ARTICLE

Pharmacological Advances in the Treatment of Schizophrenia

Javier Ballester, M.D.
Brian A. Frankel, M.D.

Schizophrenia is a devastating worldwide illness that affects approximately 1% of the global population. Despite decades of research, its pathophysiology still remains an enigma, and virtually all neurotransmitter systems have been implicated in the etiology of this disease. Since the discovery of chlorpromazine in 1950, more than 50 different drugs have been developed (1), revolutionizing the treatment of schizophrenia. So far, these drugs have proven to be effective in the treatment of positive symptoms, but unfortunately the efficacy on negative or cognitive symptoms is still minimal. The second-generation antipsychotics, introduced in the decade of 1990 (not taking into account clozapine, first introduced in 1971), promised to be effective in the treatment of negative symptoms while at the same time reducing the incidence of extrapyramidal symptoms. However they have shown to produce metabolic side effects (diabetes, hyperlipidemia), and large national-funded studies (2) have proven these drugs to be no more effective than typical or first-generation antipsychotics. This panorama has pushed researchers to look for different molecules intended to target negative or cognitive symptoms while at the same time having a more benign spectrum of side effects. The present review focuses on antipsychotic drugs currently in development (3) (Table 1).

DOPAMINE SYSTEM

Phosphodiesterase (PDE) 10A Inhibitors

The PDE enzyme specifically inactivates the intracellular second messengers cAMP and cGMP. Inhibition of PDE 10A results in potentiation of the D_1 activity and inhibition of the D_2 receptor (4). PDE 10A inhibitors are being evaluated as stand-alone drugs or as augmentation agents. Drugs targeting several members of the PDE family are already successfully introduced to the market, such as those targeting PDE3 (milrinone), PDE4 (roflumilast), or PDE5 (sildenafil). The preferential expression of PDE10A in the striatum has led efforts in investigating their role in diseases such as schizophrenia or Huntington's disease (5). Examples of current clinical trials include AMG579 (phase 2, Amgen) or OMS643762 (still recruiting patients at the time this article was accepted for publication).

D_2/D_3 Partial Agonist

Cariprazine is a dopamine D_3-preferring, D_3/D_2 receptor partial agonist. Its mechanism of action resembles the one displayed by aripiprazole, but cariprazine has more robust D_3 antagonist-partial agonist affinity (6). The D_3 receptor is an autoreceptor that appears to control the phasic, but not tonic, activity of dopamine, and it is mainly distributed in limbic areas, the ventral striatum, and the thalamus (1).

5-$HT_{1A/1B}$ Agonist

Eltoprazine is being investigated as a cognitive impairment augmentation therapy for cognitive symptoms of schizophrenia. A clinical trial is currently underway. It is also being evaluated as an antidyskinetic drug in patients treated with L-dopa and as a pro-attentional drug in attention deficit hyperactivity disorder.

L-DOPA

Based on the different affinities of dopamine receptors and on the allegedly cognitive enhancer properties of the DA_1 receptor, a clinical trial is being developed to investigate the potential effects of certain doses of L-dopa as an augmentation therapy for negative/cognitive deficits of schizophrenia (4). A meta-analysis published in 2004 has suggested that adding L-dopa might be beneficial for those patients already taking antipsychotic medication (7).

Stepholidine

Stepholidine acts as a D_2 antagonist, a D_1 agonist, and a $5HT_{1A}$ agonist and is being hypothesized as a drug effective in positive symptoms (through the D_2 receptor), as well as in cognitive symptoms (thorough the D_1 and $5HT_{1A}$ receptors) (8). There is currently an ongoing clinical trial being performed at the University of Toronto (4).

YKP1358

YKP1358 is a $D_2/D_3/5HT_{2A}$ antagonist that is currently undergoing phase 2 of clinical study (SK Bio-Pharmaceuticals). Published studies thus far have investigated the binding properties of this drug on D_2 receptors in the striatum.

GLUTAMATE SYSTEM

Bitopertin

Bitopertin is a selective inhibitor of the glycine transporter Gly-T-1 that acts by increasing the levels of glycine in the synaptic cleft and hence potentiating the *N*-methyl-D-aspartate (NMDA) receptor. A phase-2b multicenter study with more than 300 patients was reported in 2010 and showed that bitopertin improved negative symptoms in patients already taking antipsychotics (9).

TABLE 1. Antipsychotic Drugs Currently in Development

Drug	Mechanism	Status	Company	Clinical Trial ID
Dopamine system				
AMG579 OMS643762	PDE 10A inhibitor PDE 10A inhibitor	Phase 2 POC ongoing	Amgen	NCT01952132
Cariprazine	D_3/D_2 partial agonist	Phase 3	Richter Pharma AG	
DAAOI-1	DAAO catalizes D-serine and glicine	POC ongoing		NCT01390376
Eltoprazine	5-$HT_{1A/1B}$ agonist	POC ongoing		NCT01266174
L-DOPA	Dopamine stabilization	POC ongoing		NCT01636037
Stepholidine	D_2 antagonist/D_1 agonist/5HT_{1A} agonist	POC ongoing	University of Toronto	
YKP1358	D_2/D_3/5HT_{2A} antagonist	Phase 2	SK Bio-Pharmaceuticals	
Glutamate system				
Bitopertin	Inhibitor of Gly-T-1	Phase 3	Roche	NCT00616798
ADX71149	Allosteric modulator of mGluR2	Phase 2	Addex	
Memantine	NMDA antagonist	POC completed	Rio Grande	NCT00757978
Acetylcholine system				
EVP-6124 GTS-21	a7nAchR agonist a7nAchR agonist	Phase 3 Phase 3	Pfizer University of Florida/Veterans Administration	NCT01716975 NCT00100165
Xanomeline	M1/M4 agonist	POC Successful	Eli Lilly	
Hormonal systems				
Estradiol	Estrogen	Phase 2	University of Santander	NCT00206570
LY500307	Selective Estrogen Receptor Modulator	Phase 1b/2a Recruiting	University of Indiana/Eli Lilly	NCT01874756
Oxytocin	Oxytocin	POC Ongoing/Recruiting	NIMH	NCT01712646

D-Amino Acid Oxidase Inhibitors (DAAOI)

D-serine and glycine function as co-agonists of the NMDA receptor. DAAO catalyzes the oxidative deamination of these and other D-amino acids. Increasing the levels of these amino acids could trigger the NMDA receptor that might in turn improve negative and positive symptoms (10). There is currently an ongoing clinical trial using a DAAOI as a drug for treatment-resistant schizophrenia (5).

Positive Allosteric Modulator of Metabotropic Glutamate Receptors (mGluR2s)

The mGluRs are G-protein-coupled receptors that can be categorized into three different groups depending on their pre- or post-synaptic localization. Among all the different receptors, mGluR2/3 and mGluR5 are co-localized with NMDA receptors and have been suggested to play a role in the pathophysiology of schizophrenia. In 2012, Addex Therapeutics reported a phase-2a clinical study in which ADX71149 demonstrated effectiveness in patients with residual negative symptoms (11).

NMDA Antagonist

A recent meta-analysis of randomized placebo-controlled trials found that memantine (an NMDA receptor antagonist initially developed for the treatment of Alzheimer's disease) could be beneficial for the treatment of negative and cognitive effects of schizophrenia for those patients already receiving treat-

ment with antipsychotics. However, the authors concluded that these results need to be interpreted carefully because the number of studies in the literature is still low (12). Additionally, a recent comment published in the same journal questioned these results (13).

KEY POINTS/CLINICAL PEARLS

- Since the transformational discovery of chlorpromazine, changes in the pharmacological treatment of schizophrenia have been only incremental.
- Numerous drugs currently in development have targets outside the dopaminergic system.
- Numerous drugs currently in development are targeting negative and cognitive symptoms.

ACETYLCHOLINE SYSTEM

It has been suggested that one of the core cognitive deficits in patients with schizophrenia is an inability to inhibit the processing of irrelevant sensory stimuli, as measured by abnormalities in specific event-related EEG responses such as P50, N100, and the P300 potentials.

Alpha-7 nAchR Agonists

EVP-6124 is a selective CNS penetrant a7nAchR partial agonist that has shown positive and, in some cases, dose-dependent effects on P50, N100, mismatch negativity, and P300-evoked responses, as well as positive effects on domains of non-verbal learning, memory, and executive function, based on a recently published proof of concept study (14). There is currently a phase-3 study (currently recruiting participants) investigating the use of EVP-6124 as an adjunctive pro-cognitive treatment in patients with schizophrenia already receiving chronic, stable antipsychotic therapy (NCT01716975). GTS-21 (DMXB-A) is another agonist at this receptor that has reached phase-3 study (conducted at the University of Florida) and that is currently recruiting participants in another study from the Veterans Administration (NCT00100165) (15).

Muscarinic Agonists

Xanomeline is an M_1/M_4 muscarinic receptor agonist that has proven efficacy not only in improving cognitive deficits associated with Alzheimer's-type dementia but also in behavioral tests predictive of antipsychotic activity by virtue of a decrease in dopamine cell firing in the ventral tegmental area. A study published in 2008 showed that those subjects with schizophrenia treated with xanomeline improved in total Brief Psychiatric Rating Scale and total Positive and Negative Syndrome Scale (PANSS) scores and in measures of verbal learning and short-term memory function (16).

SEROTONIN SYSTEM

$5HT_3$ Antagonists

The $5HT_3$ antagonists (ondansetron, granisetron, tropisetron) are thought to modulate neurotransmitter release in mesolimbic and mesocortical dopamine neurons, but the exact mechanism of action is still unclear. A recent meta-analysis has shown that the use of $5HT_3$ antagonists might be beneficial as an add-on therapy for those patients with schizophrenia already stabilized on an antipsychotic (17). Specifically, patients showed a statistically significant improvement in PANSS general scores and on negative scores compared to placebo, with similar side effects reported (17).

HORMONES

Estrogens/Selective Estrogen Receptor Modulators (SERMS)

Numerous findings have pointed to a possible utility of estrogen in schizophrenia. On average, the age at onset is younger and the incidence is greater in males, and unlike males, females experience a second peak incidence after the age of 50. Additionally, premenopausal women experience less negative symptoms and better treatment response than men, and severe symptoms occur more often in the low-estrogen phase of the menstrual cycle. In a recent meta-analysis of four randomized-controlled trials examining estrogen augmentation of antipsychotics, it was found that estrogens were superior to placebo in reducing total symptom severity and positive symptoms (18). Given the long-term risks of estrogen usage, including endometrial hyperplasia and cancer in women and feminization in men, SERMs have been posited as possibly being a better option than estrogens. Evidence for the efficacy of SERMs, however, are not as impressive (19), and fewer studies have been conducted. Currently, there is a phase-1b/2a study being conducted at the University of Indiana in conjunction with Eli Lily investigating the use of LY500307, a selective estrogen beta agonist, in reducing negative and cognitive symptoms (NCT01874756).

Oxytocin

Oxytocin is a neuropeptide secreted by the posterior pituitary that has been well studied for its role in social attachment, behavior, and cognition. In three randomized-controlled trials of patients with schizophrenia, adjunctive intranasal oxytocin significantly reduced PANNS scores compared to placebo. One of these trials found improvement in social cognition, and another found improvement in neurocognition. All three trials, however, had small sample sizes (20). The National Institute of Mental Health is currently recruiting subjects for a study of oxytocin use in children with schizophrenia (NCT01712646).

Drs. Ballester and Frankel are both fourth-year residents in the Department of Psychiatry, Yale University, New Haven, Conn.

REFERENCES

1. George M, Amrutheshwar R, Rajkumar RP, et al: Newer antipsychotics and upcoming molecules for schizophrenia. Eur J Clin Pharmacol 2013; 69:1497–1509
2. Stroup TS, McEvoy JP, Swartz MS, et al: The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. Schizophr Bull 2003; 29:15–31
3. Geerts H: Drugs in Trials-Schizophrenia

Research Forum. http://www.schizophreniaforum.org/res/drc/drug_tables.asp (Accessed April 2014)

4. Mango D, Bonito-Oliva A, Ledonne A, et al: Phosphodiesterase 10A controls D1-mediated facilitation of GABA release from striato-nigral projections under normal and dopamine-depleted conditions. Neuropharmacology 2014; 76(pt A):127–136
5. Kehler J: Phosphodiesterase 10A inhibitors: a 2009–2012 patent update. Expert Opin Ther Pat 2013; 23:31–45
6. Citrome L: Cariprazine in schizophrenia: clinical efficacy, tolerability, and place in therapy. Adv Ther 2013; 30:114–126
7. Jaskiw GE, Popli A: A meta-analysis of the response to chronic L-dopa in patients with schizophrenia: therapeutic and heuristic implications. Psychopharmacology (Berl) 2004; 171:365–374
8. Guo Y, Zhang H, Chen X, et al: Evaluation of the antipsychotic effect of bi-acetylated l-stepholidine (l-SPD-A): a novel dopamine and serotonin receptor dual ligand. Schizophr Res 2009; 115:41–49
9. Chue P: Glycine reuptake inhibition as a new therapeutic approach in schizophrenia: focus on the glycine transporter 1 (GlyT1). Curr Pharm Des 2013; 19:1311–1320
10. Smith SM, Uslaner JM, Hutson PH: The therapeutic potential of D-amino acid oxidase (DAAO) inhibitors. Open Med Chem J 2010; 4:3–9
11. Hashimoto K, Malchow B, Falkai P, et al: Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. Eur Arch Psychiatry Clin Neurosci 2013; 263:367–377
12. Matsuda Y, Kishi T, Iwata N: Efficacy and safety of NMDA receptor antagonists augmentation therapy for schizophrenia: an updated meta-analysis of randomized placebo-controlled trials. J Psychiatr Res 2013; 47:2018–2020
13. Shim SS, Nadeem R: Are NMDA receptor antagonists beneficial in the treatment of schizophrenia? J Psychiatr Res 2014; 51:19–20
14. 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; 20:12–24
15. Olincy A, Freedman R: Nicotinic mechanisms in the treatment of psychotic disorders: a focus on the α7 nicotinic receptor. Handb Exp Pharmacol 2012; (213):211–232
16. Shekhar A, Potter WZ, Lightfoot J, et al: Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. Am J Psychiatry 2008; 165:1033–1039
17. Kishi T, Mukai T, Matsuda Y, et al: Selective serotonin 3 receptor antagonist treatment for schizophrenia: meta-analysis and systematic review. Neuromolecular Med 2014; 16:61–69
18. Begemann MJ, Dekker CF, van Luneburg M, et al: Estrogen augmentation in schizophrenia: a quantitative review of current evidence. Schizophr Res 2012; 141:179–184
19. Huerta-Ramos E, Iniesta R, Ochoa S, et al: Effects of raloxifene on cognition in postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. Eur Neuropsychopharmacol 2014; 24:223–231
20. Pedersen CA: Schizophrenia and alcohol dependence: diverse clinical effects of oxytocin and their evolutionary origin. Brain Res 2014; 1580:102–123