ARIPIPRAZOLE

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Topic Overview

Aripiprazole is an atypical, second-generation antipsychotic indicated for the treatment of schizophrenia, bipolar disorder, and treatment-resistant major depressive disorder. It is also used to manage irritability associated with autistic disorder and treat Tourette syndrome. Studies have shown that aripiprazole is associated with a lower risk of several adverse effects compared to other antipsychotic medications. Long-acting injectable formulations play an important role in treatment and patient adherence.

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Target Audience: This educational activity is for pharmacists.

How to Earn Credit: From March 3, 2023, through March 3, 2026, participants must:

1) Read the "learning objectives" and "author and planning team disclosures;"
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3) Complete the Post-test and Evaluation form. The Post-test will be graded automatically. Following successful completion of the Post-test with a score of 70% or higher, a statement of participation will be made available immediately. (No partial credit will be given.)

Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Describe** the basic pharmacological profile, indications, and clinical outcomes of aripiprazole treatment
2. **List** the different dosage forms with the dosing frequency available for aripiprazole
3. **Discuss** the benefits and risks of aripiprazole use
4. **Identify** the contraindications and potential side effects of aripiprazole

Disclosures

The following individuals were involved in the development of this activity: Amanda Mayer, PharmD, Jeff Goldberg, PharmD, BCPP, and Pamela Sardo, PharmD, B.S. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

Aripiprazole is an atypical, second-generation antipsychotic indicated for the treatment of schizophrenia, bipolar disorder, and treatment-resistant major depressive disorder. It is typically well-tolerated, and its use has extended to other psychiatric conditions in children and adults. Studies suggest aripiprazole is superior to placebo and to many first- and second-generation antipsychotics for various indications. Aripiprazole is available in oral and long-acting injectable forms, the latter of which have unique pharmacokinetic profiles that must be considered when formulating a treatment plan.

History of Aripiprazole

Aripiprazole, under the brand name Abilify, received FDA approval in 2002.[1,2] At that time, aripiprazole had a unique chemical structure that differentiated it from other available antipsychotics.[1] It was initially approved as an oral tablet for treating schizophrenia.[2] The patent expired in 2015, and oral aripiprazole has since been available as a generic medication.[2] Abilify Maintena®, a long-acting injectable (LAI), was approved for the treatment of schizophrenia in 2013.[1] Aristada® (aripiprazole lauroxil), another LAI, was approved in 2015 for the treatment of schizophrenia.[3]

Clinical Pharmacology

Mechanism of Action

Similar to other antipsychotics, the exact mechanism of action of aripiprazole is unclear. Aripiprazole is classified as a second-generation, atypical antipsychotic.[4,5] It is also known as a "prototypical third-generation antipsychotic" due to its unique characteristics.[2] Aripiprazole exhibits high affinity for D2, D3, 5-HT1A, and 5-HT2A receptors and moderate affinity for D4, 5-HT2C, 5-HT7, alpha1 adrenergic, and H1 receptors.[4] It is classified as a dopamine partial agonist due to its agonist activity at certain receptor targets, most notably D_2 autoreceptors.[4] This distinguishes it from the first-generation

dopamine antagonists.[2] Therapeutic activity is presumed to be the result of aripiprazole's partial agonist activity at D2 and 5-HT1A receptors and its antagonism at 5-HT2A receptors.[6] Aripiprazole lauroxil is a prodrug of aripiprazole.[3,7]

Pharmacokinetics

Oral Aripiprazole

The activity of oral aripiprazole is via the parent drug (aripiprazole) and to a lesser extent its major metabolite, dehydroaripiprazole.[6] Both the tablet and oral solution formulations are well-absorbed.[4,6] Peak concentrations occur between 3-5 hours post-ingestion and it has an absolute bioavailability of 87%.[4,6] Aripiprazole is highly protein-bound (>99%) and has a volume of distribution of 4.9 L/kg.[4,6] Metabolism occurs via three mechanisms: hepatic dehydrogenation and hydroxylation via CYP2D6 and CYP3A4 as well as N-dealkylation via CYP3A4.[6] The half-lives of aripiprazole and dehydroaripiprazole are 75 hours and 94 hours, respectively.[4,6] Excretion occurs primarily via feces (55%) and to a smaller extent the urine (25%).[4,6]

Long-acting Injectable

Aripiprazole dual chamber or vial (Abilify Maintena®) is a long-acting injectable. Similar to the oral formulation, the activity of the LAI is mainly due to the parent drug (aripiprazole) and, to a smaller extent, dehydroaripiprazole.[8] Due to aripiprazole's low solubility, absorption of this formulation is slow and prolonged.[4] The time to peak plasma concentration following multiple doses is 4 days after deltoid administration and 5-7 days following gluteal administration.[4,8] The half-life elimination is dose-dependent and approximately 30 days for the 300 mg dose and 47 days for the 400 mg dose.[8]

Long-acting injectable antipsychotics have a unique pharmacokinetic profile, making them particularly beneficial in the treatment of psychiatric conditions such as schizophrenia.[9] It is important for clinicians to understand

the pharmacokinetic differences between the oral and LAI forms of aripiprazole, as misunderstanding these differences may lead to poorer patient outcomes.[9] For example, the LAI forms of aripiprazole will exhibit "flip-flop" kinetics that impacts the time it takes for the drug to reach a steady state because of its slower rate of absorption.[9] 'Flip-flop' kinetics is an unusual situation where the rate of absorption, or the rate to enter the blood, is slower than its elimination.[10]

Correll, *et al.* (2021) discuss the importance of individualizing a treatment plan, utilizing an oral antipsychotic before switching to a long-acting form, knowing when it is best to make dose adjustments, understanding the different dosing schedules for the distinctive forms of aripiprazole, *e.g.*, aripiprazole lauroxil versus aripiprazole, *etc.*, and understanding that if adverse effects do present with aripiprazole, the use of a long-acting drug may prolong their duration.[9]

Long-acting Injectable: Aripiprazole lauroxil extended-release suspension Aripiprazole Lauroxil (Aristada® and Aristada Initio®)

Aripiprazole lauroxil is a prodrug of aripiprazole, with activity mainly due to aripiprazole and to a lesser extent, dehydroaripiprazole.[11] Aripiprazole lauroxil is available in two formulations - Aristada® and Aristada Initio® (aripiprazole lauroxil prodrug injection (675 mg/2.4 mL).[12] When given in the form of Aristada®, aripiprazole lauroxil appears in circulation between 5 and 6 days post-injection and is released for 36 more days.[11] When given in the form of Aristada Initio®, the day of injection is when systemic circulation starts with peak plasma exposure being about 27 days.[12] With both formulations, clinically relevant serum levels are obtained after 4 days when administered with oral aripiprazole 30 mg.[12] When supplemented with oral aripiprazole for 21 days at the start of the first dose, therapeutic concentrations are obtained within four days.[12]

The volume of distribution of aripiprazole lauroxil is 268 L.[11] It undergoes hydrolysis to form N-hydroxymethyl-aripiprazole, which subsequently undergoes water-mediated hydrolysis to aripiprazole.[11] Hepatic

metabolism involves CYP3A4 and CYP2D6.[11] The half-life elimination is approximately 53 to 57 days for Aristada® and 15 to 18 days for Aristada Initio®.[12]

Labeled and Off-Label Uses

Aripiprazole was initially approved to treat schizophrenia, but has since been approved for numerous other conditions.

Labeled Uses

The following Table 1 contains labeled uses of aripiprazole and aripiprazole lauroxil.[4,7,11] Agitation associated with schizophrenia or bipolar mania has also been listed as a labeled use; however, it is only listed for the intramuscular injection that has been taken off the market and will not be discussed further.

Table 1: Labeled Uses of Aripiprazole and Aripiprazole Lauroxil

Use	Notes
Bipolar disorder	As monotherapy or as an adjunct to lithium or valproate for acute treatment of mania or episodes with mixed features associated with bipolar disorder and maintenance treatment of bipolar disorder. May use oral formulations and Abilify Maintena.
Irritability associated with autism disorder	Treatment of irritability associated with autistic disorder in children and adolescents.
Major depressive disorder (unipolar), treatment resistant	Adjunctive treatment of unipolar major depressive disorder in patients with an inadequate response to prior antidepressant therapy

Schizophrenia	Treatment of schizophrenia. May use oral formulations, Abilify Maintena, Aristada, and Aristada Initio.
Tourette Syndrome	Treatment of Tourette syndrome in children and adolescents. Aripiprazole has been designated by the FDA as an orphan drug for this indication.

Off-Label Uses

Aripiprazole has also been used off-label for delusional disorder, delusion infestation (delusional parasitosis), Huntington disease-associated chorea, and treatment-resistant obsessive-compulsive disorder.[4] All of these uses have level C evidence, meaning evidence from observational studies (such as retrospective case series/reports providing a significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials (such as when limited options exist for a condition). Any estimate of the effect is uncertain. Use of treatment-resistant obsessive-compulsive disorder has Level C evidence along with Level G. Level G means use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.[4] Some evidence suggests aripiprazole may be useful as an add-on in the treatment of antipsychotic-induced hyperprolactinemia.[13]

Dosage and Administration

Labeled Uses

Table 2 contains the dosing regimens that are recommended for labeled uses of aripiprazole and aripiprazole lauroxil.[4,7,11,12] Dosing for off-label uses will not be stated.

Table 2: Dosing Regimens of Aripiprazole and Aripiprazole Lauroxil

Use	Dose
Bipolar disorder	*Oral formulations*: Initially 10 to 15 mg once daily. Increase dose based on response and tolerability in 5 to 10 mg/day increments at intervals of ≥1 week. Max dose of 30 mg/day. *Abilify Maintena:* Patients should first establish good tolerability with oral aripiprazole. Initial and maintenance dose is 400 mg IM once monthly. Oral aripiprazole therapy should be overlapped with injectable aripiprazole for 14 days during therapy initiation. Doses should not be given any sooner than 26 days apart. Upon stabilization, dose may be reduced to 300 mg IM if a patient is experiencing adverse effects.
Irritability associated with autism disorder	Initial dose is 2 mg/day orally. Increase dose based on response and tolerability in 5 mg/day increments no sooner than weekly. Recommended dosage range is 5 to 15 mg/day with a maximum dose of 15 mg/day orally.
Major depressive disorder (unipolar), treatment-resistant	Initial dose is 2 to 5 mg/day orally. Increase based on response and tolerability in 5 mg increments no sooner than weekly. Max dose of 15 mg/day.
Schizophrenia	*Oral Formulations:* *Adults:* Initial dose of 10 or 15 mg orally once daily. Increase based on response and tolerability in 5 mg increments no sooner than every 2 weeks. Maximum dose of 30 mg/day. *Adolescents:*Initial dose of 2 mg orally once daily, increase to 5 mg daily after 2 days, then increase to target dose of 10 mg orally once daily after 2 more days. After 10 mg dose is reached, dose can be titrated in 5 mg increments every 2 weeks based on effectiveness and tolerability. Max dose is 30 mg/day. *Abilify Maintena:* Patients should first establish good tolerability with oral aripiprazole. Initial and maintenance dose is 400 mg IM once monthly. Oral aripiprazole therapy should be

	overlapped with injectable aripiprazole for 14 days during therapy initiation. Doses should not be given any sooner than 26 days apart. Upon stabilization dose, may be reduced to 300 mg IM if a patient is experiencing adverse effects. *Aripiprazole lauroxil formulations:* With all aripiprazole lauroxil dosing options, patients should establish tolerability with oral aripiprazole prior to use. Patients who are poor CYP2D6 metabolizers should avoid use of the 675 mg Aristada Initio. *Option One - 1-day oral overlap using Aristada Initio:* Administer a single oral aripiprazole 30 mg dose, a single 675 mg dose of Aristada Initio PLUS first dose of Aristada based on current oral aripiprazole dose (see Table 3 below). Aristada dose can be given on the same day as Aristada Initio or may be given within 10 days of Aristada Initio plus oral dose. *Option two - 21-day oral overlap:* Administer oral aripiprazole for 21 days in conjunction with the first dose of Aristada based on the current oral aripiprazole dose (see Table 3 below).
Tourette Syndrome	*Weighing at least 50 kg:* Initial dose of 2 mg by mouth once daily. Increase to 5 mg daily after 2 days then increase to target dose of 10 mg daily after 5 more days. Dose may be increased at 5 mg/day increments at weekly intervals with a maximum dose of 20 mg/day. *Weighing less than 50 kg:* Initial dose of 2 mg by mouth once daily. May increase to 5 mg once daily after 2 days then increase gradually at weekly intervals if needed with a max dose of 10 mg/day.

Table 3: Converting oral aripiprazole to IM aripiprazole lauroxil (Aristada):[12]

Oral aripiprazole dose	**Initial IM Aristada dose**
10 mg/day	441 mg/month

15 mg/day	662 mg per month **or** 882 mg every 6 weeks **or** 1,064 mg every 2 months.
≥20 mg/day	882 mg every month

Dosage Forms and Strengths

The following dosage forms of aripiprazole and aripiprazole lauroxil are available in the strengths noted.[4,6-8,11]

Table 4: Dosage Forms and Strengths

Dosage form	**Strength(s)**
Aripiprazole (Abilify)	2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg
Generic aripiprazole	2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg
Aripiprazole tablets with sensors (Abilify MyCite® Starter and Maintenance Kits)[14]	2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg. Each strength comes with 30 tablets (swallow whole; do not divide, crush, or chew) plus 1 reusable pod and 7 disposable adhesive strips that connect to your smartphone.
Aripiprazole orally disintegrating tablet (Generic)	10 mg, 15 mg
Aripiprazole oral solution (Generic)	1 mg/mL (150 mL)
Aripiprazole prefilled dual chamber extended-release intramuscular syringe (Abilify Maintena®)	300 mg and 400 mg
Aripiprazole powder for suspension for	300 mg and 400 mg

extended release intramuscular Aripiprazole injection (Abilify Maintena®)	
Aripiprazole prefilled intramuscular syringe (Aristada®)	1064 mg/3.9 mL (3.9 mL); 441 mg/1.6 mL (1.6 mL); 662 mg/2.4 mL (2.4 mL); 882 mg/3.2 mL (3.2 mL)
Aripiprazole prefilled intramuscular syringe (Aristada Initio®)	675 mg/2.4 mL (2.4 mL)

Administration

Pharmacists should be familiar with administering the various dosage forms of aripiprazole appropriately.[4,6-8,11]

Oral formulation

The oral form of aripiprazole can be administered with or without food. The orally disintegrating tablet (ODT) should be placed on the tongue as soon as the tablet is removed from the packaging. Patients can take ODT aripiprazole with or without liquids. When counseling patients on the ODT formulation, patients should be told not to push tablet through the foil as this could damage the tablet.

Tablet with Sensor

Patients should be advised to swallow tablets whole and may take them with or without food. The tablets are embedded with an ingestible event marker (IEM) and come with a wearable sensor patch. This sensor is able to detect a signal from the IEM after the tablet is ingested. It then transmits data to a smartphone between 30 minutes to 2 hours after tablet ingestion. Patients will need to download Mycite app to transmit data.[14]

The patch should be applied to the left side of the body just above the lower edge of the rib cage. This should only be done when instructed by the app. Patches should not be placed where the skin is scraped, cracked, inflamed, or irritated, or in a location that overlaps the area of the most recently removed patch. Patches need to be changed weekly. The app prompts patients to change the patch and can direct patients to apply and remove the patch correctly.

Oral Solution

May be administered with or without meals. Calibrated oral measuring device should be used to draw up the dose. Once a bottle is opened it can be stored for up to 6 months, but not beyond manufacturer labeled expiration date.[15]

Aripiprazole for extended-release injectable suspension, dual chamber syringe or vial (Abilify Maintena®)

Clinicians should ensure patients tolerate oral aripiprazole prior to initiating the LAI form. This aripiprazole formulation is given intramuscularly (IM) and should *not* be administered subcutaneously or intravenously. A 1-inch needle with deltoid administration can be used for nonobese patients. For obese patients, a 1.5-inch (38 mm) needle with deltoid administration or a 2-inch (51 mm) needle with gluteal administration should be used. Patients should be instructed *not* to massage the area after administration. The injection site should be rotated between the two gluteal or deltoid muscles. Pre-filled syringes and powders come in boxes with all components needed and detailed instructions. A healthcare professional must administer injections.

Aripiprazole lauroxil extended-release injectable suspension (Aristada®)

Clinicians should ensure patients tolerate oral aripiprazole before initiating aripiprazole lauroxil. Aripiprazole lauroxil is administered intramuscularly. The 441 mg dose and the 675 mg nanocrystal dispersion dose

(Aristada Initio) should be administered via the deltoid or gluteal muscle. Other strengths should be administered in the gluteal muscle. Administration of Aristada Initio and Aristada concurrently in the same muscle should be avoided. Before administration, the syringe should be tapped at least 10 times to dislodge any settled material and then shaken vigorously ≥30 seconds to ensure a uniform suspension. If the syringe is not used within 15 minutes, it needs to be shaken again for 30 seconds. A healthcare professional must administer injections.

Contraindications

Aripiprazole treatment is contraindicated in cases where patients have any sensitivities to aripiprazole or any of the formulation components.[4]

Warnings

Important warnings and precautions should be noted before the use of aripiprazole.[4,6-8,11] A boxed warning states that elderly patients with dementia-related psychosis who use antipsychotics are at an increased risk of death. The safety of aripiprazole for use in this patient population has not been established, and is not an FDA-approved treatment.[6] Additionally, patients treated with aripiprazole for dementia-related psychosis may be at an increased risk of cerebrovascular events, including stroke and transient ischemic attack, which may lead to fatalities.[6]

Patients who discontinue aripiprazole therapy are at risk of withdrawal and rebound symptoms.[4] These patients may experience a variety of symptoms, including myalgia, psychosis, restlessness, and tremors.[4]

Aripiprazole may cause orthostatic hypotension and should be used cautiously in patients with cardiovascular disease. Heart rate and blood pressure should be monitored, and patients should be warned of the risks of dehydration or syncope.[4] Aripiprazole should be used cautiously in patients with Parkinson's disease, as they may experience worsening motor disturbances. Aripiprazole should be used cautiously in those with a history of

seizures or in patients with conditions that may lower the seizure threshold. Patients who develop neuroleptic malignant syndrome can be managed by immediately discontinuing aripiprazole and close monitoring, sometimes in an inpatient or intensive care setting.[4]

Aripiprazole has numerous additional warnings for clinicians to consider, including altered cardiac function, blood dyscrasias, CNS depression, esophageal dysmotility, falls, impulse control disorders, and temperature regulation.[4,7] The full prescribing information should always be consulted for comprehensive safety and efficacy information.

Adverse Reactions

While aripiprazole has a favorable side-effect profile compared to first-generation antipsychotics and to other atypical antipsychotics, there are important adverse reactions that need to be considered. The most common side effects noted in adult patients during clinical trials (those occurring at rates of 10% or higher) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness.[4,6,15] For pediatric patients, the most common side effects included somnolence, headache, vomiting, extrapyramidal symptoms, fatigue, increased appetite, insomnia, nausea, nasopharyngitis, and weight gain.[4.6]

In general, side effects of aripiprazole can occur on a spectrum running from sedating effects (drowsiness) to activating effects (restlessness and akathisia).[4,6,8] These effects are dose-related and risks are higher in younger children. Aripiprazole may also cause dyslipidemia, hyperglycemia, and hematologic abnormalities, including leukopenia, neutropenia, and agranulocytosis.[4] The extent of metabolic side effects is generally lower than with other antipsychotic medications.[16] Additionally, its use can lead to extrapyramidal symptoms (EPS), including drug-induced Parkinsonism, akathisia, acute dystonia, and tardive dyskinesia.[4] Previously, second generation antipsychotics were thought to have decreased risk of movement symptoms; however, this difference was not seen in recent studies that

compared second generation antipsychotics to low potency first generation antipsychotics.[17]

Post marketing reports have found an association between the use of aripiprazole and compulsive behaviors, including gambling, binge eating, shopping, or engaging in sex.[18] These effects are rare, could affect any patient regardless of history of compulsive behaviors, and may stop once aripiprazole therapy is discontinued or the dose is reduced.[18] This information is included in the package inserts for aripiprazole under patient counseling information.[12]

Adverse Reaction Case Report

Oculogyric crisis (OGC) is an acute dystonic reaction that is a relatively uncommon EPS side effect of antipsychotics and is reported as a rare potential adverse effect of aripiprazole.[19] Oculogyric crisis presents with sustained, bilateral, and upward deviation of the eyes. Episodes of OGC can last seconds to hours with associated symptoms including restlessness, agitation, malaise, fixed stare, pain, increased blinking, and neck dystonia. Risk factors for OGC include male gender, young age, use of atypical antipsychotics, and initiation or up-titration of an antipsychotic.[19]

A clinical case report from January 2023 describes a 19-year-old male who had been psychiatrically hospitalized with symptoms of his first episode of psychosis.[19] He was initiated on 5 mg of aripiprazole. Three days after initiating aripiprazole, the patient was anxious and pacing around his room. Upon physical exam, the patient was found to have intermittent eye-rolling, sustained upward conjugate gaze, and limited downward gaze. Other symptoms included frontal headache, bilateral eye pain, and anxiety. Symptoms improved within one hour of administration of 50 mg of oral diphenhydramine.[19] Oral aripiprazole was initially held upon recognition of symptoms and the patient declined to reinitiate antipsychotic medications.[19]

Drug Interactions

Aripiprazole is a major substrate of both CYP2D6 and CYP3A4.[6,8] Use of aripiprazole concomitantly with strong CYP2D6 or CYP3A4 inhibitors may increase aripiprazole concentrations and oral aripiprazole dose reductions of half the usual dose should be considered.[6] Reductions in the LAI can be considered when the use of inhibitors occurs concomitantly for more than 14 days.[8] Use of aripiprazole with strong CYP3A4 inducers can lead to decreased levels of aripiprazole and may require double the usual oral dose over 1 to 2 weeks.[6,8] Use of Abilify Maintena® should be avoided with strong CYP3A4 inducers (such as carbamazepine).[8]

Aripiprazole can increase the effects of some antihypertensive drugs due to its alpha-adrenergic antagonism when used concomitantly.[6,8] Blood pressure should be monitored closely in these cases.[6,8] Dose reductions may also be warranted. Additionally, aripiprazole should be used cautiously in patients taking lorazepam due to the potential for increased sedation and orthostatic hypotension.[6,8] Blood pressure and sedation should be monitored closely and dose adjustments should be considered.

Administration of aripiprazole with the following medications is contraindicated: brexpiprazole, cisapride, dextromethorphan with quinidine, dronedarone, fluconazole, ketoconazole, levoketoconazole, metoclopramide, pimozide, posaconazole, quinidine, and thioridazine.

Specific Populations

Pregnancy

Given its safety and efficacy profile, aripiprazole is frequently used in women of childbearing age.[20] Thus, understanding the risks and benefits of use during pregnancy is important for clinicians. Animal studies suggest risks of adverse effects on the fetus, but benefits may outweigh risks in certain patients.[4] There exists no randomized, placebo-controlled data pertaining to the use of aripiprazole in pregnancy, however, animal data and

exposure/outcome data for human fetuses is available. Studies suggest children exposed to aripiprazole during pregnancy are not at a higher risk than those exposed to other SGAs.[21-23] However, the use of antipsychotics in the third trimester has been associated with a risk of extrapyramidal symptoms and withdrawal symptoms in newborns post-delivery.[4] The American College of Obstetricians and Gynecologists (ACOG) recommends treatment with psychiatric medications during pregnancy be individualized and overseen by a multidisciplinary care team, which includes an obstetrician, mental health provider, primary care provider, and pediatrician.[24]

Lactation

Aripiprazole and dehydroaripiprazole have been found to be present in breast milk.[4] In general, breastfeeding while taking any medication is typically deemed acceptable when the relative infant dose (RID) of the medication is less than ten percent.[25] For aripiprazole, the RID has been found to be variable between 0.7% to 8.3%. Breast-fed infants should be monitored for excessive drowsiness, lethargy, and developmental delays. In deciding whether to breastfeed while taking aripiprazole, the benefits of breastfeeding should be weighed against potential risks to the infant.

Pediatric

Aripiprazole is approved for use in pediatric patients for the management of the following disorders: schizophrenia in adolescents ages 13 to 17, acute treatment of manic or mixed episodes associated with bipolar 1 disorder in pediatric patients ages 10 to 17, irritability associated with autistic disorder in pediatric patients ages 6 to 17, and treatment of Tourette Syndrome in pediatric patients ages 6 to 18 years.[14] The number of US pediatric patients receiving aripiprazole between 2014 and 2016 was found to be half a million per the FDA's pediatric focus safety review.[26] Data from meta-analyses suggests aripiprazole is superior to placebo in the treatment of behavioral impairments associated with autism, but no difference was demonstrated between aripiprazole and risperidone for this treatment.[26] The

results of four other meta-analyses found aripiprazole to be superior to placebo but not to other antipsychotics in the management of tics.[26]

Weight gain, neurological effects, extrapyramidal effects, and drowsiness are common side effects.[27] Mankoski, *et al.* (2018) found weight gain is more common in younger pediatric patients and those without previous exposure to antipsychotic medications.[27] Adverse effects such as EPS, weight gain, metabolic effects, and drowsiness may be considered more important to monitor in children and adolescents than adults.[26]

Aripiprazole does come with a boxed warning of increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. These populations should be monitored for worsening and emergence of suicidal thoughts or behaviors.[14]

Geriatric

For geriatric patients, careful monitoring and initiation doses of aripiprazole in the low range then titrating doses slowly is recommended.[4] In older patients, aripiprazole has the potential to cause or exacerbate hyponatremia or the syndrome of inappropriate antidiuretic hormone (SIADH).[28] Sodium levels should be monitored when the drug is started and during any dose adjustments.[28] If use is required in the geriatric population, reduction of other CNS depressants and implementation of fall risk strategies should be considered. The treatment of dementia-related psychosis in geriatric patients with antipsychotics is not approved and use should be avoided if possible due to increased morbidity and mortality.

Renal Impairment

No dose adjustment of aripiprazole is recommended for patients with any degree of renal impairment.[4,6] Because aripiprazole has a large volume of distribution and is protein-bound, it is unlikely to be removed via hemodialysis and no dose adjustments are recommended for these patients.[4,6] Additionally, dose adjustment is not recommended for patients undergoing peritoneal

dialysis, continuous renal replacement therapy, or sustained, low-efficiency diafiltration.[4,6]

Hepatic Impairment

No dose adjustments are recommended for patients with hepatic impairment.[4,6]

Clinical Studies

Bipolar I Disorder

The initial clinical trials of aripiprazole as an acute treatment for the onset of manic episodes in patients who had bipolar I disorder established its effectiveness for this purpose. Subsequent research, published literature, authoritative reviews, and meta-analyses have confirmed this and have reported significant efficacy in reducing the severity of manic episodes in patients who have bipolar disorder.[29-32]

Long-acting injectable aripiprazole was approved in July 2017 by the FDA as a maintenance monotherapy treatment for adults who have bipolar I disorder.[33] A double-blind, placebo-controlled, 52-week randomized withdrawal study was conducted in which patients with Bipolar 1 who were currently experiencing a manic episode were stabilized sequentially on oral aripiprazole and LAI aripiprazole 400 mg. They were then randomized to either long-acting aripiprazole 400 mg or placebo.[34] This study found that a once-a-month 400 mg IM dose of aripiprazole significantly decreased the time to recurrence of mood episodes and the rate of mood episodes.[34]

Major Depressive Disorder

Atypical antipsychotics are recommended as adjunctive agents for the treatment of major depressive disorder. Aripiprazole has been approved by the FDA as an adjunctive agent for the treatment of major depressive disorder and has a comparatively favorable benefit and risk profile. Initial clinical trials

and later research established that aripiprazole is effective and that the clinical benefits are long-lasting.[35-38]

A network meta-analysis of 65 randomized trials investigated the effectiveness of medications for augmentation of depression. Results included direct comparisons between medications and medications compared to placebo.[37] Aripiprazole demonstrated low rates of discontinuation and great benefit as an augmentation agent.[37] In another study, aripiprazole demonstrated better remission rates at week 6 over bupropion but overall similar efficacy and tolerability as augmentation therapy for patients treated for major depressive disorder who did not respond to SSRI treatment.[38]

Schizophrenia

Aripiprazole has been proven to be an effective treatment for schizophrenia.[39-45] Comparative studies of atypical antipsychotics have low to very low-quality evidence and are difficult to use clinically. However, there are definite and important differences between antipsychotics in their adverse effect profiles and their suitability for a specific patient.[39-45] A 2018 review of aripiprazole use in the treatment of schizophrenia suggests it has similar efficacy when compared to both atypical and typical antipsychotic drugs, with the exception of olanzapine and amisulpride.[40] Notably, in this review, aripiprazole was found to cause lower weight gain and fewer changes in cholesterol levels compared to risperidone, olanzapine, and clozapine and less extrapyramidal side effects than typical antipsychotics and risperidone.[40]

Long-acting injectable antipsychotics, including aripiprazole, have been effective at reducing the symptoms of schizophrenia.[43,44] Long-acting injectable antipsychotics have inherent advantages over oral formulations, such as need for less frequent dosing that would intuitively seem to help increase patient adherence.[43,44] Long-acting injectable aripiprazole therapy results in improved symptoms for patients with a favorable safety profile.[44,45]

A study published in December 2022 discusses the use of aripiprazole and its therapeutic and metabolic effects associated with gene polymorphisms.[46] Currently, a reduced dose is recommended for individuals who are CYP2D6 poor metabolizers. It has been postulated that other polymorphisms can influence the therapeutic effect of aripiprazole including CYP3A4, CYP3A5, ABCB1, DRD2, and 5-HTRs genes. Genetic variants may also help explain the increased levels of prolactin, C-peptide, insulin, and cholesterol seen in some patients.[46] Authors of this study suggest that a specific genetic profile can help determine the predicted effectiveness and tolerability of aripiprazole; however, they do admit that further extensive pharmacogenomic studies are needed to assess the true relevance of gene polymorphisms in regard to aripiprazole.[46]

Autistic Disorder

Aripiprazole has FDA approval and has been recommended for treating irritability in children who have autism spectrum disorder.[47-49] Multiple clinical trials found that aripiprazole significantly improved the Aberrant Behavior Checklist (ABC) and Clinical Global Impressions – Improvement (CGI-I) scale of children and adolescents.[48-50]

One 52-week, open-label study of aripiprazole flexible-dosing of 2–15 mg/day focused on treating irritability associated with autistic disorder in children and adolescents.[51] An estimated 38.2% of the study subjects were given concomitant antidepressants (13.4%), psychostimulants (11.5%), and antiepileptics (5.9%).[51] At week 52, the authors reported a mean change from baseline in Aberrant Behavior Checklist Irritability subscale scores was −8.0 in de novo subjects and −6.1 in prior placebo subjects; subjects who were previously on aripiprazole maintained symptom improvement that was achieved with treatment in the prior study.[51] Most subjects reportedly had a Clinical Global Impressions–Improvement score of 2 (much improved) or 1 (very much improved).[51]

The evidence suggests aripiprazole may be an effective maintenance treatment for symptoms of irritability in children with autistic disorder.[49-51] Clinicians should be informed that aripiprazole use has been associated with significant side effects including aggression, extrapyramidal symptoms, increased appetite, sedation, and weight gain.[49-51]

Tourette Syndrome

Aripiprazole was approved by the FDA for the treatment of Tourette syndrome in 2014.[52] Case reports found aripiprazole was effective in treating tics in children and adolescents with Tourette syndrome, and a clinical study measuring its effectiveness with the Yale Global Tic Severity Scale (YGTSS) and the Clinical Global Impression – Tourette Syndrome (CGI-TS) confirmed the data from earlier research.[52,53] In this study, a significant reduction was seen on the YGTSS in the treatment with aripiprazole group of total tic score compared to placebo and the CGI-TS showed 'much improved' and 'very much improved' in the treatment group. A subsequent study suggested aripiprazole could be a treatment option for children and adolescents with tic disorders.[54] Adverse events common to this age group in this study were somnolence, headache, sedation, nausea, and vomiting.[54]

Suicidal Ideation

The FDA requires a U.S. Boxed Warning about antidepressants and suicide. Aripiprazole is not categorized as an antidepressant; however, atypical antipsychotics are often prescribed for patients who have unipolar major depression. Although the FDA data analysis that was used as the basis for the U.S. Boxed Warning about antidepressants and suicide did not include information about the atypical antipsychotics, the prescribing information for aripiprazole and other atypical antipsychotics is required to include the U.S. Boxed Warning about suicide.[6,8]

There is some evidence that atypical antipsychotics may reduce the risk of suicide. To this end, certain atypical antipsychotics have a labeled use for reducing the risk of suicidal behavior in patients with schizophrenia or

schizoaffective disorder.[55] The strength of this effect and whether it truly occurs is unclear and this is also true of aripiprazole. There is encouraging evidence that aripiprazole decreases the risk of suicide, but the evidence is not conclusive.[56] Ringbäck, *et al.* (2014) reported that patients who were prescribed aripiprazole, along with patients prescribed clozapine or olanzapine, had a reduced risk of suicide compared to patients administered other antipsychotics.[55] Weisler, *et al.* (2011) reported on study subjects prescribed aripiprazole 2 mg, 10 mg, or a placebo for six weeks and suicidal ideation was noticed more in subjects who had taken the placebo.[56] A 2019 study in *JAMA Psychiatry* found no association between aripiprazole and self-harm or suicide in a study of more than 1600 patients treated with aripiprazole.[57]

Dementia-Related Psychosis

The prescribing information for many of the atypical antipsychotics has a U.S. Boxed Warning that advises clinicians that the use of these drugs in elderly patients who have dementia increases the risk of death.[6,8] This Boxed Warning was added to the prescribing information because an analysis by the FDA of 17 placebo-controlled trials found that the risk of death in the treated patients was 1.7 times that of the patients who received a placebo.[58] A systematic review evaluated data from meta-analyses focused on use of antipsychotic agents in patients with dementia.[59] Results found while these medications have some efficacy in managing aggression and agitation in this patient population, their adverse effect profile limits use.[59] In particular, aripiprazole has demonstrated some benefit in the treatment of aggression and psychosis in patients with Alzheimer's disease.[59]

Rubino, *et al.* (2020) stated that "several studies reported a decreased prevalence of antipsychotic medication use by elderly patients with dementia after the 2005 warning. However, the warning's long-term association with health outcomes in elderly patients remains unknown."[60] The authors attempted to compare the use of atypical antipsychotics with other psychiatric medications and opioids by looking at health events, cardiovascular and cerebrovascular events, falls, fractures, and mortality. According to Furey and

Wilkins (2016), no FDA-approved treatment options are available for prescribers to reference in the treatment of dementia-related behavioral disorders, such as agitation and psychosis, but there are randomized controlled trials supporting atypical antipsychotic use in cautious amounts to help control symptoms.[61] Expert consensus and professional guidelines reference second-generation antipsychotics for certain cases involving elderly patients where another treatment has failed.[61] The off-label atypical antipsychotic use for elderly patients, including those diagnosed with dementia has reportedly increased over the recent years.[61]

Look-alike/Sound-alike Concerns

The Institute for Safe Medication Practices publishes a List of Confused Drugs Names that contain look-alike, sound-alike (LASA) name pairs of medications.[62] Medications included on this list should have special safeguards in place to minimize the risk of harm. The Institute for Safe Medication Practices notes that "ARIPiprazole" could be confused with "proton pump inhibitors" or RABEprazole.[62] Pharmacists are encouraged to take steps to prevent medication errors due to these similarities.

Storage and Handling

The following storage requirements are noted for aripiprazole dosage forms.[4,7,11,14]

Table 5: Storage Recommendations

Dosage Form	Storage Requirements
Oral tablets and solution	● Store at 25°C (77°F) ○ Excursions permitted to 15°C to 30°C (59°F to 86°F) ● Use oral solution within 6 months after opening ● Do not store in humid conditions
Prefilled Dual Chamber Syringe (Abilify Maintena)	● Store below 30°C (86°F) ● Do not freeze

	● Protect from light and store in the original package
Vial for reconstitution (Abilify Maintena)	● Store unused vials at 77°F ○ Excursions permitted to 59°F to 86°F ● If the suspension is not administered immediately after reconstitution, store at room temperature in the vial (do not store in a syringe).
Mycite patch	● Store at 20°C to 25°C (68°F to 77°F) ○ Excursions permitted to 15°C to 30°C (59°F to 86°F) ○ Do not store in humid conditions ● Store wearable sensor between 15°C to 30°C (59°F to 86°F) ○ can be stored in 15% to 93% relative humidity
Aripiprazole lauroxil formulations	● Store at 20°C to 25°C (68°F to 77°F) ○ Excursions permitted to 15°C to 30°C (59°F to 86°F)

Patient Counseling

Patients who are receiving aripiprazole treatment and their caregivers should be counseled on its purpose using patient-friendly language. They should be instructed on how to take the medication appropriately and what to do in the event they miss a dose of medication. Potential side effects of the medication, including common and serious adverse reactions, should be discussed. Pharmacists should also counsel patients on ways to mitigate these side effects. Patients should be instructed to contact their prescribing physician if they experience serious side effects and to go to the closest emergency room if they experience highly concerning effects, including anaphylaxis, signs of high blood sugar, trouble controlling body movements, seizures, or blurred vision. Patients should be instructed to store aripiprazole under appropriate conditions and to refill the medication on time in order to not interrupt therapy. Pharmacists are encouraged to use the teach-back

method to ensure patient understanding. Pharmacy technicians can aid in adherence by making the refill process as smooth as possible and facilitating phone calls to patients if medication has not been picked up but is ready to be dispensed.

Summary

Aripiprazole is a second-generation, atypical antipsychotic that is best known under the brand name Abilify®. It was originally approved for the treatment of schizophrenia and bipolar I disorder, but it has also been used for other psychiatric conditions in children and adults.

Aripiprazole is available in oral and long-acting injectable forms, which have unique pharmacokinetic profiles that must be considered when formulating a treatment plan. It is important for clinicians to understand the pharmacokinetic and other differences between the oral and long-acting forms of aripiprazole. A misunderstanding of these differences may lead to poorer outcomes for patients. A long-acting injectable form of aripiprazole will impact the time it takes for the drug to reach steady state, because of its slower rate of absorption.

Aripiprazole has a favorable side-effect profile when compared to other antipsychotics. Children and adolescents have been reported to have an increase in extrapyramidal side effects when they are treated with aripiprazole. There are also recommendations clinicians should follow when switching to aripiprazole from another antipsychotic.

Course Test

1. **Aripiprazole is categorized as a second-generation**

    a. anticonvulsant.
    b. atypical antipsychotic.
    c. mood stabilizer.
    d. typical antipsychotic.

2. **Aripiprazole is available in which of the following formulations for use in schizophrenia**

    a. Aripiprazole oral tablets and solution
    b. Aripiprazole for extended-release injectable suspension
    c. Aripiprazole lauroxil extended-release injectable suspension
    d. All of the above

3. **Aripiprazole is a dopamine**

    a. antagonist.
    b. blocker.
    c. full antagonist.
    d. partial agonist.

4. **Aripiprazole is FDA-approved and used as an adjunctive therapy to treat**

    a. major depressive disorder.
    b. schizophrenia.
    c. bipolar I disorder.
    d. elderly patients with dementia-related psychosis.

5. **True or False: Abilify Mycite tablets can be crushed or chewed when taken.**

    a. True
    b. False

6. **The long-acting injectable forms of aripiprazole exhibit _____ that impacts the time it takes for the drug to reach a steady state.**

    a. rapid absorption
    b. D_2 antagonism
    c. flip-flop kinetics
    d. rapid concentration

7. **Dose guidelines for Tourette syndrome**

    a. are based on patient weight.
    b. are based on patient height.
    c. are the same as dosing for schizophrenia.
    d. have no maximum dosage.

8. **True or False: The Institute for Safe Medication Practices notes that "ARIPiprazole" could be confused with "proton pump inhibitors" or RABEprazole.**

    a. True
    b. False

9. **Patients taking aripiprazole should be counseled that**

    a. there is no risk of metabolic side effects or weight gain.
    b. only children are at risk of extrapyramidal symptoms.
    c. oculogyric crisis (OGC) is relatively common and self-resolving.
    d. an association between the use of aripiprazole and compulsive behaviors, including gambling, binge eating, shopping, or engaging in sex has been reported.

10. **When should dose adjustments be made with aripiprazole?**

    a. For hepatic impairment
    b. For renal impairment
    c. For both hepatic and renal impairment.
    d. No adjustment is needed with aripiprazole for hepatic or renal impairment.

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Healthcare professionals, including pharmacists and pharmacy technicians, must consult with their employer, healthcare facility, hospital, or other organization, for guidelines, protocols, and procedures they are to follow. The information provided in this course does not replace those guidelines, protocols, and procedures but is for academic purposes only, and this course's limited purpose is for the completion of continuing education credits.

Participants are advised and acknowledge that information related to medications, their administration, dosing, contraindications, adverse reactions, interactions, warnings, precautions, or accepted uses are constantly changing, and any person taking this course understands that such person must make an independent review of medication information prior to any patient assessment, diagnosis, treatment and/or health management. Any

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