Aripiprazole Use in Children and Adolescents
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On November 15, 2002, the newest of the atypical antipsychotics, aripiprazole, was approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia. It has subsequently been approved for use in the treatment of bipolar mania as well. This agent has been shown to be similar in efficacy to traditional antipsychotics as well as other atypical antipsychotics, but offers an improved adverse effect profile. There is growing interest in the use of aripiprazole in children with schizophrenia, schizoaffective disorder, and conduct disorders.

Mechanism of Action
Although the exact mechanism by which the atypical antipsychotics produce improvement in schizophrenia is unknown, they appear to work through interaction with both dopaminergic and serotonergic receptors within the central nervous system. Aripiprazole has a unique binding profile compared to the other atypical antipsychotics. It is a high-affinity partial agonist at both dopamine (D2) and serotonin (5-HT1A) receptors and acts as an antagonist at 5-HT2A receptors. Aripiprazole also exhibits affinity for D1, D4, 5-HT2C and 5-HT7, alpha1-adrenergic and histamine (H1) receptors.

Clinical Use
Several studies have demonstrated the efficacy of aripiprazole in the treatment of adults with schizophrenia and schizoaffective disorder. In 2002, Kane and colleagues conducted a 4-week randomized, double-blind, multicenter trial comparing aripiprazole (15 or 30 mg/day) to haloperidol (10 mg/day) or placebo in 414 adults. Both aripiprazole doses, as well as haloperidol, produced significantly greater improvements in Positive and Negative Syndrome Scale (PANSS) total, PANSS positive, PANSS-derived Brief Psychiatric Rating Scale score, and Clinical Global Impression (CGI) Severity and CGI-Improvement scores than placebo. Aripiprazole was better tolerated, with no significant extrapyramidal symptoms (EPS), prolactin elevation, weight gain, or QTc interval prolongation.

Potkin and colleagues found similar results when comparing aripiprazole to risperidone or placebo. In their 4-week multicenter trial, 404 patients were randomized to 20 or 30 mg/day aripiprazole, 6 mg/day risperidone, or placebo. Both doses of aripiprazole and risperidone produced significantly better responses than placebo on PANSS total and positive scores. PANSS negative scores were significantly better with aripiprazole. There was no significant difference in EPS rating scales or QTc intervals between aripiprazole and placebo. Additional studies of acute treatment, as well as assessments of maintenance therapy and treatment-resistant schizophrenia, have produced positive results.

Randomized trials have also been published which document the efficacy of aripiprazole in adults with acute mania associated with bipolar disorder. In 2003, Keck and colleagues published the results of a 3-week randomized, double-blind, placebo-controlled trial of aripiprazole in acute bipolar mania. A total of 262 patients were randomized to 30 mg/day aripiprazole (reduced to 15 mg/day if needed) or placebo. Aripiprazole produced significantly better improvement in Young Mania Rating Scale scores (-8.2 compared to -3.4 for placebo) and a higher response rate (40% versus 19%). Discontinuation rates and body weight were not different between groups. There were no adverse effects on serum prolactin or QTc intervals.

Aripiprazole has also been used in several other settings, including psychosis-associated with Alzheimer’s disease and treatment-resistant mood or anxiety disorders. Last year, Staller published a case report of aripiprazole in a 34 year old adult with Asperger disorder who experienced improved sociability and self-awareness, as well as reduced rigidity, anxiety, and irritability, with aripiprazole at a dose of 10 mg/day.
At this time, there is only limited information in the medical literature regarding aripiprazole use in the pediatric population. In 2003, Findling and colleagues published an abstract of their 15-day open-label study of aripiprazole in twelve children (6 to 12 years of age) and 11 adolescents (13 to 17 years of age) with conduct disorder. Improvement was noted in both Rating of Aggression Against People and/or Property (RAAPP) scale scores and CGI-Severity scores for both age groups. There were no serious adverse effects reported and no subjects discontinued treatment. The authors concluded that aripiprazole appeared to be beneficial in reducing aggressive behavior in children and adolescents with conduct disorders. Patients from the study are currently participating in a 36-month extension phase.

**Pharmacokinetics**

Aripiprazole is well absorbed after oral administration, with a bioavailability of 87%. Peak serum concentrations occur within 3 to 5 hours following an oral dose. Administration with food delays the time to peak concentrations, but does not significantly affect the extent of absorption. At steady-state, the average volume of distribution of aripiprazole in adults is 4.9 L/kg. The drug is 99% protein bound.

Aripiprazole is metabolized through three primary pathways: dehydrogenation and hydroxylation through cytochrome P450 3A4 and 2D6 (CYP3A4 and CYP2D6), and N-dealkylation through CYP3A4. The major metabolite, dehydro-aripiprazole, is active. The average elimination half-lives of aripiprazole and dehydro-aripiprazole are 47-75 hours and 94 hours, respectively. The apparent systemic clearance is 3.5 to 4 L/hr. Approximately 8% of Caucasians are poor metabolizers, lacking the ability to fully metabolize CYP2D6 substrates. These patients have a 60% higher exposure to active drug from a given dose of aripiprazole than extensive metabolizers. The average half-life in poor metabolizers is 146 hours.

The authors of the pediatric study described earlier also conducted a pharmacokinetic study of aripiprazole. Their analysis revealed a similar pharmacokinetic profile to that seen in adults. At steady-state, apparent clearance was 2.52±1.05 L/hr in children and 3.79±1.41 L/hr in adolescents. The difference between the groups was eliminated when normalized for weight.

**Adverse Effects**

In the clinical trials of adults with schizophrenia or bipolar mania, aripiprazole was well tolerated. Discontinuation due to adverse effects was similar in subjects given aripiprazole as in those given placebo (7 to 11%). The most commonly reported adverse effects after aripiprazole use included headache (31%), agitation (25%), anxiety (20%), insomnia (20%), nausea (16%), dyspepsia (15%), somnolence (12%), akathisia (12%), lightheadedness (11%), vomiting (11%), constipation (11%), asthenia (8%), EPS (6%), accidental injury (5%), myalgia (4%), tremor (4%), rhinitis or pharyngitis (4%), increased salivation (3%), coughing (3%), blurred vision (35%), peripheral edema (2%), and hypertension or orthostatic hypotension (1-2%).

Although the adverse effect profile in children has not been well studied, the small scale study reported by Findling and Blumer revealed no severe adverse effects. The authors did report excessive nausea and sedation with their initial 0.2 mg/kg dosing scheme. The incidence of these adverse effects was reduced when the authors changed to a lower dose regimen (see dosing section). Excessive sedation was also reported by Davenport and colleagues in a 9 year old, 25 kg patient given a single 15 mg (0.6 mg/kg) dose of aripiprazole. The patient became lethargic 3.5 hours after her dose, eventually becoming unresponsive, and required hospitalization for 24 hours. The mother of the patient reported seizure-like activity prior to presentation at the emergency department, but there were no seizures during admission. The child recovered without sequelae.

Seizures have been reported in a small number of patients receiving aripiprazole. In an abstract presented earlier this month, Price and colleagues reported a grand mal (tonic-clonic) seizure in a 16 year old male receiving aripiprazole for conduct disorder. The seizure occurred approximately one hour after the second 10 mg oral dose. The drug was subsequently discontinued and no further seizure activity was noted. The effect of aripiprazole in patients with known seizure disorders has not been studied.

As with all antipsychotics, there is a concern for the development of neuroleptic malignant syndrome (NMS) in patients receiving aripiprazole. The incidence of NMS is much lower with the newer atypical agents compared to traditional antipsychotics. Although only two cases of NMS were reported in clinical trials with aripiprazole prior to FDA approval, there has been an additional case report, in a 17 year old male, published earlier this month. All patients should be monitored for hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability after starting therapy.
Extrapyramidal symptoms are another well-known adverse effect of traditional antipsychotics, but appear to be rare in patients receiving aripiprazole. The partial agonist activity of aripiprazole at D₂ receptors may produce a stabilizing effect, rather than a total blockade of dopamine in the nigrostriatal tracts. In most of the premarketing clinical trials conducted in adults, the rate of EPS, including akathesia, was not significantly different in treated patients compared to placebo.¹⁻⁴

The incidence of EPS in children treated with aripiprazole is not yet known. In 2003, Lindsey and colleagues reported a case of EPS following aripiprazole use in a 16 year old girl with mental retardation and schizophrenia.¹⁶ The patient previously developed EPS with olanzapine and risperidone. She developed EPS within 24 hours of starting therapy with aripiprazole 10 mg/day. She exhibited stiffness of both arms and legs, with severe tremor, parkinsonian gait and cogwheel rigidity. On day 5, therapy was discontinued. Symptoms improved with diphenhydramine and benztropine. She was later treated with clozapine without adverse effects. The authors suggested several possible explanations for the EPS in this case, including the potential for an increased sensitivity to dopamine agonists in children. Another case of EPS with aripiprazole was recently reported in a 3 year old boy after an accidental ingestion.¹⁷

Some of the adverse effects commonly encountered with the use of other atypical antipsychotics, including weight-gain, hyperglycemia, and hyperprolactinemia appear to be less frequent with aripiprazole. In trials of adults with schizophrenia, patients receiving aripiprazole had a higher weight gain compared to those given placebo (+0.7 kg versus -0.05 kg). The percentage of patients who gained ≥ 7 % of their body weight was also greater with aripiprazole (8% versus 3%). This degree of weight-gain is relatively small compared to the other atypical antipsychotics. In a 26-week trial comparing aripiprazole and olanzapine in adults, subjects given aripiprazole had an average weight decrease of 1.37 kg, compared to an increase of 4.23 kg with olanzapine.¹⁻⁴

In the study by Potkin described earlier, aripiprazole produced no change in serum prolactin concentrations, compared to a 120% increase produced by haloperidol.⁶ Similar results have been shown in other trials. In a meta-analysis conducted by Marder and colleagues, aripiprazole produced no significant differences in serum prolactin, lipid, or glucose concentrations compared to placebo.¹² As with the lower incidence of EPS, the decreased potential for these other adverse effects may result from the partial agonist activity of aripiprazole at D₂ receptors. Patients should still be monitored for these reactions, however, particularly those with underlying diabetes or other endocrine disorders.¹⁰

In addition, all patients receiving antipsychotic agents, including aripiprazole, should be carefully evaluated for suicidal risk.⁵

**Drug Interactions**

When administered with inhibitors of CYP3A4 (such as ketoconazole and itraconazole) or CYP2D6 (such as quinidine, fluoxetine, and paroxetine), aripiprazole metabolism may be reduced, producing elevated serum concentrations. In order to avoid adverse effects, the dose of aripiprazole should be decreased by one-half in patients receiving interacting drugs. Concomitant use with CYP3A4 inducers such as carbamazepine may reduce aripiprazole serum concentrations by as much as 70%. The manufacturer recommends that the dose of aripiprazole in these patients be doubled; however, all dosage adjustments should be based on clinical response.¹,⁴ Administration of valproate with aripiprazole reduces maximum serum concentrations of aripiprazole by 25%, but no dosage adjustment is needed.²

In 2003, Preskorn described a case of a 13 year old with schizoaffective disorder who was receiving aripiprazole at a dose of 60 mg/day (twice the recommended maximum) with fluoxetine 60 mg/day. On admission, the patient had a blunted affect, was sluggish, had a diminished intensity of sensation, and was having hallucinations and delusions. The patient became more responsive after both drugs were discontinued. The author suggested that the interaction of these agents, in conjunction with the high doses used, produced the adverse effects observed and cautioned against this combination, especially in children.¹⁸

Because of its sedating properties, aripiprazole should be used with caution in patients receiving other central nervous system depressants. Concurrent administration of aripiprazole with other α₁-adrenergic antagonists may produce excessive antihypertensive effects.¹,⁴

**Dosing**

Aripiprazole (Abilify®; Bristol-Myers Squibb) is available in 5, 10, 15, 20, and 30 mg tablets. In adults, the recommended starting dose of aripiprazole for the treatment of schizophrenia is 10 to 15 mg given once daily. After two weeks,
the dose may be increased to as much as 30 mg/day as needed. In patients with bipolar disease, the usual dose is 30 mg given once daily. No dosage adjustment is needed in patients with hepatic or renal impairment.\(^1^4\)

Based on the results of the pharmacokinetic study by Blumer and colleagues, a weight-based dosing regimen has been proposed for pediatric patients: 1 mg for patients < 25 kg, 2 mg for patients between 25 and 50 kg, 5 mg for those between 50 to 70 kg, and 10 mg for patients greater than 70 kg.\(^9\) While larger clinical trials are needed to validate this dosing scheme, the conservative approach proposed by these authors appears appropriate.

**Summary**

Aripiprazole offers a new therapy for the management of patients with schizophrenia and bipolar mania. It may also have a role in the treatment of patients with Asperger syndrome, mood disorders, and conduct disorders. Preliminary reports have shown it to be useful in children and adolescents; however, several case reports suggest that careful monitoring for adverse effects is needed.

**References**


**Formulary Update**

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 12/3/04:

1. Polyethylene glycol otic cream (Kos-House Otic Cream Pac\(^\circ\)) was added to the Inpatient Formulary as an alternative to packing material.
2. Hyaluronidase (Amphadase\(^\circ\)) was added for the treatment of intravenous extravasations.
3. Ortho Tri-Cylen\(^\circ\) Lo and the Ortho-Evra\(^\circ\) patch were added to the Outpatient Formulary.
4. Class reviews of blood formation and coagulation agents, gastrointestinal agents, and eye, ear, nose, and throat agents were completed.
5. The quarterly report of the Adverse Drug Reaction Reporting Program was presented.

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