

Long-acting injectable aripiprazole for adult schizophrenia

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Depot formulation and once-monthly dosing might improve adherence in patients with schizophrenia

In February 2013, the FDA approved a long-acting IM aripiprazole formulation for treating adult schizophrenia (*Table 1*).¹ It is the fourth second-generation antipsychotic (SGA) depot formulation approved for treating schizophrenia, and the sixth depot antipsychotic if haloperidol and fluphenazine decanoate are considered.

Clinical implications

Depot medications can improve treatment adherence²; however, long-term antipsychotic use can lead to irreversible adverse effects (dyskinesias), which in some cases were reduced by using newer antipsychotics.³

How it works

Similar to other SGAs, aripiprazole's mechanism of action is unknown. Aripiprazole was developed based on the dopamine theory, in which dopamine hyperactivity in mesolimbic pathways of the brain leads to hallucinations, delusions, disorganization, and catatonia, and dopamine hypoactivity in mesocortical pathways and the prefrontal cortex causes alogia, anhedonia, autism, avolition, and problems with attention and abstract thinking.

Aripiprazole's proposed mechanism of action on dopamine receptors is that of partial agonism,¹ rather than antagonism, as is the case for other SGAs. In theory, aripiprazole antagonizes postsynaptic D2 receptors and activates presynaptic D2 autoreceptors, with subsequently decreased dopamine production and further stabilization of the dopamine system.⁴ Its antagonism of 5-HT_{2A} is similar to other SGAs.⁵

Pharmacokinetics

After depot aripiprazole is injected into the gluteal muscle, the active moiety slowly is released into circulation. The effectiveness of depot aripiprazole is attributable to its active parent drug, aripiprazole monohydrate, and its active metabolite, dehydro-aripiprazole, which is the same as oral aripiprazole. Depot aripiprazole reaches maximum concentration in 5 to 7 days. The elimination half-life of depot aripiprazole is 29.9 days for a 300-mg dose and 46.5 days for a 400-mg dose if administered monthly.¹

Aripiprazole does not undergo direct glucuronidation. It is metabolized predominantly through cytochrome P450 (CYP) 2D6 and 3A4 enzymes, which predisposes it to significant drug-drug interactions and may require dose adjustment (*Table 2, page 48*).¹

Efficacy

The ability of depot aripiprazole to sustain long-term symptom control in adult patients with schizophrenia was demonstrated in a randomized-withdrawal, double-blind, placebo-controlled trial.¹ Adults included had a DSM-IV-TR diagnosis of schizophrenia, had ≥3-year history of the illness, had undergone treatment with ≥1 antipsychotic, and had a history of relapse or symptom exacerbation when not receiving antipsychotics. Psychopathology was measured by the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression-Severity scale, the Clinical Global

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Impression-Improvement (CGI-I) scale, and the Clinical Global Impression-Severity of Suicide (CGI-SS) scale.¹

The trial lasted 52 weeks, was divided into 4 phases, and concluded early because of demonstrated efficacy.

Phase I: Conversion phase switched patients from a different antipsychotic to oral aripiprazole. This phase lasted 4 to 6 weeks and included 633 patients. An additional 210 patients already receiving aripiprazole were entered directly into Phase II.

Phase II: Open-label, oral stabilization phase included 710 patients (60% males) age 18 to 60 who had a mean PANSS score 66. Patients received 10 to 20 mg/d of oral aripiprazole until they achieved stabilization, defined as PANSS score <80, CGI-I score ≤4, and CGI-SS score <2 for 4 consecutive weeks.

Phase III: IM depot stabilization (uncontrolled single blind) included 576 patients. Patients were started on depot aripiprazole, 400 mg monthly, and continued to take 10 to 20 mg/d of oral aripiprazole for 14 consecutive days. Depot aripiprazole was decreased to 300 mg monthly if a patient developed adverse effects. Patients continued to the double-blind phase when stabilization was achieved, as evidenced by PANSS score <80, CGI-I score ≤4, and CGI-SS score <2 for 12 consecutive weeks.

Phase IV: Maintenance (double-blind, randomized, placebo-controlled) included 403 patients. Two-thirds of patients continued to take the same dose of depot aripiprazole they took in Phase III. One-third of patients were switched to placebo. The primary efficacy endpoint was time to impending relapse, defined as the first occurrence of ≥1 criteria: hospitalization due to psychosis; violence toward self, others, or property; CGI-SS score ≥4 on part I or ≥7 on part II; or CGI-I score ≥5 and any individual PANSS score >4 for disorganization, hallucinations, suspiciousness, or abnormal thought content.¹

Table 1

Depot aripiprazole: Fast facts

Brand name: Abilify Maintena
Class: Atypical antipsychotic
Indication: Adult schizophrenia
Approval date: February 28, 2013
Availability date: March 18, 2013
Manufacturer: Otsuka Pharmaceutical and Lundbeck
Dosing form: IM long-acting injection
Recommended dosage: 400 mg IM once a month; 200 to 300 mg IM if drug-drug interactions, poor cytochrome P450 2D6 metabolism, or adverse effects
Source: Reference 1

Patients randomized to continue depot aripiprazole took longer to relapse or worsening of symptoms compared with the placebo group. Of 403 patients, 10% taking an active drug and 39.6% taking placebo relapsed within 360 days of randomization. This difference was statistically significant ($P < .0001$).¹

Tolerability

One possible problem with any long-acting medication is increased duration of adverse effects (AEs), if they develop. Therefore, assessment of safety and tolerability is more important in depot formulations than in oral drugs. During the clinical trial, depot aripiprazole was well tolerated.⁶

During clinical trials, the most common AEs—insomnia (>5%), anxiety, and tremors—were mild to moderate and occurred within the first 4 weeks. Discontinuation of the medication because of AEs was low, and pain at the injection site was minimal.⁶ There were 2 deaths during the trial, which were unrelated to depot aripiprazole.⁶

Aripiprazole's activity on the D2 receptor can cause extrapyramidal AEs. In head-to-head trials, patients taking aripiprazole had fewer extrapyramidal AEs than those taking risperidone or ziprasidone, but more than patients receiving olanzapine.⁷ Its moderate

Clinical Point

Metabolism through CYP2D6 and 3A4 enzymes predisposes aripiprazole to drug-drug interactions, which may require dose adjustment



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Clinical Point

Avoid using depot aripiprazole in patients taking strong CYP3A4 inducers, such as rifampin and carbamazepine

See this article at CurrentPsychiatry.com for a table detailing aripiprazole's receptor binding profile

Table 2

Dose adjustments of depot aripiprazole

Drug-drug interaction	Adjusted dose
CYP2D6 poor metabolizers	300 mg
CYP2D6 poor metabolizers taking CYP3A4 inhibitors (ketoconazole, itraconazole, erythromycin, grapefruit juice)	200 mg
Lithium, valproate, desvenlafaxine, venlafaxine, escitalopram, dextromethorphan, omeprazole, warfarin	No significant interaction No dose adjustment
Sex, race, liver impairment, renal impairment, tobacco smokers	No dose adjustment
Patients taking 400 mg of depot aripiprazole with:	
CYP2D6 inhibitors (paroxetine, fluoxetine, quinidine) <i>or</i> CYP3A4 inhibitors (ketoconazole, itraconazole, erythromycin, grapefruit juice)	300 mg
CYP2D6 inhibitors (paroxetine, fluoxetine, quinidine) <i>and</i> CYP3A4 inhibitors (ketoconazole, itraconazole, erythromycin, grapefruit juice)	200 mg
CYP3A4 inducers (carbamazepine)	Avoid use
Patients taking 300 mg of depot aripiprazole with:	
CYP2D6 inhibitors (paroxetine, fluoxetine, quinidine) <i>or</i> CYP3A4 inhibitors (ketoconazole, itraconazole, erythromycin, grapefruit juice)	200 mg
CYP2D6 inhibitors (paroxetine, fluoxetine, quinidine) <i>and</i> CYP3A4 inhibitors (ketoconazole, itraconazole, erythromycin, grapefruit juice)	160 mg
CYP3A4 inducers (carbamazepine)	Avoid use

CYP: cytochrome P450
 Source: Adapted from reference 1

antagonism on α -adrenergic and histamine 1 (H1) receptors translates to low orthostatic hypotension, H1-mediated weight gain, and sedation. In clinical trials, weight gain and metabolic changes were comparable with placebo. In head-to-head trials, aripiprazole caused less weight gain and a higher incidence of increased cholesterol than olanzapine and risperidone, and less increase in blood glucose than olanzapine, but more than risperidone.⁸ Muscarinic 1-mediated cognitive impairment, dry mouth, constipation, urinary retention, and increased intraocular pressure were low.⁸ For a *Table* detailing aripiprazole's receptor binding profile, see this article at CurrentPsychiatry.com.

Unique clinical issues

Clinical features for depot aripiprazole can be partially deduced based on data on oral

aripiprazole. Advantages over other depot SGAs might include aripiprazole's more favorable weight and metabolic profile.

Contraindications

Depot aripiprazole is contraindicated in patients with known sensitivity to aripiprazole or other components of the formulation. Because of pharmacokinetic drug-drug interactions, using depot aripiprazole should be avoided in patients taking strong CYP3A4 inducers (eg, rifampin and carbamazepine). Dose adjustment is recommended in patients who are taking moderate CYP2D6 and 3A4 inhibitors, such as paroxetine, fluoxetine, ketoconazole, or erythromycin.¹ A "black-box" warning of increased mortality in older patients with dementia-related psychosis applies for depot aripiprazole as well as for other atypical antipsychotics.¹

Depot aripiprazole is pregnancy category C and should be used in pregnant or breast-feeding mothers only when benefits outweigh the risks. Use of depot aripiprazole in geriatric and pediatric populations has not been studied; however, patients age ≥ 65 who received oral aripiprazole, 15 mg/d, showed decreased clearance by 20%.¹

Dosing

Depot aripiprazole is available as a lyophilized powder that needs to be reconstituted in sterile water. The drug can be stored at room temperature. The kit includes two 21-gauge needles, a 1.5-inch needle for non-obese patients and a 2-inch needle for obese patients. Depot aripiprazole should be given to patients who demonstrate tolerability to oral aripiprazole. The starting and maintenance dose of depot aripiprazole is 400 mg injected into the gluteal muscle, once a month. If a patient develops an AE, decrease the monthly dose to 300 mg. Rotate the injection site between gluteal muscles to reduce AEs from injection.

Because of the potential for significant pharmacokinetic drug-drug interactions, dose adjustment is recommended for patients who are CYP2D6 poor metabolizers and those taking certain other medications (*Table 2*).¹ See this article at CurrentPsychiatry.com for the recommended dosage adjustment in the case of missed doses.

After depot aripiprazole is injected into the gluteal muscle, the patient receives 10 to 20 mg/d of oral aripiprazole for 14 consecutive days to avoid a drop in plasma concentrations into subtherapeutic levels.

Bottom Line

Depot aripiprazole is FDA-approved for treating adults with schizophrenia. The depot formulation may increase treatment adherence because it is a once-monthly IM injection. Efficacy and side effect profile are similar to oral aripiprazole, although caution is necessary because the drug stays in a patient's system longer.

Related Resource

• Abilify Maintena [package insert]. Tokyo, Japan: Otsuka Pharmaceutical Company; 2013.

Drug Brand Names

Aripiprazole • Abilify	Ketoconazole • Nizoral
Aripiprazole depot • Maintena	Lithium • Eskalith, Lithobid
Carbamazepine • Tegretol	Olanzapine • Zyprexa
Desvenlafaxine • Pristiq	Omeprazole • Prilosec
Dextromethorphan • Delsym	Paliperidone • Invega
Erythromycin • E-Mycin	Paroxetine • Paxil
Escitalopram • Lexapro	Quinidine • Quinidex
Fluoxetine • Prozac	Rifampin • Rifadin
Fluphenazine • Prolixin	Risperidone • Risperdal
Haloperidol • Haldol	Valproate • Depakote
Itraconazole • Sporanox	Venlafaxine • Effexor
	Warfarin • Coumadin
	Ziprasidone • Geodon

Disclosure

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Clinical Point

Depot aripiprazole, as well as all atypical antipsychotics, carry a 'black-box' warning of increased mortality in older patients with dementia

See this article at

CurrentPsychiatry.com

for recommended aripiprazole dosage adjustment in the case of missed doses

Table 1

Aripiprazole's receptor binding profile

	Affinity	Ki (nM) ^a	Effects associated with activity on the receptor
D2	High	0.34	Partial agonist
D3	High	0.8	Partial agonist
5-HT1A	High	1.7	Partial agonist
5-HT2A	High	3.4	Antagonist
5-HT2C	Moderate	15	Partial agonist
5-HT7	Moderate	39	Antagonist
D4	Moderate	44	Partial agonist
α1-adrenergic	Moderate	57	Antagonist
H1	Moderate	61	Antagonist
M1	No appreciable activity	>1,000	No appreciable activity

^aKi dissociation constant: lower numbers indicate higher affinity of the compound for the receptor

H1: histamine 1; M1: muscarinic 1

Source: References 1,6

Table 2

Adjusting depot aripiprazole after missed doses

	Doses missed since last injection			
	Second or third dose		Fourth or subsequent dose	
	>4 weeks and <5 weeks	>5 weeks	>4 weeks and <6 weeks	>6 weeks
Oral aripiprazole		Administer for 14 days		Administer for 14 days
Depot aripiprazole	Administer as soon as possible	Administer next injection	Administer as soon as possible	Administer next injection

Source: Reference 1