Update on New and Emerging Treatments for Schizophrenia

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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

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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]