Current PSYCHIATRY

Out of the pipeline > **Aripiprazole**

What the researchers say

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.

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Table

ARIPIPRAZOLE: FAST FACTS

Drug brand name: Abilify

Class: Atypical antipsychotic

FDA-approved indication: Schizophrenia

Approval date: Nov. 15, 2002

Manufacturer:
Bristol-Myers Squibb Co. & Otsuka America Pharmaceutical

Dosing forms:
10 mg, 15 mg, 20 mg, and 30 mg tablets

Recommended dosage:
Start at 10 to 15 mg/d for all age groups. Maintenance dosage may be the same as initial dosage or may increase over time. Maximum recommended dosage is 30 mg/d. Cross-titration with prior treatment is recommended.

Atypical 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]

continued

Table 1

ARIPIPRAZOLE'S RECEPTOR-BINDING PROFILE

Receptor type	Effect
Dopamine D2	Partial agonism
Serotonin 5HT1A	Partial agonism
Serotonin 5HT2A	Antagonism
Alpha 1A	Minimal antagonism
Muscarinic	Minimal antagonism
Histaminergic	Minimal antagonism

Table 2

POTENTIAL DRUG-DRUG INTERACTIONS WITH ARIPIPRAZOLE

Drug	Effect on plasma concentration of aripiprazole
Quinidine	Increase
Ketoconazole	Increase
Carbamazepine	Decrease
Fluoxetine	Increase
Paroxetine	Increase

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 has a relatively long half-life, so it can be taken once daily

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.[3-8]

- 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]
- A placebo-controlled, 4-week trial of aripiprazole, 20 and 30 mg/d, compared with risperidone, 6 mg/d, revealed similar efficacy with respect to symptom improvement and overall functioning.[7]
- 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]

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.[3]

Related resources

- Jordan S, Koprivica V, Chen R, et al. The antipsychotic aripiprazole is a potent, partial agonist at the human 5HT(1A) receptor. *Eur J Pharmacol* 2002;50:873-83.
- Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2002;63:763-71.

DRUG BRAND NAMES

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

DISCLOSURE

Dr. Buckley receives grant support from, is a consultant to, and is a speaker for AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Co., Eli Lilly and Co., Janssen Pharmaceutica, and Novartis Pharmaceuticals Corp.

Dr. Sinha is a consultant to Bristol-Myers Squibb Co.

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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.[9]

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.[10]

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.[6] 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.[3]

Studies have associated aripiprazole use with some weight gain, but (marginally) less than risperidone,[7] less than haloperidol,[6] and substantially less than olanzapine.[8] 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.

References

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6. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2002;63:763-71.
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Bottom Line

Aripiprazole has demonstrated efficacy and tolerability in preclinical and clinical trials of patients with schizophrenia. More information is needed on its dosing profile, its use in nonpsychotic conditions, and its efficacy compared with other atypical antipsychotics.