Abilify

Pharmacology, Warnings, Pregnancy, Lactation, Side Effects, IV Compatibility, Dosage, Additional Dosage

Pharmacology (Top)

Pharmacology

Aripiprazole is a psychotropic drug.

The mechanism of action is unknown. It is theorized that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D 2 and 5-HT1A receptors and antagonist activity at 5 HT 2 A receptors. The orthostatic hypotension reported with the use of aripiprazole may be explained by its antagonist activity at adrenergic alpha-1 receptors.

Aripiprazole in oral formulation is approved by the FDA for the treatment of schizophrenia, acute and maintenance treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate, and as adjunctive treatment of major depressive disorder. Aripiprazole as an injection is approved by the FDA for the acute treatment of agitation associated with schizophrenia or bipolar I disorder.

While not FDA approved indications, aripiprazole may be useful in the treatment of Tourette's syndrome, Asperger disorder, Alzheimer's disease associated psychosis, and relapse prevention and craving in alcohol dependent patients. It may also be useful as augmentation therapy for the treatment of refractory obsessive-compulsive disorder. However, additional studies are required in order to establish efficacy.

Pharmacokinetics

Aripiprazole is available for oral administration as a tablet, an orally disintegrating tablet, and an oral solution. According to pharmacokinetic studies, the orally disintegrating tablets are bioequivalent to the oral tablets.

The absolute oral bioavailability of the tablet is 87%.

The peak plasma concentration (Cmax) has been reported to occur within 3 to 5 hours (Tmax). Peak plasma concentrations of aripiprazole from the solution were higher than that from the tablet. The Cmax of aripiprazole and dehydro-aripiprazole increased an average of 36% and 53%, respectively, in patients with severe renal dysfunction (CrCl < 30 mL/min). However, this does not appear to have clinical significance. Slight deviations in the bioavailability of aripiprazole have been reported in patients with liver dysfunction. However, these deviations appear to be clinically insignificant.

Both aripiprazole and the active metabolite dehydro-aripiprazole are greater than 99% bound to serum proteins, primarily albumin.

The average volume of distribution following intravenous administration is 4.9 L/kg.

Specific plasma clearance data has not been reported. Single dose studies have reported that aripiprazole clearance was 20% lower in patients over 64 years of age (compared to patients from 18 to 64 years of age). However, there was no detectable age effect in the population pharmacokinetic analysis in schizophrenic patients or in pharmacokinetic data following multiple doses.

The mean elimination half-life of aripiprazole is approximately 75 hours in extensive metabolizers of CYP450

2D6 substrates and 146 hours in poor metabolizes of CYP450 2D6 substrates.

Aripiprazole is primarily metabolized via three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. CYP450 3A4 and CYP450 2D6 enzymes are responsible for dehydrogenation and hydroxylation. N-dealkylation is catalyzed by CYP450 3A4. Aripiprazole is the primary drug moiety found in the systemic circulation. The active metabolite, dehydro-aripiprazole accounts for approximately 40% of the aripiprazole in the plasma. Following a single oral dose of radiolabeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Approximately 18% of the oral dose was recovered unchanged in the feces while less than 1% of unchanged aripiprazole was excreted in the urine.

Poor metabolizers of CYP450 2D6 substrates have approximately an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to dehydro-aripiprazole compared to extensive metabolizers, which results in approximately a 60% higher exposure to the total active moieties.

There are no data on the pharmacokinetic disposition of aripiprazole in patients with moderate renal dysfunction.

There are no data concerning hemodialysis and/or peritoneal dialysis clearance of aripiprazole.

Warnings (Top)

(Severity: General Warning Exists)

In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of aripiprazole should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count less than 1000/mm3) should discontinue aripiprazole and have their WBC followed until recovery.

Aripiprazole is not approved by the FDA for use in the treatment of patients with dementia related psychosis. Collective data from 17 placebo-controlled clinical studies (n=5106) involving the use of atypical antipsychotic agents, including aripiprazole, for the treatment of behavioral disorders in the elderly patient with dementia showed a risk of death 1.6 to 1.7 times greater in the drug- treated patient than in the placebo treated patient. The average length of duration for the trials was 10 weeks with the cause of death in the majority of cases, though not all, reported as either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Similar results (i.e., increased risk of mortality with atypical antipsychotics) were reported in another meta-analysis involving elderly dementia patients that consisted of 15 randomized, placebo-controlled trials (n=3353) of 10 to 12 weeks in duration.

Clinical studies of aripiprazole administered to patients (mean age = 84 years old) with dementia related psychosis have reported increased incidence of cerebrovascular events (e.g., stroke, transient ischemic attack), including fatalities, in this population.

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Clinical studies involving the use of aripiprazole in elderly patients with Alzheimer's disease have reported a significant increase in the incidence of lethargy, somnolence (including sedation), incontinence (primarily urinary incontinence), excessive salivation, and lightheadedness as compared to placebo. The safety and efficacy of aripiprazole has not been established in patients with dementia related psychosis. In addition, esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Close clinical monitoring, particularly for the emergence of difficulty swallowing or somnolence, is recommended when aripiprazole is used in the treatment of patients at risk for aspiration pneumonia, including those with Alzheimer's disease.

Neuroleptic malignant syndrome (NMS) has been reported with the use of aripiprazole. If NMS is observed, aripiprazole should be discontinued and the patient closely monitored.

Tardive dyskinesia may develop in patients treated with antipsychotic medications. If signs and symptoms of tardive dyskinesia are observed in a patient on aripiprazole, drug discontinuation should be considered. However, some patients may require therapy with aripiprazole despite the presence of the syndrome.

Extreme cases of hyperglycemia associated with ketoacidosis, hyperosmolar coma, or death have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with aripiprazole.

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia. However, epidemiological studies (which did not include aripiprazole) have suggested an increased risk of treatment-emergent hyperglycemia related adverse events in patients treated with the atypical antipsychotics. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk.

An exhaustive review of the aripiprazole database revealed no increased signal for diabetes. But to be cautious, it is recommended that patients treated with atypical antipsychotics be monitored for signs and symptoms of diabetes. Patients with risk factors for diabetes mellitus (e.g., obesity, family history) who are starting treatment with atypical antipsychotics should undergo baseline screening and routine monitoring throughout therapy to mitigate the risk of developing serious metabolic complications.

Because aripiprazole has been associated with orthostatic hypotension, the drug should be used with caution in patients with known cardiovascular disease (including a history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, or treatment with antihypertensive medications). The safety and effectiveness of aripiprazole in patients with a recent history of myocardial infarction or unstable heart disease has not been determined in clinical studies.

Each mL of aripiprazole oral solution contains sucrose 400 mg and fructose 200 mg.

Because seizures have been reported in a small percentage of patients, the drug should be used with caution in the treatment of patients with a history of seizures or conditions that lower the seizure threshold (e.g., Alzheimer's disease). Conditions that lower the seizure threshold may be more prevalent in a population over 64

years of age.

Aripiprazole may have the potential to impair judgment, thinking, or motor skills. Somnolence has been reported with the use of aripiprazole. Therefore, patients should not drive or operate heavy machinery until they are certain aripiprazole does not adversely affect their ability to do so.

Because a disruption of the body's ability to reduce core temperature has been associated with the use of antipsychotic agents, caution is advised if aripiprazole is to be prescribed for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., strenuous exercise, exposure to extreme heat, concomitant medication(s) with anticholinergic activity, or being subject to dehydration).

Suicide is an inherent risk in psychotic illnesses and bipolar disorders. Patients should be closely supervised and dispensed the smallest quantity of drug possible while receiving aripiprazole therapy in order to reduce the risk of overdose.

Patients should be advised to avoid the intake of alcohol during aripiprazole therapy.

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia /diabetes mellitus, dyslipidemia, and body weight gain.

Pregnancy (Top)

(Severity: Major Female Pregnancy Warning)

Aripiprazole has been assigned to pregnancy category C by the FDA. Animal studies have revealed evidence of developmental toxicity, including possible teratogenic effects. There are no controlled data in human pregnancy. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization. Aripiprazole should only be given during pregnancy if the potential benefits outweigh the potential risks.

According to 1 case report, exposure to aripiprazole (10 mg/day initially then increased to 15 mg/day over 2 weeks) at week 29 of gestation until 6 days prior to delivery did not result in adverse peri- or post- natal effects.

Lactation (Top)

(Severity: Major Lactation Warning)

There are no data on the excretion of aripiprazole into human milk. The manufacturer recommends that women receiving aripiprazole should not breast-feed.

Side Effects (Top)

Nervous system

Nervous system side effects have frequently included agitation (25%), anxiety (20% to 25%), insomnia (20% to 24%), akathisia (10% to 15%), lightheadedness (11%), somnolence (11% to 12%), dizziness (11%), sedation (7%), extrapyramidal syndrome (6%), tremor (3% to 9%), restlessness (5%), increased salivation (3%),

nervousness, confusion, and abnormal gait. Twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, decreased libido, hypersomnia, dyskinesia, ataxia, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, tardive akathisia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, and slowed thinking have been reported infrequently. Blunted affect, euphoria, incoordination, hypotonia, buccoglossal syndrome, decreased reflexes, and intracranial hemorrhage have been reported rarely. Seizures have been reported in less than 0.1% to 0.3% of patients. Grand mal seizures have been reported in postmarketing experience.

Gastrointestinal

Gastrointestinal side effects have included nausea (14% to 16%), dyspepsia (15%), constipation (10% to 13%), vomiting (11% to 12%), dry mouth (5%), abdominal discomfort (3%), and salivary hypersecretion (2%). Increased appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis, gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess, fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis, mouth ulcer, oral moniliasis, eructation, fecal impaction, loose stools, abdominal distention, hematochezia, gingival pain, lower abdominal pain, oral pain, retching, fecaloma, tooth fracture, dry lip, and cholelithiasis have been reported infrequently. Esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, peptic ulcer, glossitis, melena, duodenal ulcer, cheilitis, abdominal tenderness, chapped lips, periodontitis, aptyalism, gastrointestinal pain, oral hypoesthesia, inguinal hernia, hyperchlorhydria, irritable bowel syndrome, esophagitis, gingival bleeding, glossodynia, melena, and pancreatitis have been reported rarely.

Dermatologic

Dermatologic side effects have frequently included skin ulcer, sweating, and dry skin. Pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea, cellulitis, onychomycosis, and psoriasis have been reported infrequently. Maculopapular rash, exfoliative dermatitis, folliculitis, pustular rash, and urticaria have been reported rarely.

Other 1

Other side effects have frequently included headache (31% to 32%), asthenia (7% to 8%), accidental injury (5% to 6%), fatigue (6%), pain (3%), fever (2%), peripheral edema (2%), flu syndrome, chest pain, neck pain, pelvic pain, and rigidity in the neck and/or extremities. Face edema, suicide attempt, malaise, chills, photosensitivity, arm rigidity, jaw pain, bloating, tightness (abdomen, back, extremity, head, jaw, neck, and tongue), enlarged abdomen, chest tightness, throat pain, ear pain, tinnitus, otitis media, altered taste, pyrexia, gait disturbance, edema, general physical health deterioration, feeling jittery, decreased mobility, thirst, feeling cold, difficulty in walking, facial pain, sluggishness, candidiasis, and deafness have been reported infrequently. Moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke, otitis externa, vertigo, localized inflammation, swelling, increased energy, abasia, xerosis, hyperthermia, hypothermia, septic shock, appendicitis, and neuroleptic malignant syndrome have been reported rarely.

Respiratory

Respiratory side effects have frequently included bronchitis (6%), pharyngitis (4%), rhinitis (4%), coughing (3%), sinusitis, dyspnea, pneumonia, and asthma. Epistaxis, hiccup, laryngitis, and aspiration pneumonia have been reported infrequently. Pulmonary edema, increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal passages, and hemoptysis have been reported rarely.

Musculoskeletal

Musculoskeletal side effects have frequently included arthralgia (5%), myalgia (4%), pain in extremities (4%), and muscle cramp. Myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, and myopathy have been reported infrequently. Rheumatoid arthritis, rhabdomyolysis, tendonitis, and tenosynovitis have been reported rarely.

Ocular

Ocular side effects have frequently included blurred vision (3%) and conjunctivitis. Dry eye, eye pain, cataract, blepharitis, eye redness, eye irritation, blepharospasm, visual disturbance, eye discharge, increased lacrimation, and eye hemorrhage have been reported infrequently. Diplopia, frequent blinking, ptosis, amblyopia, photophobia, eyelid function disorder, eyelid edema, and oculogyric crisis have been reported rarely.

Hypersensitivity

Hypersensitivity side effects have rarely included anaphylactic reaction, angioedema, laryngospasm, oropharyngeal spasm, pruritus, and urticaria.

Cardiovascular

Cardiovascular side effects have frequently included hypertension (2%), hypotension, bradycardia, and both ventricular and supraventricular tachycardia. Palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, cyanosis, and phlebitis have been reported infrequently. Bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, cardiomyopathy, thrombophlebitis, and cardiopulmonary failure have been reported rarely.

Hematologic

Hematologic side effects have frequently included ecchymosis and anemia. Hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, eosinophilia, and macrocytic anemia have been reported infrequently. Thrombocythemia, thrombocytopenia, idiopathic thrombocytopenic purpura, and petechiae have been reported rarely. A reversible case of elevated triglyceride levels has also been reported.

In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including aripiprazole. Agranulocytosis has also been reported.

Metabolic

Metabolic side effects have frequently included weight loss, increased creatine phosphokinase, and dehydration. Edema, hyperglycemia, hypercholesterolemia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, increased SGPT, thirst, increased BUN, hyponatremia, increased SGOT, increased creatinine, cyanosis, increased alkaline phosphatase, bilirubinemia, iron deficiency anemia, hyperkalemia, hyperuricemia, and obesity have been reported infrequently. Increased lactic dehydrogenase, hypernatremia, gout, and hypoglycemic reaction have been reported rarely.

Psychiatric

Psychiatric side effects have frequently included depression, schizophrenic reaction, hallucination, hostility, paranoid reaction, suicidal thought, manic reaction, delusions, and abnormal dream. Emotional lability, panic attack, manic depressive reaction, and visual hallucination have been reported infrequently. Obsessive thought and derealization have been reported rarely. In addition, at least one case of worsening psychosis has been

associated with aripiprazole.

Genitourinary

Genitourinary side effects have frequently included vaginitis (6%), urinary tract infection (5%), and urinary incontinence. Urinary frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency, gynecomastia, kidney calculus, albuminuria, breast pain, vaginal infection, vaginal mycosis, vaginal candidiasis, pyelonephritis, and urinary burning have been reported infrequently. Nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage, female lactation, urolithiasis, and priapism have been reported rarely.

Hepatic

Hepatic side effects have rarely included hepatitis, hepatomegaly, cholecystitis, and cholelithiasis. Jaundice has been reported in postmarketing experience.

Endocrine

Endocrine side effects have infrequently included hypothyroidism. Goiter, hyperthyroidism, and hyperparathyroidism have been reported rarely.

General

In general, the incidence of side effects does not appear to be influenced by the age, gender, or race of the patient. Side effects associated with aripiprazole are generally reported within the first week of therapy and resolve within 7 days.

Tardive dyskinesia involves involuntary, dyskinetic, repetitive movements and may be more common in the elderly, especially elderly women, receiving antipsychotics, such as aripiprazole. The exact etiology for the development of tardive dyskinesia secondary to treatment with antipsychotics is unknown. However, research has suggested that the chance of developing tardive dyskinesia and the likelihood that it will be irreversible are increased as the total duration of treatment and the total cumulative dose of antipsychotic medication administered to the patient increase. If a patient receiving aripiprazole therapy shows signs and/or symptoms of tardive dyskinesia discontinuation of therapy should be considered; however, this may not be a clinically feasible option for all patients.

The manufacturer reports elderly patients (mean = 84 years old) enrolled in placebo-controlled studies examining the use of aripiprazole for the treatment of dementia-related psychosis showed an increased incidence of cerebrovascular side effects, e.g. stroke and transient ischemia attacks, including fatalities. The incidence of these effects may be dose related.

A dose-response relationship may exist between aripiprazole and somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

A possible worsening of preexisting agitation with the initiation of aripiprazole therapy has been reported.

Two cases of aripiprazole-induced acute dystonia have been reported. In one case, symptoms resolved following treatment with trihexyphenidyl and in the other case after discontinuation of aripiprazole. Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and

at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

At least two cases of aripiprazole-induced seizures have been reported. Conditions that lower the seizure threshold, e.g., Alzheimer's dementia, may be more prevalent in a population over 64 years of age.

Several cases of aripiprazole-associated neuroleptic malignant syndrome (NMS) have been reported. It should be noted that NMS which is usually characterized by muscle rigidity, dysphagia, tremor, fever, diaphoresis, anxiety, tachycardia, labile blood pressure, and altered consciousness may present in an atypical manner with aripiprazole (i.e., delayed or late onset of typical symptoms such as hyperthermia). One identified potential risk factor for developing NMS is the period during a switch from one antipsychotic treatment to another.

Collective data gathered from 17 placebo-controlled clinical studies (n=5106) involving the use of atypical antipsychotic agents, including aripiprazole, for the treatment of behavioral disorders in the elderly patient with dementia showed a risk of death 1.6 to 1.7 times greater in the drug- treated patient than in the placebo- treated patient. The average length of duration for the trials was 10 weeks with the cause of death in the majority of cases, though not all, reported as either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Aripiprazole is not approved by the FDA for use in the treatment of behavioral disorders in elderly patients with dementia.

An increased risk of mortality, possibly due to an infection such as pneumonia, has been reported with the use of aripiprazole in the treatment of behavioral disorders in the elderly patient with dementia.

Aripiprazole may be associated with orthostatic hypotension.

Collective data gathered from 17 placebo-controlled clinical studies (n=5106) involving the use of atypical antipsychotic agents, including aripiprazole, for the treatment of behavioral disorders in the elderly patient with dementia showed a risk of death 1.6 to 1.7 times greater in the drug-treated patient than in the placebo-treated patient. The average length of duration for the trials was 10 weeks with the cause of death in the majority of cases, though not all, reported as either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Similar results (i.e., increased risk of mortality with atypical antipsychotics) were reported in another meta-analysis involving elderly dementia patients that consisted of 15 randomized, placebo-controlled trials (n=3353) of 10 to 12 weeks in duration. Aripiprazole is not approved by the FDA for use in the treatment of behavioral disorders in elderly patients with dementia.

An increased risk of mortality, possibly due to heart failure or sudden death, has been reported with the use of aripiprazole in the treatment of behavioral disorders in the elderly patient with dementia.

One case of dose-dependent incomplete right bundle-branch block has been reported following use of aripiprazole. Electrocardiographic findings returned to normal after discontinuation of aripiprazole.

A case of hypertensive crisis with tachycardia, confirmed upon rechallenge, has been reported following treatment with aripiprazole.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of aripiprazole should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.
Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count less than 1000/mm3) should discontinue aripiprazole and have their WBC followed

until recovery.

Extreme cases of hyperglycemia associated with ketoacidosis, hyperosmolar coma, or death have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with aripiprazole.

Although rare, aripiprazole-induced hyponatremia has been reported. In one case, hyponatremia developed two days after initiating therapy with aripiprazole 10 mg daily and resolved one week after discontinuation of treatment.

A possible worsening of preexisting schizoaffective disorder with the initiation of aripiprazole therapy has been reported.

Two cases of treatment-emergent psychosis and induction of mania have been reported in patients with schizoaffective disorder- bipolar type being switched to aripiprazole from high-potency dopamine receptor antagonists (i.e., perphenazine, fluphenazine). Symptoms resolved in both patients following discontinuation of aripiprazole.

One case of recurrent priapism associated with the use of aripiprazole has been reported. In this case, the first episode of priapism occurred within hours of the first dose of aripiprazole and following treatment for priapism the patient proceeded to have additional episodes of priapism over a period of 7 days even though no additional doses of aripiprazole were taken. The authors suggest that the recurrence of priapism over a week can be explained by aripiprazole's long half-life.

IV Compatibility (Top)

DESCRIPTION

D10W	D5¼S	D5½S	D5LR	D5NS	D5R	D5W	LR	NS	R	SODLAC	UNSP

Aripiprazole is available in single dose vials as a ready to use, clear, colorless, sterile, aqueous solution for intramuscular use only (2022).

STABILITY

D10W	D5¼S	D5½S	D5LR	D5NS	D5R	D5W	LR	NS	R	SODLAC	UNSP
											C

Aripiprazole should be stored at 25°C, and protected from light by storing in the original container (2022).

Source: *King's (R) Guide to Parenteral Admixtures (R)*

Dosage (Top)

Usual Adult Dose

Schizophrenia

Initial Dose: 10 or 15 mg tablet or solution orally once a day
Maintenance Dose: 10 to 30 mg per day. However, clinical trials found doses exceeding 10 or 15 mg per day

were no more effective than 10 or 15 mg per day.

Dosage increases should not be made before two weeks (the time needed to achieve steady state).

Bipolar Disorder

Starting and target dose: 15 mg tablet orally once a day as monotherapy or as adjunctive therapy with lithium or valproate. The dose can be increased to 30 mg tablet (or 25 mg solution) per day based on clinical response. The safety of doses above 30 mg per day has not been evaluated in clinical trials.

Agitated State

Treatment of agitation associated with schizophrenia or bipolar disorder (manic or mixed):
Initial dose: 5.25 mg to 15 mg IM once
If needed, dose may be repeated no more frequently than every 2 hours
Maximum dose: 30 mg IM per day

Depression

For use as adjunctive treatment for patients already taking an antidepressant:

Initial Dose: 2 mg per day to 5 mg per day
Maintenance Dose: 2 mg per day to 15 mg per day

Dose adjustments of up to 5 mg per day should occur gradually, at intervals of no less than 1 week.

The long-term efficacy of aripiprazole for the adjunctive treatment of major depressive disorder has not been established.

Usual Pediatric Dose

Schizophrenia

13 to 17 years:
Initial Dose: 2 mg tablet or solution orally once a day
After 2 days: Titrate to 5 mg per day
After 4 days: Titrate to 10 mg per day

Subsequent dosage increases should be administered in 5 mg increments.

Maintenance Dose: 10 to 30 mg per day. However, the 30 mg per day was not shown to be more effective than 10 mg per day.

Bipolar Disorder

Acute treatment of manic and mixed episodes associated with Bipolar Disorder with or without psychotic features as monotherapy or as adjunctive therapy with lithium or valproate:
10 to 17 years:
Initial Dose: 2 mg tablet or solution orally once a day
After 2 days: Titrate to 5 mg per day
After 4 days: Titrate to 10 mg per day

Subsequent dosage increases should be administered in 5 mg increments up to 30 mg tablet (or 25 mg solution) per day. However, the 30 mg per day was not shown to be more effective than 10 mg per day.

Autism

Treatment of irritability associated with autistic disorder (including aggression, deliberate self injurious behavior, temper tantrums, and quickly changing moods):
6 to 17 years:
Initial dose: 2 mg daily for 7 days, followed by 5 mg daily; subsequent dose increases may be made in 5 mg increments every 7 days, up to a maximum of 15 mg/day

Tourette's Syndrome

Tourette's syndrome, tic disorders: Children and Adolescents 7-18 years: Limited information exists in literature: Dose is not established; small, open labeled clinical trials and retrospective observational studies suggest low doses (2.5-5 mg/day) may be efficacious. Studies used the following doses: Initial dose: 1.25 to 5 mg/day; daily doses were increased by 1.25 to 2.5 mg weekly or by 5 mg every 2 weeks. Maximum dose: 15 to 20 mg/day. Reported mean required doses ranged from 3.3 to 11.7 mg/day.

Additional Dosage (Top)

Renal Dose Adjustments

No adjustment recommended

Liver Dose Adjustments

No adjustment recommended

Dose Adjustments

In general, no dosage adjustment is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function.

Precautions

Aripiprazole is not approved by the FDA for use in the treatment of dementia related psychosis. Collective data from 17 placebo-controlled clinical studies (n=5106) involving the use of atypical antipsychotic agents, including aripiprazole, for the treatment of behavioral disorders in the elderly patient with dementia showed a risk of death 1.6 to 1.7 times greater in the drug treated patient than in the placebo treated patient. The average length of duration for the trials was 10 weeks with the cause of death in the majority of cases, though not all, reported as either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Similar results (i.e., increased risk of mortality with atypical antipsychotics) were reported in another meta-analysis involving elderly dementia patients that consisted of 15 randomized, placebo-controlled trials (n=3353) of 10 to 12 weeks in duration.

Clinical studies of aripiprazole administered to patients (mean age = 84 years old) with dementia- related psychosis have reported increased incidence of cerebrovascular events (e.g., stroke, transient ischemic attack), including fatalities, in this population.

Clinical studies involving the use of aripiprazole in elderly patients with Alzheimer's disease have reported a significant increase in the incidence of lethargy, somnolence (including sedation), incontinence (primarily

urinary incontinence), excessive salivation, and lightheadedness as compared to placebo. The safety and efficacy of aripiprazole has not been established in patients with dementia- related psychosis. In addition, esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Close clinical monitoring, particularly for the emergence of difficulty swallowing or somnolence, is recommended when aripiprazole is used in the treatment of patients at risk for aspiration pneumonia, including those with Alzheimer's disease.

Neuroleptic malignant syndrome (NMS) has been reported with the use of aripiprazole. If NMS is observed, aripiprazole should be discontinued and the patient closely monitored.

Tardive dyskinesia may develop in patients treated with antipsychotic medications. If signs and symptoms of tardive dyskinesia are observed in a patient on aripiprazole, drug discontinuation should be considered. However, some patients may require therapy with aripiprazole despite the presence of the syndrome.

Extreme cases of hyperglycemia associated with ketoacidosis, hyperosmolar coma, or death have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with aripiprazole.

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia. However, epidemiological studies (which did not include aripiprazole) have suggested an increased risk of treatment-emergent hyperglycemia- related adverse events in patients treated with the atypical antipsychotics. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk.

An exhaustive review of the aripiprazole database revealed no increased signal for diabetes. But to be cautious, it is recommended that patients treated with atypical antipsychotics be monitored for signs and symptoms of diabetes. Patients with risk factors for diabetes mellitus (e.g., obesity, family history) who are starting treatment with atypical antipsychotics should undergo baseline screening and routine monitoring throughout therapy to mitigate the risk of developing serious metabolic complications.

Because aripiprazole has been associated with orthostatic hypotension, the drug should be used with caution in patients with known cardiovascular disease (including a history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, or treatment with antihypertensive medications). The safety and effectiveness of aripiprazole in patients with a recent history of myocardial infarction or unstable heart disease has not been determined in clinical studies.

Each mL of aripiprazole oral solution contains sucrose 400 mg and fructose 200 mg.

Because seizures have been reported in a small percentage of patients, the drug should be used with caution in the treatment of patients with a history of seizures or conditions that lower the seizure threshold (e.g., Alzheimer's disease). Conditions that lower the seizure threshold may be more prevalent in a population over 64 years of age.

Somnolence has been reported with the use of aripiprazole. Therefore, patients should not drive or operate heavy machinery until they are certain aripiprazole does not adversely affect their ability to do so.

Because a disruption of the body's ability to reduce core temperature has been associated with the use of antipsychotic agents, caution is advised if aripiprazole is to be prescribed for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., strenuous exercise, exposure to extreme heat, concomitant medication(s) with anticholinergic activity, or being subject to dehydration).

Suicide is an inherent risk in psychotic illnesses and bipolar disorders. Patients should be closely supervised and dispensed the smallest quantity of drug possible while receiving aripiprazole therapy in order to reduce the risk of overdose.

Patients should be advised to avoid the intake of alcohol during aripiprazole therapy.

The efficacy of aripiprazole for the maintenance treatment of schizophrenia in the pediatric population has not been determined.

Dialysis

Data not available

Other Comments

The oral solution may be given on a mg per mg basis in place of the 5, 10, 15, or 20 mg tablet strengths. Solution doses can be substituted for the tablet doses on a mg per mg basis up to 25 mg of the tablet. Patients receiving 30 mg tablets should receive 25 mg of the solution.

Aripiprazole oral tablets and oral solution may be administered with or without food.

Clinicians should instruct patients to only open the foil packet containing aripiprazole discmelt oral tablets just prior to ingestion. It is recommended not to push the tablets through the foil or to split the tablets. The tablets should not come in contact with moisture and should be handled with dry hands. The tablet should be placed under the tongue immediately following removal from the foil packet. While not recommended, a small amount of liquid may be ingested with the tablet.

Use of aripiprazole for extended periods should be periodically reevaluated for the long-term usefulness of the drug in this individual patient.

The efficacy of aripiprazole for the maintenance treatment of schizophrenia in the pediatric population has not been determined.

Each mL of the oral solution contains sucrose 400 mg and fructose 200 mg.