# Update on New and Emerging Treatments for Schizophrenia

Ganesh Gopalakrishna, MD, MHA*, Muaid H. Ithman, MD, John Lauriello, MD

**KEYWORDS**

• Schizophrenia • Advances • Antipsychotics • Cognition • Negative symptoms

**KEY POINTS**

- Review of recent advances in treatment of schizophrenia including discussion of various neurotransmitter systems.
- Review newly Food and Drug Administration–approved medications and formulations in the treatment of schizophrenia.
- Examine the evidence for of novel drugs tested in schizophrenia.

## INTRODUCTION

The serendipitous discovery in the 1950s that the phenothiazine, chlorpromazine (Thorazine) was an effective antipsychotic is often touted as one of the greatest advances of 20th-century medicine and dramatically changed the treatment and outcome of schizophrenia.[1] It set in motion a wave of drug discovery over the following 2 decades resulting in 15 approved antipsychotics in United States and 40 worldwide. Despite a concern over agranulocytosis, clozapine was reintroduced in the United States as the first second-generation antipsychotic (SGA) in the 1990s and is still the only antipsychotic shown to be effective in treatment-resistant patients. Its mechanism, which deemphasizes monodopamine blockage spurred the introduction of

Disclosure Statement: Equity ownership, profit-sharing agreements, royalties, patents: None; Research or other grants from private industry or closely affiliated nonprofit funds: Alkermes Event Monitoring Event Board—Contract paid to the University of Missouri; Advisory Panel: None; Speakers Bureau: None; Pharmaceutical CME Activity honoraria or other CME activity: RMEI LLC CME program funded through unrestricted educational grant from Janssen Scientific Affairs, LLC and Alkermes; Travel funds: None. (J. Lauriello). There is no conflict of interest to report for (G. Gopalakrishna, M.H. Ithman).

Department of Psychiatry, University of Missouri-Columbia, One Hospital Drive, Columbia, MO 65212, USA

* Corresponding author.

*E-mail address:* gopalakrishnag@health.missouri.edu

Psychiatr Clin N Am ■ (2016) ■–■

http://dx.doi.org/10.1016/j.psc.2016.01.005 **psych.theclinics.com**

0193-953X/16/$ – see front matter 

| Abbreviations and Acronyms | |
|---|---|
| AMPA | Alpha-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid |
| cAMP | Cyclic adenosine monophosphate |
| FDA | Food and Drug Administration |
| mGluR | Metabotropic glutamate receptor |
| nAChR | Nicotinic acetylcholinergic receptor |
| NMDA | *N*-methyl-D-aspartate |
| PAM | Positive allosteric modulator |
| PANSS | Positive and Negative Syndrome Scale |
| PDE | Phosphodiesterase |
| SGA | Second-generation antipsychotic |

other SGAs, which have much lower hematologic risk, but lack the exceptional efficacy.[2] Comparison studies of the first-generation antipsychotics and SGAs have demonstrated similar efficacy with the SGAs, as a group, tending to be better tolerated (especially in neurologic effects) and thus considered first-line treatment for schizophrenia.[3] Another recent advancement in treatment of schizophrenia has been the introduction of long-acting injectable (LAI) antipsychotics of some of the SGAs. Although LAIs have been available since the 1980s, the accessibility of SGA as LAIs, with fewer extrapyramidal side effects, has resulted in a renewed interest in their use. Despite the prodigious number of new antipsychotics in the previous century, only about 36% of the patients with schizophrenia reach remission.[4] About one-third of patients diagnosed with schizophrenia are considered to be treatment resistant after 2 or more adequate trials with antipsychotics.[5] So, although there has been more than 50 years of development, there remains a great need for more efficacious and better tolerated antipsychotic medications, as well as compounds that improve other impacted areas in schizophrenia (ie, cognition). This article looks at the recent advances in treatment of schizophrenia. We review newly Food and Drug Administration (FDA)–approved medications and formulations, examine the evidence for a number of novel drugs being tested in schizophrenia and describe promising compounds in the pharmaceutical pipeline.

## *Recently Approved Medications for Schizophrenia*

In 2015, 2 newly approved antipsychotics came to market, the first with a potentially breakthrough delivery method, the other a long-awaited second in class option. We review both of these drugs with the understanding that at the time of writing this article, there is limited postmarketing evidence available about their efficacy, safety, and tolerability (**Table 1**).

### *Three-month paliperidone palmitate (Invega Trinza)*

Paliperidone is the 9-OH metabolite of risperidone, first made available as LAI paliperidone palmitate in the United states for acute and maintenance treatment of schizophrenia in adults in 2009 under the trade name Invega Sustenna.[6] Paliperidone palmitate is the palmitate ester of paliperidone, in an aqueous-based nanosuspension with very low water solubility, facilitating slow dissolution after intramuscular injection.[7] In November 2014, paliperidone palmitate was approved by the FDA in the United States to treat schizoaffective disorder as monotherapy or adjunctive therapy.[8] Pivotal trial studies and subsequent postmarketing studies have shown that paliperidone palmitate to be an efficacious, safe, and well-tolerated SGA LAI that could significantly improve adherence, reduce relapse rates, enhance the rate of remission, and ultimately improve clinical outcomes in schizophrenia.[9,10]

**Table 1**
**Newly approved medications for schizophrenia**

| Agent | Mechanism of Action | Significant Results from Research | Phase of Development |
|---|---|---|---|
| Three-month paliperidone palmitate (Invega Trinza) | Blockade of both 5-HT2A and dopamine 2 receptors | Double-blind multicenter randomized trial showed reductions in relapse and safety compared with placebo | Available in the market as of May 2015 |
| Brexpiprazole (Rexulti) | Partial agonist at 5-HT1A and D2 receptors and strong antagonist at 5-HT2A | Double-blind multicenter randomized phase III trial improved PANSS scores compared with placebo | Available in the market as of May 2015 |
| Cariprazine (Vrylar) | D2 and D3 receptors antagonist-partial agonist properties, with greater affinity to D3 and 5-HT1B receptor antagonism | Three 6-week double blind multinational, multicenter phase III trials demonstrating efficacy and safety | Available in the market as of September 2015 |
| LAI of aripiprazole lauroxil (Aristada) | Prodrug of aripiprazole; D2 and 5-HT(2A) receptor antagonism, partial D2 agonist and significant 5-HT(1A) agonist actions | A 12-week multicenter, randomized, double-blind, placebo-controlled trial demonstrating evaluated the efficacy, safety and tolerability | Available in the market as of October 2015 |

*Abbreviations:* 5-HT1A, 5-hydroxytryptamine 1A; 5-HT2A, 5-hydroxytryptamine 2A; LAI, long-acting injection; PANSS, Positive and Negative Syndrome Scale.

In May 2015, the US FDA approved the 3-month paliperidone palmitate injection (Invega Trinza) to treat schizophrenia.[11] Approval was based on the results of a long-term maintenance trial designed to evaluate the efficacy and safety of the 3-month formulation of paliperidone palmitate versus placebo in delaying the time to relapse in schizophrenia symptoms in patient previously treated with once monthly paliperidone palmitate for at least 4 months.[12] The multicenter trial was conducted in 8 countries between April 2012 and April 2014. The study consisted of 4 phases: a screening phase for 3 weeks, a flexible dose open-label transition phase for 17 weeks, an open-label maintenance phase for 12 weeks, and an open-ended double-blind phase. There were 506 patients between the ages of 18 and 70 years old with the diagnosis of schizophrenia enrolled in this study; 305 patients were randomized either to 3-month paliperidone palmitate (n = 160) or placebo (n = 145). The study results showed significant difference in relapse rate in favor of the paliperidone palmitate group over the placebo group ($P<.001$). The study concluded that 3-month paliperidone palmitate significantly delayed first time relapse for at least 4 months in schizophrenic patients initially treated with once monthly paliperidone palmitate.[12] The

3-month formulation was well-tolerated compared with placebo. Of 305 patients, 183 experienced side effects (62% in the paliperidone group vs 58% in the placebo group), which included headaches (9% vs 4%), (weight gain 9% vs 3%), nasopharyngitis (6% vs 1%), and akathisia (4.5% vs 1%). Also, overall the side effect profile of the 3-month paliperidone palmitate was not much different than other marketed paliperidone formulations.

***Brexpiprazole (Rexulti)***

Brexpiprazole (Rexulti) developed by Otsuka and Lundbeck was recently approved by the US FDA as a monotherapy for the treatment of adults diagnosed with schizophrenia, in addition for use as an adjunctive to an antidepressant medication to treat adults with major depressive disorder.[13] Brexpiprazole exhibits a high affinity for serotonin, dopamine, and noradrenalin receptors, acting as a partial agonist at serotonin 5-HT1A and dopamine D2 receptors, and is a strong antagonist at serotonin 5-HT2A and noradrenalin $\alpha$1B and $\alpha$2C receptors.[14] It is the second in the class of partial agonist antipsychotics the first being aripiprazole (Abilify) also developed by Otsuka. The efficacy of brexpiprazole as a monotherapy in treatment of adults with schizophrenia was studied in a pivotal multicenter, randomized, double-blind, controlled phase III trial of fixed dose of brexpiprazole over 6 months. The study consisted of a pretreatment screening phase, a 6-week double-blind treatment period and a 30-day follow-up phase. Patients were randomized (2:3:3:3) into 1 of 4 treatment groups (1, 2, or 4 mg brexpiprazole, or placebo). The primary endpoint for this study was change from baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS) Total Score with secondary outcomes of changes in Clinical Global Impressions—Severity, Personal and Social Performance scale; PANSS positive and negative subscales; PANSS excited component and Marder Factor cores, Clinical Global Impressions—Improvement score at week 6, response rate, and discontinuation rate for lack of efficacy.[15]

There were 1005 patients aged 18 to 70 years who were screened at 64 centers in different countries, and 674 patients were randomized to double-blind treatment. In the brexpiprazole groups, 68% (n = 458) completed the study, compared with 64.1% (n = 118) in the placebo group. The most common reasons for dropping out of the treatment across all the treatment groups were withdrawal of consent to participate (12.5%), lack of efficacy (9.8%), and emergence of adverse effects (8.5%).

The study result showed that 4 mg brexpiprazole significantly improved the primary endpoint of the study compared with placebo (treatment difference, −6.47; $P = .0022$), and had similar impact to the key secondary endpoint, namely, Clinical Global Impressions—Severity versus placebo (treatment difference, −0.38; $P = .0015$). Brexpiprazole 1 and 2 mg also showed numerical improvement versus placebo, although the result was not statistically significant ($P > .05$).

The most common side effects included headache, insomnia, and agitation; the brexpiprazole groups showed lower incidence of akathisia compared with placebo (4.2%–6.5% vs 7.1%). Moderate weight gain was observed at week 6 of treatment (1.23–1.89 kg) for brexpiprazole group compared with 0.35 kg for the placebo group.

This study established the efficacy and tolerability of brexpiprazole 4 mg for the treatment of acute schizophrenia in adults, and confirmed the result of another multicenter randomized, double-blind, placebo-controlled trial. The study from Correll and colleagues[16] included patients with acute exacerbation of schizophrenia, who were randomly assigned to daily brexpiprazole at 0.25 mg, 2 mg, or 4 mg, or placebo for period of 6 weeks. The completion rate for 0.25 mg, 2 mg, and 4 mg brexpiprazole were 62%, 68%, and 67%, respectively compared with 59% for placebo group. At

week 6, patients treated with 2 mg and 4 mg of brexpiprazole showed statistically significant decrease in PANSS total score (treatment difference of -8.72 and -7.64, respectively) and CGI severity score (treatment difference of -0.33 and -0.38) compared with the placebo group. The most common side effects for brexpiprazole group was akathisia (2 mg, 4.4%; 4 mg, 7.2%; placebo, 2.2%), moderate weight gain (1.45 kg for the 2 mg group and 1.28 kg for the 4 mg group compared with 0.42 kg for the placebo group at week 6). Lipids, glucose level, and extrapyramidal symptoms rating did not show any clinical or statistically significant differences from baseline. This study indicated that brexpiprazole at dose of 2 and 4 mg/d has statistically significant efficacy compared with placebo and good tolerability for patient with an acute schizophrenia exacerbation.[16]

***Cariprazine (Vrylar)***

In September 2015, the FDA approved the use of Cariprazine in the United States for the treatment of schizophrenia and bipolar disorder in adults. Cariprazine is a new antipsychotic with D2 and D3 receptors antagonist–partial agonist properties, and an almost 10-fold greater affinity for the D3 receptor in vitro, with high occupancy for D2 and D3 receptors in vivo. It also demonstrated pure antagonism for 5-HT1B receptor with high, moderate, and low affinities for 5-HTB1, 5-HT1A, and 5-HT2A receptors respectively.[17–19]

The efficacy of cariprazine for treatment of schizophrenia was established in three 6-week clinical trials; all the trials were multinational, multicenter, double-blind studies. The 6-week double-blind trials done by Kane and colleagues[19] and Durgam and colleagues[20] demonstrated that the total PANSS score significantly improved among patient receiving cariprazine compared with placebo. Similar improvements were noted in Clinical Global Impressions—Severity scores at the end of the study. The most common treatment adverse effects were insomnia, nausea, akathisia and extrapyramidal symptoms, and most of these side effects were mild to moderate in severity. The results of the 3 studies supported the FDA's decision that cariprazine is a safe, efficacious, and well-tolerated agent in the treatment of acute exacerbation of schizophrenia in adults.

***Aripiprazole lauroxil long-acting injectable (Aristada)***

A new long-acting formulation of aripiprazole (ALLAI) was recently approved by the FDA to treat adults with schizophrenia.[21] ALLAI can be administered every 4 to 6 weeks either in the gluteal or deltoid region. ALLAI is a linker lipid ester of aripiprazole and its conversion to aripiprazole in vivo is governed by slow dissolution of the aripiprazole lauroxil particles followed by hydrolysis, resulting in a steady increase in plasma concentration and an extended blood level of aripiprazole.[22] The FDA approval is based on an international, multicenter, randomized, double-blind, placebo-controlled trial.[23] The study evaluated the efficacy, safety, and tolerability of ALLAI among 623 patients aged 18 to 70 years experiencing an acute exacerbation. Patients were randomized in a 1:1:1 ratio to receive gluteal intramuscular injection of ALLAI 441 mg, ALLAI 882 mg, or matching placebo once monthly for 12 weeks. The change in PANSS total score from baseline to day 85 was the primary efficacy outcome with change in Clinical Global Impressions—Improvement score being the secondary measure. The PANSS total score (mean $\pm$ standard error) improved significantly from baseline to day 85 in the ALLAI 441 mg (-10.9 $\pm$ 1.8; $P<.001$) and 882 (-11.9 $\pm$ 1.8; $P<.001$) mg groups compared with placebo. A significant ($P\leq.004$) improvement was noted in both active treatment arms as early as day 8 and continued throughout the treatment period. ALLAI was well-tolerated with insomnia, akathisia,

headache, and anxiety being the common side effects. The incidence of severe treatment-emergent adverse events were similar between the 3 groups. At the time of writing this article, it is not clear if ALLI (Aristada) offers any advantages over Abilify Maintena or suffers any shortcomings in comparison. The use of oral aripiprazole for overlap for 3 weeks in the pivotal study makes it likely that ALLAI will also have an oral overlap requirement. Using the every 6 week regimen can decrease the number of injections over a year compared with patients using every 4 week injections, but it is also not clear about the number of patients who can potentially use the 6 weekly injections. The package insert will likely allow some comparisons in the absence of head-to-head trials.

### *Novel Treatments in Schizophrenia*

The dopaminergic hypothesis has been the predominant explanation of the pathophysiology of schizophrenia for the last half century.[24] The hypothesis not only postulates the cause of the pathognomonic symptoms, but also the pharmacologic actions and side effects of antipsychotic medications. Hyperdopaminergic activity in the mesolimbic system is implicated in the cause of the positive symptoms (ie, hallucinations and delusions) of schizophrenia. In contrast, hypodopaminergic drive in the mesocortical system may be attributed to the negative symptoms of schizophrenia, such as anhedonia, flat affect, and social isolation. Mesolimbic antipsychotic dopaminergic blockade reduces positive psychotic symptoms but at the expense of inhibition in the hypothalamo–pituitary axis and nigrostriatal pathways leading to high prolactin levels and extrapyramidal symptoms, respectively.

Dopaminergic dysfunction, however, has not been able to account for all of the symptoms observed in schizophrenia, particularly the negative symptoms.[25] New hypotheses have been suggested that may replace or complement the dopamine hypotheses. Also, a new emphasis on improving cognition in patients with schizophrenia led to the National Institute of Mental Health funded Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) projects to promote the development of new cognitive enhancing drugs. The MATRICS project identified 9 potential target molecules belonging to 3 neurotransmitter systems: dopaminergic, cholinergic, and glutamatergic.[26]

### *Glutamate System*

The glutamate system has been a recent target for pharmacologic interventions in schizophrenia based on the proposed model of schizophrenia where dysfunction of the *N*-methyl-D-aspartate (NMDA) receptors is considered the primary convergence point in the pathology of schizophrenia (**Table 2**).[27] NMDA receptor antagonists such as phencyclidine and ketamine have shown to produce psychoticlike symptoms in healthy individuals that are similar to those seen in patients with schizophrenia.[28,29] Glutamate receptors are classified into metabotropic (mGluR) and ionotropic receptors. The metabotropic receptors are subclassified into 3 groups: group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), and group III (mGluR4-8). Similarly, the ionotropic receptors are subclassified into alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), Kainate, and NMDA receptors.[30] Glutamate has a direct excitatory influence on dopaminergic neurons in addition to indirect (through $\gamma$-aminobutyric acid interneuron) inhibitory action on the release of dopamine in some circuits.[31] This leads to increase in the mesolimbic dopaminergic activity and a decreased activity in the mesocortical circuit. Hypofunction of NMDA receptors is

implicated in the causation of schizophrenia symptomatology, particularly the negative symptoms.

***Metabotropic glutamate receptor 2/3 agonists***

Pomaglumetad methionil (LY2140023) is a potent and highly selective agonist for the metabotropic glutamate mGluR2 and mGluR3 receptors. After initial promising phase II studies showing efficacy comparable with olanzapine,[32] a series of failed phase III studies by Eli Lilly with the compound LY2140023 resulted in the discontinuation of development of this molecule for treatment of schizophrenia.[33,34] A recent exploratory analysis, which included the most recent phase III study and other integrated studies, indicated that pomaglumetad shows greater improvement among patients with early in disease or paradoxically previously treated with D2 blocking drugs compared with those receiving placebo.[35] This has raised some interesting perspectives among experts about the molecular pathology among patients diagnosed with schizophrenia.[34] Previous exposure to antipsychotics could have modified the brain structure and neuroplasticity, leading to poor response to a new medication, such as the pomaglumetad. It has also been hypothesized that there may be cohorts of patients with distinct neurochemical profiles in early stages of schizophrenia who might benefit from mGluR2/3 agonists.[34]

***Positive allosteric modulators of mGlu2***

The available mGlu2 agonists have demonstrated a lack of subtype specificity and pose a challenge for development of tolerance with chronic use.[36] This has led to the development of positive allosteric modulators (PAMs) at mGlu2/3 receptors, such as LY487379, JNJ-42153605, JNJ-40068782, and biphenylindanone A. PAMs have shown receptor selectivity, act only in the presence of endogenous ligands, and are considered to overcome the rapid desensitization of the receptors.[37] These molecules have been tested in various preclinical trials.[38,39] ADX71149/JNJ4041183 has been the most successful PAM thus far after passing a phase IIa clinical study demonstrating safety, tolerability, and efficacy on negative symptoms in schizophrenia.[37]

***Ampakines***

Ampakines are PAMs of the synaptic AMPA glutamate receptors that facilitate glutamate neurotransmission.[40] CX516, a prototype of the ampakines, was compared with placebo in 4-week, double-blind study and failed to demonstrate the efficacy as a single agent.[41] Despite an earlier study suggesting positive effects on measures of attention and memory,[42] CX516 did not separate from the placebo arm with regard to PANSS total score and was not effective for cognition among 105 patients with schizophrenia when added to clozapine, olanzapine, or risperidone.[43]

## *Glycine System*

Glycine is a coagonist and essential neurotransmitter for the activation of NMDA receptor (see **Table 2**).[31] Multiple small clinical trials, with limited power, tested a high dose of glycine and gylcine site agonists such as D-cycloserine, as an adjunct to existing treatments.[44–50] Some of these studies showed improvements in various domains in schizophrenia symptomatology among patients using the adjunctive glycine and glycine agonists compared with treatment as usual supporting the hypoglutaminergic hypothesis of schizophrenia. Sarcosine is a naturally occurring, nonselective glycine reuptake inhibitor. Sarcosine also demonstrated positive results as an adjunctive treatment to antipsychotics in multiple short-term studies.[51–53]

**Table 2**
**Medications acting on the glutamate and glycine system**

| Agent | Mechanism of Action | Significant Results from Research | Phase of Development |
|---|---|---|---|
| Glutamate system | | | |
| Metabotropic glutamate receptor (mGluR) 2/3 agonists (Pomaglumetad methionil) | Highly selective agonist for the metabotropic glutamate mGluR2 and mGluR3 receptors | Initial promising phase II studies showing efficacy comparable with olanzapine followed by a series of failed phase III studies | Discontinuation of development |
| Positive allosteric modulators of mGlu2 | Modulators of the mGlu receptors | Tested in various preclinical trials; ADX71149/ JNJ4041183 has been the most successful PAM thus far after passing a phase IIa clinical study | Results awaited on further studies by Addex |
| Ampakines (CX516) | Positive allosteric modulators of the synaptic AMPA glutamate receptors that facilitate glutamate neurotransmission | Compared with placebo in 4-week double blind study failed to demonstrate the efficacy as a single agent. Despite an earlier study suggesting improvement of attention and memory, CX516 did not separate from the placebo arm in regards to PANSS total score and was not effective for cognition when added to clozapine, olanzapine, or risperidone | Discontinuation of development |
| Glycine system | | | |
| Glycine, D-cycloserine, D-serine | Coagonist and essential neurotransmitter for the activation of NMDA receptor | A metaanalysis of all available double-blind, placebo controlled trials showed that glycine, D-serine and sarcosine improved psychopathology overall, whereas D-cycloserine had no effect. Despite showing benefit when added to risperidone or olanzapine, none of these drugs add therapeutic advantage over placebo when added to clozapine | No further development |
| Sarcosine | Naturally occurring, nonselective GRI | | |

| | | | |
|---|---|---|---|
| Bitopertin | GRI | An 8-week phase II study showed significantly reduced negative symptoms among the patients taking bitopertin compared with placebo. Followed by 2 failed phase III trials. A combined phase II/III trial (the CandleLyte study) compared bitopertin with placebo and zyprexa and failed to demonstrate efficacy on PANSS total score. | Removal of the drug from the pipeline of Roche in 2014 |
| Sodium benzoate | Inhibitor of the D-amino acid oxidase increasing levels of D-serine in the synapse improving NMDA functioning | Antipsychotic effects from sodium benzoate noted in the PCP model of schizophrenia in mice. A randomized, double blind, placebo controlled study in Taiwan showed improved a variety of positive, negative, and neurocognitive symptoms. | Further studies required |

*Abbreviations:* AMPA, alpha-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid; GRI, glycine reuptake inhibitor; mGluR, metabotropic glutamate receptor; NMDA, *N*-methyl-D-aspartate; PANSS, Positive and Negative Syndrome Scale; PCP, phencyclidine.

A metaanalysis of all available double-blind, placebo-controlled trials evaluating the efficacy of NMDA-enhancing molecules on schizophrenia showed that glycine, D-serine, and sarcosine improved psychopathology overall, and D-cycloserine had no effect.[54] Despite showing benefit when added to risperidone or olanzapine, none of these drugs have shown to add therapeutic advantage over placebo when added to clozapine.[54,55]

One of the avenues to enhance the NMDA receptor functioning is to increase the availability of glycine at modulatory sites on the NMDA receptors through the inhibition of glycine transporter-1 on glial cells.[56] This propelled the development and testing of glycine transporter-1 inhibitors as a potential treatment of schizophrenia. We review 2 important molecules in the glycine system that increase the synaptic glycine or D-serine concentration.

***Bitopertin***

Bitopertin is a glycine reuptake inhibitor that has demonstrated enhanced NMDAR signaling.[57] An 8-week, double-blind, randomized, placebo-controlled, proof-of-concept, multicenter, phase II study was conducted with 323 patients with schizophrenia who were stable on antipsychotic treatment but had significant negative symptoms. Bitopertin significantly reduced the negative symptoms among the patients taking either 10 mg/d or 30 mg/d dosing compared with placebo.[58] Unfortunately, this was followed by 2 failed phase III trials, resulting in the removal of the drug from the pipeline of Roche in 2014.[59] A combined phase II/III trial (the CandleLyte study) compared bitopertin to placebo and Zyprexa with 301 patients over 4 weeks. This study failed to demonstrate statistically significant separation between the 3 arms on the primary endpoint of change from baseline in mean PANSS total score.[60]

***Sodium benzoate***

NMDA receptor functioning can be enhanced by increasing the levels of D-serine in the synapse by inhibiting the D-amino acid oxidase, which metabolizes D-serine.[61] Sodium benzoate, a common food preservative, is one such D-amino acid oxidase inhibitor. An animal study examined the effects of sodium benzoate on behavioral abnormalities in mice after administration of phencyclidine. The study suggested that antipsychotic effects were noted from sodium benzoate in the phencyclidine model of schizophrenia in mice without increasing D-serine levels in the brain.[62] A randomized, double-blind, placebo-controlled study in Taiwan compared the efficacy of sodium benzoate as an adjunct to antipsychotics in subjects with schizophrenia. Sodium benzoate improved a variety of positive, negative, and neurocognitive symptoms, including a 21% improvement in PANSS total score compared with placebo.[63]

## *Phosphodiesterase System*

Phosphodiesterases (PDEs) are a family of enzymes regulating signal transduction of neuronal membranes by maintaining the homeostasis of intracellular cyclic nucleotides by degrading cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate.[64] PDE10A is 1 member of the PDE family that is highly expressed in the bodies and the dendrites of medium spiny projection neurons in the striatum with minimal distribution outside the brain.[65] Parallels with D2 receptor functioning makes the PDE10A inhibitors a potential candidate for intervention in schizophrenia.[34] Also, the role of cAMP responsive element binding protein and the cAMP signaling has been demonstrated in neurodevelopment and neuroprotection.[66,67] Multiple PDE10A inhibitors are in development by various pharmaceutical companies with many of the patents directed toward improving negative and cognitive symptoms in schizophrenia

(Table 3).[68] Based on preclinical trials, and despite moderate adverse events, the use of PDE10A inhibitors like MP-10 and papaverine was expected to yield an antipsychotic effect along with beneficial effects on negative and cognitive symptoms.[69] However, a 4-week placebo and positive controlled randomized double-blind multicenter trial investigating fixed doses of MP-10/PF-02545920 at 5 and 15 mg failed to demonstrate the efficacy of MP-10 compared with placebo, whereas risperidone showed clear benefit.[70] This has led to further examination of the rationale and mechanism of action of this group of molecules. The discovery of PET ligands has led to assess a clinical trial studying the occupancy of PDE10A receptors by MP-10, which is completed and the results are awaited.[71]

Other PDE inhibitors are also being tested for use in treatment of negative and cognitive symptoms of schizophrenia (see Table 3). PDE5 inhibitors like sildenafil, a popular erectile dysfunction drug, have been hypothesized to improve the negative and cognitive symptoms.[72] Goff and colleagues[73] studied the cognitive effects of sildenafil on 15 clinically stable patients treated with various antipsychotics compared with placebo. After the administration of sildanefil 50 mg, 100 mg, and placebo in randomized order, cognitive functioning was tested 3 postbaseline sessions and another assessment for delayed recall after 48 hours. The study failed to demonstrate the cognitive enhancing effects of sildenafil among patients compared with placebo.[73] Another 8-week trial in Iran comparing sildenafil with placebo as an adjunctive therapy to risperidone demonstrated superiority of sildenafil in improving negative and PANSS total scores.[74] Intra-Cellular Therapies, Inc, is developing PDE1 inhibitors to improve cognition among patients with schizophrenia.[75]

### *Nicotinic Cholinergic System*

Nicotinic acetylcholinergic receptors (nAChRs) mediate multiple modulatory functions in diverse synaptic and nonsynaptic locations throughout the human brain with roles in development and neuronal plasticity, contributing to learning, memory, and attention.[76] One of the subtypes of these receptors, α-7 nAChR, has been associated with P50 sensory gating found to be impaired in patients with schizophrenia. The impairment is implicated in the attention deficits and lack of attention sustainment seen in patients with schizophrenia and their unaffected relatives.[77–83]

Nicotine receptor agonists that selectively target the α-7 subtype are being tested by various pharmaceutical companies for efficacy in improving the cognitive impairment associated with schizophrenia (see Table 3). DMXB-A, a partial α-7 nicotinic cholinergic agonist showed promising results in improving neurocognition in a proof-of-concept study.[84] This has not been replicated in subsequent larger studies, but instead showed improvement of negative symptoms in patients with schizophrenia.[85] Another 4-week placebo-controlled study was recently completed with sustained release DXMB-A; the results are pending.[86,87] The beneficial effect on negative symptoms was replicated with other α-7 partial agonists including TC-5619 in an exploratory trial with 185 outpatients in the United States and India.[88] However, a 24-week randomized trial with 477 outpatients from 64 sites in the United States, Russia, Ukraine, Hungary, Romania, and Serbia comparing TC-5619 with placebo showed no benefit in negative or cognitive symptoms of schizophrenia.[89]

Tropisetron is a[90] 5-HT3 antagonist with high-affinity partial agonism at α-7 nAChR.[91] A short-term double-blind placebo-controlled trial with 40 patients demonstrated that tropisetron improved auditory sensory gating P50 deficits in nonsmoking individuals and cognitive functioning.[92] Subsequent studies evaluating tropisetron as an adjunctive treatment to oral antipsychotics showed that tropisetron significantly improved the overall cognitive along with P50 deficits[93] and negative symptoms

**Table 3**
**Medications acting on the PDE system and nicotinergic system**

| Agent | Mechanism of Action | Significant Results from Research | Phase of Development |
|---|---|---|---|
| PDE system | | | |
| PDE10A inhibitors (eg, MP-10 and papaverine) | Regulates signal transduction of neuronal membranes by maintaining the homeostasis of intracellular cyclic nucleotides by degrading cAMP and cGMP | Preclinical trials suggested an antipsychotic effect along with beneficial effects on negative and cognitive symptoms with. A 4-week placebo- and positive-controlled randomized double-blind multicenter trial of MP-10 failed to demonstrate the efficacy compared with placebo while risperidone showed clear benefit. | Multiple PDE10A inhibitors in pharmaceutical pipeline with many of the patents directed toward improving negative and cognitive symptoms in schizophrenia |
| PDE5 inhibitors (eg, sildenafil) | | A study of 15 clinically stable failed to demonstrate the cognitive enhancing effects of sildenafil among patients compared with placebo. | Discontinuation of development |
| PDE1 inhibitors | | — | Intra-Cellular Therapies, Inc. is developing PDE1 inhibitors |
| Nicotinic cholinergic system | | | |
| DMXB-A | $\alpha$-7 nAChR agonists improve the deficits with P50 sensory gating | Promising results in the proof of concept study not replicated in larger studies. | Discontinuation of development |
| TC-519 | | A 24-week multicenter trial comparing TC-5619 to placebo showed with benefit in negative or cognitive symptoms | |

| | | | |
|---|---|---|---|
| Tropisetron | 5-HT3 antagonist with high-affinity partial agonism at α-7 nAChR | Metaanalysis of double-blinded, randomized, placebo-control trials showed that 5HT-3 receptor antagonists improved psychopathology | Results of a large randomized controlled trial awaited |
| EVP-6124 (Encenicline) | Highly selective partial agonist of α-7 nAChR | Phase II study showed Encenicline was well-tolerated at single doses of ≤180 mg | Phase III trials are under way |
| ABT-126 | Partial agonist of α-7 nAChR | Completion of 3 phase II studies and terminating another phase II trial in 2014 | Removed from the pipeline |
| PAM of nicotinergic system (eg, JNJ-39393406, AVL-3288) | Increase the potency and efficacy of the agonist-induced responses | JNJ-39393406 showed positive results on cognition and improved sensory gating deficits in animal studies but failed to demonstrate its effect on P50 deficits in a multicenter, randomized, double blind, placebo controlled study | AVL-3288 is currently being tested for safety, tolerability and pharmacokinetics in a phase I study |

*Abbreviations:* cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; 5HT-3, 5-hydroxytryptamine 3; nAChR, neuronal nicotinic acetylcholine receptor; PDE, phosphodiesterase.

compared with patients taking placebo.[94] A recent metaanalysis of double-blinded, randomized, placebo-controlled trials showed that 5HT-3 receptor antagonists improved psychopathology (especially negative symptoms) in patients with schizophrenia compared with placebo.[95] A large randomized controlled trial comparing tropisetron with placebo as an adjunctive treatment has been completed and the results are pending.[90]

EVP-6124 (Encenicline) is a highly selective partial agonist of α-7 nAChR with good penetrability across the blood–brain barrier.[96] In a proof-of-concept study, encenicline was compared with placebo as an adjunctive treatment to oral antipsychotics. Encenicline was well-tolerated among patients and showed positive results in various measures.[97] Based on this study, a phase II single ascending dose study was conducted to evaluate the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles in healthy male volunteers. Encenicline was well-tolerated at single doses of up to 180 mg with dose-dependent pharmacodynamic effects on the central nervous system.[98] Phase III trials are under way by Forum pharmaceuticals for this drug currently.

ABT-126 is a partial agonist developed by Abbvie at α-7 nAChR that has been studied for improving cognition in Alzheimer's disease and schizophrenia.[87] After completing 3 phase II studies[99–101] and terminating another phase II trial in 2014,[102] the drug is not listed in Abbvie's pipeline. AQW051, a Novartis product, is highly selective agonist with high affinity toward α-7 nAChR.[103] Two double-blind randomized placebo-controlled phase II studies have been completed so far, but the results have not been published.[104,105] Similar to ABT-126, Novartis Pharmaceuticals does not list AQW051 in their pipeline.

PAMs are also being developed in the nicotinergic system not only to increase the potency and efficacy of the agonist induced responses, but also to alter the desensitization properties of the agonist. JNJ-39393406 showed positive results on cognition and improved sensory gating deficits in animal studies but failed to demonstrate its effect on P50 deficits in a multicenter, randomized, double-blind, placebo-controlled study.[106] AVL-3288 another PAM is currently being tested for safety, tolerability, and pharmacokinetics in a single-center, randomized, double-blind, placebo-controlled, dose-escalating phase I study.[107]

### *Other Compounds*

#### *Blonanserin*

Blonanserin is an SGA with 5HT-2A, D2, and D3 antagonistic activity with minimal effect on histaminic and muscarinic receptors (**Table 4**).[108] It has been approved for schizophrenia and has been used in Japan since 2008 and in Korea since 2009. A systemic review in 2012 showed that blonanserin had a lower risk of hyperprolactinemia than the other pooled antipsychotics. Although blonanserin was better tolerated with respect to dizziness and akathisia, it had a higher risk of akathisia compared with risperidone. Recently, an 8-week study comparing risperidone and blonanserin showed that blonanserin was similar to risperidone in efficacy but improved quality of life compared with risperidone.[109] The Japan Useful Medication Program for Schizophrenia (JUMPS) is a 104 week, open-label, multicenter, randomized, comparative study underway in Japan, comparing treatment with either aripiprazole, blonanserin, or paliperidone in patients with schizophrenia aged 20 years or older. The primary endpoint is treatment discontinuation rate for any causes.

#### *Minocycline*

Antioxidant aberration has been implicated in the pathophysiology of schizophrenia. Microglia are key sources of free radicals leading to brain injury in various areas.[110]

**Table 4**
**Other drugs**

| Agent | Mechanism of Action | Significant Results from Research | Phase of Development |
|---|---|---|---|
| Blonanserin | 5HT-2A, D2, and D3 antagonistic activity | Similar to risperidone in efficacy but improved quality of life. A large 104-week study is under way. | Approved for schizophrenia in Japan since 2008 and in Korea since 2009 |
| Minocycline | Inhibitor of microglial activation and rescue neurogenesis | Two randomized, double-blind, placebo-controlled studies showed efficacy of minocycline as an adjunctive treatment in early phase of schizophrenia. | Further studies required |

*Abbreviation:* 5HT-2A, 5-hydroxytryptamine 2A.

Microglia are also the intrinsic immune competent cells of the brain implicated in cytokine-induced impairment of adult neurogenesis in key areas like hippocampus.[111] The minocycline is a known inhibitor of microglial activation and rescue neurogenesis (see **Table 4**).[111,112] An open-label study of 22 patients by Miyaoka and colleagues[113] demonstrated significant clinical improvements on PANSS among patient using adjunctive minocycline. The effects were sustained at 4 weeks after the completion of the study without adverse events.[113] Two randomized, double-blind, placebo-controlled studies showed efficacy of minocycline as an adjunctive treatment in early phase of schizophrenia with respect to negative symptoms albeit their methodology had some limitations.[114,115]

### *Pharmaceutical Pipeline*

According to a report by America's Biopharmaceutical Research Companies published in 2014, there are about 36 developing medications among various pharmaceutical companies.[116] Eight of them are in the spectrum of being in phase III studies or being currently marketed. As noted, there have been a number of drugs that have been dropped from the pipeline owing to disappointing results in clinical trials in various phases.

PDE10A inhibitors and $\alpha$-7 nAChR modulators constitute the majority of these molecules in the pipeline. Some 5-HT2A antagonists, similar to lurasidone and iloperidone, which are already in the market, are also noted in the pipeline.

## SUMMARY

Schizophrenia has posed a substantial challenge not only for patients and their families, but also the medical profession for many centuries. The last century has witnessed significant strides in development of treatments for schizophrenia and outcomes of these patients. But there are a large number of patients still struggling from with ongoing symptoms and for some progressively worsening course illness, necessitating the pursuit of better treatments.

The paradigm shift of focusing on specific symptom domains of schizophrenia like cognition and negative symptoms has been reflected in the research and also by the drugs in the pipeline of several of pharmaceutical companies. The marketing of these medications eventually may result in change about how schizophrenia is treated in the future.

## REFERENCES

1. Lopez-Munoz F, Alamo C, Cuenca E, et al. History of the discovery and clinical introduction of chlorpromazine. Ann Clin Psychiatry 2005;17(3):113–35.
2. Shen WW. A history of antipsychotic drug development. Compr Psychiatry 1999; 40(6):407–14.
3. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009; 373(9657):31–41.
4. AlAqeel B, Margolese HC. Remission in schizophrenia: critical and systematic review. Harv Rev Psychiatry 2012;20(6):281–97.
5. Meltzer HY. Treatment-resistant schizophrenia–the role of clozapine. Curr Med Res Opin 1997;14(1):1–20.
6. Janssen, D.o.O.-M.-J.P., Inc, Invega® Sustenna® (paliperidone palmitate) extended-release injectable suspension. United States prescribing information. 2010. Available at: http://www.invegasustenna.com/invegasustenna/shared/pi/invegasustenna.pdf. Accessed August 9, 2015.
7. Gilday E, Nasrallah HA. Clinical pharmacology of paliperidone palmitate a parenteral long-acting formulation for the treatment of schizophrenia. Rev Recent Clin Trials 2012;7(1):2–9.
8. Janssen, D.o.O.-M.-J.P., Inc. U.S FDA approves supplemental new drug applications for once monthly long-acting therapy Invega Sustenna (paliperidone palmitate) for the treatment of schizoaffective disorder. 2014.
9. Hough D, Gopal S, Vijapurkar U, et al. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res 2010;116(2–3): 107–17.
10. Kramer M, Litman R, Hough D, et al. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. Int J Neuropsychopharmacol 2010;13(5):635–47.
11. Johnson&Johnson. U.S. FDA approves Invega Trinza™, first and only four-times-a-year treatment for schizophrenia. 2015. Available at: http://www.jnj.com/news/all/US-FDA-Approves-INVEGA-TRINZA-First-and-Only-Four-Times-A-Year-Treatment-for-Schizophrenia. Accessed August 9, 2015.
12. Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. JAMA Psychiatry 2015;72(8):830–9.
13. FDA new release. Rexulti was approved by the U.S Food and drug administration as a mono-therapy for adult schizophrenia treatment, in addition as an adjunctive to an antidepressant medication to treat adults with major depressive disorder (MDD) on July 10th 2015. 2015.
14. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther 2014;350(3):589–604.

15. Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr Res 2015;164(1–3):127–35.
16. Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2015;172(9):870–80.
17. Altinbas K, Guloksuz S, Oral ET. Clinical potential of cariprazine in the treatment of acute mania. Psychiatr Danub 2013;25(3):207–13.
18. Gyertyan I, Kiss B, Sághy K, et al. Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. Neurochem Int 2011;59(6):925–35.
19. Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: results from an international, phase III clinical trial. J Clin Psychopharmacol 2015;35(4):367–73.
20. Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. Schizophr Res 2014;152(2–3):450–7.
21. FDA new release. FDA approves new injectable drug to treat schizophrenia. 2015. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465801.htm. Accessed October 7, 2015.
22. Turncliff R, Hard M, Du Y, et al. Relative bioavailability and safety of aripiprazole lauroxil, a novel once-monthly, long-acting injectable atypical antipsychotic, following deltoid and gluteal administration in adult subjects with schizophrenia. Schizophr Res 2014;159(2–3):404–10.
23. Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. J Clin Psychiatry 2015;76(8):1085–90.
24. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III–the final common pathway. Schizophr Bull 2009;35(3):549–62.
25. Laruelle M, Risinger R, Nasrallah HA, et al. Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol Psychiatry 1999;46(1):56–72.
26. Marder SR. The NIMH-MATRICS project for developing cognition-enhancing agents for schizophrenia. Dialogues Clin Neurosci 2006;8(1):109–13.
27. 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):108–21.
28. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991;148(10):1301–8.
29. Lahti AC, Holcomb HH, Medoff DR, et al. Ketamine activates psychosis and alters limbic blood flow in schizophrenia. Neuroreport 1995;6(6):869–72.
30. Gibert-Rahola J, Villena-Rodriguez A. Glutamatergic drugs for schizophrenia treatment. Actas Esp Psiquiatr 2014;42(5):234–41.
31. Citrome L. Unmet needs in the treatment of schizophrenia: new targets to help different symptom domains. J Clin Psychiatry 2014;75(Suppl 1):21–6.
32. Patil ST, Zhang L, Martenyi F, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized phase 2 clinical trial. Nat Med 2007;13(9):1102–7.
33. Downing AM, Kinon BJ, Millen BA, et al. A double-blind, placebo-controlled comparator study of LY2140023 monohydrate in patients with schizophrenia. BMC Psychiatry 2014;14:351.

34. Dunlop J, Brandon NJ. Schizophrenia drug discovery and development in an evolving era: are new drug targets fulfilling expectations? J Psychopharmacol 2015;29(2):230–8.
35. Kinon BJ, Millen BA, Zhang L, et al. Exploratory analysis for a targeted patient population responsive to the metabotropic glutamate 2/3 receptor agonist pomaglumetad methionil in schizophrenia. Biol Psychiatry 2015;78(11):754–62.
36. Lavreysen H, Ahnaou A, Drinkenburg W, et al. Pharmacological and pharmacokinetic properties of JNJ-40411813, a positive allosteric modulator of the mGlu2 receptor. Pharmacol Res Perspect 2015;3(1):e00096.
37. Hopkins CR. Is there a path forward for mGlu2 positive allosteric modulators for the treatment of schizophrenia? ACS Chem Neurosci 2013;4(2):211–3.
38. Cid JM, Tresadern G, Vega JA, et al. Discovery of 3-cyclopropylmethyl-7-(4-phenylpiperidin-1-yl)-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (JNJ-42153605): a positive allosteric modulator of the metabotropic glutamate 2 receptor. J Med Chem 2012;55(20):8770–89.
39. Galici R, Echemendia NG, Rodriguez AL, et al. A selective allosteric potentiator of metabotropic glutamate (mGlu) 2 receptors has effects similar to an orthosteric mGlu2/3 receptor agonist in mouse models predictive of antipsychotic activity. J Pharmacol Exp Ther 2005;315(3):1181–7.
40. Wezenberg E, Verkes RJ, Ruigt GS, et al. Acute effects of the ampakine farampator on memory and information processing in healthy elderly volunteers. Neuropsychopharmacology 2007;32(6):1272–83.
41. Marenco S, Egan MF, Goldberg TE, et al. Preliminary experience with an ampakine (CX516) as a single agent for the treatment of schizophrenia: a case series. Schizophr Res 2002;57(2–3):221–6.
42. Goff DC, Leahy L, Berman I, et al. A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia. J Clin Psychopharmacol 2001;21(5):484–7.
43. Goff DC, Lamberti JS, Leon AC, et al. A placebo-controlled add-on trial of the Ampakine, CX516, for cognitive deficits in schizophrenia. Neuropsychopharmacology 2008;33(3):465–72.
44. Evins AE, Amico E, Posever TA, et al. D-Cycloserine added to risperidone in patients with primary negative symptoms of schizophrenia. Schizophr Res 2002;56(1–2):19–23.
45. Goff DC, Tsai G, Manoach DS, et al. D-cycloserine added to clozapine for patients with schizophrenia. Am J Psychiatry 1996;153(12):1628–30.
46. Goff DC, Tsai G, Levitt J, et al. A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. Arch Gen Psychiatry 1999;56(1):21–7.
47. Duncan EJ, Szilagyi S, Schwartz MP, et al. Effects of D-cycloserine on negative symptoms in schizophrenia. Schizophr Res 2004;71(2–3):239–48.
48. Heresco-Levy U, Javitt DC, Ermilov M, et al. Double-blind, placebo-controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia. Br J Psychiatry 1996;169(5):610–7.
49. Heresco-Levy U, Javitt DC, Ermilov M, et al. Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Arch Gen Psychiatry 1999;56(1):29–36.
50. Heresco-Levy U, Ermilov M, Lichtenberg P, et al. High-dose glycine added to olanzapine and risperidone for the treatment of schizophrenia. Biol Psychiatry 2004;55(2):165–71.

51. Lane HY, Lin CH, Huang YJ, et al. A randomized, double-blind, placebo-controlled comparison study of sarcosine (N-methylglycine) and D-serine add-on treatment for schizophrenia. Int J Neuropsychopharmacol 2010;13(4):451–60.
52. Lane HY, Chang YC, Liu YC, et al. Sarcosine or D-serine add-on treatment for acute exacerbation of schizophrenia: a randomized, double-blind, placebo-controlled study. Arch Gen Psychiatry 2005;62(11):1196–204.
53. Tsai G, Lane HY, Yang P, et al. Glycine transporter I inhibitor, N-methylglycine (sarcosine), added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 2004;55(5):452–6.
54. Tsai GE, Lin PY. Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis. Curr Pharm Des 2010;16(5):522–37.
55. Singh SP, Singh V. Meta-analysis of the efficacy of adjunctive NMDA receptor modulators in chronic schizophrenia. CNS Drugs 2011;25(10):859–85.
56. Hashimoto K. Glycine transporter-1: a new potential therapeutic target for schizophrenia. Curr Pharm Des 2011;17(2):112–20.
57. Pinard E, Alanine A, Alberati D, et al. Selective GlyT1 inhibitors: discovery of [4-(3-fluoro-5-trifluoromethylpyridin-2-yl)piperazin-1-yl][5-methanesulfonyl-2-(( S)-2,2,2-trifluoro-1-methylethoxy)phenyl]methanone (RG1678), a promising novel medicine to treat schizophrenia. J Med Chem 2010;53(12):4603–14.
58. Umbricht D, Alberati D, Martin-Facklam M, et al. Effect of bitopertin, a glycine reuptake inhibitor, on negative symptoms of schizophrenia: a randomized, double-blind, proof-of-concept study. JAMA Psychiatry 2014;71(6):637–46.
59. Kingwell K. Schizophrenia drug gets negative results for negative symptoms. Nat Rev Drug Discov 2014;13(4):244–5.
60. Bugarski-Kirola D, Wang A, Abi-Saab D, et al. A phase II/III trial of bitopertin monotherapy compared with placebo in patients with an acute exacerbation of schizophrenia - results from the candlelyte study. Eur Neuropsychopharmacol 2014;24(7):1024–36.
61. Betts JF, Schweimer JV, Burnham KE, et al. D-amino acid oxidase is expressed in the ventral tegmental area and modulates cortical dopamine. Front Synaptic Neurosci 2014;6:11.
62. Matsuura A, Fujita Y, Iyo M, et al. Effects of sodium benzoate on pre-pulse inhibition deficits and hyperlocomotion in mice after administration of phencyclidine. Acta Neuropsychiatr 2015;27(3):159–67.
63. Lane HY, Lin CH, Green MF, et al. Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. JAMA Psychiatry 2013;70(12):1267–75.
64. Siuciak JA. The role of phosphodiesterases in schizophrenia: therapeutic implications. CNS Drugs 2008;22(12):983–93.
65. Coskran TM, Morton D, Menniti FS, et al. Immunohistochemical localization of phosphodiesterase 10A in multiple mammalian species. J Histochem Cytochem 2006;54(11):1205–13.
66. Sakamoto K, Karelina K, Obrietan K. CREB: a multifaceted regulator of neuronal plasticity and protection. J Neurochem 2011;116(1):1–9.
67. Mantamadiotis T, Lemberger T, Bleckmann SC, et al. Disruption of CREB function in brain leads to neurodegeneration. Nat Genet 2002;31(1):47–54.
68. Kehler J. Phosphodiesterase 10A inhibitors: a 2009-2012 patent update. Expert Opin Ther Pat 2013;23(1):31–45.

69. Grauer SM, Pulito VL, Navarra RL, et al. Phosphodiesterase 10A inhibitor activity in preclinical models of the positive, cognitive, and negative symptoms of schizophrenia. J Pharmacol Exp Ther 2009;331(2):574–90.
70. DeMartinis N, Banerjee A, Kumar V, et al. Poster #212 results of a phase 2A proof-of-concept trial with a PDE10A inhibitor in the treatment of acute exacerbation of schizophrenia. Schizophr Res 2012;136(Suppl 1):S262.
71. ClinicalTrials.gov, N. A study to evaluate the PDE10 enzyme occupancy following a single dose of PF-02545920 In healthy male volunteers (PET). 2014.
72. Rodefer JS, Saland SK, Eckrich SJ. Selective phosphodiesterase inhibitors improve performance on the ED/ID cognitive task in rats. Neuropharmacology 2012;62(3):1182–90.
73. Goff DC, Cather C, Freudenreich O, et al. A placebo-controlled study of sildenafil effects on cognition in schizophrenia. Psychopharmacology (Berl) 2009; 202(1–3):411–7.
74. Akhondzadeh S, Ghayyoumi R, Rezaei F, et al. Sildenafil adjunctive therapy to risperidone in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled trial. Psychopharmacology (Berl) 2011;213(4):809–15.
75. Deal watch: intra-cellular therapies and Takeda to develop PDE1 inhibitors for schizophrenia. Nat Rev Drug Discov 2011;10(5):329.
76. Dani JA, Bertrand D. Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. Annu Rev Pharmacol Toxicol 2007; 47:699–729.
77. Freedman R, Adler LE, Gerhardt GA, et al. Neurobiological studies of sensory gating in schizophrenia. Schizophr Bull 1987;13(4):669–78.
78. Judd LL, McAdams L, Budnick B, et al. Sensory gating deficits in schizophrenia: new results. Am J Psychiatry 1992;149(4):488–93.
79. Clementz BA, Geyer MA, Braff DL. P50 suppression among schizophrenia and normal comparison subjects: a methodological analysis. Biol Psychiatry 1997; 41(10):1035–44.
80. Siegel C, Waldo M, Mizner G, et al. Deficits in sensory gating in schizophrenic patients and their relatives. Evidence obtained with auditory evoked responses. Arch Gen Psychiatry 1984;41(6):607–12.
81. Waldo MC, Adler LE, Freedman R. Defects in auditory sensory gating and their apparent compensation in relatives of schizophrenics. Schizophr Res 1988;1(1): 19–24.
82. Potter D, Summerfelt A, Gold J, et al. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. Schizophr Bull 2006;32(4): 692–700.
83. Patterson JV, Hetrick WP, Boutros NN, et al. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. Psychiatry Res 2008;158(2): 226–47.
84. Olincy A, Harris JG, Johnson LL, et al. Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. Arch Gen Psychiatry 2006;63(6):630–8.
85. Freedman R, Olincy A, Buchanan RW, et al. Initial phase 2 trial of a nicotinic agonist in schizophrenia. Am J Psychiatry 2008;165(8):1040–7.
86. ClinicalTrials.gov. Nicotinic receptors and schizophrenia. 2015.
87. Hashimoto K. Targeting of alpha7 nicotinic acetylcholine receptors in the treatment of schizophrenia and the use of auditory sensory gating as a translational biomarker. Curr Pharm Des 2015;21(26):3797–806.

88. Lieberman JA, Dunbar G, Segreti AC, et al. A randomized exploratory trial of an alpha-7 nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. Neuropsychopharmacology 2013;38(6):968–75.
89. Walling D, Marder SR, Kane J, et al. Phase 2 trial of an alpha-7 nicotinic receptor agonist (tc-5619) in negative and cognitive symptoms of schizophrenia. Schizophr Bull 2016;42(2):335–43.
90. ClinicalTrials.gov. NCT00435370. Effectiveness of tropisetron plus risperidone for improving cognitive and perceptual disturbances in schizophrenia. 2014.
91. Macor JE, Gurley D, Lanthorn T, et al. The 5-HT3 antagonist tropisetron (ICS 205-930) is a potent and selective alpha7 nicotinic receptor partial agonist. Bioorg Med Chem Lett 2001;11(3):319–21.
92. Shiina A, Shirayama Y, Niitsu T, et al. A randomised, double-blind, placebo-controlled trial of tropisetron in patients with schizophrenia. Ann Gen Psychiatry 2010;9:27.
93. Zhang XY, Liu L, Liu S, et al. Short-term tropisetron treatment and cognitive and P50 auditory gating deficits in schizophrenia. Am J Psychiatry 2012;169(9):974–81.
94. Noroozian M, Ghasemi S, Hosseini SM, et al. A placebo-controlled study of tropisetron added to risperidone for the treatment of negative symptoms in chronic and stable schizophrenia. Psychopharmacology (Berl) 2013;228(4):595–602.
95. Kishi T, Mukai T, Matsuda Y, et al. Selective serotonin 3 receptor antagonist treatment for schizophrenia: meta-analysis and systematic review. Neuromolecular Med 2014;16(1):61–9.
96. Prickaerts J, van Goethem NP, Chesworth R, et al. EVP-6124, a novel and selective alpha7 nicotinic acetylcholine receptor partial agonist, improves memory performance by potentiating the acetylcholine response of alpha7 nicotinic acetylcholine receptors. Neuropharmacology 2012;62(2):1099–110.
97. Preskorn SH, Gawryl M, Dgetluck N, et al. Normalizing effects of EVP-6124, an alpha-7 nicotinic partial agonist, on event-related potentials and cognition: a proof of concept, randomized trial in patients with schizophrenia. J Psychiatr Pract 2014;20(1):12–24.
98. Barbier AJ, Hilhorst M, van Vliet A, et al. Pharmacodynamics, pharmacokinetics, safety, and tolerability of encenicline, a selective alpha7 nicotinic receptor partial agonist, in single ascending-dose and bioavailability studies. Clin Ther 2015;37(2):311–24.
99. ClinicalTrials.gov. NCT01678755. A phase 2 study to evaluate ABT-126 for the treatment of cognitive deficits in schizophrenia. 2015.
100. ClinicalTrials.gov. NCT01655680. A study to evaluate ABT-126 for the treatment of cognitive deficits in schizophrenia. 2015.
101. ClinicalTrials.gov. NCT01095562. Safety and efficacy study for cognitive deficits in adult subjects with schizophrenia. 2013.
102. ClinicalTrials.gov. NCT01834638. Long-term safety and efficacy of ABT-126 in subjects with schizophrenia: an extension study for subjects completing study M10–855 (NCT01655680). 2014.
103. Feuerbach D, Pezous N, Weiss M, et al. AQW051, a novel, potent and selective alpha7 nicotinic ACh receptor partial agonist: pharmacological characterization and phase I evaluation. Br J Pharmacol 2015;172(5):1292–304.
104. ClinicalTrials.gov. NCT01730768. A study to evaluate the effects of once daily doses of AQW051 on cognition, in stable schizophrenia patients. 2015.
105. NCT01163227. Effect of AQW051 on cognitive function in patients with chronic stable schizophrenia. 2013.

106. Winterer G, Gallinat J, Brinkmeyer J, et al. Allosteric alpha-7 nicotinic receptor modulation and P50 sensory gating in schizophrenia: a proof-of-mechanism study. Neuropharmacology 2013;64:197–204.
107. NCT01851603. Phase I study to evaluate the safety and pharmacokinetics of oral doses of anvylic-3288 in healthy subjects (AVL3288). 2015.
108. Tenjin T, Miyamoto S, Ninomiya Y, et al. Profile of blonanserin for the treatment of schizophrenia. Neuropsychiatr Dis Treat 2013;9:587–94.
109. Hori H, Yamada K, Kamada D, et al. Effect of blonanserin on cognitive and social function in acute phase Japanese schizophrenia compared with risperidone. Neuropsychiatr Dis Treat 2014;10:527–33.
110. Kato TA, Hyodo F, Yamato M, et al. Redox and microglia in the pathophysiology of schizophrenia. Yakugaku Zasshi 2015;135(5):739–43 [in Japanese].
111. Mattei D, Djodari-Irani A, Hadar R, et al. Minocycline rescues decrease in neurogenesis, increase in microglia cytokines and deficits in sensorimotor gating in an animal model of schizophrenia. Brain Behav Immun 2014;38:175–84.
112. Zhu F, Liu Y, Zhao J, et al. Minocycline alleviates behavioral deficits and inhibits microglial activation induced by intrahippocampal administration of granulocyte-macrophage colony-stimulating factor in adult rats. Neuroscience 2014;266:275–81.
113. Miyaoka T, Yasukawa R, Yasuda H, et al. Minocycline as adjunctive therapy for schizophrenia: an open-label study. Clin Neuropharmacol 2008;31(5):287–92.
114. Chaudhry IB, Hallak J, Husain N, et al. Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. J Psychopharmacol 2012;26(9):1185–93.
115. Levkovitz Y, Mendlovich S, Riwkes S, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry 2010;71(2):138–49.
116. America's Biopharmaceutical Research Companies. Medicines in development for mental health. Washington DC: Pharmaceutical Research and Manufacturers of America; 2014.