Aripiprazole has demonstrated efficacy in schizophrenia, with fewer and less-severe side effects than older antipsychotics. Here are evidence-based insights on using this new agent in clinical practice.

A typical antipsychotics have enhanced outcomes in schizophrenia while helping patients avert the troublesome motor effects associated with older agents. Some side effects, such as weight gain and prolactin elevation, have remained a concern, however.

Aripiprazole, a novel antipsychotic recently FDA-approved for treating schizophrenia, exhibited efficacy and tolerability in preclinical and clinical trials.

How aripiprazole works
Aripiprazole’s mechanism of action is important to our understanding of the dopamine hypothesis of antipsychotic effect.1

The dopamine hypothesis remains the predominant explanation of how antipsychotics work.2 However, the evolution of antipsychotic therapy has led to further refinement of the dopamine hypothesis, including selective dopamine (D4) antagonism, rapid dissociation from dopamine receptors, dopamine-serotonin receptor system interactions, dopamine-GABA system interactions, and now (with aripiprazole) partial agonist effects at dopamine (and selective serotonin) receptors.1,2
Aripiprazole has demonstrated efficacy in clinical studies of patients with schizophrenia and schizoaffective disorder.1,2 Table 1 describes the agent’s receptor-binding profile.

Unlike other antipsychotics, which appear to act through dopamine receptor antagonism, aripiprazole is a potent partial agonist at both the dopamine (D2) and serotonin (5HT1A) receptors.1,2 Table 1 describes the agent’s receptor-binding profile.

The agent offers 78% bioavailability. It is metabolized through the hepatic microenzyme system, specifically the cytochrome P450 enzymes 2D6 and 3A4. Use of nicotine does not alter the agent’s plasma levels. Its active moiety is aripiprazole with minor contributions from the derivative dehydro-aripiprazole.

Aripiprazole therapy can be started at 10 or 15 mg/d; the starting dosage—15 mg/d in most cases—may also suffice as maintenance therapy for many patients. If the patient does not respond, it is prudent to wait several weeks before increasing the dosage beyond 15 mg/d.

The FDA-approved maximum dosage for aripiprazole is 30 mg/d. However, information from clinical trials indicates that increasing the dosage from 15 to 30 mg/d does not enhance the antipsychotic’s efficacy.3,4 Because of its absorption properties, the agent can be taken with or without food.

Aripiprazole has a relatively long half-life (75 hours), so it can be administered once daily. This provides an advantage when switching treatments. Some information suggests that patients may be switched directly to aripiprazole,5 although cross-titration is recommended.3

Although data in clinical populations are insufficient, studies in normal volunteers suggest that aripiprazole can be given at regular dosages to older patients and to those with renal or hepatic impairment.3

Table 2 highlights potential drug-drug interactions with agents that can influence the hepatic microenzyme system.

**Efficacy**

Aripiprazole has demonstrated efficacy in clinical studies of patients with schizophrenia and schizoaffective disorder.1,2

- In a placebo-controlled, 4-week trial, patients who received aripiprazole, 15 to 30 mg/d, or haloperidol, 10 mg/d, reported similar improvements in positive and negative symptoms, psychopathology, and overall function.6
- Aripiprazole and olanzapine demonstrated comparable efficacy in a 28-week study. However, patients in the aripiprazole group showed greater improvement at 8 weeks and sustained improvement through 28 weeks in a measure of verbal memory.8
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Researchers have not yet compared aripiprazole with clozapine, quetiapine, or ziprasidone. Also, information on the dosing, efficacy, and tolerability of aripiprazole in patients with first-episode or treatment-refractory schizophrenia is limited. According to the manufacturers’ prescription information, aripiprazole’s long-term efficacy in schizophrenia treatment has not been established. Data on 1-year treatment with aripiprazole appear encouraging.1
Studies have associated aripiprazole use with some weight gain, but (marginally) less than risperidone, less than haloperidol, and substantially less than olanzapine. Direct comparisons with other atypicals are not yet available.

Aripiprazole’s effect on glucose metabolism has not been determined, but early information suggests a favorable profile with respect to metabolic indices. Aripiprazole does not appear to elevate prolactin or cause cardiac QTc prolongation. Sedation appears to be the most pronounced side effect; this effect also appears to increase with higher dosages.

As has happened with the other atypicals, the pattern of use for aripiprazole will unfold over time as clinicians gain experience with using this agent in distinct patient groups.

Related resources


**DRUG BRAND NAMES**

- Carbamazepine • Tegretol
- Clozapine • Clozaril
- Fluoxetine • Prozac
- Haloperidol • Haldol
- Ketoconazole • Nizoral
- Olanzapine • Zyprexa
- Paroxetine • Paxil
- Quetiapine • Seroquel
- Risperidone • Risperdal
- Ziprasidone • Geodon

**DISCLOSURE**

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Preliminary data suggest that aripiprazole may help treat nonpsychotic conditions, although which ones has yet to be determined. A 3-week, placebo-controlled study demonstrated that aripiprazole, 30 mg/d, helped ameliorate symptoms of mania.

**Tolerability**

Aripiprazole’s side-effect profile, revealed in preclinical and clinical trials, suggests that the drug could be well tolerated among a broad range of patients.

In the 4-week, placebo-controlled comparison with haloperidol, rates of extrapyramidal symptoms (EPS) among aripiprazole-treated patients were much lower than those in the haloperidol group and similar to those in the placebo group. There is no evidence that higher dosages of aripiprazole lead to increased EPS. It is also not known whether aripiprazole will cause EPS in children and in patients older than 65, who are more susceptible than other age groups to antipsychotic-induced motor side effects.

Aripiprazole is believed to be less likely than typical antipsychotics to induce tardive dyskinesia, but more long-term information is needed.

**References**