**CME Background**
Articles are selected for credit designation based on an assessment of the educational needs of CME participants, with the purpose of providing readers with a curriculum of CME articles on a variety of topics throughout each volume. Activities are planned using a process that links identified needs with desired results.

To obtain credit, read the article, correctly answer the question in the Posttest, and complete the Evaluation. The Posttest and Evaluation are available at PSYCHIATRIST.COM (**Keyword: April**).

**CME Objectives**
After studying this article, you should be able to:

- Compare the mechanism of action of antipsychotic agents when choosing medications for individual patients
- Analyze the role of NMDA receptors in schizophrenia

**Accreditation Statement**
The CME Institute of Physicians Postgraduate Press, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

**Credit Designation**
The CME Institute of Physicians Postgraduate Press, Inc., designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

*Note:* The American Academy of Physician Assistants (AAPA) accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 1 hour of Category I credit for completing this program.

**Date of Original Release/Review**
This educational activity is eligible for *AMA PRA Category 1 Credit*™ through April 30, 2017. The latest review of this material was March 2014.

**Financial Disclosure**
All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past year, Alan J. Gelenberg, MD, Editor in Chief, has been a consultant for Allergan, Forest, and Zynx Health; has received grant/research support from Pfizer; and has been a stock shareholder of Healthcare Technology Systems. No member of the CME Institute staff reported any relevant personal financial relationships. **Faculty financial disclosure appears at the end of the article.**

This COMMENTARY section of The Journal of Clinical Psychiatry presents the highlights of the planning teleconference series "Making Connections Between Science and Symptoms in Schizophrenia," which was held in January and February 2014. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Genentech. The opinions expressed herein are those of the faculty and do not necessarily reflect the opinions of the CME provider and publisher or the commercial supporter.

*J Clin Psychiatry 2014;75(4):347–348*

***Online ahead of print:*** *March 7, 2014 (doi:10.4088/JCP.13078co8c).*


# Schizophrenia: Mechanism of Action of Current and Novel Treatments

*Christoph U. Correll, MD, and John M. Kane, MD*

Antipsychotics are effective for managing the positive symptoms of schizophrenia, but no medications are approved for treating the negative and cognitive symptoms that can persist, despite an adequate treatment response. This Commentary series explains the neuroscience behind schizophrenia in order to identify novel treatment targets that may address the wide range of symptoms in schizophrenia. This concluding section focuses on the mechanism of action of currently available antipsychotics and how targeting *N*-methyl-D-aspartate (NMDA) receptors may address currently less-treatable aspects of this condition.

## MECHANISM OF ACTION OF ANTIPSYCHOTICS

When prescribing any medication, clinicians should consider 3 aspects of pharmacology that affect the patient's response to the drug:

- *pharmacokinetics*—the activity that the body has on the drug
- *pharmacodynamics*—the activity that the drug has on the body
- the interaction between the drug and the individual patient's unique genetics, age, disease variables, and environment.[1]

Unfortunately, predicting individual pharmacokinetic and pharmacodynamic reactions to a certain drug remains difficult. However, knowledge of the pharmacology of antipsychotics can help clinicians anticipate their clinical effectiveness and optimize patient outcomes by balancing efficacy and side effects.

Each one of these 3 pharmacologic aspects can be broken down further to help explain the mechanism of action of antipsychotic medications. Pharmacokinetic parameters include absorption/elimination, concentration, and half life, among others. The amount of plasma concentration needed for drug efficacy varies from patient to patient. In addition, even though the same dosage might be given to 2 patients, the amount of drug absorbed and available at the neurotransmitter target might be different. Knowing the half life can help clinicians determine how many doses or days are needed to reach a steady state of medication concentration. Once the steady state is reached, clinicians can ascertain whether the patient has side effects or efficacy at the dose and take further action.

Pharmacodynamic considerations include:

- *affinity*—how well the drug binds to the receptor
- *relative binding affinity*—how well the drug binds to a secondary receptor relative to the primary target receptor
- *intrinsic activity*—what the medication does at the receptor.[1]

Intrinsic activity can be (partial) agonism (stimulation = increasing transmission above basal tone), inverse agonism (decreasing transmission below basal tone), or antagonism (blockade = preventing stimulation or reduction of transmission). All but one currently approved antipsychotics are $D_2$ receptor–antagonists. The only current exception is aripiprazole, which is a partial $D_2$ agonist (with 2 others, cariprazine and brexpiprazole, being evaluated by the US Food and Drug Administration [FDA] or in development). However, according to present knowledge, only 1 of the 6 pertinent dopamine pathways in the brain is implicated in psychosis. Dopamine blockade in the other pathways can cause a wide range of adverse effects, such as extrapyramidal side effects (EPS),

secondary negative symptoms, secondary cognitive symptoms, and hyperprolactinemia.[2,3] In fact, a high level of $D_2$ occupancy predicts EPS.[4] Unfortunately, a medication cannot target only 1 dopamine pathway, so other strategies must be used to balance $D_2$ blockade in the other 5 pathways.

One strategy to counter undesired $D_2$ blockade is to target other neurotransmitters. The typical, first-generation antipsychotics have a higher affinity for dopamine receptors than for any other type of receptor, as does aripiprazole, which has intrinsic $D_2$ partial agonism to counter excessive $D_2$ antagonism. Some atypical antipsychotics have a higher affinity for certain serotonergic and α-adrenergic receptors than dopamine receptors, and other atypicals also have higher affinity for muscarinic and histaminergic receptors.[1] These differences in binding affinity relative to $D_2$ blockade can help reduce adverse effects of pure dopamine antagonism, but also explain various side effect profiles related to the extradopaminergic activity.

Another strategy to avoid unwanted $D_2$ blockade–related side effects that may also address other schizophrenia symptoms relies on the glutamate hypothesis of the disorder and involves targeting NMDA receptors.

## NMDA RECEPTORS AS A NOVEL TREATMENT TARGET

Noncompetitive NMDA receptor antagonists, such as ketamine and phencyclidine (PCP), have been shown to induce schizophrenia-like psychosis as well as negative and cognitive symptoms.[5,6] Therefore, the glutamate hypothesis proposes that dysfunctional NMDA receptor–mediated neurotransmission in the glutamate pathway is at least one relevant aspect of the pathogenesis of schizophrenia.[7]

Glutamate is the most prominent neurotransmitter in the brain.[6] NMDA is an ionotropic glutamate receptor that plays a large role in memory formation, synaptic plasticity, and circuit formation and maturation during brain development. During the maturation process, NMDA receptors are particularly vulnerable to genetic and environmental risk factors (eg, altered glycine and D-serine levels, glutathione depletion, developmental neurotoxicity, metabolic variations), both of which can cause low NMDA functioning.[6] As a result, NMDA receptor hypofunction can lead to sensory deficits, generalized cognitive deficits, impaired learning and memory, thought disorder, negative symptoms, positive symptoms, gating deficits, executive dysfunction, and dopamine dysregulation, an established mechanism implicated in the symptoms of psychosis.[6] In addition to dopamine, NMDA also regulates the downstream release of other common neurotransmitters, including glutamate and γ-aminobutyric acid (GABA), which are thought to be involved in the pathophysiology of schizophrenia.[6] Because glutamate, glycine, and D-serine are required for NMDA receptors to properly function, disturbances in any of these modulatory systems could potentially lead to specific NMDA receptor–related impairments or NMDA-mediated neurotransmitter impairments seen in schizophrenia.

Thus, NMDA receptor hypofunction provides a potential explanation for the constellation of symptoms of schizophrenia, including positive, negative, and cognitive symptoms, as well as neuropsychological dysfunction. Targeting this neurotransmitter system with pharmacotherapy may help to mediate the downstream release of other neurotransmitters, such as glutamate, GABA, and dopamine, which in turn may moderate the symptoms of schizophrenia.

**Clinical Points**

- Antipsychotics cannot selectively affect the specific dopamine ($D_2$) pathways; therefore, novel treatments are needed that target other neurotransmitter systems that can counter undesired dopamine pathway blocking effects.
- *N*-methyl-D-aspartate (NMDA) hypofunction affects several neurotransmitter systems, such as glutamate, γ-aminobutyric acid (GABA), and dopamine, and may provide a potential therapeutic target to address the positive, negative, and cognitive symptoms of schizophrenia.

***Drug names:*** aripiprazole (Abilify), ketamine (Ketalar and others).
***Disclosure of off-label usage:*** Dr Kane has determined that, to the best of his knowledge, brexpiprazole, cariprazine, and ketamine are not approved by the FDA for the treatment of schizophrenia.
***Author affiliations:*** From the Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks; the Department of Psychiatry, Hofstra North Shore-Long Island Jewish School of Medicine, Hempstead; and Behavior Health Services, North Shore-Long Island Jewish Health System, New Hyde Park, New York (Dr Kane); and the Recognition and Prevention Program (RAP), The Zucker Hillside Hospital, Glen Oaks; the Department of Psychiatry and Molecular Medicine, Hofstra-North Shore-Long Island Jewish School of Medicine, Hempstead; and the Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, New York (Dr Correll).
***Financial disclosure:*** **Dr Kane** is a consultant for Amgen, Alkermes, Bristol-Myers Squibb, Azur, Gerson Lehman, Eli Lilly, Lundbeck, MedAvante, Merck, Novartis, Otsuka, Johnson & Johnson, Janssen, Pierre Fabre, Roche, Reviva, Shire, Sunovion, Targacept, Jazz, Intracellular Therapies, and Forest; is a member of the speakers/advisory boards for Otsuka, Janssen, Bristol-Myers Squibb, and Novartis; and is a shareholder of MedAvante. **Dr Correll** is a consultant for Alexza, Bristol-Myers Squibb, Eli Lilly, Genentech, Gerson Lehman, IntraCellular Therapies, Lundbeck, MedAvante, Pfizer, Otsuka, Roche, Takeda, and Teva; has received grant/research support from Bristol-Myers Squibb, Otsuka, Janssen, Novo Nordisk, NIMH, and Feinstein Institute for Medical Research; has received honoraria from Bristol-Myers Squibb, Cephalon, GlaxoSmithKline, and Janssen; and is a member of the speakers/advisory boards for Actelion, Alexza, Bristol-Myers Squibb, Genentech, IntraCellular Therapies, Lundbeck, MedAvante, Merck, Otsuka, Pfizer, Roche, and Sunovion.

### REFERENCES

1. Correll CU. *Eur Psychiatry.* 2010;25(suppl 2):S12–S21.
2. Inoue A, Nakata Y. *Jpn J Pharmacol.* 2001;86(4):376–380.
3. Sesack SR, Carr DB. *Physiol Behav.* 2002;77(4–5):513–517.
4. Kapur S, Zipursky R, Jones C, et al. *Am J Psychiatry.* 2000;157(4):514–520.
5. Krystal JH, Karper LP, Seibyl JP, et al. *Arch Gen Psychiatry.* 1994;51(3):199–214.
6. Kantrowitz JT, Javitt DC. *Brain Res Bull.* 2010;83(3–4):108–121.
7. Snyder MA, Gao WJ. *Front Cell Neurosci.* 2013;7:31.

## CME INSTITUTE™ POSTTEST

**To obtain credit, go to** PSYCHIATRIST.COM **(Keyword: April) to take this Posttest and complete the Evaluation.**

1. **In the brain, almost all currently available antipsychotic medications have which of the following actions on dopamine pathways in the brain:**
   a. Block only 1 of 6 pathways
   b. Block all 6 pathways
   c. Stimulate only 1 of 6 pathways
   d. Stimulate all 6 pathways