ABSTRACT

The pharmacologic management of schizophrenia has dramatically improved over the past 50 years. While the first-generation, or conventional, antipsychotic medications were found to be helpful in reducing the positive symptoms of the disorder, they had little effect on negative and cognitive symptoms. Additionally, the first-generation agents were associated with the troubling neurologic side effects of extrapyramidal symptoms (EPS) and tardive dyskinesia. The development of second-generation, or atypical antipsychotic drugs, greatly expanded pharmacologic treatment options. These agents were found to effectively treat both positive and negative symptoms of schizophrenia, with a lower incidence of EPS and tardive dyskinesia. However, many of the atypical agents are associated with their own types of distressing side effects, particularly metabolic and endocrine adverse effects.

While both conventional and atypical antipsychotic agents block dopamine D2 receptors, atypical agents also block 5-HT2A serotonergic receptors. This dual serotonin/dopamine antagonism is believed to bestow the efficacy and safety profiles observed with these compounds. The antipsychotic agent aripiprazole, newly approved by the US Food and Drug Administration, represents the most recent development in the treatment of schizophrenia. Aripiprazole is a dopamine partial agonist and has demonstrated efficacy in controlling positive, negative, and cognitive symptoms of schizophrenia.

When determining which antipsychotic therapy to employ, it is important to consider efficacy not only in positive symptoms but also in negative and cognitive symptoms. Other factors to consider include safety, tolerability, and quality-of-life issues. Healthcare providers must work collaboratively with patients to determine optimal therapy, monitor adverse effects, and increase rates of adherence to treatment.

Schizophrenia is a devastating mental illness that significantly impacts all aspects of daily functioning. While positive symptoms, such as delusions, hallucinations, and thought disorders, may be the most dramatic in presentation, other symptom domains, such as negative symptoms (eg, flat affect, social withdrawal, diminished speech) and cognitive symptoms (eg, diminished capacity for concentration, abstraction, memory, organization) also contribute to patients’ overall impairment. Advanced practice nurses must therefore consider all symptom domains when making treatment decisions and evaluating treatment response.
Prior to the advent of antipsychotic drugs in the 1950s, treatments for schizophrenia had limited efficacy, and many were potentially harmful to the patients. Such treatments included insulin shock, lobotomy, physical restraint, and electroconvulsive therapy. With insulin shock, patients received a large dose of insulin to induce hypoglycemic convulsions and coma. Lobotomy included cutting vital pathways in the brain that mediated consciousness and thought processes in order to control disturbed behavior. Physical restraint was commonly used, as were inhumane methods of administering electroconvulsive therapy. Ongoing developments in the understanding of the pathophysiology of schizophrenia have since led to improved treatments and the development of antipsychotic medication.

**FIRST-GENERATION (CONVENTIONAL OR TYPICAL) ANTIPSYCHOTIC AGENTS**

The 1950s marked the introduction of the first antipsychotic drug, chlorpromazine, which revolutionized schizophrenia treatment. Over the next 15 years, other conventional antipsychotic drugs were developed, such as thioridazine, fluphenazine, haloperidol, and loxapine. The conventional antipsychotic drugs are effective in reducing the positive symptoms of schizophrenia but have minimal impact on negative or cognitive symptoms. Side effects of conventional agents include extrapyramidal symptoms (EPS), tardive dyskinesia, sedation, weight gain, orthostatic hypotension, increased prolactin levels, tachycardia, dry mouth, constipation, and blurred vision.

From a scientific perspective, however, the conventional antipsychotic agents set the framework for a hypothesis regarding the pathophysiology of schizophrenia—the dopamine hypothesis. This theory purports that more dopamine is produced in the brain of patients with schizophrenia compared with the brain of individuals without the disorder, and this increased level of dopamine induces the symptoms associated with schizophrenia. Further research found that dopamine functions along 4 major pathways (Figure 1). The mesolimbic pathway connects the midbrain ventral tegmental area to the nucleus accumbens, the area of the brain responsible for the positive symptoms under conditions of dopamine hyperactivity. The mesocortical pathway, which connects to the frontal lobes, mediates both positive and negative symptoms of psychosis. This pathway connects the midbrain ventral tegmental area to the limbic system. The nigrostriatal pathway, which is responsible for movement and motor activity, connects the substantia nigra in the lower part of the brain with the striatum. The tuberoinfundibular pathway, which regulates neuroendocrine functioning, connects the hypothalamus to the anterior pituitary gland. All of these pathways utilize dopamine.

The conventional antipsychotic drugs block dopamine D₂ receptors in the mesolimbic pathway, thereby resolving positive symptoms; however, they also block dopamine receptors in the nigrostriatal pathway (the substantia nigra nucleus in the basal ganglia), which may cause movement disorders (EPS and tardive dyskinesia). The negative and cognitive symptoms of schizophrenia are related to the hypoactivity of dopaminergic pathways in the mesocortical system. Antagonism of the tuberoinfundibular pathway leads to an increase in prolactin levels, a common side effect of antipsychotic medication. Conventional antipsychotics have limited efficacy in reducing negative and cognitive symptoms.

**SECOND-GENERATION (ATYPICAL) ANTIPSYCHOTIC AGENTS**

In an effort to improve the side-effect profiles and efficacy of conventional antipsychotic drugs, second-
Advanced studies in nursing

In the 1980s, atypical antipsychotic agents were developed and introduced, beginning with clozapine. Like conventional agents, atypical antipsychotic agents block dopamine D2 receptors; however, the atypical agents bind less tightly to these receptors and operate via additional therapeutic mechanisms. Clozapine has significant antagonist effects at D1, D2, D4, and monoamine receptors. It increases the synaptic release of acetylcholine, which is thought to enhance its therapeutic effect. Additionally, this agent has proven effective in patients who were previously nonresponsive to pharmacologic treatment. An interesting and unexpected effect of clozapine is that it appears to decrease cigarette smoking in patients who respond to treatment. It has been hypothesized that patients with schizophrenia who smoke heavily are attempting self-medication, as nicotine briefly improves several aspects of brain function. In this sense, clozapine's action on acetylcholine may mimic the cholinergic effect of nicotine.

In regard to safety, clozapine has a dramatically lower incidence of EPS and tardive dyskinesia than conventional antipsychotic medications as well as a virtual absence of prolactin elevation. However, clozapine is associated with the development of agranulocytosis in some patients, resulting in a fatality rate of 0.013%. Because of this potentially fatal side effect, the US Food and Drug Administration (FDA) imposed a black-box warning regarding this blood dyscrasia and requires mandatory monitoring of leukocyte counts weekly throughout treatment and for at least 4 weeks after therapy is discontinued. Other warnings include risks of significant orthostatic hypotension and respiratory arrest, moderate-to-severe weight gain, seizures, and myocarditis. Despite these adverse events, clozapine possesses substantially enhanced therapeutic effects that justify its use.

After the introduction of clozapine, several additional atypical antipsychotic agents followed, including risperidone (1994), olanzapine (1996), quetiapine (1997), and ziprasidone (2001). In addition to blocking dopamine D2 receptors, the atypical agents also block 5-HT2A serotonergic receptors. As a group, the atypical agents demonstrate efficacy in both positive and negative symptoms and may also enhance cognition. A meta-analysis comparing olanzapine, quetiapine, risperidone, and sertindole with conventional antipsychotic drugs and placebo found olanzapine and risperidone were slightly more effective than haloperidol, whereas quetiapine and sertindole were equal in efficacy to haloperidol (measured in Brief Psychiatric Rating Scale [BPRS] scores). Ziprasidone has demonstrated efficacy equal to haloperidol in 2 studies, both using the BPRS measure.

**Side Effects**

Compared with conventional agents, atypical antipsychotic drugs have a lower incidence of EPS and tardive dyskinesia and fewer anticholinergic effects. Most do not exert an effect on serum prolactin levels. Atypical agents, however, are associated with other adverse effects, such as weight gain, diabetes, and QTc prolongation.

Other side effects associated with atypical antipsychotic drugs include increased lipid levels (specifically triglycerides) and disturbances in glucose metabolism. Reports indicate that the risk of diabetes might be twice as high among some of the atypical agents compared with conventional antipsychotic medications.

**New-Generation Antipsychotic Agents: Dopamine Partial Agonists**

Despite the advances with the atypical antipsychotic drugs, there is still an unmet need for well-tolerated pharmacologic agents that demonstrate efficacy in all symptom domains. Dopamine partial agonists may accomplish this challenge. The optimal management of dopaminergic dysregulation associated with psychosis would decrease dopaminergic activity in the mesolimbic pathway, increase dopaminergic activity in the mesocortical pathway, and show little or no effect on the nigrostriatal or tuberoinfundibular pathways.

**Aripiprazole**

Aripiprazole, the first agent of the newest generation of antipsychotic drugs, has a unique mechanism of action identified as dopamine partial agonism. It is hypothesized that dopamine partial agonists have high affinity for the D2 receptor but reduced intrinsic activity. The dopamine partial agonists appear to have higher affinity for the presynaptic autoreceptor compared with the postsynaptic receptor; hence, they reduce dopamine synthesis and are released through an agonist action at the dopamine autoreceptor. Also, such agents have lower intrinsic activity at the postsynaptic receptor than its natural ligand dopamine, resulting in a diminished dopaminergic signal at postsynaptic sites, effectively delivering a reduced message. Aripiprazole is a dopamine D2 receptor partial agonist with partial agonist activity at serotonin 5-HT1A receptors.
receptors and antagonist activity at 5-HT<sub>2A</sub> receptors. Because of its unique mechanism of action, Burris and colleagues have described aripiprazole as a dopamine-serotonin system stabilizer. Aripiprazole has shown efficacy in improving the positive, negative, and cognitive symptoms of schizophrenia with low potential for EPS, weight gain, sedation, hyperprolactinemia, or prolongation of QT<sub>c</sub> interval.

**Efficacy Data**

Five short-term placebo-controlled trials with aripiprazole were conducted. The FDA requirements stipulate that a medication must be statistically more effective than placebo in at least 2 placebo-controlled trials to indicate sufficient efficacy for approval. Kane and colleagues reported on a 4-week, double-blind, randomized study comparing aripiprazole 15 mg daily and 30 mg daily with placebo, with haloperidol 10 mg daily as an active control in 414 patients with schizophrenia or schizoaffective disorder. Aripiprazole (at both doses) and haloperidol produced statistically significant improvements from baseline in the Positive and Negative Syndrome Scale (PANSS) Total, PANSS Positive, PANSS Negative, PANSS-derived BPRS, Clinical Global Impressions (CGI)-Severity of Illness, and mean CGI-Improvement scores compared with placebo ($P \leq .05$). Both aripiprazole and haloperidol separated from placebo for PANSS Total scores at week 2 (Figure 2). Unlike haloperidol, however, aripiprazole was not associated with significant EPS or prolactin elevation at endpoint compared with placebo.

Similar findings were noted in a 4-week, double-blind, randomized study by Potkin and colleagues, which compared aripiprazole 20 mg daily and 30 mg daily with placebo, using risperidone 6 mg daily as an active control. Both active treatments were significantly better than placebo on all efficacy measures. Separation from placebo occurred at week 1 for PANSS Total and Positive scores with both aripiprazole and risperidone, and for PANSS Negative scores with aripiprazole. Aripiprazole demonstrated levels of EPS similar to placebo throughout the study. Notably, mean prolactin levels decreased with aripiprazole but significantly increased 5-fold with risperidone. Mean change in QT<sub>c</sub> interval did not differ significantly from placebo with either active treatment group. The aripiprazole and risperidone groups showed a similar low incidence of clinically significant weight gain.

**Cognitive Function**

As identified earlier, cognitive dysfunction also significantly impacts patients with schizophrenia. Although cognitive deficits are numerous in patients with schizophrenia, only recently have they been identified as targets for pharmacotherapy. Cognitive symptoms were previously thought to be associated with, or a consequence of, positive symptoms, but current research findings indicate that cognitive symptoms are independent of positive symptoms.

Cognitive dysfunction in schizophrenia can be divided into severe, moderate, and mild impairment, based on the mean or average performance of normal individuals similar in age and educational attainment. Areas of severe cognitive impairments (2 to 3 standard deviations [SD] below the mean) include the following: serial learning, executive functioning, vigilance, motor speed, and verbal fluency. Areas of moderate cognitive impairments (1 to 2 SD below the mean) include distractibility, delayed recall, visuomotor skills, immediate memory span, and working memory. Areas of mild impairments (0.5 to 1 SD below the mean) include perceptual skills, delayed recognition memory, con-
frontation naming, and verbal and full-scale intelligence quotient scores. It is important to note that the cognitive abilities of word recognition, reading, and long-term factual memory are typically unaffected and intact.

**GENERAL COGNITIVE EFFECTS OF CONVENTIONAL VERSUS ATYPICAL ANTIPSYCHOTIC AGENTS**

**CONVENTIONAL ANTIPSYCHOTIC AGENTS**

Conventional antipsychotic agents demonstrate little efficacy in remediating cognitive dysfunction in schizophrenia. Patients taking conventional agents often experience an initial worsening of attention span, but attention span might improve slightly after several weeks of treatment. Generally, treatment with conventional antipsychotic drugs may lead to a worsening of motor functions. Other cognitive functions may either remain stable or deteriorate with conventional antipsychotic treatment, with an absence of “practice effects” (the ability to learn by repeated exposure).15-18 The little observed improvement or worsening of cognitive deficits with conventional antipsychotic treatment in combination with the high prevalence of unpleasant side effects contributes to nonadherence and symptom exacerbations.14

**ATYPICAL ANTIPSYCHOTIC AGENTS AND PARTIAL DOPAMINE AGONISTS**

Atypical antipsychotic agents have been shown to have a more positive effect on the cognitive deficits in schizophrenia compared with their conventional counterparts. Studies of atypical agents have demonstrated enhancement over conventional antipsychotic drugs in at least one cognitive domain.19,20 The various atypical agents appear to have differential effects on certain aspects of cognitive functioning (eg, executive functioning, working memory, vigilance). Studies comparing atypical antipsychotic drugs have yielded further information regarding the specific benefits associated with each agent. For example, Cornblatt and colleagues compared aripiprazole 30 mg daily with olanzapine 10 mg and 15 mg daily in a 26-week open-label study in patients with schizophrenia or schizoaffective disorder (n = 255).21 Patients were taking a stable dose of an antipsychotic agent for at least 1 month prior to enrollment and had not been hospitalized for at least 2 months. Although there was no statistical difference between the aripiprazole and olanzapine groups in symptoms, as evidenced by PANSS scores, there were observed differences in cognition. By week 8, statistically significant improvements in secondary verbal memory were observed in the patients taking aripiprazole. This significant separation was maintained until study end. Secondary verbal memory is the ability to acquire, store, and retrieve verbal information for more than a few minutes; it is therefore important for activities of daily living, sustaining employment, and overall functioning.

**MAINTENANCE THERAPY**

**CONVENTIONAL AND ATYPICAL ANTIPSYCHOTIC AGENTS**

Clinical data regarding the efficacy of long-term treatment with conventional antipsychotic drugs on relapse have been minimal. In the 1970s, there was great concern about the development of tardive dyskinesia associated with antipsychotic medications. An active debate emerged as to whether the risk for the development of tardive dyskinesia outweighed the benefits of antipsychotic treatment. After analyzing data from 3 large trials, the American Psychiatric Association Task Force on Tardive Dyskinesia concluded that the benefits of preventing relapse with conventional antipsychotic drugs outweighed the associated risk of developing tardive dyskinesia.22

Since that time, several antipsychotic agents have been approved for long-term maintenance treatment of schizophrenia. To receive FDA approval for a “maintenance” indication in schizophrenia, antipsychotic agents must be proven effective for 6 months to 1 year or longer. To date, olanzapine, risperidone, ziprasidone, and aripiprazole are approved for this indication.

**PARTIAL DOPAMINE AGONISTS**

Aripiprazole received an indication for maintaining stability in patients with schizophrenia based on a study by Pigott and colleagues, in which 310 stable patients with schizophrenia were enrolled in a randomized double-blind study to receive either 15 mg daily of aripiprazole or placebo for 6 months.23 At 26 weeks, the time to relapse was significantly longer for the patients taking aripiprazole compared with placebo (P < .001). Kasper and colleagues examined the effects of aripiprazole over a 52-week period among 1294 acutely ill patients.24 The patients were randomized to either aripiprazole 30 mg daily or haloperidol 10 mg daily. The patients taking aripiprazole were less likely to discontinue medication compared with those
taking haloperidol. At 6 months, changes in PANSS Total and PANSS Positive scores were comparable between the 2 groups; however, there was a statistically significant ($P < .05$) improvement in PANSS Negative scores with aripiprazole compared with haloperidol (Figure 3).24 Aripiprazole was also more effective than haloperidol in reducing depressive symptoms, as shown by a significantly greater improvement from baseline in Montgomery-Asberg Depression Rating Scale scores ($P < .05$). Response rates (defined as at least a 30% improvement in PANSS Total for at least 4 weeks) were significantly higher in the aripiprazole group ($P = .003$).

**Conclusions**

Antipsychotic treatment has changed dramatically over the past 50 years. From their start as pure dopamine D$_2$ antagonists, to serotonin/dopamine antagonists, and now to partial dopamine agonists, medications to treat psychosis have changed in their mechanism of action as well as expected benefits. Antipsychotic medications are now assessed for their effects on positive symptoms, negative symptoms, and cognitive symptoms. They are also evaluated for their overall safety and tolerability in addition to their effects on the individual’s quality of life. If a change to the newer antipsychotic medications is indicated, nurses must work collaboratively with patients when a change in medication is being considered. Education regarding the drug’s mechanisms of action, potential benefits, and possible side effects will enhance the likelihood that a medication change is understood and accepted. As the scope of our knowledge regarding the pathophysiology of schizophrenia improves, so do our pharmacologic treatment options. There is now a wide array of antipsychotic medications available to advanced practice nurses to help individuals with psychotic illnesses.

**References**


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