Current PSYCHIATRY

IM aripiprazole for acute agitation

Richard C. Josiassen, PhD, and Rita A. Shaughnessy, MD, PhD

In recent clinical trials, a new intramuscular (IM) form of the second-generation antipsychotic (SGA) aripiprazole has controlled agitation in adults with schizophrenia or bipolar mania without causing significant side effects (***Table 1***).[1-3]

Fast-acting injectable has shown efficacy 45 to 60 minutes after dosing in randomized, controlled studies

Table 1

IM aripiprazole: Fast facts

Brand name: Abilify
Class: Second-generation antipsychotic
Indication: Acute agitation associated with schizophrenia or type I bipolar disorder (mixed or manic episodes)
Manufacturer: Otsuka America Pharmaceutical (marketed in collaboration with Bristol-Myers Squibb)
Dosing forms: 1.3-mL vial of clear, aqueous solution containing 9.75 mg of active drug
Recommended dosage: 9.75 mg every 2 hours as needed; do not exceed 30 mg across 24 hours

Clinical implications

Rapid intervention is critical to protecting the patient and caregivers when violent and/or destructive behavior accompanies agitation. IM aripiprazole substantially reduced agitation within 45 to 60 minutes of dosing in randomized, double-blind, placebo-controlled studies.[1-3]

How it works

Whereas other SGAs have relatively little effect on D_2 (dopamine) receptors and relatively high 5-HT_{2A} (serotonin) receptor affinities, aripiprazole appears to work via partial D_2 receptor agonism. The medication:

- blocks D_2 receptors in brain regions where dopamine is overactive in schizophrenia, such as the mesolimbic pathway. This produces an antipsychotic effect.
- maintains or moderately boosts dopamine activity as needed in regions such as the nigrostriatal pathway. This reduces the risk of motor side effects and might improve negative and cognitive schizophrenia symptoms.

Aripiprazole is a partial 5-HT_{1A} receptor agonist and—like other SGAs—a 5-HT_{2A} receptor antagonist. These receptor subtypes have been implicated in antipsychotic action. In particular, partial 5-HT_{1A} receptor agonism is thought to help:

- reduce anxiety
- lessen depressive, negative, and cognitive symptoms
- decrease extrapyramidal symptom (EPS) liability.[4]

Aripiprazole also has moderate affinity for histaminic and alpha-adrenergic receptors and no appreciable effect on cholinergic muscarinic receptors.[5-8]

Dr. Josiassen is chief scientific officer, Arthur P. Noyes Research Foundation, Norristown, PA, and adjunct professor of psychiatry, University of Pennsylvania, Philadelphia.

Dr. Shaughnessy is associate professor of psychiatry, Drexel University College of Medicine, Philadelphia, and medical consultant, Arthur P. Noyes Research Foundation.

continued

Table 2

Agitation, symptom improvement 2 hours after aripiprazole or haloperidol injection

Assessment scale	IM aripiprazole, 9.75 mg	IM haloperidol, 6.5 mg	Placebo
PANSS-EC mean score decrease (P < 0.001)	7.27	7.75	4.78
CGI-I mean score (P < 0.01)	2.42	2.37	3.10

PANSS-EC: Positive and Negative Syndrome Scale Excited Component; CGI-I: Clinical Global Impression of Improvement

Source: Adapted from reference 2

Clinical Point

Monitor aripiprazole dosing in patients taking carbamazepine, fluoxetine, or paroxetine

Pharmacokinetics

IM aripiprazole's activity has been attributed to its parent drug and to a lesser extent its major metabolite, dehydroaripiprazole. Both moieties act on D_2 receptors, and dehydroaripiprazole accounts for 40% of the parent drug's exposure in plasma.

Mean elimination half-lives for aripiprazole and dehydroaripiprazole are approximately 75 and 94 hours, respectively, allowing for daily administration. Both active moieties reach steady-state concentration within 14 days of dosing. Because aripiprazole accumulation is predictable after a single dose and its pharmacokinetics are dose-proportional at steady state, higher doses are not always more effective and could increase side-effect risk.

Aripiprazole is metabolized mainly through the liver by cytochrome P-450 2D6 and 3A4 isozymes. This requires careful monitoring when prescribing the drug concomitantly with:

- agents that induce CYP 3A4—such as carbamazepine—which could diminish aripiprazole's effectiveness by increasing its clearance and decreasing aripiprazole blood levels
- CYP 3A4 inhibitors such as ketoconazole or CYP 2D6 inhibitors such as quinidine, fluoxetine, or paroxetine, which can inhibit aripiprazole elimination[9] and increase the risk of adverse events.

Similarly, aripiprazole could be efficacious at lower-than-therapeutic dosages when taken with medications that raise aripiprazole blood levels.

Read about other new drugs and innovations at CurrentPsychiatry.com

- Click on 'Browse Back Issues'
- Then click on 'Out of the Pipeline' under 'Browse by Category'

Efficacy

In 3 randomized, placebo-controlled, double-blind trials, IM aripiprazole reduced agitation in inpatients with schizophrenia, schizoaffective disorder, or type I bipolar disorder with manic or mixed episodes, with or without psychotic features.

In each trial, IM aripiprazole was as effective as comparable dosages of haloperidol or lorazepam IM preparations. Patients were moderately to severely agitated based on Positive and Negative Syndrome Scale Excited Component (PANSS-EC) assessments, which gauged impulse control, tension, hostility, uncooperativeness, and excitement.

Patients could receive up to 3 injections within 24 hours but had to wait ≥2 hours for the second injection so that investigators could record follow-up PANSS-EC scores. Clinical Global Impression of Improvement (CGI-I) scale scores were a key secondary measure.

Examination of population subsets in the studies showed no differential response based on age, race, or gender.

Tran-Johnson et al[1] followed 357 patients with schizophreniform disorders, schizophrenia, or schizoaffective disorders.

Two hours after initial injection, mean PANSS-EC scores decreased approximately 3 points with placebo and 4 to 6.5 points

among patients receiving 7.5 mg of IM haloperidol or 5.25, 9.75, or 15 mg of IM aripiprazole. Agitation improved significantly after 45 minutes among patients receiving 9.75 mg of IM aripiprazole, compared with 105 minutes in the IM haloperidol group.

Prevalence of EPS across 24 hours with haloperidol was 19.3%, compared with an average 5.2% among all IM aripiprazole groups, suggesting that IM aripiprazole carries a substantially lower EPS risk.

Andrezina et al[2] followed 448 patients with schizophrenia or schizoaffective disorder. Two hours after injection, patients in both treatment groups showed much greater improvement compared with placebo based on mean PANSS-EC score decreases and mean CGI-I scores (***Table 2***).

Prevalence of EPS was 1.7% with IM aripiprazole, 2.3% with placebo, and 12.6% with IM haloperidol. Prevalence of EPS-related adverse events was 0% with IM aripiprazole, 1.6% with placebo, and 16.5% with IM haloperidol.

Zimbroff et al[3] gave IM aripiprazole, 9.75 or 15 mg; IM lorazepam, 2 mg; or placebo to 301 patients with type I bipolar disorder with manic or mixed episodes.

Two hours later, all 3 treatment groups showed significantly greater agitation improvement as shown by PANSS-EC scores, compared with placebo (***Table 3***).

Across 2 hours, oversedation—defined as an Agitation-Calmness Evaluation Scale score of 8 or 9—was less prevalent among patients receiving IM aripiprazole, 9.75 mg (6.7%), compared with IM aripiprazole, 15 mg (17.3%), or IM lorazepam (19.1%).

Safety and tolerability

IM aripiprazole was well tolerated in clinical trials and did not cause excessive sedation[10] or injection-site pain.[1-3]

Most frequently reported adverse events were headache (12% with IM aripiprazole vs 7% with placebo), nausea (9% vs 3%), dizziness (8% vs 5%), and somnolence (7% vs 4%).

Table 3

Agitation improvement 2 hours after aripiprazole or lorazepam injection

IM preparation	PANSS-EC mean score decrease
Aripiprazole, 9.75 mg	8.7
Aripiprazole, 15 mg	8.7
Lorazepam, 2 mg	9.6
Placebo	5.6

PANSS-EC: Positive and Negative Syndrome Scale Excited Component

Source: Adapted from reference 3

Prevalence of akathisia or dystonia among all IM aripiprazole groups in the 3 trials was 2% and <1%, respectively, compared with 0% among the placebo groups. Prevalence of nonakathisia-related EPS was 2% among the IM aripiprazole and placebo groups.

No clinically significant ECG abnormalities were reported among the aripiprazole groups.[1-3,11]

Dosing

Start at 9.75 mg every 2 hours as needed, but do not exceed 30 mg/d across 24 hours. Controlled studies have not evaluated efficacy or safety of more-frequent injections or safety of total daily doses >30 mg.

Try a lower dose (5.25 mg) for patients who are elderly or small in body size or have reacted adversely to other antipsychotics. If necessary, give another 5.25 mg in 2 hours. If the patient is still agitated 2 hours after the second dose, consider a third dose at 9.75 mg. Again, do not exceed 30 mg over 24 hours. Obtain lower doses by administering a portion of the vial.

Transitioning to oral Tx

If IM aripiprazole reduces psychotic symptoms as well as acute behaviors, switch the patient to oral aripiprazole once the risk of violence has diminished.[12] If psychosis does not improve with IM aripiprazole,

Clinical Point

Start with 5.25 mg of IM aripiprazole if the patient is elderly or small in body size or has reacted adversely to other antipsychotics

Clinical Point

Oral and IM aripiprazole doses are equivalent; a patient receiving 20 mg IM can take the same dose orally within 24 hours

weigh clinical factors before choosing an oral antipsychotic.

Only one controlled trial[12] has examined transitioning from IM aripiprazole to an oral antipsychotic. In the randomized study, 448 patients receiving IM aripiprazole, 9.75 mg; IM haloperidol, 6.5 mg; or placebo for agitation secondary to schizophrenia or schizoaffective disorder were transitioned to the oral preparation of the drug they were receiving: aripiprazole, 10 to 15 mg/d, or haloperidol, 7.5 to 10 mg/d. Placebo-group patients transitioned to oral aripiprazole.

Over 4 days, both oral treatments provided continued efficacy, suggesting that:

- patients receiving IM aripiprazole can be conveniently switched to the oral preparation
- IM and oral aripiprazole are equally safe.

Oral and IM aripiprazole doses are equivalent and the pharmacokinetics are comparable. For example, a patient receiving 20 mg/d of IM aripiprazole can take 20 mg of oral aripiprazole within 24 hours of the last injection.

Related Resources

- Allen MH, Currier GW, Carpenter D, et al. Expert consensus guidelines: treatment of behavioral emergencies. *J Psychiatr Pract* 2005;11(suppl 1):5-108.
- Currier GW, Citrome LL, Zimbroff DL, et al. Intramuscular aripiprazole in the control of agitation. *J Psychiatr Pract* 2007;13:159-69.

Drug Brand Names

Aripiprazole IM • Abilify
Carbamazepine • Tegretol, others
Fluoxetine • Prozac
Haloperidol • Haldol
Ketoconazole • Nizoral
Lorazepam • Ativan
Paroxetine • Paxil
Quinidine • Quinaglute

Disclosures

Dr. Josiassen was principal investigator and Dr. Shaughnessy a co-investigator on a pre-approval clinical trial of IM aripiprazole. Both have conducted sponsor- and investigator-initiated studies for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Janssen, Novartis Pharmaceuticals Corp., Organon, Otsuka America Pharmaceuticals, Otsuka Maryland Research Institute, Pfizer, and Yamanuchi.

Acknowledgments

This article was supported in part by the Arthur P. Noyes Research Foundation.

The authors thank Margit Kacso, Cara Bendler, Dawn Filmyer, and Jon Weinstein for their technical and editorial assistance in preparing this article.

References

1. Tran-Johnson TK, Sack DA, Marcus RN, et al. Efficacy and safety of intramuscular aripiprazole inpatients with acute agitation: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2007;68:111-9.
2. Andrezina R, Josiassen RC, Marcus R, et al. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology (Berl)* 2006;188:281-92.
3. Zimbroff DL, Marcus RN, Manos G, et al. Management of acute agitation in patients with bipolar disorder: efficacy and safety of intramuscular aripiprazole. *J Clin Psychopharmacol* 2007;27:171-6.
4. Stark AD, Jordan S, Allers KA, et al. Interaction of the novel antipsychotic aripiprazole with HT1A and 5-HT2A receptors: functional receptor-binding and in vivo electrophysiological studies. *Psychopharmacol* 2007;190:373-82.
5. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther* 2002;302:381-9.
6. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology* 2003;28:1400-11.
7. Jordan S, Koprivica V, Dunn R, et al. In vivo effects of aripiprazole on cortical and striatal dopaminergic and serotonergic function. *Eur J Pharmacol* 2004; 483:45-53.
8. Hirose T, Uwahodo Y, Yamada S, et al. Mechanism of action of aripiprazole predicts clinical efficacy and a favourable side-effect profile. *J Psychopharmacol* 2004;18:375-83.
9. *Physicians' desk reference, 61st ed*. Montvale, NJ: Thomson PDR; 2007.
10. Currier GW, Crandall D, Archibald D, et al. Intramuscular (IM) aripiprazole controls agitation in patients with schizophrenia or bipolar I disorder without excessive sedation. Paper presented at: Annual Meeting of the American Psychiatric Association; May 20-25, 2006; Toronto, Canada.
11. Currier GW, Citrome LL, Zimbroff DL, et al. Intramuscular aripiprazole in the control of agitation. *J Psychiatr Pract* 2007;13:159-69.
12. Daniel DG, Currier GW, Zimbroff DL, et al. Efficacy and safety of oral aripiprazole compared with haloperidol in patients transitioning from acute treatment with intramuscular formulations. *J Psychiatr Pract* 2007;13:170-7.

Bottom Line

In randomized, placebo-controlled studies, IM aripiprazole reduced agitation in patients with schizophrenia or bipolar disorder 45 to 60 minutes after dosing. Sedation and involuntary movement were less prevalent than with other injectable preparations used to treat acute behaviors. Start at 9.75 mg every 2 hours as needed; do not exceed 30 mg across 24 hours.