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).1,2

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

How it works

Whereas other SGAs have relatively little effect on D₂ (dopamine) receptors and relatively high 5-HT₁A (serotonin) receptor affinities, aripiprazole appears to work via partial D₂ receptor agonism. The medication:

- blocks D₂ 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-HT₁A receptor agonist and—like other SGAs—a 5-HT₂A receptor antagonist. These receptor subtypes have been implicated in antipsychotic action. In particular, partial 5-HT₁A receptor agonism is thought to help:

- reduce anxiety
- lessen depressive, negative, and cognitive symptoms
- decrease extrapyramidal symptom (EPS) liability.1

Aripiprazole also has moderate affinity for histaminic and alpha-adrenergic receptors and no appreciable effect on cholinergic muscarinic receptors.3,4

Table 1

<table>
<thead>
<tr>
<th>IM aripiprazole: Fast facts</th>
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<tbody>
<tr>
<td>Brand name: Abilify</td>
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<tr>
<td>Class: Second-generation antipsychotic</td>
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<tr>
<td>Indication: Acute agitation associated with schizophrenia or type I bipolar disorder (mixed or manic episodes)</td>
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<tr>
<td>Manufacturer: Otsuka America Pharmaceutical (marketed in collaboration with Bristol-Myers Squibb)</td>
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<tr>
<td>Dosing forms: 1.3-mL vial of clear, aqueous solution containing 9.75 mg of active drug</td>
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<tr>
<td>Recommended dosage: 9.75 mg every 2 hours as needed; do not exceed 30 mg across 24 hours</td>
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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\(^6\) 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.

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

**Table 2**

<table>
<thead>
<tr>
<th>Assessment scale</th>
<th>IM aripiprazole, 9.75 mg</th>
<th>IM haloperidol, 6.5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS-EC mean score decrease (P &lt; 0.001)</td>
<td>7.27</td>
<td>7.75</td>
<td>4.78</td>
</tr>
<tr>
<td>CGI-I mean score (P &lt; 0.01)</td>
<td>2.42</td>
<td>2.37</td>
<td>3.10</td>
</tr>
</tbody>
</table>

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

**Source:** Adapted from reference 2
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 al1 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 al3 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 sedation10 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>
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<tr>
<th>IM preparation</th>
<th>PANSS-EC mean score decrease</th>
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<tr>
<td>Aripiprazole, 9.75 mg</td>
<td>8.7</td>
</tr>
<tr>
<td>Aripiprazole, 15 mg</td>
<td>8.7</td>
</tr>
<tr>
<td>Lorazepam, 2 mg</td>
<td>9.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.6</td>
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PANSS-EC: Positive and Negative Syndrome Scale

**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.

**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.2 If psychosis does not improve with IM aripiprazole,
Out of the Pipeline

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

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.

Bottom Line

References

Drug Brand Names
Aripiprazole IM - Abilify
Carbamazepine - Tegretol, others
Haloperidol - Prozac
Ketoconazole - Quinidine, Quinaglute
Lexapro - Paroxetine - Paxil
Lorazepam - Ativan, others
Olanzapine - Zyprexa
Quetiapine - Seroquel
Risperidone - Risperdal
Sertindole - Serlon, others
Sulpiride - Serapip, others
Valproic acid - Depakene, others
Zuclopenthixol - Clopal, others
Zyprexa Zubs

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Disclosures
Dr. Josiassen was principal investigator and Dr. Shaughnnessy 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 Yamanouchi.

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