventions.
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Outcomes for individuals with schizophrenia are often bleak. Most are unemployed,[1] and many are homeless.[2] Although the treatments typically used by individuals with schizophrenia are generally effective for controlling the positive symptoms of the disorder, these treatments do little to improve the cognitive impairments that are characteristic of schizophrenia, and cognitive impairments have a greater impact on functional outcomes than positive symptoms.[3] Effective treatment of cognitive impairment may be the key to improving long-term outcomes for individuals with schizophrenia. To accomplish this goal, a combination of behavioral and pharmacologic treatments will very likely be required.[4,5] This article describes some emerging behavioral and pharmacologic interventions that may improve cognition, and therefore outcomes, in patients with schizophrenia.

BEHAVIORAL INTERVENTIONS FOR COGNITIVE IMPAIRMENT

The human brain is extremely malleable. At birth, the prefrontal cortex is essentially a blank slate waiting to be inscribed by the individual's perceptual, cognitive, and emotional experiences.[6] The neurodevelopment of individuals with neuropsychiatric illnesses shows a range of abnormalities that ultimately leads to impaired cognition, perception, and affective experience. As neuropsychiatric illnesses progress, they often follow a chronic, relapsing, and worsening course, suggesting that the brain is learning increasingly maladaptive associations, which leads key neural systems into increasingly dysfunctional "configurations."[6] Until recently, neuroscientists believed that the impaired neural system functioning of individuals with schizophrenia was irreversible, but investigation has shown that this idea is not accurate.[7]

Challenges for Effective Behavioral Interventions

Effective behavioral interventions to target neural system dysfunction must address several challenges unique to individuals with schizophrenia.[6] One challenge is that the learning mechanisms in the brains of some individuals with schizophrenia may show some abnormalities, as it appears that certain genes contributing to schizophrenia affect neuroplasticity.[6] Another challenge is that multiple neural systems involved in schizophrenia are related to functioning. An effective behavioral intervention, therefore, must address the impaired learning ability of individuals with schizophrenia and must also change key maladaptive patterns of neural function via intensive and repetitive practice.[6]

Guideline Recommendations for Behavioral Interventions

Behavioral interventions such as cognitive-behavioral therapy have been found to be effective adjunctive treatments for the treatment of positive symptoms of schizophrenia when pharmacologic treatment alone has been unsuccessful.[8] Similarly, targeted adjunctive behavioral treatment may succeed in improving cognitive impairments and functioning. The American Psychiatric Association (APA) *Practice Guideline for the Treatment of Patients With Schizophrenia*[9] stated that psychosocial treatments can be used to prevent relapse and promote recovery. These psychosocial interventions include family psychoeducation, assertive community treatment, supported employment, social skills training, peer support, cognitive-behavioral therapy, and cognitive remediation.

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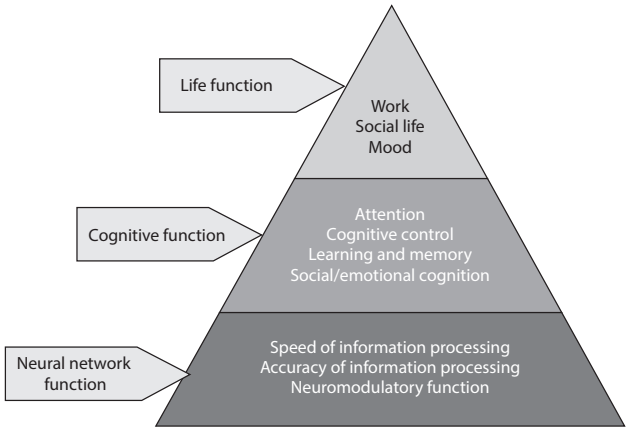
Table 1. Comparison of Results from Meta-Analyses of Cognitive Remediation Studies in Schizophrenia

	McGurk et al[11]	Grynszpan et al[12]	Wykes et al[13]
Number of studies included	26	16	40
Date range of studies	1968–2006	1991–2007	1973–2010
Intervention studied	Cognitive remediation	Computer-assisted cognitive remediation	Cognitive remediation
Cognitive effect size	0.41	0.38	0.45

Figure 1. Translating Neural Network Function Into Improved Real-World Behavior[a]



[a]Based on Vinogradov et al.[6]

New Directions in Behavioral Interventions: Cognitive Remediation and Cognitive Training

Cognitive remediation. In the years since the APA released the schizophrenia treatment guidelines, research on cognitive remediation for schizophrenia has grown. This type of behavioral treatment seeks to improve functioning by improving the underlying cognitive processes through behavioral training.[10] Cognitive remediation can be aimed at training individuals with schizophrenia to compensate for cognitive impairments by learning ways to bypass them, or it can be aimed at restoring cognitive functioning by repairing specific underlying impairments, thus tapping into the brain's ability to repair and change throughout the lifetime.[10]

The most recent meta-analyses[11] that have investigated cognitive remediation approaches in schizophrenia have found modest benefits (Table 1).[11–13] However, drawing specific conclusions about the benefit of cognitive remediation from these meta-analyses is difficult because most of the studies used small sample sizes and varied greatly in terms of interventions (or combinations of interventions) studied, study design (eg, control conditions, blinding), analytic methods, and treatment duration, setting, and intensity.[6] Cognitive remediation as most often discussed in practice usually has a broad treatment perspective, meaning that it attempts to improve multiple cognitive systems at once using multiple strategies.[7]

Cognitive training. The concept of cognitive training is similar to cognitive remediation but focuses on the notion of harnessing physiological mechanisms of brain plasticity that are present in everyone, as opposed to the notion of remediating abnormalities that are present only in a clinical group. As such, it often uses a more specifically targeted approach to the neural systems that are the focus of training. In other words, this approach attempts to address specific neural system abnormalities that are involved in the pathophysiology of schizophrenia, using targeted training strategies to improve or enhance cognitive performance.[6]

This approach to cognitive training often provides targeted, intense training that is aimed at improving perceptual and preattentive processing.[6] The individual earns rewards by completing thousands of precisely defined perceptual training events that are individualized to be at the threshold of that learner's ability. Each set of exercises is designed to strengthen a particular neural system, such as visual or auditory perception. Exercise difficulty is continuously adjusted so that each learner is performing at 80% accuracy. This ensures that a dense reward schedule is maintained, which improves neuromodulatory functioning, but participants make enough mistakes to remain challenged and drive learning.[6] Ultimately, the goal of cognitive training is to improve neural network functioning, which should then lead to improved cognitive functioning, and finally to better life functioning (Figure 1).[6]

In other words, ideal cognitive training for people with schizophrenia targets well-defined and appropriately constrained cognitive operations that are tied to underlying deficits of the illness. The basic principles can be elucidated as follows: (1) Training must carry learners to the boundaries between what they can and cannot do and must be progressive and of sufficient duration. (2) Advances must be made in small steps that cumulatively add up to big gains. (3) Training must be applied so that learners get certain and immediate feedback about whether they have been successful. (4) Learners must be motivated to be engaged in the training activity.

In an effort to implement these cognitive training principles, Fisher and colleagues have conducted several trials.[14–16] For example, Fisher and colleagues[14] conducted a double-blind, randomized, controlled trial using a cognitive training regimen designed to improve auditory processing and verbal learning in individuals in the early stages of schizophrenia. On average, participants were within 2 years of illness onset; the 86 participants had a mean age of 21 years. At baseline, participants showed impairments in overall global cognition, with the most pronounced deficits in verbal learning

Clinical Points

- Improved cognitive functioning should be a treatment goal for all patients with schizophrenia.
- Effective treatment for cognitive impairment should include a combination of pharmacotherapy and behavioral interventions.
- Behavioral interventions should target distinct, well-defined cognitive operations, be progressive, and include continual challenges and rewards for the learner.

and memory, visual learning and memory, and speed of processing. The cognitive training consisted of computerized activities designed to improve speed and accuracy of auditory information processing. The activities also engaged auditory and working memory[14] as investigators have found that these cognitive domains are correlated with community functioning.[15] The difficulty level of the training exercises adjusted to each participant's performance so that the learner was able to continuously maintain an 80%–85% correct performance level and remain challenged and engaged.[14] Animation and points were used to reward correct performance and increase motivation. The control group completed various commercial computer games. All participants were asked to spend 1 hour per weekday on the exercises at home on loaned laptops, for a total of 40 hours over 8 weeks. After 8 weeks, the individuals who completed the cognitive training exercises showed significantly greater improvement than the control group in global cognition ($P < .01$), verbal memory ($P < .01$), and problem solving ($P < .05$).[14] The global cognition effect size for completers was 0.73. The gains in problem solving were interesting because this ability was not directly targeted by the training program. Another notable finding was that the participants who engaged in computer games showed decrements in verbal learning and memory. This may be because the highly visual nature of the computer games drew resources away from these individuals' verbal learning and memory abilities.[14]

Cognitive gains can also be achieved in individuals with schizophrenia who are older and have been ill for many years. A study[15] of auditory training to improve verbal memory was conducted in 55 chronically ill patients with schizophrenia who were clinically stable; their mean ages were 43 years in the cognitive training group and 45 years in the control group. After 10 weeks and 50 hours of computer exercises, patients who engaged in active cognitive training showed greater gains than control participants in global cognition ($P < .01$), verbal learning and memory ($P < .01$ for both), and verbal working memory ($P < .05$).[15] The global cognition effect size was 0.86, indicating that the brains of individuals with schizophrenia who have been ill for extended periods of time and undergone a variety of treatments are still amenable to cognitive training. However, the patients did not show significant improvements in problem solving, suggesting that the brains of the younger subjects may demonstrate more plasticity and are able to generate more generalized gains than the older subjects.[15] Fisher and colleagues conducted an additional study[16] in which 32 adult patients with schizophrenia received targeted cognitive training and then underwent 6-month follow-up. The investigators found that gains in verbal learning/memory were still apparent at 6-month follow-up, and improved functional outcomes were associated with improved cognition.[16] Durable gains in processing speed and global cognition were found only in those who had continued the cognitive training for 50 additional hours (100 total).

The growing ubiquity of portable digital technology is making cognitive training through mobile devices a practical form of treatment. Many software programs and apps are available, and a nonprofit guide providing expert reviews and unbiased perspectives for consumers and practitioners is available at www.psyberguide.org.

Emerging Pharmacologic Treatment Options for Cognitive Impairment

The pathophysiologic mechanisms underlying schizophrenia are extremely complex, and numerous treatment targets have been explored.[17] Dopamine is perhaps the most widely studied neurotransmitter involved in the pathology and treatment of schizophrenia. Antipsychotic medications primarily used to treat schizophrenia all target dopamine. Although these drugs are helpful for controlling the positive symptoms of this disorder, they do little to alleviate negative or cognitive symptoms. Furthermore, some of the treatments that improve the positive symptoms of schizophrenia may actually limit a patient's ability to benefit from behavioral interventions intended to improve cognitive functioning. Vinogradov and colleagues[18] found that serum anticholinergic levels were negatively correlated with an individual's response to cognitive training. The study participants were 49 individuals with schizophrenia receiving stable doses of medication, which varied depending on their psychiatrists' prescriptions. Serum anticholinergic levels, which remained constant during the trial, had a greater effect on global cognition scores than age, IQ, or symptom severity, indicating that medications with anticholinergic effects may hinder ability to experience cognitive improvement.[18]

Because of the limitations and drawbacks of existing treatments, research into new pharmacologic agents that will be more effective for improving cognitive functioning is ongoing, as is research into the pathogenesis of cognitive impairments. Dysfunction and dysregulation of a number of neurotransmitters and receptors including dopamine, glutamate, *N*-methyl-D-aspartate (NMDA), nicotinic acetylcholine, γ-aminobutyric acid (GABA), and kynurenic acid have been implicated in cognitive impairments[17,19] and are being investigated as potential treatment targets. The glutamatergic system and the nicotinic-cholinergic system are 2 of the most promising targets for cognitive functioning; treatments for social cognition are also being investigated.

Treatments Targeting the Glutamatergic System

Several aspects of the glutamatergic system are believed to be involved in schizophrenia. Glutamate is the primary excitatory neurotransmitter in the brain. Bustillo and colleagues[20] used proton echoplanar spectroscopic imaging to measure glutamate in the brains of individuals with schizophrenia and found that higher glutamate concentrations were correlated with better cognitive performance. Glutamate acts at a number of receptors throughout the brain, but the NMDA receptors are particularly relevant for schizophrenia.[21] Drugs such as phencyclidine and ketamine that act by blocking neurotransmission at NMDA glutamate receptors (NMDAR) have been found to cause symptoms similar to those of schizophrenia, such as sensory disturbances and

cognitive impairment. This finding contributed to the NMDA receptor hypofunction theory of schizophrenia, which also partially accounts for the dopamine dysfunction found in schizophrenia.

Glutamate neurons can excite dopamine neurons when connected directly, or inhibit dopamine when connected indirectly, through GABA neurons.[17] Hypofunctioning of NMDARs can prevent glutamate from exciting dopamine, leading to insufficient dopamine, which results in the cognitive and negative symptoms of schizophrenia.[17] NMDAR hypofunction can also impede the release of GABA. The GABA levels are then insufficient to adequately inhibit dopamine, leading to excess dopamine and producing the positive symptoms of schizophrenia.[17,21]

Research into potential treatments targeting glutamate and NMDARs is ongoing, but results thus far have been modest and mixed. The Cognitive and Negative Symptoms in Schizophrenia Trial[22] examined 2 agents that act at NMDARs, glycine and D-cycloserine, but failed to find any significant differences between these agents and placebo on cognitive scores. A more recent meta-analysis[23] uncovered more promising results. Singh and Singh[23] found that the NMDAR modulators D-serine, *N*-acetylcysteine, and sarcosine were effective for negative and total symptoms of schizophrenia, including cognitive symptoms such as poor attention and conceptual disorganization, when added to antipsychotics other than clozapine. They discovered that glycine had similar benefits when added to non-clozapine antipsychotics, but actually worsened symptoms when used with clozapine.[23] Although glutamatergic agents do show some promise for improving negative symptoms in schizophrenia, more research is needed.

Treatments Targeting the Nicotinic-Cholinergic System

Individuals with schizophrenia are known to have difficulty focusing attention, which may be related to impairments in sensory gating caused by dysfunction in the nicotinic-cholinergic system.[24] Normally, when people are presented with an auditory stimulus, they will experience a P50 auditory-evoked response (an event-related potential occurring 40 to 70 milliseconds after a stimulus), but their response to additional auditory stimuli occurring quickly after the first will be diminished. In individuals with schizophrenia, P50 suppression is diminished, leading to difficulties sustaining attention. The P50 suppression is mediated by acetylcholine, primarily at α_7 nicotinic receptors, and is enhanced by nicotine in individuals with schizophrenia.[24]

Another indicator of the involvement of the nicotinic-cholinergic system in schizophrenia is the high rate of smoking in this population. The rate of tobacco use is higher in individuals with schizophrenia than in the general population, and individuals with schizophrenia tend to be heavier smokers and have more difficulty quitting.[24] This high level of smoking may be related to abnormalities in the number and functioning of nicotinic receptors, which in turn affect multiple neurotransmitter systems including serotonin, dopamine, norepinephrine, glutamate, GABA, and acetylcholine.[24] Thus, for individuals with schizophrenia, tobacco use may help alleviate the negative symptoms of the disorder and improve cognitive functioning. Tobacco use, however, is associated with a host of health risks. Nicotine replacement (eg, gum, patch) is also not a practical long-term treatment because the benefits are not sustained and it is highly addictive.

Clozapine has also been found to enhance P50 suppression, perhaps because it increases acetylcholine levels in the hippocampus, but clozapine use is limited because of its side effect profile and the need for close monitoring during treatment.[24] Donepezil, an acetylcholinesterase inhibitor already used in patients with Alzheimer's disease, has been investigated as a potential adjunctive treatment to enhance cognition in schizophrenia. Zhu and colleagues[25] added 5 mg/d of donepezil to patients' established antipsychotic treatment (either risperidone or olanzapine), and, after 12 weeks, they found that adjunctive donepezil was associated with significantly greater improvement than adjunctive placebo in working memory, speed of processing, and visual learning and memory ($P \leq .008$). Thus, cognitive functioning in schizophrenia appears to be enhanced when acetylcholine levels are increased.

Treatments targeting nicotinic receptors have the potential to help individuals with schizophrenia both by diminishing their dependence on tobacco and by normalizing sensory gating, which should lead to better attention and improved cognitive functioning.[24] In particular, α_7 nicotinic acetylcholine receptor modulators have shown promise in this area. A partial agonist at the α_7 receptor called 3-(2,4-dimethoxybenzylidene)-anabaseine, or DMXBA, has been extensively studied in animal models and initial clinical trials. These studies[24] have found that administration of DMXBA is associated with reversal of sensory gating deficits and improvement on a number of measures of learning and memory. Freedman and colleagues[26] conducted a placebo-controlled trial of DMXBA in people with schizophrenia and found that those receiving the active drug showed nonsignificant improvement on attention/vigilance and working memory. These results are promising, but the trial was small and further investigation is needed.

Encenicline, originally known as EVP-6124, is also an agonist of α_7 nicotinic acetylcholine receptors that is under investigation for treating schizophrenia. Encenicline enhances the response of α_7 receptors to endogenous acetylcholine and may also have a modulatory effect on dopamine and glutamate.[27] In a pilot study,[28] individuals receiving encenicline in addition to their normal antipsychotic exhibited improved performance on cognitive tests measuring nonverbal learning, memory, and executive function. In a larger study, Keefe et al[27] found that, after 12 weeks of treatment with an antipsychotic and encenicline, participants showed significant improvement on a number of cognitive tests, including the Overall Cognition Index (OCI; $P = .034$), the Schizophrenia Cognition Rating Scale (SCoRS; $P = .011$), and the Cognition Impairment domain of the Positive and Negative Symptoms Scale ($P = .0098$). In both studies,[27,28] encenicline was well tolerated.

In consideration of the growing body of evidence suggesting that α_7 nicotinic agonists can improve cognition in schizophrenia, Deutsch and colleagues[29] undertook a study investigating an alternative method for targeting the α_7 nicotinic receptor by using a combination of galantamine and cytidine diphosphate (CDP)-choline. Galantamine, which is used to treat Alzheimer's disease, is a positive allosteric modulator and cholinesterase inhibitor that is able to enhance neurotransmission without altering endogenous neurotransmitter function. CDP-choline provides a dietary source of supplemental choline that can mimic the effects of acetylcholine at receptor sites. Because chronic exposure to an agonist can reduce receptor sensitivity, the investigators sought to determine if the combination of galantamine and CDP-choline could enhance choline binding while maintaining the receptor's sensitivity, leading to improvements in negative symptoms and cognitive impairment. After 16 weeks of treatment, the participants receiving active treatment did not show any significant improvement in negative symptoms, but they did show improvement in overall functioning ($P = .05$) and free verbal recall ($P = .04$) compared with those receiving placebo,[29] indicating that further investigation of this treatment strategy may be warranted.

Treatments Targeting Social Cognition

Social cognition, which encompasses the ability to understand and intuit the thoughts, feelings, and actions of others, is known to be impaired in individuals with schizophrenia, leading to poor social functioning. These impairments can cause individuals to have difficulties with both personal and occupational relationships.[30] Antipsychotic treatment does not improve social cognition, which has led researchers to investigate other agents that might lead to improvements in this area. One of these agents is the neuropeptide oxytocin, which is known to be associated with bonding and social behaviors in mammals. Woolley and colleagues[30] conducted a study that found that, after receiving an intranasal dose of oxytocin, individuals with schizophrenia showed improved controlled social cognition, which involves the ability to use careful deliberation to understand indirectly expressed emotions, thoughts, and intentions ($P = .004$). This improvement was not observed in the healthy controls. The participants did not show any improvement in automatic social cognition, which requires rapid interpretation of emotional cues from the voice, face, and body. Controlled social cognition is important for interpersonal and occupational functioning.[30] Davis and colleagues[31] conducted a trial of oxytocin as part of their research on social performance in schizophrenia. Prior to social cognitive skills training, half of the subjects received oxytocin and the other half received placebo. All participants had schizophrenia and were clinically stable on antipsychotic medications. The investigators found that the participants who received oxytocin experienced greater improvement in empathic accuracy, a high-level social cognitive process, than those who received placebo ($P = .03$). Thus, oxytocin may be helpful for some individuals with schizophrenia, but further investigation is needed.

CONCLUSION

The importance of improving cognitive functioning for recovery from schizophrenia cannot be overstated. Unfortunately, the antipsychotics typically used to control the positive symptoms of schizophrenia leave the negative and cognitive symptoms largely unchanged. To remedy this unmet need, a combination of behavioral and pharmacologic interventions will most likely be required, and new research into these areas is promising. Investigators are using insights from neuroscience to develop effective, targeted behavioral treatments such as cognitive training that are harnessing the brain's ability to heal and rewire itself to improve cognitive performance. Investigations into the pathophysiology of schizophrenia are building on knowledge of the underpinnings of this disorder and revealing new targets for potential pharmacologic treatments. All of these discoveries and advances are bringing the field closer to its ultimate goal, which is enabling individuals with schizophrenia to achieve recovery and live full, functional lives.

Drug names: clozapine (Clozaril, FazaClo, and others), donepezil (Aricept and others), galantamine (Razadyne and others), ketamine (Ketalar and others), olanzapine (Zyprexa and others), risperidone (Risperdal and others).

Disclosure of off-label usage: Dr Schulz has determined that D-cycloserine, DMXBA, D-serine, donepezil, encenicline, galantamine, ketamine, *N*-acetylcysteine, oxytocin, and sarcosine are not approved by the US Food and Drug Administration for the treatment of schizophrenia.

REFERENCES

1. Rosenheck R, et al. *Am J Psychiatry*. 2006;163(3):411–417.
2. Folsom D, Jeste DV. *Acta Psychiatr Scand*. 2002;105(6):404–413.
3. Green MF. *Am J Psychiatry*. 1996;153(3):321–330.
4. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Schizophrenia*, 2nd ed. *Am J Psychiatry*. 2004;161(suppl 2):1–114.
5. Swerdlow NR. *Neuropsychopharmacology*. 2012;37(1):310–311.
6. Vinogradov S, et al. *Neuropsychopharmacology*. 2012;37(1):43–76.
7. Vinogradov S, et al. *Biol Psychiatry*. 2013;73(10):935–937.
8. Zimmermann G, et al. *Schizophr Res*. 2005;77(1):1–9.
9. American Psychiatric Association. Guideline Watch: Practice Guideline for the Treatment of Patients With Schizophrenia. September 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia-watch.pdf.
10. Barlati S, et al. *Schizophr Res Treatment*. 2013;2013:156084.
11. McGurk SR, et al. *Schizophr Bull*. 2009;35(2):319–335.
12. Grynszpan O, et al. *Psychol Med*. 2011;41(1):163–173.
13. Wykes T, et al. *Am J Psychiatry*. 2011;168(5):472–485.
14. Fisher M, et al. *Schizophr Bull*. 2015;41(1):250–258.
15. Fisher M, et al. *Am J Psychiatry*. 2009;166(7):805–811.
16. Fisher M, et al. *Schizophr Bull*. 2010;36(4):869–879.
17. Citrome L. *J Clin Psychiatry*. 2014;75(suppl 1):21–26.
18. Vinogradov S, et al. *Am J Psychiatry*. 2009;166(9):1055–1062.
19. Petrova NN, Dorofeykova MV. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2014;114(11):116–123.
20. Bustillo JR, et al. *Biol Psychiatry*. 2011;69(1):19–27.
21. Kantrowitz JT, Javitt DC. *Brain Res Bull*. 2010;83(3-4):108–121.
22. Buchanan RW, et al. *Am J Psychiatry*. 2007;164(10):1593–1602.
23. Singh SP, Singh V. *CNS Drugs*. 2011;25(10):859–885.
24. Martin LF, et al. *Psychopharmacology (Berl)*. 2004;174(1):54–64.
25. Zhu W, et al. *Neuropsychiatr Dis Treat*. 2014;10:1317–1323.
26. Freedman R, et al. *Am J Psychiatry*. 2008;165(8):1040–1047.
27. Keefe RS, et al. *Neuropsychopharmacology*. 2015;40(13):3053–3060. 10.1038/npp.2015.17
28. Preskorn SH, et al. *J Psychiatr Pract*. 2014;20(1):12–24.
29. Deutsch SI, et al. *Schizophr Res*. 2013;148(1-3):138–144.
30. Woolley JD, et al. *Psychoneuroendocrinology*. 2014;47:116–125.
31. Davis MC, et al. *Neuropsychopharmacology*. 2014;39(9):2070–2077.