

DRUGDEX-EV 2240

MICROMEDEX

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**ARIPIPRAZOLE**

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**0.0] Overview**

**1] Class**

**a)]** This drug is a member of the following class(es):

Antipsychotic

**2] Dosing Information**

**a)] Adult**

**1)]** Oral solution mg-per-mg dose same as tablet up to 25 mg; for 30-mg tablet, use oral solution at 25 mg [6]

**2)]** Orally disintegrating tablet dosing same as oral tablets [6]

**a)]** Bipolar I disorder, Adjunctive therapy with [lithium](#) or [valproate](#)

**1)]** Initial, 10 to 15 mg orally once a day; target, 15 mg once a day; may increase to MAX 30 mg/day [23][24]

**b)]** Bipolar I disorder, Monotherapy, manic or mixed episodes

**1)]** Initial and target dose, 15 mg orally once a day; may increase to MAX dose of 30 mg/day [23][24]

**c)]** [Borderline personality disorder](#)

**1)]** (Monotherapy) 15 mg/day orally (off-label dosage) [8]

**2)]** (Combination therapy) 10 to 15 mg/day orally added to sertraline 100 to 200 mg/day (off-label dosage) [9]

**d)]** [Drug-induced hyperprolactinemia](#), Caused by antipsychotics

1j) 5 mg orally once daily (off-label dosage) [2]

e) **Major depressive disorder**, Adjunctive treatment in patients receiving antidepressants

1j) Initial, 2 to 5 mg orally once daily; may adjust in increments up to 5 mg/day at intervals of 1 week or more; usual dosage, 2 to 15 mg/day; periodically assess the need for continued treatment [3][4]

f) **Schizophrenia**

1j) (Oral) Initial, 10 to 15 mg orally once daily; may increase after 2 weeks at each dose strength to a MAX 30 mg/day; efficacy not significantly greater with doses above 15 mg/day [11][12]

2j) (Extended-release injection) Establish tolerability with oral aripiprazole first (may take up to 2 weeks). Initial and maintenance dose, 400 mg IM once monthly; give oral aripiprazole (or continue another antipsychotic in patients with known aripiprazole tolerance) after the initial injection and continue for 14 consecutive days [14]

b) **Pediatric**

1j) Oral solution mg-per-mg dose same as tablet up to 25 mg; for 30-mg tablet, use oral solution at 25 mg [6]

2j) Orally disintegrating tablet dosing same as oral tablets [6]

a) **Autistic disorder** - Psychomotor agitation

1j) (6 to 17 years) Initial, 2 mg orally once daily, then increase to 5 mg/day; may adjust to effect in up to 5-mg/day increments at a minimum of 1-week intervals to 10 mg/day or 15 mg/day; periodically assess the need for continued treatment [3][4]

b) **Bipolar I disorder, Monotherapy, manic or mixed episodes**

1j) (10 years or older) Initial, 2 mg orally once a day for 2 days, then 5 mg once a day for 2 days, then target dose of 10 mg once a day; MAX dose 30 mg/day, titrated in 5-mg/day increments [23][24]

c) **Gilles de la Tourette's syndrome**

1j) (6 to 18 years, less than 50 kg) Initial, 2 mg orally once daily for 2 days, then increase to target dose of 5 mg once daily; if tics not controlled, may increase to 10 mg/day in intervals of not less than 1 week; periodically assess the need for continued treatment [3][4]

2j) (6 to 18 years, 50 kg or greater) Initial, 2 mg orally once daily for 2 days, then increase to 5 mg once daily for 5 days; on day 8 increase to target dose of 10 mg once daily; if

tics not controlled, may increase to 20 mg/day in increments of 5 mg/day at intervals not less than 1 week; periodically assess the need for continued treatment [3][4]

**d) Schizophrenia**

**1)**(13 to 17 years) Initial, 2 mg orally once daily; increase to 5 mg after 2 days and to 10 mg (target dose) after 2 more days; MAX 30 mg/day; efficacy not greater at 30 mg/day compared with 10 mg/day [11][12]

**3) Contraindications**

**a)** Hypersensitivity to [aripiprazole](#) [3][4][36]

**4) Serious Adverse Effects**

**a)** [Agranulocytosis](#)

**b)** [Angioedema](#)

**c)** At risk for suicide

**d)** [Cardiorespiratory arrest](#)

**e)** [Cardiorespiratory failure](#)

**f)** Cerebrovascular accident

**g)** [Diabetic ketoacidosis](#)

**h)** Increased body temperature

**i)** [Leukopenia](#)

**j)** [Myocardial infarction](#)

**k)** [Neuroleptic malignant syndrome](#)

**l)** [Neutropenia](#)

**m)** [Pancreatitis](#)

**n)** Prolonged QT interval

**o)** [Rhabdomyolysis](#)

**p)** Seizure

**q)** Suicidal behavior

**r)** [Tardive dyskinesia](#)

**s)** [Transient ischemic attack](#)

**5) Clinical Applications**

**a)** FDA Approved Indications

- 1) [Autistic disorder](#) - Psychomotor agitation
- 2) Bipolar I disorder, Adjunctive therapy with [lithium](#) or [valproate](#)
- 3) Bipolar I disorder, Monotherapy, manic or mixed episodes
- 4) [Gilles de la Tourette's syndrome](#)
- 5) [Major depressive disorder](#), Adjunctive treatment in patients receiving antidepressants
- 6) [Schizophrenia](#)

**b) Non-FDA Approved Indications**

- 1) [Borderline personality disorder](#)
- 2) [Drug-induced hyperprolactinemia](#), Caused by antipsychotics

**1.0] Dosing Information**

[Drug Properties](#)  
[Storage and Stability](#)  
[Adult Dosage](#)  
[Pediatric Dosage](#)

**1.1] Drug Properties**

**A)** Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

**B)** Synonyms

[Aripiprazole](#)

**C)** Orphan Drug Status

1) Orphan drug designation: Treatment of [Tourette syndrome](#)

**D)** Physicochemical Properties

1) Molecular Weight

a) 448.38 [3][4]

2) pH

a) Solution for [IM injection](#): 4.3 [3][4]

3) Melting point: 139 to 139.5 degrees C [423]

**1.2] Storage and Stability**

**A)** Preparation

1) Intramuscular route

**a)) Extended-Release Prefilled Dual-chamber Syringe**

**1)) Preparation**

- a))** Push plunger slightly to engage threads and then rotate plunger rod fully to release diluent; the middle stopper will arrive at indicator line on syringe [37].
- b))** Shake vertically and vigorously for 20 seconds to uniformly suspend milky-white particles [37].
- c))** Twist and pull off the over-cap and tip-cap, then snugly place patient-appropriate needle on syringe and expel any air so that suspension fills needle base [37].
- d))** Do not use prefilled syringes for reduced doses; obtain 160- and 200-mg doses only from vials for reconstitution [37].

**2)) Administration**

- a))** Inject full contents of syringe immediately upon reconstitution [37].
- b))** Use 2-inch needle for gluteal administration in obese patients, a 1.5-inch needle for gluteal administration in nonobese patients or for deltoid administration in obese patients, or a 1-inch needle for deltoid administration in nonobese patients [19].
- c))** For IM use only; inject slowly, into gluteal or deltoid muscle; rotate sites between the 2 deltoid or gluteal muscles. Do not massage injection site [19].

**b)) Extended-Release Vial**

**1)) Preparation**

- a))** Use the provided diluent for reconstitution, sterile water for injection [36].
- b))** Reconstitute 400-mg vial with 1.9 mL of sterile water for injection (SWFI) and the 300-mg vial with 1.5 mL of SWFI; discard excess SWFI [36].
- c))** Shake vigorously for 30 seconds to uniformly suspend particles [36].
- d))** Inject immediately upon reconstitution. Do not store reconstituted suspension in a syringe. If immediate use is not possible, maintain vial at room temperature and resuspend particles by shaking for 60 seconds prior to injection [36].
- e))** Withdraw dose-appropriate volume of reconstituted suspension: 2 mL for 400 mg; 1.5 mL for 300 mg; 1 mL for 200 mg; and 0.8 mL for 160 mg [36].
- f))** Obtain 160- and 200-mg doses only from vials for reconstitution; do not use prefilled syringes for reduced doses [37].

**2)) Administration**

**a)** Use 2-inch needle for gluteal administration in obese patients, a 1.5-inch needle for gluteal administration in nonobese patients or for deltoid administration in obese patients, or a 1-inch for deltoid administration in nonobese patients [19].

**b)** For IM use only; inject slowly, into gluteal or deltoid muscle; rotate sites between the 2 deltoid or gluteal muscles [19].

**2)** Oral route

**a)** [Aripiprazole](#) may be taken without regard to meals [11][12].

**B)** Intramuscular route

**1)** Powder for Suspension, Extended Release

**a)** Store prefilled dual chamber syringe in original package below 30 degrees C (86 degrees F). Do not freeze and protect from light [37].

**b)** Store vial at a controlled room temperature of 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). After reconstitution, keep vial at room temperature [37].

**2)** Solution

**a)** Store in original container at a controlled room temperature of 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from light [63].

**C)** Oral route

**1)** Solution

**a)** Store at a controlled room temperature of 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Use within 6 months after opening, but not beyond the expiration date [63].

**2)** Tablet/Tablet, Disintegrating

**a)** Store at a controlled room temperature of 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [38].

**1.3]** Adult Dosage

**1.3.1]** Normal Dosage

**1.3.1.A]** Important Note

**b)** Beers Criteria: Avoid use in elderly [1].

**1.3.1.B]** Intramuscular route

**1.3.1.B.1] Bipolar disorder - Psychomotor agitation****a) Immediate-Release Aripiprazole For Injection**

- 1) The marketing and distribution of Abilify(R) immediate-release injection for IM use has been discontinued, with estimated product availability until 06/15/15. This decision is not related to product safety or efficacy [31].
- 2) Usual dose: 9.75 mg IM (range, 5.25 mg to 15 mg); additional benefit not observed for 15 mg compared with 9.75 mg [32]
- 3) Second dose: Cumulative doses up to 30 mg/day may be administered if a second dose is required; however, the efficacy of repeated doses in agitated patients has not been systematically evaluated [32].
- 4) Maximum: The safety of total daily doses greater than 30 mg or injections administered more frequently than every 2 hours have not been adequately evaluated [32].
- 5) Ongoing therapy: Oral aripiprazole 10 mg to 30 mg/day should replace aripiprazole injection as soon as possible [32].

**1.3.1.B.2] Psychomotor agitation - Schizophrenia****a) Immediate-Release Aripiprazole For Injection**

- 1) The marketing and distribution of Abilify(R) immediate-release injection for IM use has been discontinued, with estimated product availability until 06/15/15. This decision is not related to product safety or efficacy [31].
- 2) Usual dose: 9.75 mg IM (range, 5.25 to 15 mg); additional benefit not observed for 15 mg compared with 9.75 mg [32]
- 3) Second dose: Cumulative doses up to 30 mg/day may be administered if a second dose is required; however, the efficacy of repeated doses in agitated patients has not been systematically evaluated [32].
- 4) Maximum: The safety of total daily doses greater than 30 mg or injections administered more frequently than every 2 hours have not been adequately evaluated [32].
- 5) Ongoing therapy: Oral aripiprazole 10 mg to 30 mg/day should replace aripiprazole injection as soon as possible [32].

**1.3.1.B.3] Schizophrenia****a) Extended-Release Aripiprazole For Injection**

- 1) Prior to initiation: Establish tolerability with oral formulation in aripiprazole-naïve patients (may take up to 2 weeks). Administer concurrent oral aripiprazole 10 to 20 mg daily (or continue alternative antipsychotic for patients with known aripiprazole tolerance) for 14 consecutive days following initial IM dose [14].
- 2) Initial and maintenance dose: 400 mg IM in the deltoid or gluteal muscle once monthly (no sooner than 26 days after prior injection) [19]

### 1.3.1.C] Oral route

#### 1.3.1.C.1] Bipolar I disorder, Adjunctive therapy with **lithium** or **valproate**

- a) Usual dose (acute treatment): 10 to 15 mg orally once a day as adjunct to **lithium** or **valproate**; target dose, 15 mg orally once a day; may be increased to 30 mg/day based on response, but larger doses have not been evaluated for safety [23][24].
- b) Maintenance dose: Same as needed to stabilize the individual during acute treatment, but assess at regular intervals to determine the need for ongoing treatment [23][24].

#### 1.3.1.C.2] Bipolar I disorder, Monotherapy, manic or mixed episodes

- a) Usual dose: 15 mg orally once a day; may increase to 30 mg/day based on response [23][24].
- b) Maintenance dose: Use the same dose needed to stabilize the patient during acute treatment; periodically assess benefit of continued therapy [23][24].

#### 1.3.1.C.3] **Borderline personality disorder**

- a) Off-label dosage, monotherapy: 15 mg/day orally [8]
- b) Off-label dosage, combination therapy: 10 to 15 mg/day orally added to **sertraline** 100 to 200 mg/day [9]

#### 1.3.1.C.4] **Drug-induced hyperprolactinemia, Caused by antipsychotics**

- a) Off-label dosage: 5 mg orally once daily [2]

#### 1.3.1.C.5] **Major depressive disorder, Adjunctive treatment in patients receiving antidepressants**

- a) Initial dose: 2 to 5 mg orally once daily [3][4]
- b) Dose titration: May increase in increments of 5 mg/day in no less than 1-week intervals based on patient tolerability and efficacy to the usual dose range of 2 to 15 mg/day [3][4]
- c) Duration: Periodically assess the need for maintenance therapy [3][4].

#### 1.3.1.C.6] **Schizophrenia**

- a) Initial and target dose: 10 or 15 mg orally once daily, with or without meals [11][12]; doses of 10 to 30 mg daily have been effective in patients with acutely relapsed **schizophrenia** or **schizoaffective disorder** [20][21][22][16], but efficacy was not significantly greater above 10 to 15 mg daily [11][12].
- b) Dose adjustment: Allow at least 2 weeks at each dose strength [11][12].
- c) Maximum dose: 30 mg orally per day [11][12]
- d) Duration: Assess need for maintenance therapy at regular intervals; 15 mg/day for up to 26 weeks was beneficial in studies [11][12].
- e) Switching from other antipsychotics: Previous treatment may be discontinued immediately or gradually, but keep duration of antipsychotic drug overlap to a minimum; specific data are not available [11][12].

#### 1.3.1.C.7) Oral Solution

- a) The marketing and distribution of **Abilify(R)** oral solution use has been discontinued, with estimated product availability until 05/15/15. This decision is not related to product safety or efficacy [31].



- b)) Oral solution may be substituted with oral tablets on a mg-per-mg basis up to a 25-mg dose. Convert 30-mg tablets to 25 mg of oral solution [6].

#### 1.3.1.C.8)) Orally Disintegrating Tablet

- a)) Dosing with orally disintegrating tablets is the same as for the oral tablets [6].

#### 1.3.2] Dosage in Renal Failure

A)) Dosage adjustment in patients with renal impairment [36] (GFR between 15 and 90 mL/min) is not necessary [3][4].

#### 1.3.3] Dosage in Hepatic Insufficiency

A)) Dosage adjustment in patients with hepatic impairment [36] (Child-Pugh score between 5 and 15) is not necessary [3][4].

#### 1.3.4] Dosage in Geriatric Patients

A)) Adjustment is not necessary [3][4][36].

#### 1.3.6] Dosage in Other Disease States

A)) Abilify Maintena(TM) Extended-Release IM Injection

##### 1)) Adverse Reaction

- a)) Consider reduction from 400 to 300 mg IM once monthly [36].

##### 2)) Concomitant with Strong CYP2D6 or Strong CYP3A4 Inhibitors

- a)) Concomitant use for more than 14 days: Reduce the 400-mg dose to 300 mg IM once monthly OR reduce the 300-mg dose to 200 mg IM once monthly. Upon withdrawal of the inhibitor, an increase may be necessary [36].

##### 3)) Concomitant with a Combination of CYP2D6 and CYP3A4 Inhibitors

- a)) Concomitant use for more than 14 days: Reduce the 400-mg dose to 200 mg IM once monthly OR reduce the 300-mg dose to 160 mg IM once monthly. Upon withdrawal of the inhibitor, an increase may be necessary [36].

##### 4)) Missed Doses

- a)) If the second or third scheduled dose is missed with more than 4 but less than 5 weeks elapsed since last dose, administer the next dose as soon as possible. If more than 5 weeks have elapsed, restart concomitant oral aripiprazole for 14 days with the next injection [36].
- b)) If the fourth or any subsequently scheduled dose is missed with more than 4 but less than 6 weeks elapsed since last dose, administer the next dose as soon as possible. If more than 6 weeks have elapsed, restart concomitant oral aripiprazole for 14 days with the next injection [36].

##### 5)) Poor CYP2D6 Metabolizers

a) Reduce to 300 mg IM once monthly OR if taking a concomitant CYP3A4 inhibitor, reduce to 200 mg IM once monthly. If the concomitant CYP3A4 inhibitor is withdrawn, a dose increase may be necessary. No adjustment is necessary if duration of concomitant use is less than 14 days [36].

## **B) Oral Tablets and Oral Disintegrating Tablets**

### **1) Concomitant with Strong CYP3A4 Inhibitors**

a) Reduce to 50% the usual dose. When the inhibitor is discontinued, increase the dose. In patients with [major depressive disorder](#), administer without adjustment [3][4].

### **2) Concomitant with CYP3A4 Inducers**

a) Double the usual dose over 1 to 2 weeks. When the inducer is withdrawn, reduce to original dose over 1 to 2 weeks. In patients with [major depressive disorder](#), administer without adjustment [3][4].

### **3) Concomitant with Strong CYP2D6 Inhibitors**

a) Reduce to at least 50% the usual dose. When the inhibitor is discontinued, increase the dose. In patients with [major depressive disorder](#), administer without dose adjustment. In patients with [major depressive disorder](#), administer without adjustment [3][4].

### **4) Concomitant with Combination CYP3A4 and CYP2D6 Inhibitors**

a) Reduce to 25% the usual dose regardless of the strength of inhibition. Further adjustment may be needed based on clinical evaluation. When the inhibitor is discontinued, increase the [ariprazole](#) dose. In patients with [major depressive disorder](#), administer without adjustment [3][4].

### **5) Poor CYP2D6 Metabolizers**

a) Reduce to 50% the usual dose (further adjustment may be needed based on clinical evaluation) OR if using a concomitant strong CYP3A4 inhibitor, reduce to 25% the usual dose. In patients with [major depressive disorder](#), administer without adjustment [3][4].

## **1.4] Pediatric Dosage**

### **1.4.1] Normal Dosage**

#### **1.4.1.A] Important Note**

j) Beers Criteria: Avoid use in elderly [1].

#### **1.4.1.B] Oral route**

##### **1.4.1.B.1] [Autistic disorder](#) - Psychomotor agitation**

a) 6 to 17 Years

- 1) Initial dose: 2 mg orally once daily, increased to 5 mg/day [3][4]
- 2) Dose titration (manufacturer dosing): May increase in 5-mg/day increments, at intervals of not less than 1 week, to 10 or 15 mg/day [3][4]
- 3) Dose titration (study dosing): Begin at 2 mg/day for the first week and increase to 5 mg/day for the second week; thereafter, weekly increases in 5-mg/day increments to the target dose [7]
- 4) Duration has not been evaluated; periodically assess the need for continued therapy [3][4].

#### **1.4.1.B.2] Bipolar I disorder, Adjunctive therapy with lithium or valproate**

##### **a) 10 Years or Older**

- 1) Usual dose (acute treatment): 2 mg orally once a day for 2 days, titrated to 5 mg orally once a day for 2 days, then further titrated to the target dose of 10 mg/day; may increase in 5-mg/day increments to a maximum of 30 mg/day; larger doses have not been evaluated for safety [23][24].
- 2) Maintenance dose: Same as needed to stabilize the individual during acute treatment, but assess at regular intervals to determine the need for ongoing treatment [23][24].

#### **1.4.1.B.3] Bipolar I disorder, Monotherapy, manic or mixed episodes**

##### **a) 10 Years Or Older**

- 1) Usual dose: 2 mg orally once a day for 2 days, then titrated to 5 mg orally once a day for 2 days, and titrated to the target dose of 10 mg orally once a day [23][24].
- 2) Dose titration: 5-mg/day increments based on response [23][24]
- 3) Maintenance dose: Use the same dose needed to stabilize the patient during acute treatment; periodically assess benefit of continued therapy [23][24].

#### **1.4.1.B.4] Gilles de la Tourette's syndrome**

##### **a) 6 to 18 years, Weight less than 50 kg**

- 1) Initial and target dose: 2 mg orally once daily for 2 days, then increase to 5 mg orally once [3][4]
- 2) Maximum dose: If tics are not controlled, may increase to 10 mg/day in intervals of not less than 1 week [3][4]
- 3) Duration: Periodically assess the need for continued treatment [3][4].

##### **b) 6 to 18 years, Weight 50 kg or Greater**

- 1) Initial and target dose: 2 mg orally once daily for 2 days, then increase to 5 mg orally once daily for 5 days, and then to 10 mg orally once daily on day 8 [3][4]
- 2) Maximum dose: If tics are not controlled, may increase to 20 mg/day in increments of 5 mg/day at intervals of not less than 1 week [3][4]
- 3) Duration: Periodically assess the need for continued treatment [3][4].

**1.4.1.B.5] Schizophrenia****a)] 13 to 17 Years**

- 1)] Initial and target dose: 2 mg/day orally once daily, then increase to 5 mg after 2 days and then to 10 mg after an additional 2 days [11][12]
- 2)] Maintenance dose: 10 mg per day [11][12]
- 3)] Dose titration: 5-mg increments [11][12]
- 4)] Maximum dose: 30 mg orally per day; however, no additional benefit was seen with the 30-mg dose [11][12]
- 5)] Duration: Efficacy not studied beyond 6 weeks in pediatric patients; based on adult data, therapy can be continued beyond acute response, but at the lowest dose necessary to maintain remission; periodically assess need for therapy [11][12].
- 6)] Switching from other antipsychotics: Previous treatment may be discontinued immediately or gradually, but keep duration of antipsychotic drug overlap to a minimum; specific data are not available [11][12].

**1.4.1.B.6)] Oral Solution**

- a)] The marketing and distribution of **Abilify(R)** oral solution use has been discontinued, with estimated product availability until 05/15/15. This decision is not related to product safety or efficacy [31].
- b)] Oral solution may be substituted with oral tablets on a mg-per-mg basis up to a 25-mg dose. Convert 30-mg tablets to 25 mg of oral solution [6].

**1.4.1.B.7)] Orally Disintegrating Tablets**

- a)] Dosing with orally disintegrating tablets is the same as for the oral tablets [6].

**1.4.2] Dosage in Renal Failure**

A)] Dosage adjustment in patients with **renal impairment** (GFR between 15 and 90 mL/min) is not necessary [3][4].

**1.4.3] Dosage in Hepatic Insufficiency**

A)] Dosage adjustment in patients with **hepatic impairment** (Child-Pugh score between 5 and 15) is not necessary [3][4].

**1.4.5] Dosage in Other Disease States****A)] Concomitant with Strong CYP3A4 Inhibitors**

- 1)] Reduce to 50% the usual dose. When the inhibitor is discontinued, increase the **aripiprazole** dose [3][4].

**B)] Concomitant with CYP3A4 Inducers**

- 1)] Double the usual dose over 1 to 2 weeks. When the inducer is withdrawn, reduce to original dose over 1 to 2 weeks [3][4].

**C) Concomitant with Strong CYP2D6 Inhibitors**

**1) Reduce to at least 50% the usual dose. When the inhibitor is discontinued, increase the dose [3][4].**

**D) Concomitant with Combination CYP3A4 and CYP2D6 Inhibitors**

**1) Reduce to 25% the usual dose regardless of strength of inhibition. Further adjustment may be needed based on clinical evaluation. When the inhibitor is withdrawn, increase the [aripiprazole](#) dose [3][4].**

**E) Poor CYP2D6 Metabolizer**

**1) Reduce to 50% the usual dose. Further adjustment may be needed based on clinical evaluation. If concurrently taking a strong CYP3A4 inhibitor, reduce [aripiprazole](#) to 25% the usual dose [3][4].**

**2.0] Pharmacokinetics**

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

**2.1] Onset and Duration****A) Onset****1) Initial Response**

**a) [Schizophrenia](#), oral: 1 week (10 to 30 mg daily) [167][168]**

**1) In phase II studies involving hospitalized schizophrenic patients, significant improvement (including negative symptoms) was seen after one week of therapy with aripiprazole 30 mg daily. With lower doses (2 or 10 mg daily), symptom improvement was not seen until week 2 or 3, and benefits were less substantial [167].**

**2.2] Drug Concentration Levels****A) Peak Concentration**

**1) IM, single-dose: 19% higher than oral tablet [169]**

**a) Following an IM dose, the geometric mean Cmax was on average 19% higher than the Cmax after an oral tablet administration [169].**

**b) When the extended-release [aripiprazole](#) suspension was injected into the deltoid and gluteal muscles, the rate of absorption (Cmax) was 31% higher from the deltoid muscle compared with gluteal muscle. However at steady state, the Cmax was similar for both injection sites [19].**

**2) Pediatrics**

**a) Oral, multiple-dose, children (6 to 12 years old): 1 mg: 21.8 ng/mL; 2 mg 48.8 ng/mL; 5 mg: 138 ng/mL [170]**

**1) In an open-label pharmacokinetic study of aripiprazole in children (6 to 12 years old) with conduct disorder, the Cmax on day 14 was 21.8 nanograms/milliliter (ng/mL), 48.8 ng/mL, and 138 ng/mL, following oral, once daily dosing of aripiprazole 1 mg (n=3),**

2 mg (n=5), and 5 mg (n=3), respectively. The C<sub>max</sub> was linearly proportional to dose administered. On day 14, the C<sub>max</sub> was 2- to 4-fold higher than the C<sub>max</sub> observed on day 1 [170].

**3j) Oral, multiple-dose, adolescents (13 to 17 years old):** 2 mg: 43.8 ng/mL; 5 mg 73.1 ng/mL; 10 mg: 136 ng/mL; 15 mg: 194.2 ng/mL [170]

**a)** In an open-label [pharmacokinetic study](#) of [aripiprazole](#) in adolescents (13 to 17 years old) with conduct disorder, the C<sub>max</sub> on day 14 was 43.8 nanograms/milliliter (ng/mL), 73.1 ng/mL, 136 ng/mL, and 194.2 ng/mL, following oral, once daily dosing of [aripiprazole](#) 1 mg (n=3), 2 mg (n=5), and 5 mg (n=3), respectively. The C<sub>max</sub> was linearly proportional to dose administered. On day 14, the C<sub>max</sub> was 2- to 4-fold higher than the C<sub>max</sub> observed on day 1 [170].

## **B) Time to Peak Concentration**

**1j) IM: 1 to 3 hours** [169]

**a)** In 2 studies of healthy subjects, the median times to peak plasma concentrations following IM [aripiprazole](#) administrations were 1 and 3 hours [169].

**b)** Steady-state is reached within 14 days [169].

**2j) IM, extended-release suspension: 5 to 7 days (gluteal muscle injection); 4 days (deltoid muscle injection)** [19]

**a)** The median T<sub>max</sub> was 5 to 7 days following an injection of extended-release [aripiprazole](#) suspension into the gluteal muscle and was 4 days following an injection into the deltoid muscle. Steady state concentrations are achieved by the fourth dose regardless of the injection site [19].

**3j) Oral: 3 to 5 hours** [168][169].

**a)** In healthy subjects receiving once-daily doses of 5 and 20 mg, mean peak plasma levels on day 14 were 77 and 302 nanograms/mililiter, respectively, and occurred in 3 to 5 hours [168].

**b)** With a titrated dosing schedule of 10 mg daily for 2 days, then 20 mg daily for 2 days, and finally 30 mg daily for 10 days, the mean peak plasma concentration on day 14 was 452 nanograms/mililiter (3 hours) [168].

**c) Pediatrics**

**1j) Oral, multiple-dose, children (6 to 12 years old): 2 to 4 hours** [170]

**a)** In an open-label pharmacokinetic study of aripiprazole in children (6 to 12 years old) with conduct disorder, the T<sub>max</sub> on day 14 was 4 hours, 2 hours and 2 hours following oral, once daily dosing of aripiprazole 1 mg (n=3), 2 mg (n=5), and 5 mg (n=3), respectively [170].

**b)** Steady-state appears to be reached with 14 days of once-daily dosing [170].

**4) Oral, multiple-dose, adolescents (13 to 17 years old): 2 to 4 hours [170]**

**a)** In an open-label pharmacokinetic study of aripiprazole in adolescents (13 to 17 years old) with conduct disorder, the T<sub>max</sub> on day 14 was 2 hours, 4 hours, 3 hours, and 2 hours, following oral, once daily dosing of aripiprazole 2 mg (n=2), 5 mg (n=5), 10 mg (n=3), and 15 mg (n=1), respectively [170].

**b)** Steady-state appears to be reached with 14 days of once-daily dosing [170].

**C) Area Under the Curve****1) IM, single-dose: similar over 24 hours to oral tablet; linear over 1 to 45 mg dose range [169]**

**a)** The aripiprazole AUC in the first 2 hours after an IM injection was 90% greater than the AUC after the same dose as a tablet; however, both routes had similar systemic exposure over 24 hours. When IM aripiprazole doses were administered to stable patients with schizophrenia or schizoaffective disorder, the pharmacokinetics of aripiprazole were linear over a dose range of 1 to 45 mg [169].

**b)** When the extended-release aripiprazole suspension was injected into the deltoid and gluteal muscles following a single dose, the extent of absorption (AUC(t) and AUC(infinity)) were similar for both injection sites and was also similar at steady state [19].

**2) IM, multiple-dose, extended-release suspension, 300 and 400 mg: approximate dose-proportional increases [36]**

**a)** Approximate dose-proportional increases in aripiprazole and dehydro-aripiprazole AUC parameters were seen after every 4-week aripiprazole IM extended-release suspension injections of 300 and 400 mg [36].

**b) Pediatrics**

**1) Oral, multiple-dose, children (6 to 12 years old): 1 mg: 471 ng x hr/mL; 2 mg 827 ng x hr/mL; 5 mg: 2217 ng x hr/mL [170]**

**a)** In an open-label pharmacokinetic study of aripiprazole in children (6 to 12 years old) with conduct disorder, the AUC on day 14 was 471 nanograms (ng) x hr/mL, 827 ng x hr/mL, and 2217 ng x hr/mL, following oral, once daily dosing of aripiprazole 1 mg (n=2), 2 mg (n=5), and 5 mg (n=3), respectively. The AUC was linearly proportional to dose administered. On day 14, the AUC was three- to 6-fold higher than the AUC observed on day 1 [170].

**3) Oral, multiple-dose, adolescents (13 to 17 years old): 2 mg: 800 ng x hr/mL; 5 mg 1340 ng x hr/mL; 10 mg: 2387 ng x hr/mL; 15 mg: 3879 ng x hr/mL**

**a)** In an open-label pharmacokinetic study of aripiprazole in adolescents (13 to 17 years old) with conduct disorder, the AUC on day 14 was 800 nanograms (ng) x hr/mL, 1340 ng x hr/mL, 2387 ng x hr/mL, and 3879 ng x hr/mL, following oral, once daily dosing of aripiprazole 2 mg (n=2), 5

mg (n=5), 10 mg (n=3) and 15 mg (n=1), respectively. The AUC was linearly proportional to dose administered. On day 14, the AUC was 3- to 6-fold higher than the AUC observed on day 1 [170].

## 2.3] ADME

### 2.3.1] Absorption

#### A)] Bioavailability

1)] Oral: tablet, 87%; solution, well-absorbed [169].

2)] Intramuscular: 100% after a 5-mg [IM injection](#) [169].

a)] A comparative bioavailability study which compared the pharmacokinetics of a 30 mg [aripiprazole](#) tablet with 30 mg of the oral solution found that plasma concentrations of [aripiprazole](#) were higher with the solution than with the tablet. In healthy subjects, mean maximum plasma concentration and area under the curve values were 22% and 14% higher with the solution as compared with the tablet formulation [169].

b)] [Pharmacokinetic studies](#) with the orally disintegrating [aripiprazole](#) tablet indicate that they are bioequivalent to [aripiprazole](#) tablets [171].

#### B)] Effects of Food

1)] Absorption unaffected [169]

a)] Peak serum levels and AUC of [aripiprazole](#) and dehydroaripiprazole are not significantly affected when [aripiprazole](#) is given with food. The time to peak serum levels is delayed (by 3 hours for [aripiprazole](#) and by 12 hours for dehydroaripiprazole) [169].

### 2.3.2] Distribution

#### A)] Distribution Sites

1)] Protein Binding

a)] Albumin: greater than 99% [169]

1)] At therapeutic concentrations, aripiprazole and dehydroaripiprazole (major metabolite) are greater than 99% bound to serum proteins (primarily albumin) [169].

#### B)] Distribution Kinetics

1)] Volume of Distribution

a)] 404 L or 4.9 L/kg [169]

1)] The steady-state volume of distribution following IV administration is 404 L or 4.9 L/kg [169].



### 2.3.3] Metabolism

#### A) Metabolism Sites and Kinetics

##### 1) Liver: extensive via CYP3A4 and CYP2D6[3]

a) Metabolic pathways include dehydrogenation and hydroxylation via CYP3A4 and CYP2D6; N-dealkylation also occurs via CYP3A4. [Aripiprazole](#) is the primary compound in plasma [3].

b) Poor metabolizers (CYP2D6) have been identified (speculated as 8% of Caucasians and 3% to 8% of Black/African Americans); these patients have approximately a 60% greater exposure to dehydro-aripiprazole and 200% greater exposure to [aripiprazole](#) [3].

#### B) Metabolites

##### 1) Dehydroaripiprazole (active) [169]

a) Major metabolite, representing about 40% of [aripiprazole](#) AUC in plasma. This metabolite has affinities for D2 receptors similar to the parent compound and appears to contribute to pharmacologic activity [169].

#### C) Other

##### 1) Metabolic Enzymes and Transporters

##### a) Substrate of CYP2D6 and CYP3A4

1) In extensive CYP2D6 metabolizers, a 4.5-fold increase in C<sub>max</sub> and AUC can be expected when aripiprazole is administered with both strong CYP2D6 and CYP3A4 inhibitors. In poor CYP2D6 metabolizers, a 3-fold increase can be expected with coadministration of aripiprazole and strong CYP3A4 inhibitors [3].

### 2.3.4] Excretion

#### A) Kidney

##### 1) Renal Excretion (%)

a) 25% of dose (less than 1% unchanged [aripiprazole](#)) [169]

1) The renal excretion of aripiprazole is 25% of the dose with less than 1% unchanged aripiprazole [169].

#### B) Feces

1) 55% of a dose (about 18% unchanged [aripiprazole](#)) [169]

a) Fecal elimination is 55% of the dose with about 18% unchanged [aripiprazole](#) [169].

#### C) Total Body Clearance

**1J) Pediatrics**

**aJ)** children (6 to 12 years old): 0.05 to 0.11 L/hr/kg; adolescents (13 to 17 years old) 0.03 to 0.07 L/hr/kg [170]

**1J)** When normalized for body weight, the oral clearance of aripiprazole is similar across age groups. In an open-label pharmacokinetic study of aripiprazole in children (6 to 12 years old) with conduct disorder, the apparent oral clearance on day 14 following oral once daily dosing of aripiprazole 1 mg (n=2), 2 mg (n=5), and 5 mg (n=3) was 0.11 L/hr/kg, 0.07 L/hr/kg and 0.05 L/hr/kg, respectively. In adolescents (13 to 17 years old) the apparent oral clearance on day 14 was 0.05 L/hr/kg, 0.07 L/hr/kg, 0.05 L/hr/kg, and 0.03 L/hr/kg, following oral, once daily dosing of aripiprazole 1 mg (n=2), 2 mg (n=5), and 5 mg (n=3), respectively [170].

**2.3.5] Elimination Half-life****AJ) Parent Compound**

**1J)** 75 hours (extensive metabolizers) [169]; 29.9 days (300 mg extended-release IM suspension, gluteal injection); 46.5 days (400 mg extended-release IM suspension, gluteal injection) [19]

**aJ)** An elimination half-life of 146 hours has been reported in poor metabolizers [169]. Following every 4-week [aripiprazole](#) extended-release 300 mg and 400 mg suspension [IM injection](#) into the gluteal muscle, mean [aripiprazole](#) terminal t(1/2) was 29.9 days and 46.5 days, respectively [19].

**BJ) Metabolites**

**1J)** Active metabolite, dehydro-aripiprazole: 94 hours [169]

**3.0] Cautions**

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

**3.0.A] Black Box WARNING**

Intramuscular (Powder for Suspension)

**Increased Mortality In Elderly Patients With Dementia-Related Psychosis**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

Aripiprazole extended-release suspension for IM injection is not approved for the treatment of patients with dementia-related psychosis [19].

**Oral (Tablet; Tablet, Disintegrating; Solution)****Increased Mortality In Elderly Patients With Dementia-Related Psychosis And Suicidal Thoughts And Behaviors With Antidepressant Drugs**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [4][3].

**Intramuscular (Solution)****Increased Mortality In Elderly Patients With Dementia-Related Psychosis And Suicidal Thoughts And Behaviors With Antidepressant Drugs**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [3].

**3.1] Contraindications**

**A)** Hypersensitivity to [aripiprazole](#) [3][4][36]

**3.2] Precautions**

**A)** Black box warning: Dementia-related [psychosis](#), not approved for use due to increased risk of death in elderly [3][4][36]

**B)** Black box warning: [Suicidal ideation](#) and behavior or worsening depression may occur, especially in children, adolescents, and young adults (age 24 years or younger), particularly during first few months of therapy or following dose change; monitoring recommended and therapy discontinuation may be required [3][4].

**C)** Beers Criteria: Avoid use for behavioral problems of [dementia](#) or [delirium](#) in elderly as antipsychotics may increase risk of cerebrovascular accident and mortality (unless nonpharmacological measures fail and the patient is a threat to self or others). Avoid use in elderly patients with a history of falls or fractures (unless safer alternatives are not available), or cognitive impairment due to risk of adverse CNS effects, syncope, ataxia, and impaired

psychomotor performance, and in patients with [Parkinson Disease](#) as symptoms may worsen. If used, caution is advised and monitoring is recommended as SIADH or [hyponatremia](#) may occur or be exacerbated [1].

**D))** Body temperature: Inability to reduce core body temperature has been reported with antipsychotics especially following strenuous exercise, exposure to extreme heat, concomitant anticholinergic medication, or dehydration [3][4][36].

**E))** Cardiovascular: Orthostatic hypotension has been reported; increased risk with preexisting [cardiovascular](#) or [cerebrovascular disease](#), conditions with predisposition to hypotension (eg, dehydration, [hypovolemia](#)), and concomitant use of antihypertensives [3][4][36].

**F))** Concomitant use: Avoid [aripiprazole](#) extended-release injection and CYP3A4 inducers, including [carbamazepine](#), for greater than 14 days [36].

**G))** CYP2D6 metabolism: Poor metabolizers of CYP2D6 require dose reduction [3][4].

**H))** Dosage and duration: Higher cumulative dose and longer treatment duration increase risk of potentially irreversible [tardive dyskinesia](#) [3][4][36].

**I))** Endocrine and metabolic: Patients with preexisting or risk factors for [diabetes mellitus](#), including [obesity](#) and family history of [diabetes](#), may experience [hyperglycemia](#) or worsening of glucose control; monitoring recommended [3][4][36].

**J))** Endocrine and metabolic: Severe [hyperglycemia](#), sometimes in association with [ketoacidosis](#), [hyperosmolar coma](#), or death, has been reported with atypical antipsychotics [3][4][36].

**K))** Endocrine and metabolic: [Dyslipidemia](#) has been reported [3][4][36].

**L))** Endocrine and metabolic: Weight gain has been reported; monitoring recommended [3][4][36].

**M))** Gastrointestinal: [Dysphagia](#) has been reported and may result in [aspiration pneumonia](#) due to [esophageal dysmotility](#) [3][4].

**N))** Hematologic: [Agranulocytosis](#), [leukopenia](#), and [neutropenia](#) have been reported in patients with risk factors (eg, history of low WBC, [leukopenia](#), or [neutropenia](#)); monitoring recommended and discontinuation may be necessary [3][4][36].

**O))** Immunologic: [Allergic reactions](#) have been reported, including [anaphylaxis](#) [3][4][36].

**P))** Musculoskeletal: [Tardive dyskinesia](#) has been reported and may be irreversible; discontinuation may be required [3][38][36].

**Q))** [Neuroleptic malignant syndrome](#): Has been reported; may require discontinuation of therapy and medical management; reinstitute therapy carefully with monitoring [3][4][36].

**R))** Neurologic: Seizures have been reported; increased risk with a history of seizures and conditions that may lower seizure threshold [3][4][36].

**S))** Phenylketonurics: Oral disintegrating tablets contain [phenylalanine](#) [4].

**T))** Psychiatric: Compulsive behaviors and impaired impulse control (eg, urges to gamble, binge eat, shop, increased sexual urges, other intense urges) have been reported; monitoring recommended and dose reduction or discontinuation may be necessary [39].

**U))** Psychiatric: Patients with [bipolar disorder](#) are at increased risk of precipitation of a mixed or [manic episode](#); rule out disorder prior to initiating therapy [3][4].

**V))** Special populations: Elderly patients are at increased risk of potentially irreversible [tardive dyskinesia](#), especially women [3][4][36].

### 3.3] Adverse Reactions

#### 3.3.1] Cardiovascular Effects

##### 3.3.1.A] Angina pectoris

1)) Incidence: 0.1% to 1% [36]

2)) Clinical Trials

a)) Indications not specified (oral route; at least 2 mg/day): between 1/1000 and 1/100 patients [36]

**3.3.1.B] Atrioventricular block**

1) Incidence: 0.1% to 1% [36]

2) Clinical Trials

a) Indications not specified (oral route; at least 2 mg/day): between 1/1000 and 1/100 patients [36]

**3.3.1.C] Bradyarrhythmia**

1) Incidence: Less than 0.1% [14]

2) Adult Clinical Trials

a) **Schizophrenia** (IM route, extended-release): less than 0.1%[14]

3) Adult Case Reports

a) Symptomatic bradycardia developed in an 18-year-old women with **bipolar disorder** following 3 days of **aripiprazole** and resolved with IV fluid and **aripiprazole** discontinuation. The patient was admitted for treatment of psychotic symptoms due to medication nonadherence with **ziprasidone** 80 mg/day; resting heart rate was 69 beats per minute (bpm) and blood pressure was 127/72 mmHg. **Ziprasidone** was switched to **aripiprazole** 15 mg/day (which was increased to 20 mg/day on day 2) and **lithium** carbonate 600 mg twice daily for mood stabilization. The patient developed **sinus bradycardia**, a syncopal episode, a heart rate of 35 bpm, blood pressure of 80/42 mmHg, and a QTc interval of 444 msec. She was administered normal saline and monitored until her heart rate stabilized. **Aripiprazole** was discontinued and **lithium** was continued. She had a resting heart rate was 56 bpm and blood pressure of 108/63 mmHg at discharge [42].

**3.3.1.D] Cardiorespiratory arrest**

1) Incidence: 0.1% to 1% [36]

2) Clinical Trials

a) Indications not specified (oral route; at least 2 mg/day): between 1/1000 and 1/100 patients [36]

**3.3.1.E] Cardiorespiratory failure**

1) Incidence: 0.1% to 1% [36]

2) Clinical Trials

a) Indications not specified (oral route; at least 2 mg/day): between 1/1000 and 1/100 patients [36]

**3.3.1.F] Myocardial infarction**

1) Incidence: 0.1% to 1% [36]

2) Clinical Trials

a) Indications not specified (oral route; at least 2 mg/day): between 1/1000 and 1/100 patients [36]

**3.3.1.G] Orthostatic hypotension**

1) Incidence: 0.2% to 4% [14][47][44]

2) General Information

- a)) Use caution in patients with known [cardiovascular disease](#) or conduction abnormalities, or conditions which would predispose patients to hypotension [44].

### 3)) Adult Clinical Trials

a)) Indications not specified (oral route): 1% vs 0.3% with placebo; 4% vs 2% with placebo (significant orthostatic change in blood pressure; a decrease of at least 20 mmHg in systolic blood pressure accompanied by an increase in heart rate of 25 or greater when changing from a supine to standing position) [44]

b)) Agitation associated with [schizophrenia](#) or bipolar mania (IM route, immediate-release): 3% vs 2% with placebo (significant orthostatic change in blood pressure; a decrease of at least 20 mmHg in systolic blood pressure accompanied by an increase in heart rate of 25 or greater when changing from a supine to standing position) [44]

c)) [Schizophrenia](#) (IM route, extended-release): 0.2% [14]

### 4)) Adolescent Clinical Trials

a)) Indications not specified (oral route; aged 6 to 17 years): 0.5% vs 0% with placebo; 0.2% vs 1% with placebo (significant orthostatic change in blood pressure; a decrease of at least 20 mmHg in systolic blood pressure accompanied by an increase in heart rate of 25 or greater when changing from a supine to standing position) [48][47]

#### 3.3.1.H) [Paroxysmal supraventricular tachycardia](#)

##### 1)) Adult Case Reports

a)) [Paroxysmal supraventricular tachycardia](#) developed in 19-year-old man after receiving [aripiprazole](#) for 3 days for acute psychotic symptoms. The patient was hospitalized because of psychotic symptoms, was neuroleptic naive, and had a family history of [arrhythmia](#). During the first 3 days of hospitalization, ECG and vital signs were normal except for mild [tachycardia](#) (pulse rate of 100 to 104 beats per minutes [bpm]), and a [risperidone](#) trial resulted in [oculogyric crisis](#). [Aripiprazole](#) 10 mg/day was initiated along with [lorazepam](#) 3 mg/day and biperidin 6 mg/day. Three days following [aripiprazole](#) initiation, the patient started to experience chest pain and tightness, and was found to have a heart rate of 178 bpm. His blood pressure was 98/65 mmHg, and a respiratory rate of 16 breaths/min. ECG revealed [paroxysmal supraventricular tachycardia](#). He responded to [propranolol](#) 10 mg 1 hour later. [Aripiprazole](#) was switched to flupentixol 12 mg/day. The patient's mental status resolved along with no further issues of chest pain or tightness at 9 months following discharge [43].

##### 3.3.1.I) [Prolonged QT interval](#)

1)) Incidence: 0.1% to 1% [44]

##### 2)) General Information

- a)) Use caution in patients with known [cardiovascular disease](#) or conduction abnormalities, or conditions which would predispose patients to hypotension [44].

##### 3)) Clinical Trials

a)) Indications not specified (oral route; at least 2 mg/day): between 1/1000 and 1/100 patients [44]

##### 4)) Adult Case Reports

a) Aripiprazole-induced QT prolongation was reported in a 69-year-old woman receiving treatment for [bipolar disorder](#). QTc at baseline was 433 msec. The patient had been treated ineffectively with [lithium](#), [risperidone](#), and [olanzapine](#). [Quetiapine](#) 200 mg at bedtime was subsequently started with significant improvement in mood and psychotic symptoms; however, there was no ECG performed before starting [quetiapine](#) trial. After 9 months on [quetiapine](#), the patient reported progressive dizziness and ECG revealed a QTc of 448 msec. The patient was switched to [aripiprazole](#) titrated to 7 mg/day. Dizziness persisted and a subsequent QTc increased to 482 msec 2 months after starting [aripiprazole](#). Because of the increased QTc, [aripiprazole](#) was reduced to 2 mg/day and 11 days later, the ECG showed a QTc of 492 msec. [Aripiprazole](#) was completely discontinued and 13 days later the QTc was 438 msec. This case had a Naranjo score of 6, indicating that the QT prolongation was probably related to [aripiprazole](#). [Divalproex](#) was proposed as maintenance treatment thereafter [45].

### 3.3.1.J] Tachycardia

1) Incidence: Up to 2% [14][44]

2) General Information

a) Use caution in patients with known [cardiovascular disease](#) or conduction abnormalities, or conditions which would predispose patients to hypotension [44].

3) Adult Clinical Trials

a) Agitation associated with [schizophrenia](#) or bipolar mania (IM route; immediate-release, 5.25 mg/day or greater): 2% vs less than 1% with placebo [44]

b) [Schizophrenia](#) (IM route, extended-release): 0.1% to 1% [14]

### 3.3.1.K] Torsades de pointes

1) Adult Case Reports

a) [Cardiac arrest](#) due to [torsade de pointes](#) occurred after 5 days of [aripiprazole](#) 2.5 mg/day in a 42-year-old man with [schizophrenia](#), [hypertension](#), [diabetes](#), and previous [stroke](#). The patient was admitted 30 days prior with severe sepsis, complicated by [renal failure](#), [adrenal insufficiency](#), adult [respiratory distress syndrome](#), and an episode of QT-interval prolongation, with QTc of 644 milliseconds (msec), after a single dose of [quetiapine](#) 400 mg. Upon arrival to the emergency department, ECG revealed a QTc interval of 528 msec and 23 days later, his baseline QTc was 414 msec. Five days following initiation of [aripiprazole](#), ECG revealed [torsade de pointes](#) and a QTc interval of 624 msec. When normal sinus rhythm was restored following [cardiac arrest](#), [aripiprazole](#) was discontinued. Subsequent [cardiac catheterization](#) did not reveal any significant disease and QTc interval on 1, 5, and 14 days later was 537, 472, and 450 msec. The Naranjo probability score of causality assessment rated this adverse event as probable [46].

## 3.3.2] Dermatologic Effects

### 3.3.2.A] Acneiform drug eruption

1) A 23-year-old man developed acneiform drug eruptions 10 days after starting [aripiprazole](#) treatment for [paranoid schizophrenia](#). The patient had a 3-year history of symptoms suggestive of [paranoid schizophrenia](#). In the past had received an adequate trial of [risperidone](#) with poor response, and then was treated with [aripiprazole](#) 20 mg/day with a good response. After 1 month of treatment with [aripiprazole](#), the patient had discontinued medication himself and remained symptomatic for 1 year. The patient was



readmitted for aggravation of symptoms and upon admission his laboratory analysis revealed normal [hemogram](#), serum electrolytes, renal function and liver function. For acute control of his aggression, the patient was initially treated with injectable [haloperidol](#) 10 mg and [promethazine](#) 25 mg intramuscularly twice daily for 4 days. The patient was restarted on [aripiprazole](#) with gradual titration to 15 mg/day over 4 days. After 10 days of [aripiprazole](#) treatment, the patient developed papulopustular eruptions over his forehead and nasal bridge (which worsened with sunlight exposure) The patient had no past history of the eruptions or [aripiprazole](#) exposure in the past 1 year. The patient was diagnosed with aripiprazole-induced acneiform eruptions. [Aripiprazole](#) was discontinued and the patient was switched to oral [haloperidol](#) 10 mg/day with good response. Consequently, the affected regions were treated with topical retinoic acid 0.25 mg ointment. Within 10 days after discontinuing the [aripiprazole](#), there was complete resolution of the acneiform eruptions with mild scarring. Because the patient was previously exposed to [aripiprazole](#) and there was a rapid development of the acneiform lesions, the acneiform drug eruption may have been mediated through a Type III allergic mechanism although no clinical signs of allergy were noted [71].

### 3.3.2.B] Injection site pain

- 1) Incidence: 5% [14]
- 2) Adult Clinical Trials

a) [Schizophrenia](#) (IM route, extended release): 5% vs 1% with placebo [14]

### 3.3.2.C] Rash

- 1) Incidence: 2% [44]
- 2) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with [schizophrenia](#) or bipolar mania received either oral [aripiprazole](#) (doses 2 mg/day or greater) (n=399) or placebo (n=197), rash was reported in 2% of patients receiving [aripiprazole](#) compared with 1% of patients receiving placebo [44].

## 3.3.3] Endocrine/Metabolic Effects

### 3.3.3.A] Decreased [HDL](#) level

- 1) Incidence: 3.7% to 13.5% [3][4][14]
- 2) Adult Clinical Trials

a) [Major depressive disorder](#) (oral route): [HDL cholesterol](#) change from normal to low, 5.3% with [aripiprazole](#) plus antidepressant therapy vs 3.5% with antidepressant therapy only [3][4]

b) [Schizophrenia](#) (IM route, extended release): [HDL cholesterol](#) change from normal to low, 13.5% vs 12.6% with placebo [14]

### 3) Pediatric Clinical Trials

a) [Tourette disorder](#) (oral route; age 6 to 18 years): [HDL cholesterol](#) change from normal to low: 3.7% vs 3% with placebo [3][4]

### 3.3.3.B] Decreased prolactin level

- 1) Incidence: Less than 0.1% [14]
- 2) Adult Clinical Trials

a) [Schizophrenia](#) (IM route, extended-release): Less than 0.1% [14]

### 3.3.3.C] [Diabetes mellitus](#)



**1) General Information**

a) Blood glucose fluctuation, [diabetic ketoacidosis](#), [hyperglycemia](#), and [diabetes mellitus](#) have been reported with [aripiprazole](#) treatment [36][38][63].

**2) Prevention and Management**

a) Order fasting blood glucose testing for patients who develop symptoms of [hyperglycemia](#) [36][38][63].

b) [Hyperglycemia](#) may resolve with drug continuation, but some patients may require continued antidiabetic treatment [36][38][63].

c) Monitor patients with [diabetes](#) or with risk factors for [diabetes](#) (eg, [obesity](#), family history of [diabetes](#)) for worsening glucose control; order fasting blood glucose testing at the initiation and periodically during [aripiprazole](#) treatment [36][38][63].

d) Monitor weight in all adult, adolescent, and pediatric patients and compare weight gain in pediatric patients with expected normal growth [36][38][63].

**3) Adult Clinical Trials**

a) Unspecified indication (oral route): [diabetes mellitus](#) including increased blood [insulin](#), decreased carbohydrate tolerance, [non-insulin-dependent diabetes mellitus](#), [impaired glucose tolerance](#), glycosuria, glucose urine, and glucose urine present, 0.1% to 1% [38][63]

**3.3.3.D) Diabetic ketoacidosis**

**1) Incidence:** Less than 0.1% [36][38][63]

**2) General Information**

a) [Hyperglycemia](#) has been reported and in some cases was associated with [ketoacidosis](#), [hyperosmolar coma](#), or death [36][38][63].

**3) Prevention and Management**

a) Monitor patients for symptoms of [hyperglycemia](#), including polydipsia, polyuria, [polyphagia](#), and weakness [36][38][63].

b) Perform fasting blood glucose testing in patients who develop symptoms of [hyperglycemia](#) [36][38][63].

c) [Hyperglycemia](#) may resolve with antipsychotic drug discontinuation, but some patients require continued antidiabetic treatment [36][38][63].

**4) Adult Clinical Trials**

a) Unspecified indication (oral route): Less than 0.1% [36][38][63]

**5) Adult Clinical Trials**

a) A 44-year-old, obese, African-American man developed new-onset [diabetes](#) and [diabetic ketoacidosis](#) (DKA) within 16 days of initiating [aripiprazole](#) treatment for [schizoaffective disorder](#). The patient had [schizoaffective disorder](#) for 16 years, [hyperlipidemia](#), [obesity](#) (BMI upon admission was 43.3 kg/m(2)), no personal or family history of [diabetes](#), and no other current medications. Upon admission to the hospital psychiatric service for exacerbation of [schizoaffective disorder](#) symptoms (auditory hallucinations), treatment with [fluphenazine](#) was initiated. On day 3, the [fluphenazine](#) dose was increased and [valproic acid](#) was added. By day 27, the patient

continued to experience auditory hallucinations and aripiprazole 15 mg/day was added. The patient was also receiving benztropine for akathisia and atorvastatin for hyperlipidemia. On day 28 the aripiprazole was increased to 30 mg/day. On day 43, after 16 days of aripiprazole treatment, the patient experienced an episode of urinary incontinence. On day 44, the patient refused to eat, experienced somnolence and upper extremity weakness, lost the ability to take his medication or drink fluids without assistance. On day 45, the patient was lethargic, stopped communicating, had difficulty walking, and had not received substantial oral intake for 48 hours. Laboratory analysis revealed hyperglycemia, metabolic acidosis, moderate serum ketone levels, elevated serum creatinine, bilirubinemia plasma hyperosmolality, and A1C was 14.9%. The patient was diagnosed with DKA and all psychiatric medications were discontinued. The patient was given IV insulin and fluids and fluphenazine, benztropine, and haloperidol as needed for agitation. The metabolic acidosis and azotemia resolved, and the IV insulin was changed to subQ long-acting insulin. Discharge medications were metformin, insulin glargine, insulin aspart, benztropine, fluphenazine, divalproex sodium, and escitalopram. Within 4 months after hospital discharge, the patient still required insulin [64].

**b)** A case of new-onset diabetes and diabetic ketoacidosis with elevated lipase was described in a 33-year-old, schizophrenic, African-American man following treatment with aripiprazole. Prior to current presentation, the patient had been on aripiprazole therapy for 18 months (dose was not available) and had a BMI of 32 kg/m(2) prior to taking aripiprazole. The patient presented with fatigue, dyspepsia, and epigastric abdominal pain. The patient had progressively gained weight since initiating aripiprazole treatment and his current BMI was 41 kg/m(2). Laboratory tests indicated hyperglycemia, diabetic ketoacidosis, and hyperlipasemia. The patient did not have a personal or family history of diabetes mellitus. Aripiprazole was discontinued and the patient was treated with IV fluids and insulin. A diagnosis of aripiprazole-induced diabetes and elevated lipase, secondary to diabetic ketoacidosis, was made and the patient was discharged home with haloperidol and insulin glargine. Six months after discontinuation of aripiprazole, the patient's BMI had decreased to 33 kg/m(2) and, while still diabetic, his insulin requirements were reduced [65].

### 3.3.3.E] Hyperglycemia

**1)** Incidence: 0.8% to 8% [14][3][4]

**2)** General Information

**a)** Extreme cases with ketoacidosis, hyperosmolar coma, or death, has been reported with atypical antipsychotics [3][4].

**b)** Resolution may not occur with antipsychotic discontinuation, necessitating continued antidiabetic treatment [3][4]

**3)** Prevention and Management

**a)** Monitor all patients for hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness; if symptoms develop, test fasting blood glucose [3][4].

**b)** Perform baseline and periodic fasting blood glucose testing for patients with risk factors for diabetes mellitus (eg, family history, obesity) [3][4].

**c)** Regularly monitor patients with established diagnosis of diabetes mellitus [3][4].

**4)** Adult Clinical Trials

a) **Schizophrenia** or bipolar mania, pooled data (oral route): Change in fasting glucose from baseline, normal to high, 3.8% vs 3.6% with placebo; change from borderline to high, 17.6% vs 9.2% with placebo. Median exposure was 42 days [3][4][36].

b) **Major depressive disorder** (oral route): Change in fasting glucose from baseline, normal to high, 1% with aripiprazole plus antidepressant therapy vs 1% with antidepressant therapy only; change from borderline to high, 11.8% vs 8.1% with placebo. Median exposure was 42 days [3][4].

c) **Schizophrenia** (IM route, extended release): Change in fasting glucose from baseline, normal to high, 8% vs 0% with placebo; change from borderline to high, 3% vs 9.1% with placebo [14]

#### 5) Pediatric Clinical Trials

a) **Schizophrenia** or bipolar mania, pooled data (oral route; age 10 to 17 years): Change in fasting glucose from baseline, normal to high, 0.8% vs 1.8% with placebo; change from borderline to high, 4.5% vs 0% in placebo. Median exposure was 43 days [3][4]

b) **Tourette disorder** (oral route; age 6 to 18 years): Change in fasting glucose from baseline, normal to high, 3.4% vs 1.7% with placebo. Median exposure was 56 days [3][4]

### 3.3.3.F] Hyperprolactinemia

#### 1) Adult Case Reports

a) An 18-year-old woman with **bipolar affective disorder** developed prolactinemia after 3 months of therapy with aripiprazole and lithium. Upon diagnosis of **bipolar disorder**, she had normal menstrual periods and received risperidone and sodium valproate for 1 month with no **menstrual irregularities**. Therapy was changed to aripiprazole (up to 15 mg/day) and lithium because of weight gain. After 3 months, she had developed **oligomenorrhea** and extrapyramidal symptoms of resting hand tremors and cogwheel rigidity; serum prolactin was 50 International Units/mL. Lithium was continued, aripiprazole was stopped, and quetiapine was initiated. One month later, serum prolactin was 11.6 nanograms/mL; 2 months later, it was 8.8 ng/mL. Naranjo probability scale score was 7, indicating a probable association between **hyperprolactinemia** and aripiprazole [67].

### 3.3.3.G] Hyponatremia

1) Incidence: 0.1% to 1% [36][38][63]

#### 2) Adult Clinical Trials

a) Unspecified indication (oral route): 0.1% to 1% [36][38][63]

#### 3) Adult Clinical Trials

a) **Hyponatremia** was reported in a 69-year-old man when aripiprazole was added to sodium valproate maintenance therapy for **bipolar affective disorder**. His comorbid conditions included **diabetes mellitus** treated with metformin and glibenclamide, and **hypothyroidism** treated with thyroxine supplements. While he was treated with a stable dose of sodium valproate, he experienced a **relapse** of manic symptoms and aripiprazole 10 mg/day was added. He developed persistent hiccoughs 2 days later and had a serum sodium level of 122 mEq/L, serum potassium level of 4.5 mEq/L, and urine specific gravity of 1.01. The patient admitted to drinking 3 to 4 L per day of water for the previous 3 weeks. When aripiprazole was withheld and water intake was restricted to 1.5 L/day, sodium levels stabilized to 133 mEq/L. However, sodium levels dropped again to 120 mEq/L one day following rechallenge with aripiprazole 10 mg/day. Once the patient

discontinued [aripiprazole](#) and was initiated on [quetiapine](#) (dose titrated to 400 mg/day over 2 weeks), his sodium levels gradually normalized to 135 mEq/L one week later with spontaneous resolution of hiccoughs. Fluid restriction was then stopped. During the following 8 months, the patient remained euthymic with normal sodium levels [66].

### 3.3.3.H] Increased prolactin level

1) Incidence: 0.1% to 1% [38][63]

2) Adult Clinical Trials

a) Unspecified indication (oral route): 0.1% to 1% [38][63]

### 3.3.3.I] Metabolic syndrome

See Drug Consult reference: Antipsychotic Agents - [Metabolic Syndrome](#)

### 3.3.3.J] Raised low density lipoprotein cholesterol

1) Incidence: 9.6% [14]

2) Adult Clinical Trials

a) [Schizophrenia](#) (IM route, extended release): Fasting [LDL cholesterol](#) change from normal to high, 1.7% vs 2% with placebo; fasting [LDL cholesterol](#) change from borderline to high, 9.6% vs 2.4% with placebo [14]

### 3.3.3.K] Serum cholesterol raised

1) Incidence: 1.1% to 3.6% [14][3][4]

2) Adult Clinical Trials

a) [Schizophrenia](#) (IM route, extended release): Total cholesterol change from normal to high, 3.6% vs 2.7% with placebo; total cholesterol change from borderline to high, 22.2% vs 10.5% with placebo [14]

3) Pediatric Clinical Trials

a) [Autistic disorder](#) (oral route; age 6 to 17 years): Total cholesterol change from normal to high, 1.1% vs 0% with placebo [3][4]

b) [Schizophrenia](#) or [bipolar disorder](#), pooled data (oral route; age 10 to 17 years): Total cholesterol change from normal to high, 1.4% vs 0% with placebo [3][4]

c) [Tourette disorder](#) (oral route; age 6 to 18 years): Total cholesterol change from normal to high, 1.2% vs 0% with placebo [3][4]

### 3.3.3.L] Serum triglycerides raised

1) Incidence: 5.3% to 9.7% [14][3][4]

2) Adult Clinical Trials

a) [Schizophrenia](#) or [bipolar mania](#) (oral route): Fasting [triglycerides](#) change from normal to high, 7.4% vs 7% with placebo [3][4]

b) [Major depressive disorder](#) (oral route): Fasting [triglycerides](#) change from normal to high, 9.7% with [aripiprazole](#) plus antidepressant therapy vs 4.1% with antidepressant therapy only [3][4]

c) **Schizophrenia** (IM route, extended release): Fasting **triglycerides** change from normal to high, 7.1% vs 5.1% with placebo; change from borderline to high, 27.3% vs 26.7% with placebo [14]

### 3) Pediatric Clinical Trials

a) **Tourette disorder** (oral route; age 6 to 18 years): Fasting **triglycerides** change from normal to high, 5.3% vs 3.6% with placebo [3][4]

### 3.3.3.M] Syndrome of inappropriate antidiuretic hormone secretion

#### 1) Adult Case Reports

a) A 60-year-old male with **schizophrenia** developed SIADH after 2 weeks of **aripiprazole** therapy in a hospital setting. The patient was admitted for management of psychiatric symptoms with a recent history of 3 weeks without psychiatric medication, and no history of **diabetes** or alcoholism. **Aripiprazole** 10 mg/day was initiated with gradual dose titration over 10 days to 20 mg/day. Four days after the dose was increased to 20 mg/day, laboratory tests indicated the patient's serum sodium had decreased to 126 mEq/L from a baseline of 142 mEq/L on admission. The patient remained clinically stable, with no signs of overhydration or dehydration, despite a further decrease in the serum sodium to 120 mEq/L over the next 2 days. Additional laboratory data indicated a serum osmolality of 274 milliosmoles (mOsm)/kg, **urine osmolality** of 740 mOsm/kg, urine specific gravity of 1.02, and urine sodium of 113 mEq/L (24-hour urine output was 1500 mL). Concomitant medications included **atenolol** and multivitamins, which have not been associated with **hyponatremia**. The patient was placed on water restriction for 3 days before **aripiprazole** was discontinued. The SIADH resolved within one week after **aripiprazole** was discontinued [68].

### 3.3.3.N] Weight decreased

1) Incidence: 4% [14]

#### 2) Adult Clinical Trials

a) **Schizophrenia** (IM route, extended release): 4% vs 2% with placebo; trial duration was 12 weeks [14]

### 3.3.3.O] Weight increased, 7% or greater

1) Incidence: 2.5% to 21.5% [14][3][4]

#### 2) Prevention and Management

a) Monitor weight in all patients; assess pediatric growth against expected normal growth [3][4].

#### 3) Adult Clinical Trials

a) **Schizophrenia** (oral route): 8.1% vs 3.2% with placebo; trial duration was 4 to 6 weeks [3][4][36]

b) **Major depressive disorder** (oral route): 5.2% with **aripiprazole** plus antidepressant therapy vs 0.6% with antidepressant therapy only; trial duration was 6 weeks [3][4]

c) **Schizophrenia** (IM route, extended release): 21.5% vs 8.5% with placebo; trial duration was 12 weeks [14]

#### 4) Pediatric Clinical Trials

a) **Autistic disorder** (oral route; age 6 to 17 years): 26.3% vs 7.1% with placebo; median exposure was 56 days [3][4]

b) **Schizophrenia** or bipolar mania, pooled data (oral route; age 10 to 17 years): 2.5% vs 1.6% with placebo; median exposure was 43 days [3][4]

c) **Tourette disorder** (oral route; age 6 to 18 years): 20% vs 7.6%; median exposure was 57 days [3][4]

### 3.3.4] Gastrointestinal Effects

#### 3.3.4.A] Abdominal discomfort

1) Incidence: 2% to 3%[14] to 3% [36]

2) Adult Clinical Trials

a) **Schizophrenia** or bipolar mania, pooled data (oral route): 3% vs 2% with placebo [36]

b) **Schizophrenia** (IM route, extended release): 2% vs 1% with placebo [14]

#### 3.3.4.B] Constipation

1) Incidence: 5% to 11% [14][44]

2) Adult Clinical Trials

a) **Major depressive disorder** (oral route): 5% with **aripiprazole** plus antidepressant therapy vs 2% with antidepressant therapy only [44]

b) **Schizophrenia** or bipolar mania (oral route): 11% vs 7% with placebo [36][44]

c) **Schizophrenia** (IM route, extended release): 10% vs 7% with placebo [14]

#### 3.3.4.C] Diarrhea

1) Incidence: 3% [14][44]

2) Adult Clinical Trials

a) **Schizophrenia** (IM route, extended release): 3% vs 2% with placebo [14]

3) Pediatric Clinical Trials

a) **Schizophrenia** or bipolar mania (oral route; age 10 to 17 years): 3% vs 0% with placebo [44]

#### 3.3.4.D] Dysphagia

1) **Esophageal dysmotility** and aspiration have occurred with **aripiprazole** use. **Dysphagia** was reported infrequently in aripiprazole-treated patients in premarketing clinical trials. Nonetheless, like other antipsychotic drugs, **aripiprazole** should be used cautiously in patients at risk for **aspiration pneumonia** [36][44].

#### 3.3.4.E] Excessive salivation

1) Incidence: 3.1% to 8.1% [44]

2) In a short-term study of **aripiprazole** as adjunctive therapy for **bipolar disorder**, **salivary hypersecretion** was reported in 4% of patients receiving **aripiprazole** 15 mg/day or 30 mg/day orally (n=253) compared with 2% of patients receiving placebo (n=130). Patients received **lithium** or **valproate** therapy in addition to **aripiprazole** or placebo for up to 6 weeks [44].

3b) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania received either aripiprazole 10 mg or 30 mg/day orally or placebo, salivary hypersecretion was reported in 8.1% of the aripiprazole 30-mg group and 3.1% of the 10-mg group compared with 0% of the placebo group [44].

4b) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar mania received either oral aripiprazole (doses 2 mg/day or greater) (n=399) or placebo (n=197), salivary hypersecretion was reported in 4% of patients receiving aripiprazole compared with 1% of patients receiving placebo [44].

5b) A 27-year-old man with bipolar affective disorder and current-episode mania with mood-congruent psychotic symptoms treated with valproate sodium 1 gram/day developed sialorrhea 3 months after the institution of aripiprazole 10 mg/day for persistent psychotic symptoms. The patient did not present with any associated sign suggestive of extrapyramidal syndrome. A significant reduction in sialorrhea was noted one week after receiving trihexyphenidyl 2 mg/day [69].

#### 3.3.4.F] Increased appetite

1b) Incidence: 3% to 7% [3][4]

2b) Adult Clinical Trials

a) Major depressive disorder (oral route): 3% with aripiprazole plus antidepressant therapy vs 2% with antidepressant therapy only [3][4]

3b) Pediatric Clinical Trials

a) Tourette disorder (oral route; age 6 to 18 years): 7% vs 1% with placebo [3][4]

b) All pediatric indications, pooled data (oral route; age 6 to 18 years): 7% vs 3% with placebo [3][4]

#### 3.3.4.G] Indigestion

1b) Incidence: 9% [36]

2b) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either oral aripiprazole 2 mg/day or greater (n=1843) or placebo (n=1166), dyspepsia was reported in 9% of patients receiving aripiprazole compared with 7% of patients receiving placebo [36].

#### 3.3.4.H] Nausea

1b) Incidence: 8% to 15% [36][44]

2b) Adult Clinical Trials

a) Agitation in schizophrenia or bipolar mania (IM route): 9% vs 3% with placebo [3][4]

b) Bipolar mania (oral route): 8% with aripiprazole plus lithium or valproate vs 5% with placebo plus lithium or valproate [3][4]

c) Schizophrenia or bipolar mania, pooled data (oral route): 15% vs 11% with placebo [3][4]

3b) Pediatric Clinical Trials

a) Bipolar mania (oral route; age 10 to 17 years): 11% vs 4% with placebo [3][4]

b) Tourette disorder (oral route; age 6 to 18 years): 11% vs 4% with placebo [3][4]

c) All pediatric indications, pooled data (oral route; age 6 to 18 years): 8% vs 4% with placebo [3][4]



**3.3.4.I] Pancreatitis**

1) Incidence: Lss than 0.1% [36]

2) **Pancreatitis** has been observed during clinical trials with a frequency of less than 1/1000 patients who received multiple oral doses of **aripiprazole** at least 2 mg/day within the database of 13,543 adult patients [36].

**3.3.4.J] Toothache**

1) Incidence: 4% [36]

2) In a pooled analysis of trials in which adult patients with **schizophrenia** or bipolar mania received either oral **aripiprazole** 2 mg/day or greater (n=1843) or placebo (n=1166), toothache was reported in 4% of patients receiving **aripiprazole** compared with 3% of patients receiving placebo [36].

**3.3.4.K] Vomiting**

1) Incidence: 3% to 11% [14][44]

2) Adult Clinical Trials

a) **Bipolar disorder** (oral route): 4% with **aripiprazole** plus **lithium** or **valproate** vs 0% with placebo plus **lithium** or **valproate** [44]

b) **Schizophrenia** or bipolar mania (oral route): 11% vs 6% with placebo [44]

c) Agitation associated with **schizophrenia** or bipolar mania (oral route): 3% vs 1% with placebo [44]

d) **Schizophrenia** (IM route, extended release): 3% vs 1% with placebo [14]

**3.3.4.L] Xerostomia**

1) Incidence: 2% to 5% [14][36][44]

2) Adult Clinical Trials

a) **Bipolar disorder** (oral route): 2% with **aripiprazole** plus **lithium** or **valproate** vs 1% with placebo plus **lithium** or **valproate** [44]

b) **Schizophrenia** or bipolar mania (oral route): 5% vs 4% with placebo [44]

c) **Schizophrenia** (IM route, extended release): 4% vs 2% with placebo [14]

3) Pediatric Clinical Trials

a) **Schizophrenia** or bipolar mania (oral route; age 10 to 17 years): 2% vs 1% with placebo [44]

**3.3.5] Hematologic Effects****3.3.5.A] Agranulocytosis**

1) **Agranulocytosis** has been reported during clinical and postmarketing use of oral **aripiprazole**. The potential risk factors include a history of low WBC and drug-induced **leukopenia** or **neutropenia**. These patients should have frequent monitoring of CBC during the first few months of treatment [36][40].

**3.3.5.B] Leukopenia**



1) Incidence: Less than 1% [40]

2) **Leukopenia** has been reported in less than 1% of patients receiving **aripiprazole** treatment [40].

3) **Leukopenia** has been reported during clinical and postmarketing use of oral **aripiprazole**. The potential risk factors include a history of low WBC and drug-induced **leukopenia** or **neutropenia**. These patients should have frequent monitoring of CBC during the first few months of treatment [36][40].

4) A case report described **leukopenia** in a 32-year-old man following treatment with **risperidone** and **aripiprazole**. The patient, who had a long history of **paranoid schizophrenia**, had been initiated on **risperidone** 2 mg/day a few years earlier. Although he reported no side effects and the results of his annual physical exam were normal, laboratory assessment showed a WBC and absolute neutrophil count (ANC) of  $2.8 \times 10^9$  and  $1.27 \times 10^9$ , respectively. Risperidone-induced **leukopenia** was suspected and the patient agreed to reduce the **risperidone** dose to 1 mg/day. A few weeks later, a lab workup showed WBC count and ANC at  $2.7 \times 10^9$  and  $1.22 \times 10^9$ , respectively. Subsequently, **risperidone** was discontinued and the patient was initiated on **aripiprazole** 10 mg daily. He was evaluated every 4 weeks and reported no adverse effects. Six months later, his WBC count and ANC were  $2.4 \times 10^9$  and  $0.85 \times 10^9$ , respectively, and **aripiprazole** was discontinued. Two weeks later, he experienced **paranoid delusions**, irritable mood, and auditory hallucinations for which he was hospitalized. Upon admission, his WBC count and ANC were  $6.4 \times 10^9$  and  $1.29 \times 10^9$ , respectively. He was discharged after being reinitiated on **aripiprazole** 10 mg/day. At a follow-up appointment, his WBC count and ANC were again low ( $2.9 \times 10^9$  and  $1.29 \times 10^9$ , respectively). It was decided to discontinue **aripiprazole** and treat the patient with **paliperidone** 6 mg and **lithium** 300 mg. Subsequent to the medication change, his WBC count and ANC increased to  $3.3 \times 10^9$  and  $1.42 \times 10^9$ . A full hematologic workup was pending at the time of this publication [41].

### 3.3.5.C] **Neutropenia**

1) Incidence: Less than 1% [40]

2) **Neutropenia** has been reported in less than 1% of patients receiving **aripiprazole** treatment [40].

3) **Neutropenia** has been reported during clinical and postmarketing use of oral **aripiprazole**. The potential risk factors include a history of low WBC and drug-induced **leukopenia** or **neutropenia**. These patients should be evaluated for signs of infection, and frequent monitoring of CBC during the first few months of treatment is recommended. Patients with severe **neutropenia** (absolute neutrophil count less than  $1000/\text{mm}^3$ ) should discontinue **aripiprazole** and have their WBC followed at discontinuation of treatment until recovery [36][40].

### 3.3.5.D] **Thrombocytopenia**

1) Incidence: Up to 1% [14][40]

2) Adult Clinical Trials

a) Indication not specified (oral or IM route): less than 1% [40]

b) **Schizophrenia** (IM route, extended-release): less than 0.1% [14]

## 3.3.6] **Hepatic Effects**

### 3.3.6.A] **Drug-induced liver disease**

1) Incidence: Less than 0.1% [14]

2) Adult Clinical Trials

a) **Schizophrenia** (IM route, extended-release): less than 0.1% [14]

## 3.3.7] **Immunologic Effects**

**3.3.7.A] Hypersensitivity reaction**

1) Incidence: Up to 0.1% [14]

2) Adult Clinical Trials

a) **Schizophrenia** (IM route, extended-release): Less than 0.1% [14]

3) Postmarketing

a) **Allergic reactions** (ie, **anaphylactic reaction**, **angioedema**, **laryngospasm**, **pruritus/urticaria**, or oropharyngeal spasm) have been observed rarely in postmarketing surveillance of oral **aripiprazole** [36][44].

**3.3.8] Musculoskeletal Effects****3.3.8.A] Arthralgia**

1) Incidence: 2% to 4% [14][44]

2) Adult Clinical Trials

a) **Major depressive disorder** (oral route): 4% with **aripiprazole** plus antidepressant therapy vs 3% with antidepressant therapy only [44]

b) **Schizophrenia** (IM route, extended release): 4% vs 1% with placebo [14]

3) Pediatric Clinical Trials

a) **Schizophrenia** or bipolar mania (oral route; age 10 to 17 years): 2% vs 0% with placebo [44]

**3.3.8.B] Backache**

1) Incidence: 4% [14]

2) Adult Clinical Trials

a) **Schizophrenia** (IM route, extended release): 4% vs 2% with placebo [14]

**3.3.8.C] Muscle rigidity**

1) Incidence: 4% [36]

2) In a pooled analysis of trials in which adult patients with **schizophrenia** or bipolar mania received either oral **aripiprazole** 2 mg/day or greater (n=1843) or placebo (n=1166), musculoskeletal stiffness was reported in 4% of patients receiving **aripiprazole** compared with 3% of patients receiving placebo. Patients with **schizophrenia** received acute therapy up to 6 weeks and patients with bipolar mania received treatment up to 3 weeks [36].

**3.3.8.D] Musculoskeletal pain**

1) Incidence: 3% [14]

2) Adult Clinical Trials

a) **Schizophrenia** (IM route, extended release): 3% vs 1% with placebo [14]

**3.3.8.E] Myalgia**

1) Incidence: 2% to 3% [14][44]

2) Adult Clinical Trials

a) **Major depressive disorder** (oral route): 3% with **aripiprazole** plus antidepressant therapy vs 1% with antidepressant therapy only [44]

b) **Schizophrenia** (IM route, extended release): 4% vs 2% with placebo [14]

c) **Schizophrenia** or bipolar mania, pooled data (oral route): 2% vs 1% with placebo [36]

### 3.3.8.F] Pain in limb

1) Incidence: 4% [36]

2) In a pooled analysis of trials in which adult patients with **schizophrenia** or bipolar mania received either oral **aripiprazole** 2 mg/day or greater (n=1843) or placebo (n=1166), pain in extremity was reported in 4% of patients receiving **aripiprazole** compared with 2% of patients receiving placebo. Patients with **schizophrenia** received acute therapy up to 6 weeks and patients with bipolar mania received treatment up to 3 weeks [36].

### 3.3.8.G] Rhabdomyolysis

1) Incidence: Less than 0.1% [14]

2) Adult Clinical Trials

a) **Schizophrenia** (IM route, extended-release): Less than 0.1% [14]

3) Adult Case Report

a) A 31-year-old Taiwanese man developed **rhabdomyolysis** within 1 month of starting **aripiprazole** therapy for **schizophrenia**. Thirty days after starting **aripiprazole** 15 mg/day, the patient was found lying on the floor with intermittent consciousness and muscle weakness. Although he was afebrile and had blood pressure of 113/68 mmHg, his pulse and respiratory rate were slightly elevated at 120 beats/min and 18 breaths/min, respectively. Neurological examination showed slurred and incoherent speech, periodic disorientation, and weakness of both lower extremities. Laboratory results revealed elevated levels of **creatinine kinase** (CK) (maximum, 19,660 international units) and serum glutamate oxaloacetate transaminase (maximum, 238 international units/L), a WBC count of 16,620/mm<sup>3</sup>, the presence of myoglobin in his urine, and a negative **toxicology screen**. **Aripiprazole** was discontinued and daily treatment with high-volume IV solution replacement, which improved his consciousness, began. His serum CK level dropped to 6348 international units after 3 days and it continued to normalize following discharge. The **rhabdomyolysis** resolved with **aripiprazole** discontinuation [72].

### 3.3.8.H] Spasm

1) Incidence: 2% [36]

2) In a pooled analysis of trials in which adult patients with **schizophrenia** or bipolar mania received either oral **aripiprazole** 2 mg/day or greater (n=1843) or placebo (n=1166), muscle spasms were reported in 2% of patients receiving **aripiprazole** compared with 1% of patients receiving placebo. Patients with **schizophrenia** received acute therapy up to 6 weeks and patients with bipolar mania received treatment up to 3 weeks [36].

## 3.3.9] Neurologic Effects

### 3.3.9.A] Akathisia

1) Incidence: 2% to 25% [14][44]

**2) Adult Clinical Trials**

- a) Agitation associated with [schizophrenia](#) or bipolar mania (IM route): 2% vs 0% with placebo [44]
- b) [Bipolar disorder](#) (oral route): 19% with [aripiprazole](#) plus [lithium](#) or [valproate](#) vs 5% with placebo plus [lithium](#) or [valproate](#) [44]
- c) Bipolar mania (oral route): 13% vs 4% with placebo [44]
- d) [Major depressive disorder](#) (oral route): 25% with [aripiprazole](#) with antidepressant therapy vs 4% with antidepressant therapy only [44].
- e) [Schizophrenia](#) (oral route): 10 to 30 mg/day, 55% increased risk compared with placebo; 49% increased risk compared with older second generation antipsychotics (ie, [olanzapine](#), [risperidone](#), [ziprasidone](#)) in a meta-analysis of 11 studies [62]
- f) [Schizophrenia](#) or bipolar mania (oral route): 13% vs 4% with placebo [44]
- g) [Schizophrenia](#) (IM route, extended release): 11% vs 4% with placebo [14]

**3) Pediatric Clinical Trials**

- a) Bipolar mania (oral route; age 10 to 17 years): 11.1% vs 8.2% with placebo [44]
- b) [Schizophrenia](#) or bipolar mania (oral route; age 10 to 17 years): 9% vs 4% with placebo [44]

**3.3.9.B| Cerebrovascular accident****1) General Information**

- a) Cerebrovascular adverse events (eg, [stroke](#), [transient ischemic attack](#)), included fatalities [3][4]
- b) There was a significant dose response relationship for cerebrovascular adverse events in elderly aripiprazole-treated patients (age range, 78 to 88 years) [3][4]

**2) Adult Clinical Trials**

- a) Dementia-related [psychosis](#) (unapproved use; oral route; mean age, 84 years): Cerebrovascular adverse events (eg, [stroke](#), [transient ischemic attack](#)), including fatalities, occurred with greater incidence vs placebo [3][4]

**3.3.9.C| Dizziness****1) Incidence: 4% to 10% [14][44]****2) Adult Clinical Trials**

- a) Agitation associated with [schizophrenia](#) or bipolar mania (IM route): 8% vs 5% with placebo [44]
- b) [Bipolar disorder](#) (oral route): 4% with [aripiprazole](#) plus [lithium](#) or [valproate](#) vs 1% with placebo plus [lithium](#) or [valproate](#) [44]
- c) [Major depressive disorder](#) (oral route): 4% with [aripiprazole](#) plus antidepressant therapy vs 2% with antidepressant therapy only [44]
- d) [Schizophrenia](#) or bipolar mania, pooled data (oral route): 10% vs 7% with placebo [44]

e) **Schizophrenia** (IM route, extended release): 4% vs 2% with placebo [14]

### 3j) Pediatric Clinical Trials

a) Bipolar mania (oral route; age 10 to 17 years) 5% vs 1% with placebo [44]

b) **Schizophrenia** or bipolar mania (oral route; age 10 to 17 years): 5% vs 2% with placebo [44]

### 3.3.9.D] Dystonia

1j) Incidence: 2% [44]

2j) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with **schizophrenia** or bipolar mania received either **aripiprazole** (doses 2 mg/day or greater) (n=399) or placebo (n=197), **dystonia** was reported in 2% of patients receiving **aripiprazole** compared with 0% of patients receiving placebo [44].

3j) Dystonic symptoms, including spasm of the neck muscles, sometimes progressing to tightness of the throat, difficulty swallowing, difficulty breathing, and/or protrusion of the tongue, may occur in susceptible individuals during the first few days of treatment with **aripiprazole**. Symptoms occur more frequently and with greater severity with higher doses of first-generation antipsychotic drugs, although they can occur at low doses. Males and younger patients are at higher risk for acute **dystonia** [36].

4j) A 25-year-old female with **schizophrenia** developed characteristics associated with tardive **dystonia** following **aripiprazole** treatment. The patient was diagnosed with **schizoaffective disorder** that included 2 previous psychotic episodes and 3 previous **manic episodes**. She had a past medication history of changing to various antipsychotic medications due to adverse events which included skin rashes with **carbamazepine**, weight gain with **olanzapine**, **galactorrhea** and severe extrapyramidal symptoms with **risperidone**, and tremors and drowsiness with **valproate**. Because the patient had a recurrence of mania with **quetiapine**, the patient switched to **lithium**. **Lithium** was reduced to 450 mg/day because of memory loss and vomiting. The patient remained on **lithium** for 8 months with additional adverse effects. **Aripiprazole** 10 mg/day was added to **lithium** therapy due to a **manic episode**. After 4 weeks of treatment, **aripiprazole** was increased to 15 mg/day. After 2 months of **lithium** and **aripiprazole** therapy, she presented with backward arching with muscle spasms over the latissimus dorsi, which worsened over time. The patient did not experience any other symptoms such as: perioral tongue movements, facial grimacing, or difficulty in breathing or chewing. However, the Extrapyramidal Symptom Rating Scale (ESRS) demonstrated that she was suffering from moderate to severe levels of extrapyramidal symptoms. The patient was started on trihexyphenidyl 6 mg daily and the **aripiprazole** was discontinued. After 2 weeks, her **dystonia** improved and she had a ESRS score of zero. After 4 weeks, **clozapine** was added to the **lithium** treatment, which was titrated to 150 mg/day to treat her mood and psychotic symptoms. She remained symptom free 1 year after stopping **aripiprazole** therapy [53].

5j) A 10-year-old boy with **bipolar disorder** developed **dystonia** following **aripiprazole** treatment. The child was admitted to a psychiatric care unit because of high energy and violent, impulsive behaviors with aggression toward his family and peers. His current medications included **divalproex** 20 mg/kg per day divided three times daily plus **guanfacine** 0.5 mg three times daily. **Divalproex** was discontinued and **aripiprazole** 5 mg twice daily for mood stabilization was initiated the following day. Three days after initial **aripiprazole** therapy, the patient developed neck pain and stiffness with abnormal jaw sensations. Upon examination, his symptoms were consistent with acute torticollis. His neck symptoms completely resolved within 30 minutes of **benztropine** 1 mg administration and **aripiprazole** discontinuation. The patient did not have any recurrence of **dystonia** after he was treated with **quetiapine** 150 mg three times daily with **bupropion** SR 200 mg daily for mood disorder [54].

### 3.3.9.E] Extrapyramidal sign

1j) Incidence: 2% to 27.3% [36][44]

- 2)) In a short-term study of [aripiprazole](#) as adjunctive therapy for [bipolar disorder](#), [extrapyramidal disorder](#) was reported in 5% of patients receiving [aripiprazole](#) 15 mg/day or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients received [lithium](#) or [valproate](#) therapy in addition to [aripiprazole](#) or placebo for up to 6 weeks [44].
- 3)) In pooled data of 2 placebo-controlled trials of adult patients with [major depressive disorder](#) receiving [aripiprazole](#) 2 mg to 20 mg/day for up to 6 weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), [extrapyramidal disorder](#) occurred in 2% versus 0% of patients, respectively [44].
- 4)) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania received oral [aripiprazole](#) 15 or 30 mg/day (n=917) or placebo (n=753), [extrapyramidal disorder](#) was reported in 5% of aripiprazole-treated patients compared with 2% of placebo-treated patients [44].
- 5)) In a pooled analysis of trials in which adult patients with [schizophrenia](#) or bipolar mania received either oral [aripiprazole](#) 2 mg/day or greater (n=1843) or placebo (n=1166), [extrapyramidal disorder](#) was reported in 5% of patients receiving [aripiprazole](#) compared with 3% of patients receiving placebo [36][44].
- 6)) In a short-term, placebo-controlled trial in which pediatric patients age 13 to 17 years with [schizophrenia](#) received either [aripiprazole](#) or placebo, [extrapyramidal disorder](#) was reported in 21.6% of the 30-mg [aripiprazole](#) group and 13% of the 10-mg [aripiprazole](#) group compared with 5% of the placebo group [44].
- 7)) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania received either oral [aripiprazole](#) 10 mg or 30 mg/day or placebo, [extrapyramidal disorder](#) was reported in 27.3% of the [aripiprazole](#) 30-mg group and 12.2% of the 10-mg group compared with 3.1% of the placebo group [44].
- 8)) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with [schizophrenia](#) or bipolar mania received either [aripiprazole](#) (doses 2 mg/day or greater) (n=399) or placebo (n=197), [extrapyramidal disorder](#) was reported in 19% of patients receiving [aripiprazole](#) compared with 4% of patients receiving placebo [44].
- 9)) A case report described the development of extrapyramidal symptoms (EPS) in a 56-year-old schizophrenic woman following treatment with [aripiprazole](#). The patient, who presented with psychiatric symptoms of paranoid and [persecutory delusions](#), auditory hallucinations, and perplexed mood, was started on [aripiprazole](#) 10 mg once daily. The dose was increased to 15 mg once daily the second week and then to 30 mg once daily the third week. Five weeks after the initiation of [aripiprazole](#), including 3 weeks at the 30 mg dose, the patient developed stiffness of the trunk and limbs, parkinsonian-gait, mask-like facial expression, and [hypersalivation](#). None of these symptoms had been documented in this patient prior to [aripiprazole](#) therapy, and the patient had not received treatment with any other antipsychotic agents previously. [Akathisia](#) was absent, and acute [dystonia](#) was ruled out based on absence of opisthotonos, torticollis, [oculogyric crisis](#), and the time of onset. Subsequently, the [aripiprazole](#) dose was reduced to 15 mg daily and [procyclidine](#) 5 mg was added, which prompted resolution of the stiffness. However, the patient continued to hypersalivate and her psychotic symptoms did not improve. [Aripiprazole](#) treatment was stopped 7 days after the onset of EPS and nightly [olanzapine](#) therapy was initiated, starting with 2.5 mg for 3 days, followed by 5 mg thereafter. The [hypersalivation](#) resolved 10 days after discontinuation of [aripiprazole](#) and no further EPS symptoms were observed. While the exact mechanism for this adverse event was not elucidated, an idiosyncratic reaction to [aripiprazole](#), rather than a general side effect, was postulated as a possible cause for this effect [55].
- 10)) Extrapyramidal symptoms have been minimal during oral [aripiprazole](#) therapy of [schizophrenia](#) in unpublished studies [56][57][58][59]. In one 4-week study, the overall incidence of extrapyramidal side effects with [aripiprazole](#) 15 or 30 mg daily was similar to that in the placebo group; at least one dose of [benztropine](#) was required in 11 to 17% of patients receiving these doses of [aripiprazole](#), compared to 36% assigned to [haloperidol](#) 10 mg daily [56]. The frequency of extrapyramidal symptoms was also lower with [aripiprazole](#) than [haloperidol](#) in a phase II study [57].



See Drug Consult reference: Neuroleptic-Induced Extrapyramidal Reactions

### 3.3.9.F] Headache

1) Incidence: 10% to 27% [4][3]

2) Adult Clinical Trials

a) Agitation in [schizophrenia](#) or bipolar mania (IM route): 12% vs 7% with placebo [3]

b) [Schizophrenia](#) or bipolar mania, pooled data (oral route): 27% vs 23% with placebo [4][3]

3) Pediatric Clinical Trials

a) [Schizophrenia](#) or bipolar mania (oral route): 16% vs 13% with placebo [44].

b) [Tourette disorder](#) (oral route; age 6 to 18 years): 10% vs 3% with placebo [3][4]

c) All pediatric indications, pooled data (oral route; 6 to 18 years): 12% vs 10% with placebo [4][3]

### 3.3.9.G] Insomnia

1) Incidence: 8% to 18% [36][44]

2) In a short-term study of [aripiprazole](#) as adjunctive therapy for [bipolar disorder](#), insomnia was reported in 8% of patients receiving [aripiprazole](#) 15 mg/day or 30 mg/day orally (n=253) compared with 4% of patients receiving placebo (n=130). Patients received [lithium](#) or [valproate](#) therapy in addition to [aripiprazole](#) or placebo for up to 6 weeks [44].

3) In pooled data of 2 placebo-controlled trials of adult patients with [major depressive disorder](#) receiving oral [aripiprazole](#) 2 mg to 20 mg/day for up to 6 weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), insomnia occurred in 8% versus 2% of patients, respectively [44].

4) In a pooled analysis in which adult patients with [schizophrenia](#) or bipolar mania received either oral [aripiprazole](#) 2 mg/day or greater (n=1843) or placebo (n=1166), insomnia was reported in 18% of patients receiving [aripiprazole](#) compared with 13% of patients receiving placebo [36][44].

### 3.3.9.H] Sedated

1) Incidence: 3% to 21% [14][4][3]

2) General Information

a) [Aripiprazole](#) has the potential to impair judgement, thinking, or motor skills [4][3][36].

3) Adult Clinical Trials

a) Agitation in [schizophrenia](#) or bipolar mania (IM route): 3% vs 2% [3]

b) Bipolar mania (oral route): 8% vs 3% with placebo [4][3]

c) Bipolar mania (oral route): 4% with [aripiprazole](#) plus [lithium](#) or [valproate](#) vs 2% with placebo plus [lithium](#) or [valproate](#) [4][3]

d) [Major depressive disorder](#) (oral route): 4% with [aripiprazole](#) plus antidepressant therapy vs 2% with antidepressant therapy only [4][3]

e) [Schizophrenia](#) (oral route): Somnolence including sedation, 12.6% (30 mg); 7.5% (20 mg); 8.7% (15 mg); and 8.5% (10 mg) vs 7.1% placebo [4][3]

f) **Schizophrenia** or bipolar mania, pooled data (oral route): 7% vs 4% with placebo [4][3]

g) **Schizophrenia** (IM route, extended release): 5% vs 1% with placebo [14]

#### 4) Pediatric Clinical Trials

a) **Autistic disorder** (oral route; age 6 to 17 years): 21% vs 4% with placebo [4][3]

b) **Tourette disorder** (oral route; age 6 to 18 years): 13% vs 6% with placebo [4][3]

c) All pediatric indications, pooled data (oral route; age 6 to 18 years): 9% vs 2% with placebo [4][3]

### 3.3.9.I] Seizure

1) Incidence: Up to 0.3% [14][44]

#### 2) General Information

a) Use cautiously in patients with a history of seizures or conditions with lower the seizure threshold (eg, **Alzheimer dementia**) [44][14].

b) Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older [14].

#### 3) Adult Clinical Trials

a) Indication not specified (oral route): 0.1% [44]

b) Indication not specified (IM route): 0.2% [44]

c) **Schizophrenia** (IM route, extended-release): Less than 0.1% [14]

d) Various indications (oral route): Among patients with **schizophrenia**, an affective disorder, or **dementia** (Study N=60,121), the incidence of seizures among patients receiving monotherapy with **aripiprazole**, amisulpride, **risperidone**, or sulpiride was 24.1 per 10,000 person-years, 12.4 per 10,000 patient-years among patients with past use of any antipsychotic (greater than 90 days since last prescription), and 11.7 per 10,000 person-years among patients with no history of antipsychotic use [61].

#### 4) Pediatric Clinical Trials

a) Indication not specified (oral route; age 10 to 17 years): 0.3% [44]

### 3.3.9.J] Somnolence

1) Incidence: 6% to 26.3% [4][3]

#### 2) Adult Clinical Trials

a) Agitation in **schizophrenia** or bipolar mania (IM route): 7% vs 4% with placebo [3]

b) **Major depressive disorder** (oral route): 6% with **aripiprazole** plus antidepressant therapy vs 4% with antidepressant therapy alone [3][4]

c) **Schizophrenia** (oral route): Somnolence including sedation, 12.6% (30 mg); 7.5% (20 mg); 8.7% (15 mg); and 8.5% (10 mg) vs 7.1% placebo [4][3]

d) **Schizophrenia** or bipolar mania, pooled data (oral route): 5% vs 3% [4][3]

#### 3) Pediatric Clinical Trials



- a) **Autistic disorder** (oral route; age 6 to 17 years): 10% vs 4% [4][3]
- b) **Bipolar mania** (oral route; age 10 to 17 years): 23% (overall); 26.3% (30 mg); and 19.4% (10 mg) vs 3.1% with placebo [4][3]
- c) **Schizophrenia** (oral route; age 13 to 17 years): 21.6% (30 mg) and 11% (10 mg) vs 6% with placebo [4][3]
- d) **Tourette disorder** (oral route): 13% vs 1% with placebo [3][4]
- e) All pediatric indications, pooled data (oral route; age 6 to 18 years): 16% vs 4% with placebo [3][4]

#### 4) Pediatric Case Report

- a) Excessive somnolence requiring hospitalization was observed in a 9-year-old girl weighing 25 kg within 3.5 hours of initiation of **aripiprazole** at a dose of 15 mg/day (0.6 mg/kg/day) for the treatment of **oppositional defiant disorder**. Although optimal dosing in pediatric patients has not been established, this dose is up to three times higher than doses used in a clinical study including children of similar body weight to this patient (ie, 0.2 mg/kg/day or 2 to 5 mg/day) [60].

#### 3.3.9.K] **Tardive dyskinesia**

- 1) **Tardive dyskinesia** may develop in patients treated with antipsychotic drugs, with a higher prevalence in the elderly, particularly elderly women. The risk of developing **tardive dyskinesia** and the likelihood of it becoming irreversible appear to increase as treatment duration and the total cumulative dose of the drug increase. Although less common, the condition can develop after relatively brief treatment periods at low doses. **Tardive dyskinesia** may remit upon discontinuation of the antipsychotic drug; however, the antipsychotic drug itself may mask the underlying process. **Aripiprazole** should be prescribed at the lowest dose and the shortest duration of therapy to produce a satisfactory clinical response to minimize the occurrence of **tardive dyskinesia**. If a patient receiving **aripiprazole** therapy develops symptoms of **tardive dyskinesia**, consideration should be given to discontinuing the drug. Some patients may require **aripiprazole** treatment regardless of the presence of **tardive dyskinesia** [36][44].
- 2) In a retrospective case series, **tardive dyskinesia**, manifesting primarily as ora-buccal-lingual stereotypy, occurred with **aripiprazole** therapy in 8 patients (5 female; average age 55.8 years) in treatment for **bipolar disorder**, **depression**, stress-induced anxiety or anger/irritability (n=236). Duration of therapy was known in 7 patients and ranged from 4 to 72 months; doses of 5 mg/day and 20 mg/day were known in 2 patients. In 5 patients, there was no history of previous therapy with other agents known to cause TD symptoms; these cases were considered to have a definite relationship between **aripiprazole** use and TD symptoms. In 3 patients, the correlation was deemed probable, as they had been exposed to other neuroleptics before symptoms emerged, including **quetiapine** (n=2), **ziprasidone** (n=1), **haloperidol** (n=1), **fluphenazine** (n=1), **risperidone** (n=1), **mesoridazine** (n=1), **olanzapine** (n=1), and **metoclopramide** (n=1). No spontaneous improvement was noted following **aripiprazole** discontinuation in 5 of the 7 patients with follow-up data available (range, 4 to 72 months); of these, one patient's symptoms worsened. Moderate symptom improvement occurred with tetrabenazine treatment in all 4 patients with available follow-up data (n=5) [49].
- 3) A 53-year-old neuroleptic-naïve female developed **tardive dystonia** following treatment with **aripiprazole**. She was a past IV heroin user and was positive for **hepatitis C**. She was taking **aripiprazole** 5 mg/day (the only neuroleptic), **clonazepam** 1 mg twice daily, **escitalopram** 20 mg/day, and **propranolol** 10 mg twice daily. Neurological testing was unremarkable except for involuntary continuous truncal spasms. Flexing of her trunk with occasional extension of her pelvis occurred primarily during sitting or standing,

and disappeared when lying down. Although she had no signs of [choreiform movements](#), she developed mild facial masking, mild bradykinesia, and walked without arm swing. [Aripiprazole](#) was substituted with tetrabenazine 25 mg twice daily. This resulted in a significant reduction in [dystonia](#) but a mild increase in her [parkinsonism](#). The benefit of tetrabenazine failed to sustain, and therapy was subsequently discontinued 2 months later [50].

4) A 46-year-old female experienced oromandibular [tardive dyskinesia](#) following administration of [aripiprazole](#) to manage her treatment-resistant depression. At time of presentation, the patient had been experiencing depression symptoms consistently for 2 years while taking [duloxetine](#) (up to 120 mg/day) with only partial response. A low-dose of [ziprasidone](#) (40 mg/day) was administered, but discontinued 2 weeks later due to [akathisia](#) and adverse effects. [Ziprasidone](#) was then switched to [aripiprazole](#) (a gradual dose increase to 15 mg/day). Several weeks later, the patient had attained full resolution of her depression. After 15 months of continued remission with [duloxetine](#) and [aripiprazole](#), the patient began to develop involuntary lateral jaw movements, primarily on her left side at a rate of 2 to 3 movements every few minutes. Notably, she had no dentition problems or prior history of nervous or motor tics. Following a series of tests, [aripiprazole](#) was tapered and discontinued. Subsequently, the patient's lateral movements completely resolved 8 weeks later. Based on the Naranjo Scale, the probability score of oromandibular [tardive dyskinesia](#) directly related to [aripiprazole](#) was 5 on a 12-point scale [51].

5) Two case reports (involving Taiwanese women, ages 41 and 52 years) suggest a relationship between use of [aripiprazole](#) and [tardive dyskinesia](#). The first patient was maintained on amisulpride 200 mg/day no adverse effects. However, she was concerned over [amenorrhea](#) following amisulpride treatment. A combination of amisulpride 200 mg/day and [aripiprazole](#) 10 mg/day was initiated and the patient's mental stability and menstrual cycle remained stable. After 11 months of therapy, the patient presented with Parkinsonian symptoms including rabbit syndrome, mask face and hand tremor, which persisted for 4 months. Amisulpride was withdrawn and [aripiprazole](#) 15 mg/day was given. Dyskinetic symptoms developed 3 months after amisulpride discontinuation. However, the patient was reluctant to change medication since her psychotic symptoms were under control. Some of her dyskinetic symptoms improved and sustained after 21 months of [aripiprazole](#) therapy. The second patient, who had discontinued all the psychotropic medications (sulpiride 50 to 200 mg/day for 6 years) was admitted due to reoccurring psychotic symptoms. Upon admission, [aripiprazole](#) 5 mg/day was initiated titrating up to 10 mg/day in one week. She was discharged on this dose. After 2 months of [aripiprazole](#) treatment, the patient developed buccal [dyskinesia](#) (involuntary chewing and crunching movements). [Diphenhydramine](#) 150 mg/day was added to her regimen and her symptoms improved and eventually disappeared within 3 to 4 months [52].

### 3.3.9.L] [Transient ischemic attack](#)

#### 1) General Information

- a) Cerebrovascular adverse events (eg, [stroke](#), [transient ischemic attack](#)), included fatalities [3][4]
- b) There was a significant dose response relationship for cerebrovascular adverse events in elderly aripiprazole-treated patients (age range, 78 to 88 years) [3][4]

#### 2) Adult Clinical Trials

- a) Dementia-related [psychosis](#) (unapproved use; oral route; mean age, 84 years): Cerebrovascular adverse events (eg, [stroke](#), [transient ischemic attack](#)), including fatalities, occurred with greater incidence vs placebo [3][4]

### 3.3.9.M] Tremor

- 1) Incidence: 2% to 11.8% [14][44]
- 2) Adult Clinical Trials

- a) Bipolar mania (oral route): 6% vs 3% with placebo [44]
- b) Bipolar disorder (oral route): 9% with aripiprazole plus lithium or valproate vs 6% with placebo plus lithium or valproate [44]
- c) Major depressive disorder (oral route): 5% with aripiprazole plus antidepressant therapy vs 4% with antidepressant therapy only [44]
- d) Schizophrenia or bipolar mania (oral route): 5% vs 3% with placebo [44]
- e) Schizophrenia (IM route, extended release): 3% vs 1% with placebo [14]

### 3) Pediatric Clinical Trials

- a) Schizophrenia or bipolar mania (oral route; age 10 to 17 years) 5% vs 2% with placebo [44]
- b) Schizophrenia (oral route; age 13 to 17 years): 11.8% (30 mg) and 2% (10 mg) vs 2% with placebo [44]

## 3.3.10] Ophthalmic Effects

### 3.3.10.A] Blurred vision

- 1) Incidence: 3% to 8% [36][44]
- 2) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either oral aripiprazole 2 mg/day or greater (n=1843) or placebo (n=1166), blurred vision was reported in 3% of patients receiving aripiprazole compared with 1% of patients receiving placebo [36][44].
- 3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral aripiprazole 2 mg to 20 mg/day for up to 6 weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), blurred vision occurred in 6% versus 1% of patients, respectively [44].
- 4) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania received either aripiprazole 10 mg or 30 mg/day orally or placebo, blurred vision was reported in 8% of the aripiprazole group (n=197) compared with 0% of the placebo group (n=97) [44].
- 5) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar mania received either oral aripiprazole (doses 2 mg/day or greater) (n=399) or placebo (n=197), blurred vision was reported in 5% of patients receiving aripiprazole compared with 0% of patients receiving placebo [44].

### 3.3.10.B] Oculogyric crisis

- 1) Incidence: 0.1% to 1% [14]
- 2) Adult Clinical Trials

- a) Schizophrenia (IM route, extended-release): 0.1% to 1%[14]

## 3.3.12] Psychiatric Effects

### 3.3.12.A] Agitation

- 1) Incidence: 19% [36]
- 2) Adult Clinical Trials

- a) Schizophrenia or bipolar mania, pooled data (oral route): 19% vs 17% with placebo [36].

**3.3.12.B| Anxiety**

1) Incidence: 4% to 17% [36][44]

2) Adult Clinical Trials

a) **Bipolar disorder** (oral route): 4% with **aripiprazole** plus **lithium** or **valproate** vs 1% with placebo plus **lithium** or **valproate** [44]

b) **Schizophrenia** or bipolar mania, pooled data (oral route): 17% vs 13% with placebo [36][44].

**3.3.12.C| At risk for suicide**

1) General Information

a) In placebo-controlled trials of patients with **major depressive disorder** or other psychiatric disorders, antidepressant drugs were associated with an increased risk of suicidality among pediatric patients (14 additional cases per 1000 patients treated) and adults 18 to 24 years old (5 additional cases per 1000 patients treated); the absolute risk of suicidality was highest in patients with **major depressive disorder** [44].

2) Prevention and Management

a) Carefully monitor patients for clinical worsening of depression, suicidality, and unusual changes in behavior, which may be precursors to suicidality, especially if symptoms are severe, abrupt, or unusual. This is especially crucial during the initial few months of antidepressant therapy and during dose changes [44].

b) Because a suicide attempt is inherently possible in patients with a psychotic illness or **bipolar disorder**, high-risk patients on **aripiprazole** therapy should receive close supervision [44].

3) Adult Clinical Trials

a) **Schizophrenia** (IM route, extended-release): **Suicidal ideation**, less than 0.1% [14]

**3.3.12.D| Compulsive gambling**

1) General Information

a) Serious impulse control problems, particularly pathological gambling, have occurred with **aripiprazole** products [39].

b) Increased risk in patients with a personal or family history of **obsessive-compulsive disorder**, **impulse control disorder**, **bipolar disorder**, impulsive personality, alcoholism, drug abuse or other addictive behaviors [39]

c) Uncontrollable urges have stopped within days to weeks after **aripiprazole** dosage reduction or discontinuation [39].

2) Management

a) Consider dosage reduction or discontinuation if new or increased compulsive behaviors develop [39]

3) Adult and Pediatric Case Reports

a) Since marketing approval of the first **aripiprazole** product in November 2002, case reports (N=184) of compulsive behaviors and serious impulse control problems have been identified

by the US Food and Drug Administration. Pathological gambling (n=164) was the most commonly reported compulsive behavior among the case reports. No history of pathological gambling was reported for the majority of patients and the uncontrollable urge to gamble started after [aripiprazole](#) therapy was initiated. The urge to gamble stopped within days to weeks after [aripiprazole](#) discontinuation or dosage reduction. One patient who was rechallenged with [aripiprazole](#) indicated that the uncontrollable urge to gamble reappeared [39].

**b))** Pathological gambling (PG) was described in a case series of 8 adult patients receiving [aripiprazole](#) for either [schizophrenia](#) or [bipolar disorder](#), who also had a history of addictive disorders or gambling prior to [aripiprazole](#) use. The cases were identified from a cohort of 166 patients receiving treatment for PG, and causality was rated as possible on the Naranjo adverse drug reaction probability scale in 7 patients and doubtful in 1. PG began within days to a few months after [aripiprazole](#) initiation or titration and PG decreased within days to a few months after [aripiprazole](#) discontinuation or dose reduction in 7 of the 8 patients [74].

### 3.3.12.E] Feeling nervous

**1))** Incidence: 3% [44]

**2))** Adult Clinical Trials

**a))** [Major depressive disorder](#) (oral route): Feeling jittery, 3% with [aripiprazole](#) plus antidepressant therapy vs 1% with antidepressant therapy only [44]

### 3.3.12.F] [Impulse control disorder](#)

**1))** General Information

**a))** Serious impulse control problems have been reported with [aripiprazole](#) products, including urges to gamble, binge eat, shop, and have sex [39].

**b))** Increased risk in patients with a personal or family history of [obsessive-compulsive disorder](#), [impulse control disorder](#), [bipolar disorder](#), impulsive personality, alcoholism, drug abuse or other addictive behaviors [39]

**c))** Uncontrollable urges have stopped within days to weeks after [aripiprazole](#) dosage reduction or discontinuation [39].

**2))** Management

**a))** Consider dosage reduction or discontinuation if new or increased compulsive behaviors develop [39]

**3))** Adult and Pediatric Case Reports

**a))** Since marketing approval of the first [aripiprazole](#) product in November 2002, case reports (N=184) of compulsive behaviors and serious impulse control problems have been identified by the US Food and Drug Administration: Pathological gambling (n=164), compulsive sexual behavior (n=9), compulsive buying (n=4), compulsive eating (n=3), and multiple impulse control problems (n=4). No history of pathological gambling was reported for the majority of patients who experienced this urge, and the uncontrollable behaviors started after [aripiprazole](#) therapy was initiated. The urges stopped within days to weeks after [aripiprazole](#) discontinuation or dosage reduction. Four patients who were rechallenged with [aripiprazole](#) indicated the uncontrollable urges reappeared [39].

b)] A case series of 2 patients described behavioral changes, including new or worsened impulsive behaviors (excessive shopping and [hypersexuality](#)), that occurred during [aripiprazole](#) use for [bipolar disorder](#) and resolved with [aripiprazole](#) discontinuation. First, a 57-year-old man was initiated on [aripiprazole](#) 3 mg/day for emergent depressive symptoms, in addition to on-going [lithium](#) carbonate 1000 mg/day and [carbamazepine](#) 600 mg/day. Within a week the patient reported hypersexual urges. Upon discontinuation of [aripiprazole](#), his [hypersexuality](#) resolved. One year later, [aripiprazole](#) was reinstated at 3 mg/day, titrated to 6 mg/day one week later. Two weeks later his depression improved, but [hypersexuality](#) returned. Again [aripiprazole](#) was discontinued and his [hypersexuality](#) urges subsequently resolved. The second case described a 53-year-old woman, maintained on [lithium](#) carbonate 600 mg/day, [perphenazine](#) 4 mg/day, and [amoxapine](#) 50 mg/day. She was euthymic when [amoxapine](#) was reduced and discontinued. The patient became depressed approximately 2 months later, and [amoxapine](#) 10 mg/day was initiated. The patient became talkative, developed insomnia and excessive shopping as a result. [Amoxapine](#) was discontinued and [aripiprazole](#) initiated at 6 mg/day and titrated to 12 mg/day. The urge to shop continued to increase over the next 2 weeks, and [aripiprazole](#) was discontinued and within 2 weeks the urges to shop resolved [73].

### 3.3.12.G] Restlessness

1)] Incidence: 2% to 12% [36][44]

2)] Adult Clinical Trials

a)] Bipolar mania (oral route): 6% vs 3% with placebo [44]

b)] Bipolar mania (oral route): 2% with [aripiprazole](#) plus [lithium](#) or [valproate](#) vs 1% with placebo plus [lithium](#) or [valproate](#) [44]

c)] [Major depressive disorder](#) (oral route): 12% with [aripiprazole](#) plus antidepressant therapy vs 2% with antidepressant therapy only [44]

d)] [Schizophrenia](#) or bipolar mania, pooled data (oral route): 5% vs 3% with placebo [36][44]

### 3.3.12.H] Suicidal behavior

1)] General Information

a)] Adult and pediatric patients with [major depressive disorder](#) may experience unusual changes in behavior and onset of suicidal behavior (suicidality). Antidepressant therapy may be associated with the emergence of suicidality and inducing worsening of depression in patients, especially during the early treatment phase and in children, adolescents, and young adults ages 18 to 24 years [44].

2)] Prevention and Management

a)] Carefully monitor patients for clinical worsening of depression, suicidality, and unusual changes in behavior, which may be precursors to suicidality, especially if symptoms are severe, abrupt, or unusual. This is especially crucial during the initial few months of antidepressant therapy and during dose changes [44].

### 3.3.15] Respiratory Effects

#### 3.3.15.A] [Cough](#)



1) Incidence: 3% [36]

2) In a pooled analysis of trials in which adult patients with [schizophrenia](#) or bipolar mania received either oral [aripiprazole](#) 2 mg/day or greater (n=1843) or placebo (n=1166), [cough](#) was reported in 3% of patients receiving [aripiprazole](#) compared with 2% of patients receiving placebo. Patients with [schizophrenia](#) received acute therapy up to 6 weeks and patients with bipolar mania received treatment up to 3 weeks [36].

### 3.3.15.B] Hiccoughs

1) In a single case report, the administration of [aripiprazole](#) appeared to induce hiccups in a 28-year-old male with organic [bipolar affective disorder](#). The patient had a history of [measles](#), accidental [insecticide poisoning](#), episodic illness, and a closed head injury, which left him with peritraumatic amnesia (retrograde and anterograde), left-sided [hemiparesis](#), and behavioral problems. On admission, testing revealed increased tone, grade 4 power and exaggerated left upper and lower tendon jerks. [Carbamazepine](#) 800 mg daily and [olanzapine](#) 10 mg/day were initiated with resolution of symptoms within a month's time. Due to excessive sedation, [olanzapine](#) was discontinued and [aripiprazole](#) 10 mg/day was added to the patient's existing drug regimen. Within 3 to 4 hours of [aripiprazole](#) initiation, the patient developed continual hiccups. The patient skipped the next dose of [aripiprazole](#) was advised, and within 30 hours following the last dose, the hiccups subsided. Upon [aripiprazole](#) rechallenge, the patient began experiencing hiccups again within a few hours. [Aripiprazole](#) was replaced with gradual dose titration of [quetiapine](#) 200 mg/day and [carbamazepine](#) 1000 mg/day. No further symptoms had reoccurred at 1 month follow-up [70].

### 3.3.15.C] Nasal congestion

1) Incidence: 2% [14]

2) Adult Clinical Trials

a) [Schizophrenia](#) (IM route, extended release): 2% vs 1% with placebo [14]

### 3.3.15.D] Nasopharyngitis

1) Incidence: 9% [3][4]

2) Pediatric Clinical Trials

a) [Tourette disorder](#) (oral route, age 6 to 18 years): 9% vs 0% with placebo [3][4]

### 3.3.15.E] Pain in throat

1) Incidence: 3% [36]

2) In a pooled analysis of trials in which adult patients with [schizophrenia](#) or bipolar mania received either oral [aripiprazole](#) 2 mg/day or greater (n=1843) or placebo (n=1166), pharyngolaryngeal pain was reported in 3% of patients receiving [aripiprazole](#) compared with 2% of patients receiving placebo. Patients with [schizophrenia](#) received acute therapy up to 6 weeks and patients with bipolar mania received treatment up to 3 weeks [36].

### 3.3.15.F] Upper respiratory infection

1) Incidence: 4% to 6% [14] to 6% [44]

2) Adult Clinical Trials

a) [Major depressive disorder](#) (oral route): 6% with [aripiprazole](#) plus antidepressant therapy vs 4% with antidepressant therapy only [44]

b) [Schizophrenia](#) (IM route, extended release): 4% vs 2% with placebo [14]

### 3.3.16] Other

#### 3.3.16.A] Angioedema

1) Incidence: 0.1% to less than 1% [36]

2) Angioedema has been observed during clinical trials with a frequency between 1/1000 and 1/100 patients who received multiple oral doses of aripiprazole at least 2 mg/day within the database of 13,543 adult patients [36].

#### 3.3.16.B] Death

1) Elderly patients with dementia-related psychosis (unapproved use) treated with aripiprazole had a 1.6- to 1.7-times greater risk of death compared with placebo (4.5% vs 2.6%) in 17 placebo-controlled clinical studies (modal duration 10 weeks). The cause of death varied, but most were associated with cardiovascular events, including heart failure, or infectious events, including pneumonia [36][44].

2) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined [77].

3) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio



1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study [78].

**4)** The findings of one meta-analysis suggest that there may be a small increased risk of death associated with the use of atypical antipsychotic agents for the treatment of **dementia** in elderly patients. The study analysis (n=5110), including 15 randomized, double-blind, placebo-controlled, parallel group trials of antipsychotic use (ie, **aripiprazole** (n=3), **olanzapine** (n=5), **quetiapine** (n=3), **risperidone** (n=5)) in elderly patients (weighted mean age, 81.2 years) with **dementia**, found that death occurred more often in patients receiving atypical antipsychotic therapy as compared with placebo (118 (3.5%) vs 40 (2.3%), respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receiving atypical antipsychotics as compared with placebo was 1.54 (95% CI, 1.06 to 2.23; p=0.02), and the risk difference was 0.01 (95% CI, 0.004 to 0.02; p=0.01). Overall, the relative risk associated with atypical antipsychotic use was 1.65 (95% CI, 1.19 to 2.29; p=0.003); however this increased risk was only identified when all drugs were pooled for analysis; meta-analyses of individual drugs did not show a statistically significant increased risk. A similar dropout rate was observed between antipsychotic- and placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in dropouts found by meta-analysis [79].

**5)** The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all time points studied after beginning therapy (within 180 days: RR, 1.37; 95% CI, 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with **dementia** (RR, 1.29; 95% CI, 1.15 to 1.45), without **dementia** (RR, 1.45; 95% CI, 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided [80].

### 3.3.16.C] Fatigue

**1)** Incidence: 2% to 17% [4][3][36]

**2)** Adult Clinical Trials

**a)** Agitation in **schizophrenia** or bipolar mania (IM route): 2% vs 1% with placebo [3]

**b)** **Major depressive disorder** (oral route): 8% with **aripiprazole** plus antidepressant therapy vs 4% with antidepressant therapy only [3]

**c)** **Schizophrenia** or bipolar mania, pooled data (oral route): 6% vs 4% with placebo [4][3][36]

**3)** Pediatric Clinical Trials

**a)** **Autistic disorder** (oral route; age 6 to 17 years): 17% to 2% [4][3]

**b)** Bipolar mania (oral route; age 10 to 17 years): 11% vs 4% with placebo [4][3]

**c)** **Tourette disorder** (oral route; age 6 to 18 years): 8% vs 0% with placebo [3][4]

**d)** All pediatric indications, pooled data (oral route; age 6 to 18 years): 10% vs 2% with placebo [4][3]

### 3.3.16.D] Increased body temperature

1J) Disruption of the body's ability to reduce core body temperature has been associated with antipsychotic agents. Aripiprazole should be prescribed with appropriate care in patients who will be experiencing conditions that may contribute to an elevated core body temperature (eg, exercising strenuously, exposure to extreme heat, or dehydration) [36][44].

### 3.3.16.E] Neuroleptic malignant syndrome

1J) Neuroleptic malignant syndrome (NMS) has been reported rarely in the worldwide clinical database in patients on aripiprazole therapy. NMS symptoms may include hyperpyrexia, muscle rigidity, altered mental status, evidence of autonomic instability, elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The diagnosis of patients with NMS is complicated; differential diagnosis should account for the possibility of both serious illness and untreated extrapyramidal signs, as well as central anticholinergic toxicity, heat stroke, drug fever, and primary CNS pathology. If NMS is diagnosed, antipsychotic drugs and other concomitant drugs that are not essential should be immediately discontinued. The patient should be monitored and receive intensive treatment for presenting symptoms and any concomitant serious medical problems. Following recovery from NMS, the patient may require antipsychotic drug treatment and reintroduction of such therapy should be carefully considered and the patient closely monitored for the possible recurrence of NMS [36][44].

2J) Neuroleptic malignant syndrome (NMS) was reported in a 71-year-old female with pre-hypertension and paranoid schizophrenia. She was admitted due to an abrupt change in her baseline mental status, skin flushing, and worsening tardive dyskinesia including grimacing, tongue protrusion, lip sucking, and upper extremity choreiform movements. In the previous 9 months, the patient was receiving aripiprazole 15 mg/day with only subtle elevations of abnormal buccal oral muscle movement and upper arm athetosis 4 weeks prior to admission. Despite aripiprazole dose reduction to 10 mg/day 8 days prior to hospitalization and a 1-week treatment of benzotropine 1 mg/day for extrapyramidal reactions, her clinical conditions worsened. Physical examination revealed a rectal temperature of 106.5 Fahrenheit, pulse of 137 beats per minute, respiratory rate of 22 breaths per minute, and fluctuating blood pressure ranging between 99/54 mmHg and 147/100 mmHg. The patient exhibited distress, marked muscle rigidity, choreoathetoid movements, and progressively worsening slurred speech that became muted. CPK rose from 78 units/L at admission to 103 units/L eight hours later. Further assessment revealed no leukocytosis, unremarkable metabolic panel, urine analysis, and normal aged-consistent atrophic changes on brain CT. Consequently, she was diagnosed with NMS and aripiprazole was discontinued. She was given intravenous hydration, supportive cooling therapy, bromocriptine 2.5 mg every 8 hours, benzotropine 1 mg/day, and lorazepam 1 to 2 mg as needed. Five days later, the patient stabilized aside from tardive dyskinesia, and was then transferred to the care of her psychiatrist in a psychiatric hospital [75].

3J) In a case report, a 14-year-old girl with psychotic depression and mental retardation developed partial neuroleptic malignant syndrome following aripiprazole treatment. The patient had no prior experience with any extrapyramidal symptoms with her past medications of risperidone and olanzapine during previous hospitalizations. She did not experience any side effects from quetiapine 300 mg daily which was discontinued 2 weeks prior to receiving aripiprazole 5 mg daily. Within 48 hours of aripiprazole initiation, the patient presented with tremors, drooling, severe cogwheel rigidity, unsteady gait, incontinence, and agitation. The patient was disoriented and had slurred, incoherent speech with fluctuating consciousness with 31 respirations per minute (rpm) and a pulse of 131 beats per minute (bpm). The patient's serum creatine phosphokinase (CPK) increased to 23,340 international units without myoglobinuria. However, her temperature and blood pressure were within normal parameters. Her white blood cell count was also within normal limits (9300 per millimeter cubed (mm<sup>3</sup>) of blood) and urine toxicology screen was negative. Along with other supportive measures, the patient was treated with sodium bicarbonate to

alkalinize the urine. After 2 days, the patients CPK decreased to 6157 international units and continued to decline. [Lorazepam](#) 2 mg every 4 hours was administered to treat the tremors and agitation. The patient eventually recovered and returned to baseline [76].

### 3.3.16.F] Pain

1) Incidence: 3% [36]

2) In a pooled analysis of trials in which adult patients with [schizophrenia](#) or bipolar mania received either oral [aripiprazole](#) 2 mg/day or greater (n=1843) or placebo (n=1166), pain was reported in 3% of patients receiving [aripiprazole](#) compared with 2% of patients receiving placebo. Patients with [schizophrenia](#) received acute therapy up to 6 weeks and patients with bipolar mania received treatment up to 3 weeks [36].

## 3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding

### A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential [risk to the fetus](#).

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Administer [aripiprazole](#) to pregnant women only if the maternal benefit justifies the fetal risk. Encourage women exposed to [aripiprazole](#) during pregnancy to participate in a clinical surveillance program sponsored by the National Pregnancy Registry for Atypical Antipsychotics. The program can be accessed by calling 1-866-961-2388 or visiting <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/> [3][4].

4) Literature Reports

a) There are no adequate and well-controlled studies of [aripiprazole](#) use in pregnant women. Maternal use of antipsychotic drugs during the third trimester of pregnancy has been associated with an increased risk of neonatal extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) following delivery. Severity of these adverse effects have ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care [3][4].

b) A systematic review of the literature found no significant correlation between first-trimester exposure to [aripiprazole](#) and risk of [congenital malformations](#). However, due to the low number of exposed infants, the risk estimate is considered imprecise. Of 100 pregnancies with first-trimester exposure, 5 malformations were observed, resulting in a malformation rate of 5% [165].

c) In the case of a 27-year-old, medically healthy, schizoaffective woman, exposure to [aripiprazole](#) during different trimesters of pregnancy was not associated with fetal toxicity. The patient was being effectively treated with [aripiprazole](#) 15 mg/day when she conceived. At week 8 of gestation, [aripiprazole](#) was withdrawn following a risk-to-benefit analysis. However, at week 20 of gestation,

the patient suffered a schizophrenic [relapse](#) and following a revised risk-to-benefit analysis, [aripiprazole](#) was re-initiated at 10 mg/day which was continued throughout the pregnancy. The patient's overall weight gain at full term was 10 kg. Ultrasound scans and laboratory tests for serum glucose, thyroid function, and routine hematology during the pregnancy were normal. Although spontaneous labor occurred at term, development of unexplained fetal distress in the form of [tachycardia](#) prompted a [cesarean section](#) which resulted in the birth of a male infant weighing 3.25 kg. Failure to establish lactation led to the infant being bottle-fed from birth. At the 6-month follow-up, the infant had achieved normal milestones [166].

d) RATS, RABBITS: Oral [aripiprazole](#) doses up to 10 times the maximum recommended human dose on a mg/m(2) basis administered during organogenesis resulted in slightly [prolonged gestation](#) and a slight delay in fetal development, including fetal weight decreases and delayed skeletal ossification in rat offspring. Delays in skeletal ossification and decreased fetal weights also occurred with IV administration at doses of 27 mg/kg/day during organogenesis. In rabbits, increased abortions, increased fetal mortality, decreased fetal weight, fused sternbrae, and minor skeletal variations were reported with oral [aripiprazole](#) doses up to 65 times the MRHD on a mg/m(2) basis, and maternal toxicity, decreased fetal weight, increased fetal abnormalities (mostly skeletal), and decreased fetal skeletal ossification were reported with IV doses up to 19 times the MRHD on a mg/m(2) basis. The no-effect dose was 6 times the MRHD on mg/m(2) basis [3][4].

e) [Aripiprazole](#) administration in rats with oral doses 10 times the maximum recommended human dose (MRHD) from gestation day 17 through postpartum day 21 resulted in slight maternal toxicity, slightly [prolonged gestation](#), an increase in stillbirths, a decrease in pup weight that persisted into adulthood, and a decrease in survival. [Aripiprazole](#) administration in rats with IV doses of 8 mg/kg/day and 20 mg/kg/day from gestation day 6 through postpartum day 20 resulted in increased stillbirths, and doses of 20 mg/kg/day resulted in decreased early postnatal pup weights and survival [3][4].

## B) Breastfeeding

### 1) Micromedex Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

### 2) Clinical Management

a) [Aripiprazole](#) is excreted in human breast milk. Either discontinue [aripiprazole](#) or discontinue nursing, considering the importance of the drug to the mother [3][4].

### 3) Drug Levels in Breastmilk

#### a) Active Metabolites

##### 1) Dehydro-aripiprazole [169]

## 3.5] Drug Interactions

### 3.5.1] Drug-Drug Combinations

#### 3.5.1.A] Alfentanil

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [alfentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [alfentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 7) Probable Mechanism: additive CNS depression

#### 3.5.1.B] Alfuzosin

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.C] Amifampridine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#)[111].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#)[111].
- 7) Probable Mechanism: additive QT-interval prolongation

#### 3.5.1.D] Amiodarone

- 1) Interaction Effect: increased risk of QT prolongation and [torsades de pointes](#)

- 2)) Summary: Avoid the concomitant administration of [amiodarone](#) and a QT prolonging agent since it may result in additive effects on the QT interval and increase the risk of [torsades de pointes](#). Due to the long half-life of [amiodarone](#), this interaction is possible even after the discontinuation of [amiodarone](#)[149].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Avoid the concomitant administration of [amiodarone](#) and a QT prolonging agent since it may result in additive effects on the QT interval and increase the risk of [torsades de pointes](#). Due to the long half-life of [amiodarone](#), this interaction is possible even after the discontinuation of [amiodarone](#)[149].
- 7)) Probable Mechanism: additive effects on QT interval

#### 3.5.1.E] Amisulpride

- 1)) Interaction Effect: increased risk of [torsades de pointes](#)
- 2)) Summary: The concomitant use of amisulpride with other agents that may induce [torsade de pointes](#) is contraindicated. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of [torsade de pointes](#)[142].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of amisulpride with other agents that may induce [torsade de pointes](#) is contraindicated. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of [torsade de pointes](#)[142].
- 7)) Probable Mechanism: additive QT prolongation

#### 3.5.1.F] Amitriptyline

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.G] Anagrelide

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).



- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

#### **3.5.1.H) Apomorphine**

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

#### **3.5.1.I) Arsenic Trioxide**

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

#### **3.5.1.J) Asenapine**

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.K] [Astemizole](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.L] [Atazanavir](#)

1) Interaction Effect: increased [aripiprazole](#) exposure; increased risk for QT-interval prolongation

2) Summary: [Aripiprazole](#) is a CYP3A4 substrate, [atazanavir](#) is a strong CYP3A4 inhibitor, and both drugs are known to prolong QTc-interval[88][92]. Although this interaction has not been specifically studied, concurrent use of [aripiprazole](#) with [ketoconazole](#), another strong CYP3A4 inhibitor, resulted in increased AUC values of both [aripiprazole](#) and its active metabolite, dehydro-aripiprazole, by 63% and 77%, respectively. Coadministration of [aripiprazole](#) with [atazanavir](#) may result in a similar effect and increase risk for QT-interval prolongation and other serious cardiac adverse events. If coadministration is required, reduce the [aripiprazole](#) dose to one-half of its normal dose. For concomitant use in poor CYP2D6 metabolizers or with a 2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If concurrent [atazanavir](#) is discontinued, the dose of [aripiprazole](#) should then be increased [88]. Increased monitoring may be warranted.

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [aripiprazole](#) and a strong CYP3A4 inhibitor, such as [atazanavir](#), has resulted in increased [aripiprazole](#) concentrations[88]. Additionally, both drugs are known to prolong the QTc-interval [88][92], and coadministration may increase risk of serious cardiac adverse events. If concurrent use is required, reduce the [aripiprazole](#) dose to one-half of the normal dose. For coadministration in poor CYP2D6 metabolizers or with a 2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of the normal dose. If concurrent [atazanavir](#) is discontinued, the dose of [aripiprazole](#) should then be increased [88]. Increased monitoring may be warranted.

7) Probable Mechanism: inhibition of CYP3A4-mediated [aripiprazole](#) metabolism; additive effects on QT interval

8) Literature Reports



- a) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days (strong CYP3A4 inhibitor) with a single dose of [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively [88].

#### 3.5.1.M] [Azithromycin](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.N] [Bedaquiline](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.O] [Bepridil](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated[161], as coadministration may increase the risk of [ventricular arrhythmias](#).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated[161], as coadministration may increase the risk of [ventricular arrhythmias](#).
- 7) Probable Mechanism: additive QT-interval prolongation

#### 3.5.1.P] [Boceprevir](#)

- 1) Interaction Effect: increased exposure of [aripiprazole](#)

2J) Summary: Aripiprazole is metabolized by CYP2D6 and CYP3A4 enzymes. Coadministration with CYP3A4 inhibitors may inhibit aripiprazole elimination causing increased blood concentrations and increased risk for toxicity, including QT-interval prolongation. During drug interaction studies, coadministration of aripiprazole and ketoconazole, a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of aripiprazole and its active metabolite. If aripiprazole is coadministered with a CYP3A4 inhibitor, reduce the aripiprazole dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of aripiprazole should then be increased[88]. Dosage reductions are required if long-acting aripiprazole injection is used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If aripiprazole and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of aripiprazole is required.[19].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of aripiprazole and a CYP3A4 inhibitor may result in increased aripiprazole plasma levels and increased risk for toxicity, including QT-interval prolongation. If coadministration of aripiprazole and a CYP3A4 inhibitor is required, reduce the aripiprazole dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of aripiprazole should then be increased[88]. Dosage reductions are required if long-acting aripiprazole injection is used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If aripiprazole and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of aripiprazole is required.[19].

7J) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of aripiprazole

8J) Literature Reports

aJ) During drug interaction studies, coadministration of ketoconazole 200 mg/day for 14 days with single dose aripiprazole 15 mg resulted in a 63% and 77% increase in the AUC of aripiprazole and its active metabolite, respectively. Studies have not yet been conducted with higher ketoconazole doses (ie, 400 mg/day) [88].

### 3.5.1.Q] Bromazepam

1J) Interaction Effect: increased risk of respiratory or cardiovascular depression

2J) Summary: Concomitant use of bromazepam with another CNS depressant should be avoided due to increased risk for respiratory or cardiovascular depression and profound sedation[98].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of bromazepam, which is a CNS depressant, with another CNS depressant may result in respiratory or cardiovascular depression and profound sedation. Due to the added CNS depressant effects, avoid use of bromazepam and other CNS depressants[98].

7J) Probable Mechanism: additive CNS depression

### 3.5.1.R] Bromopride

1J) Interaction Effect: increased risk of extrapyramidal reactions

2J) Summary: Concomitant use of bromopride and other drugs that may cause extrapyramidal reactions is contraindicated[81].

3J) Severity: contraindicated

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of bromopride and other drugs that may cause extrapyramidal reactions is contraindicated[81].
- 7) Probable Mechanism: additive extrapyramidal side effects

### 3.5.1.S] Buprenorphine

- 1) Interaction Effect: increased risk of [respiratory depression](#)
- 2) Summary: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[134][135] and monitor for signs of [respiratory depression](#), sedation, and hypotension [134].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[134][135] and monitor for signs of [respiratory depression](#), sedation, and hypotension [134].
- 7) Probable Mechanism: additive [respiratory depression](#)

### 3.5.1.T] Bupropion

- 1) Interaction Effect: increased exposure of [aripiprazole](#)
- 2) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes. Coadministration with CYP2D6 inhibitors may inhibit [aripiprazole](#) elimination causing increased blood concentrations. If [aripiprazole](#) is coadministered with a CYP2D6 inhibitor, dose reduction of the oral CYP2D6 inhibitor is required immediately, and dose reduction of [aripiprazole](#) long-acting injection is required when concurrent use exceeds 14 days. If [aripiprazole](#) and the CYP2D6 inhibitor are concurrently used with a strong CYP3A4 inhibitor, further dose reduction of [aripiprazole](#) is required. If the concurrent CYP2D6 inhibitor is discontinued, [aripiprazole](#) dose should then be increased[14][88]. Dosage adjustments with concomitant use are not recommended if low-dose [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [88].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [aripiprazole](#) with a CYP2D6 inhibitor may result in increased [aripiprazole](#) plasma levels. Dose reduction of oral [aripiprazole](#) is required immediately during concurrent use of a CYP2D6 inhibitor, and dose reduction of [aripiprazole](#) long-acting injection is required when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP2D6 inhibitor are concurrently used with a strong CYP3A4 inhibitor, further dose reduction of [aripiprazole](#) is required. If the concurrent CYP2D6 inhibitor is discontinued, the dose of [aripiprazole](#) should then be increased[14][88]. Specific dosage adjustments are not recommended if low-dose oral [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [88].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [aripiprazole](#)
- 8) Literature Reports

- a) During drug interaction studies, coadministration of [quinidine](#) 166 mg/day for 13 days with a single dose of [aripiprazole](#) 10 mg resulted in a 112% increase in [aripiprazole](#) AUC. The AUC of dehydro-aripiprazole, the active metabolite of [aripiprazole](#), was decreased by 35% [88]

**3.5.1.U] Buserelin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[153][154][155]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[153][154][155].
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.V] Butorphanol**

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [butorphanol](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [butorphanol](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 7) Probable Mechanism: additive CNS depression

**3.5.1.W] Carbamazepine**

- 1) Interaction Effect: decreased exposure of [aripiprazole](#)
- 2) Summary: Coadministration of [aripiprazole](#) and this drug, a strong CYP3A4 inducer, may result in decreased [aripiprazole](#) plasma levels. Avoid coadministration of long-acting [aripiprazole](#) injection with strong CYP3A4 inducers for more than 14 days[19]. During drug interaction studies, coadministration of [aripiprazole](#) and [carbamazepine](#) (a strong CYP3A4 inducer) resulted in decreased AUC and Cmax concentrations of [aripiprazole](#) and its active metabolite. As a similar reaction cannot be ruled out, double the normal [aripiprazole](#) dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased over 1 to 2 weeks to the original level [4][3].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [aripiprazole](#) and this drug, a strong CYP3A4 inducer, may result in decreased [aripiprazole](#) plasma levels. Avoid coadministration of long-acting [aripiprazole](#) injection

with strong CYP3A4 inducers for more than 14 days[19]. Double the normal [aripiprazole](#) dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased over 1 to 2 weeks to the original level [4][3].

7J) Probable Mechanism: induction of CYP3A4-mediated metabolism of [aripiprazole](#)

8J) Literature Reports

aJ) During drug interaction studies, coadministration of [aripiprazole](#) 30 mg/day and [carbamazepine](#) 200 mg twice daily resulted in a 70% decrease in the AUC and Cmax of both [aripiprazole](#) and its active metabolite [88].

bJ) Coadministration of [carbamazepine](#), a strong CYP3A4 inducer, twice daily with [aripiprazole](#) once daily decreased plasma concentrations of [aripiprazole](#) and its active metabolite, dehydro-aripiprazole by 64% and 68%, respectively. In this [pharmacokinetic study](#), 18 patients with [schizophrenia](#) (mean age 35.8 years) on a fixed dose of [aripiprazole](#) (12 mg (n=3) or 24 mg (n=18)) once daily for 3 to 5 weeks were started on [carbamazepine](#) 200 mg twice daily for 1 week. Blood samples were analyzed before [carbamazepine](#) initiation and 1 week after completion. The mean [carbamazepine](#) plasma concentration achieved was 9.3 mcg/mL. A review of CYP2D6 genotypes showed no association between genotypes and changes in [aripiprazole](#) and dehydro-aripiprazole plasma concentrations. The concentration ratio of [aripiprazole](#) to dehydro-aripiprazole did not change during the study. Because [carbamazepine](#) is a potent inducer of CYP3A4, the most likely mechanism for this interaction is CYP3A4 induction [102].

### 3.5.1.X] Ceritinib

1J) Interaction Effect: increased exposure of CYP3A substrate

2J) Summary: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate[130].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate[130].

7J) Probable Mechanism: inhibition of CYP3A-mediated metabolism of drug by ceritinib

### 3.5.1.Y] Chloroquine

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

**3.5.1.Z] Chlorpromazine**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.AA] Ciprofloxacin**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.AB] Cisapride**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[103].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[103].
- 7) Probable Mechanism: additive QT-interval prolongation

**3.5.1.AC] Citalopram**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes); increased risk of QT-interval prolongation



2j) Summary: [Citalopram](#) is a serotonergic antidepressant, [aripiprazole](#) is an antipsychotic with partial agonist activity at serotonin (1A) receptors, both are associated with QTc-interval prolongation[108][88], and concurrent use should be avoided [108]. Although this combination has not been studied, a 64-year-old man receiving [citalopram](#) experienced serotonin toxicity after just one 5-mg dose of [aripiprazole](#) [109], and coadministration may increase risk for QT-interval prolongation. If concurrent use is required, monitor ECG, electrolytes, and for serotonergic effects, especially during initiation and around dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops [108].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: [Citalopram](#) is a serotonergic known to cause dose-dependent QT-interval prolongation, and coadministration with another QT-prolonging drug, such as [aripiprazole](#), should be avoided[108]. Additionally, [serotonin syndrome](#) has been reported with concurrent use [109]. If coadministration is required, monitor ECG, electrolytes, and for serotonergic effects, especially during initiation and around dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion) [108].

7j) Probable Mechanism: additive serotonergic effects; additive effects on QT interval

8j) Literature Reports

a) A case report described serotonin toxicity in 64-year-old man following the concomitant use of [citalopram](#) and [aripiprazole](#). The patient, who had [coronary heart disease](#) and [hypertension](#), presented to the emergency room (ER) with agitation, diaphoresis, tremors, and nausea more than 1 hour after taking his first dose of [aripiprazole](#) 5 mg in combination with [citalopram](#) 60 mg. Adherence with antihypertensives and a statin was reported, and [citalopram](#) dose had not changed in many years. While in the ER, the patient was somnolent but oriented and physical exam revealed blood pressure fluctuations, dilated pupils, diffuse fasciculations, upper-extremity postural tremors, cogwheel rigidity, diffuse hyperreflexia with clonus elicited at both knees and ankles, and appendicular ataxia that prevented the patient from standing independently. Laboratory and [brain imaging](#) studies were unremarkable, including CPK, [TSH](#), and urine toxicology. All symptoms and clinical findings resolved within 24 hours of stopping psychiatric medications and treatment with [cyproheptadine](#) and supportive care [109].

### 3.5.1.AD] [Clarithromycin](#)

1j) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT-interval prolongation

2j) Summary: Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor, such as [clarithromycin](#), may result in increased [aripiprazole](#) plasma levels. During drug interaction studies, coadministration of [ketoconazole](#) (also a CYP3A4 inhibitor) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in an increase in the AUC of [aripiprazole](#) and its active metabolite. As a similar reaction cannot be ruled out with [clarithromycin](#), reduce the [aripiprazole](#) dose to one-half of its normal dose when these agents are coadministered. For concomitant use of [aripiprazole](#) and [clarithromycin](#) in poor CYP2D6 metabolizers, the [aripiprazole](#) dose should be reduced to one-quarter of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with [clarithromycin](#) and/or the CYP2D6 inhibitor is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Additionally, concurrent use of

aripiprazole and QT-prolonging drugs, including clarithromycin, may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of aripiprazole and a CYP3A4 inhibitor, such as clarithromycin, may result in increased aripiprazole plasma levels. Reduce the aripiprazole dose to one-half of its normal dose when these agents are coadministered. For concomitant use of aripiprazole and clarithromycin in poor CYP2D6 metabolizers, the aripiprazole dose should be reduced to one-quarter of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with clarithromycin and/or the CYP2D6 inhibitor is discontinued, the dose of aripiprazole should then be increased[88]. Additionally, concurrent use of aripiprazole and QT-prolonging drugs, including clarithromycin, may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of aripiprazole; additive QT-interval prolongation

8) Literature Reports

a) During drug interaction studies, coadministration of ketoconazole 200 mg/day for 14 days with single dose aripiprazole 15 mg resulted in a 63% and 77% increase in the AUC of aripiprazole and its active metabolite, respectively. Studies have not yet been conducted with higher ketoconazole doses (ie, 400 mg/day) [88].

### 3.5.1.AE] Clobazam

1) Interaction Effect: increased aripiprazole plasma concentrations

2) Summary: The concomitant use of aripiprazole, a CYP2D6 substrate[23], and clobazam, a CYP2D6 inhibitor, may increase aripiprazole plasma concentrations [87]. If administered concomitantly, reduce the aripiprazole dose by one-half. If therapy with clobazam is discontinued, the dose of aripiprazole should then be increased [23].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of aripiprazole, a CYP2D6 substrate[23], and clobazam, a CYP2D6 inhibitor, may result in increased aripiprazole plasma levels [87]. If administered concomitantly, reduce the aripiprazole dose by one-half. If therapy with clobazam is discontinued, the dose of aripiprazole should then be increased [23].

7) Probable Mechanism: inhibition of CYP2D6-mediated aripiprazole metabolism by clobazam

### 3.5.1.AF] Clomipramine

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution



because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AG] [Clonidine](#)

1) Interaction Effect: induction or exacerbation of orthostatic regulation disturbances

2) Summary: Coadministration of [clonidine](#) with neuroleptics, such as [aripiprazole](#)[63], may result in orthostatic regulation disturbance induction or exacerbation [85][86] and should be approached with caution.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [clonidine](#) and neuroleptics, such as [aripiprazole](#)[63], may induce or exacerbate orthostatic regulation disturbances (eg, dizziness, fatigue, orthostatic hypotension) [85][86] and should be approached with caution.

7) Probable Mechanism: unknown

### 3.5.1.AH] [Clozapine](#)

1) Interaction Effect: increase risk of QT-interval prolongation; increased plasma levels of [aripiprazole](#), [clozapine](#), or both

2) Summary: [Aripiprazole](#) and [clozapine](#) are CYP2D6 substrates associated with QTc-interval prolongation[88][157]. Concomitant use of [clozapine](#) with other drugs metabolized by CYP2D6, such as [aripiprazole](#), can increase plasma levels of one or both drugs [157]. Although this interaction has not been studied, coadministration may increase [aripiprazole](#) or [clozapine](#) exposure and result in additive prolongation effects on the QT interval. Use caution with concomitant use and monitor the patient closely for QT-interval prolongation. Lower doses than usually prescribed for either drug may be required. Discontinue [clozapine](#) if the QTc-interval exceeds 500 milliseconds [157]

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [clozapine](#) with another drug known to prolong QT interval, such as [aripiprazole](#), may result in additive effects on the QT interval and increase the risk of serious cardiac events, including [ventricular arrhythmias](#) and [torsade de pointes](#). Additional reason to use caution with concurrent use is that use of [clozapine](#) with another drug metabolized by CYP2D6, such as [aripiprazole](#), may increase plasma levels of one or both drugs. Lower doses than usually prescribed for either [clozapine](#) or other CYP2D6 substrates may be required[157].

7) Probable Mechanism: additive effects on QT; competitive substrate inhibition

### 3.5.1.AI] [Cobicistat](#)

1) Interaction Effect: increased [aripiprazole](#) concentrations

2) Summary: [Aripiprazole](#) is metabolized by both CYP3A4 and CYP2D6 enzymes. Therefore, caution is advised when using [aripiprazole](#) concomitantly with a strong CYP3A4 inhibitor and CYP2D6 inhibitor such as [cobicistat](#) as this may result in elevated [aripiprazole](#) plasma concentrations. The coadministration of [ketoconazole](#), a strong CYP3A4 inhibitor, resulted in increased AUC values of both [aripiprazole](#) and its active metabolite, dehydro-aripiprazole, by 63% and 77%, respectively. If concomitant use of [aripiprazole](#) and [cobicistat](#) is required, reduce the [aripiprazole](#) dose to one-quarter of its normal dose and adjust to clinical response. If therapy with [cobicistat](#) is discontinued, the dose of [aripiprazole](#) should then be increased[63].

- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Caution is advised when using [aripiprazole](#), a CYP3A4 and CYP2D6 substrate, concomitantly with a strong CYP3A4 inhibitor and CYP2D6 inhibitor such as cobicistat as this may result in elevated [aripiprazole](#) plasma concentrations. If concomitant use is required, reduce the [aripiprazole](#) dose to one-quarter of its normal dose and then adjust to clinical response. If therapy with cobicistat is discontinued, the dose of [aripiprazole](#) should then be increased[63].
- 7J) Probable Mechanism: inhibition of CYP3A4- and 2D6-mediated [aripiprazole](#) metabolism
- 8J) Literature Reports
  - aJ) Although not specifically studied with cobicistat, coadministration of [ketoconazole](#) (a known strong CYP3A4 inhibitor) 200 mg daily for 14 days with a single 15 mg [aripiprazole](#) dose resulted in increased AUC values of both [aripiprazole](#) and its active metabolite, dehydro-aripiprazole, by 63% and 77%, respectively [63].

### 3.5.1.AJ] [Codeine](#)

- 1J) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2J) Summary: The concomitant use of [codeine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [codeine cough](#) medications with CNS depressants[110].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Reserve concomitant use of [codeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [codeine cough](#) medications with CNS depressants[110].
- 7J) Probable Mechanism: additive CNS depression

### 3.5.1.AK] [Conivaptan](#)

- 1J) Interaction Effect: increased exposure of [aripiprazole](#)
- 2J) Summary: Coadministration of [aripiprazole](#), a CYP3A substrate, and [conivaptan](#), a strong CYP3A inhibitor, may increase [aripiprazole](#) exposure[151] and risk for toxicity, eg, QT prolongation. [Ketoconazole](#), a strong CYP3A inhibitor, increased exposure of [aripiprazole](#) and its active metabolite [88] and [conivaptan](#) increased the AUC of CYP3A substrates [midazolam](#), [simvastatin](#), and [amlodipine](#). Avoid use of [conivaptan](#) with drugs eliminated mainly by CYP3A metabolism, and initiate treatment with a CYP3A substrate no sooner than 1 week after completion of [conivaptan](#) therapy [151]. If coadministration of [aripiprazole](#) and a CYP3A inhibitor is required, reduce [aripiprazole](#) to one-half of its normal dose, and increase the dose when the CYP3A inhibitor is discontinued [88]. Dosage reduction of long-acting [aripiprazole](#) injection is only required when concurrent use exceeds 14 days [19].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical

**6j) Clinical Management:** Coadministration of [aripiprazole](#), a CYP3A substrate, and [conivaptan](#), a strong CYP3A inhibitor, may increase [aripiprazole](#) exposure[151][88] and increase risk for toxicity, including QT-interval prolongation [88]. Avoid concomitant use of [conivaptan](#) with drugs eliminated mainly by CYP3A metabolism and initiate treatment with a CYP3A substrate no sooner than 1 week after completion of [conivaptan](#) therapy [151]. If coadministration of [aripiprazole](#) and a CYP3A inhibitor is required, reduce [aripiprazole](#) to one-half of its normal dose and increase the dose when the CYP3A inhibitor is discontinued [88]. Dosage reduction for long-acting [aripiprazole](#) injection is only required when concurrent use exceeds 14 days [19].

**7j) Probable Mechanism:** inhibition of CYP3A-mediated metabolism of [aripiprazole](#)

**8j) Literature Reports**

**a)j)** During drug interaction studies, coadministration of the strong CYP3A inhibitor [ketoconazole](#) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

**b)j)** The strong CYP3A inhibitor [conivaptan](#) 40 mg/day increased AUC of [midazolam](#), a CYP3A substrate, by approximately 100% with a 1-mg IV dose and by 200% with a 2-mg oral dose [151].

**c)j)** [Conivaptan](#) 30 mg/day tripled the AUC of [simvastatin](#), a CYP3A substrate [151].

**d)j)** [Conivaptan](#) 40 mg orally twice daily doubled the AUC and half-life of [amlodipine](#), a CYP3A substrate [151].

### 3.5.1.ALj Crizotinib

**1j)** Interaction Effect: increased [aripiprazole](#) exposure; increased risk for QT-interval prolongation

**2j)** Summary: Coadministration of crizotinib with another drug known to prolong the QT-interval, such as [aripiprazole](#) should be avoided. In addition, crizotinib is a CYP3A4 inhibitor[89] and [aripiprazole](#) is a drug extensively metabolized by CYP3A4; therefore concomitant use may significantly increase [aripiprazole](#) concentrations [88]. If concomitant use is clinically indicated, consider periodic ECG and [electrolyte monitoring](#) during therapy. If QTc is greater than 500 msec on at least 2 separate ECGs, withhold crizotinib until recovery to baseline or until QTc is less than 481 msec, then resume at a lower dose. Permanently discontinue crizotinib if QTc is greater than 500 msec or if the QTc changes by at least 60 msec from baseline and is associated with [torsade de pointes](#), [polymorphic ventricular tachycardia](#), or signs or symptoms of serious [arrhythmia](#) [89]. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor reduce the [aripiprazole](#) dose to one-quarter of its normal dose with dose adjustments based on clinical response [88].

**3j)** Severity: major

**4j)** Onset: unspecified

**5j)** Substantiation: theoretical

**6j)** Clinical Management: Coadministration of crizotinib with another drug known to prolong the QT-interval, such as [aripiprazole](#) should be avoided[89]. In addition, crizotinib is a CYP3A4 inhibitor [89] and [aripiprazole](#) is a drug extensively metabolized by CYP3A4; therefore concomitant use may significantly increase [aripiprazole](#) concentrations [88]. If concomitant use is clinically indicated, consider periodic ECG and [electrolyte monitoring](#) during therapy. If QTc is greater than 500 msec on at least 2 separate ECGs, withhold crizotinib until recovery to baseline or until QTc is less than 481 msec, then resume at a lower dose. Permanently discontinue crizotinib if QTc is greater than 500 msec or if the QTc changes by at least 60 msec from baseline and is associated with [torsade de pointes](#), [polymorphic ventricular tachycardia](#), or signs or symptoms of serious [arrhythmia](#) [89]. If coadministration includes a CYP3A4 inhibitor and a

CYP2D6 inhibitor reduce the [aripiprazole](#) dose to one-quarter of its normal dose with dose adjustments based on clinical response [88].

7J) Probable Mechanism: inhibition of CYP3A4-mediated [aripiprazole](#) metabolism by crizotinib; additive QT effects

8J) Literature Reports

aJ) In a [pharmacokinetic study](#), coadministration of crizotinib (250 mg twice daily for 28 days) with oral [midazolam](#) resulted in a 3.7-fold increase in mean [midazolam](#) AUC compared with [midazolam](#) administered alone. This clinical study with a CYP3A4 substrate suggests that crizotinib is a moderate CYP3A4 inhibitor [89].

### 3.5.1.AM] [Cyclobenzaprine](#)

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AN] [Dabrafenib](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: Dabrafenib, as a single agent, has potential to prolong the QT interval; therefore, concomitant use with other drugs that can prolong the QT interval may cause additive effects on the QT interval[156]. Therefore, caution should be exercised with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of dabrafenib with other drugs that cause QT-interval prolongation may result in additive effects on the QT interval[156]. Exercise caution with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).

7J) Probable Mechanism: additive QT prolongation

### 3.5.1.AO] [Dasatinib](#)

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AP] Degarelix

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[153][154][155]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[153][154][155].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AQ] Delamanid

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AR] Desipramine

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution

because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AS] Deslorelin

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[153][154][155]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[153][154][155].

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AT] Dihydrocodeine

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [dihydrocodeine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[110].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [dihydrocodeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[110].

7) Probable Mechanism: additive CNS depression

### 3.5.1.AU] Disopyramide

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution



because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AV] Dofetilide

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AW] Dolasetron

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AX] Domperidone

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

**3.5.1.AY] Donepezil**

- 1) Interaction Effect: increased risk of QT-interval prolongation and [torsade de pointes](#)
- 2) Summary: [Donepezil](#) has been associated with QT-interval prolongation[131][132]. Use caution when administering [donepezil](#) concomitantly with other drugs that cause QT-interval prolongation.
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: [Donepezil](#) has been associated with QT-interval prolongation[131][132]. Use caution when administering [donepezil](#) concomitantly with other drugs that cause QT-interval prolongation
- 7) Probable Mechanism: additive QT-interval prolongation

**3.5.1.AZ] Doxepin**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.BA] Doxylamine**

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[146][147]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[146][147]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 7) Probable Mechanism: additive CNS depression

**3.5.1.BB] Dronedarone**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[123].
- 3) Severity: contraindicated



- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[123].
- 7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.BC] [Droperidol](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BD] [Ebastine](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BE] [Efavirenz](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Consider alternatives to [efavirenz](#) when used concomitantly with another drug that prolongs the QT interval or has a known risk of [torsade de pointes](#), because additive effects on the QT interval may occur. In a QT study of 58 healthy subjects, the mean C<sub>max</sub> in patients with the CYP2B6 \*6/\*6 genotype was 2.25-fold higher than the mean C<sub>max</sub> in those with the CYP2B6 \*1/\*1 genotype and the mean QTc interval prolongation was 8.7 milliseconds in subjects with the CYP2B6 \*6/\*6 genotype[141].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: Consider alternatives to efavirenz when used concomitantly with another drug that prolongs the QT interval or has a known risk of torsade de pointes, because additive effects on the QT interval may occur[141].
- 7) Probable Mechanism: additive effects on the QT interval
- 8) Literature Reports

a) In a QT study of healthy subjects (N=58) enriched for CYP2B6 polymorphisms, a positive association between efavirenz concentration and QTc prolongation was observed. Following administration of efavirenz 600 mg/day for 14 days, the mean Cmax in subjects with the CYP2B6 \*6/\*6 genotype was 2.25-fold higher than the mean Cmax in subjects with the CYP2B6 \*1/\*1 genotype and the mean QTc interval prolongation was 8.7 milliseconds in subjects with the CYP2B6 \*6/\*6 genotype [141].

### 3.5.1.BF] Enzalutamide

- 1) Interaction Effect: decreased exposure of aripiprazole
- 2) Summary: Coadministration of aripiprazole and this drug, a strong CYP3A4 inducer, may result in decreased aripiprazole plasma levels. Avoid coadministration of long-acting aripiprazole injection with strong CYP3A4 inducers for more than 14 days[19]. During drug interaction studies, coadministration of aripiprazole and carbamazepine (a strong CYP3A4 inducer) resulted in decreased AUC and Cmax concentrations of aripiprazole and its active metabolite. As a similar reaction cannot be ruled out, double the normal aripiprazole dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the aripiprazole dose should be decreased over 1 to 2 weeks to the original level [4][3].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of aripiprazole and this drug, a strong CYP3A4 inducer, may result in decreased aripiprazole plasma levels. Avoid coadministration of long-acting aripiprazole injection with strong CYP3A4 inducers for more than 14 days[19]. Double the normal aripiprazole dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the aripiprazole dose should be decreased over 1 to 2 weeks to the original level [4][3].
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism of aripiprazole
- 8) Literature Reports

a) During drug interaction studies, coadministration of aripiprazole 30 mg/day and carbamazepine 200 mg twice daily resulted in a 70% decrease in the AUC and Cmax of both aripiprazole and its active metabolite [88].

b) Coadministration of carbamazepine, a strong CYP3A4 inducer, twice daily with aripiprazole once daily decreased plasma concentrations of aripiprazole and its active metabolite, dehydro-aripiprazole by 64% and 68%, respectively. In this pharmacokinetic study, 18 patients with schizophrenia (mean age 35.8 years) on a fixed dose of aripiprazole (12 mg (n=3) or 24 mg (n=18)) once daily for 3 to 5 weeks were started on carbamazepine 200 mg twice daily for 1 week. Blood samples were analyzed before carbamazepine initiation and 1 week after completion. The mean carbamazepine plasma concentration achieved was 9.3 mcg/mL. A review of CYP2D6 genotypes showed no association between genotypes and changes in aripiprazole and dehydro-aripiprazole plasma concentrations. The concentration ratio of aripiprazole to dehydro-aripiprazole did not change during the study. Because carbamazepine is a potent inducer of CYP3A4, the most likely mechanism for this interaction is CYP3A4 induction [102].

**3.5.1.BG| Eribulin**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.BH| Erythromycin**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.BI| Escitalopram**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.BJ| Famotidine**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BK] [Felbamate](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BL] [Fentanyl](#)

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death[106]. Severe hypotension has been reported with coadministration of [fentanyl](#) and [midazolam](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [107]. Due to the risk of additive CNS effects, use caution, monitor patients closely, and reduce the dose of one or both when these agents are administered concomitantly [106].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [fentanyl](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Due to the added CNS depressant effects, exercise caution if coadministration of [fentanyl](#) and another CNS depressant is required. Carefully monitor patients receiving concomitant [fentanyl](#) and other CNS depressants and adjust dosage of one or both agents[106].
- 7) Probable Mechanism: additive CNS depression

**3.5.1.BM] Fingolimod**

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

**3.5.1.BN] Flecainide**

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

**3.5.1.BO] Flibanserin**

- 1)) Interaction Effect: additive CNS depression
- 2)) Summary: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[150].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[150].
- 7)) Probable Mechanism: additive CNS depression

**3.5.1.BP] Fluconazole**

- 1)) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT-interval prolongation

2) Summary: Using [fluconazole](#) (a strong CYP3A4 inhibitor) together with a CYP3A4 substrate known to prolong the QT interval, such as [aripiprazole](#), is contraindicated[140]. Concomitant use may result in elevated plasma concentrations of [aripiprazole](#), increasing the risk for QT prolongation. If coadministration is required, reduce the [aripiprazole](#) dose to one-half the usual dose. For coadministration in poor CYP2D6 metabolizers or with a 2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with [fluconazole](#) is discontinued, increase the dose of [aripiprazole](#) [88].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Using [fluconazole](#) together with a CYP3A4 substrate known to prolong the QT interval, such as [aripiprazole](#), is contraindicated[140]. Concomitant use may result in elevated plasma concentrations of [aripiprazole](#), increasing the risk for QT prolongation. If coadministration is required, reduce the [aripiprazole](#) dose to one-half the usual dose. For coadministration in poor CYP2D6 metabolizers or with a 2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with [fluconazole](#) is discontinued, increase the dose of [aripiprazole](#) [88].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [aripiprazole](#); additive QT-interval prolongation

### 3.5.1.BQ] Fluoxetine

1) Interaction Effect: increased [aripiprazole](#) exposure and increased risk for QT-interval prolongation

2) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes. Coadministration with CYP2D6 inhibitors, such as [fluoxetine](#), may inhibit [aripiprazole](#) elimination causing increased blood concentrations. If [aripiprazole](#) is coadministered with [fluoxetine](#), dose reduction of oral [fluoxetine](#) is required immediately, and dose reduction of [aripiprazole](#) long-acting injection is required when concurrent use exceeds 14 days. If [aripiprazole](#) and [fluoxetine](#) are concurrently used with a strong CYP3A4 inhibitor, further dose reduction of [aripiprazole](#) is required. If concurrent [fluoxetine](#) is discontinued, [aripiprazole](#) dose should then be increased[14][88]. Dosage adjustments with concomitant use are not recommended if low-dose [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [88]. Additionally, coadministration may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted [94]

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [aripiprazole](#) with [fluoxetine](#) may result in increased [aripiprazole](#) plasma levels. Dose reduction of oral [aripiprazole](#) is required immediately during concurrent use of [fluoxetine](#), and dose reduction of [aripiprazole](#) long-acting injection is required when concurrent use exceeds 14 days. If [aripiprazole](#) and [fluoxetine](#) are concurrently used with a strong CYP3A4 inhibitor, further dose reduction of [aripiprazole](#) is required. If concurrent [fluoxetine](#) is discontinued, the dose of [aripiprazole](#) should then be increased[14][88]. Specific dosage adjustments are not recommended if low-dose oral [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [88]. Additionally, coadministration may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted [94].

7) Probable Mechanism: inhibition of CYP2D6- and CYP3A4-mediated [aripiprazole](#) metabolism by [fluoxetine](#); additive effects on QT interval

8) Literature Reports

a) During drug interaction studies, coadministration of [quinidine](#) 166 mg/day for 13 days (a strong CYP2D6 inhibitor) with a single dose of [aripiprazole](#) 10 mg resulted in a 112% increase in



aripiprazole AUC. The AUC of dehydro-aripiprazole, the active metabolite of aripiprazole, was decreased by 35% [88]

b) During drug interaction studies, coadministration of ketoconazole 200 mg/day for 14 days (a strong CYP3A4 inhibitor) with single dose aripiprazole 15 mg resulted in a 63% and 77% increase in the AUC of aripiprazole and its active metabolite, respectively [88].

### 3.5.1.BR] Formoterol

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BS] Foscarnet

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BT] Fosphenytoin

- 1) Interaction Effect: decreased aripiprazole exposure and increased risk of QT-interval prolongation
- 2) Summary: Approach coadministration of aripiprazole and fosphenytoin with caution. Fosphenytoin is a prodrug of phenytoin. Phenytoin is a strong CYP3A4 inducer and has been associated with QT interval prolongation[160]. Aripiprazole is a CYP3A4 substrate and has been associated with QT interval prolongation. During drug interaction studies, coadministration of aripiprazole 30 mg/day and carbamazepine 200 mg twice daily (a strong CYP3A4 inducer) decreased the AUC and Cmax of aripiprazole and its active metabolite by 70% [88]. Avoid coadministration of long-acting aripiprazole injection with strong CYP3A4 inducers for more than 14 days [19]. If concurrent use is required with oral aripiprazole, double the normal aripiprazole dose, then clinically evaluate the need for additional dosage



increases during coadministration. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased to 10 to 15 mg [88]. Consider periodic monitoring for [ventricular arrhythmia](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [aripiprazole](#) and a CYP3A4 inducer, such as [fosphenytoin](#), may decrease [aripiprazole](#) exposure and efficacy. Additionally, both [aripiprazole](#) [88] and [fosphenytoin](#) are known to prolong the QT interval [160]. Avoid coadministration of long-acting [aripiprazole](#) injection with strong CYP3A4 inducers for more than 14 days [19]. If concurrent use is required with oral [aripiprazole](#), initially double the normal [aripiprazole](#) dose, then clinically evaluate the need for additional dosage increases during coadministration. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased to 10 to 15 mg [88]. Consider periodic monitoring for [ventricular arrhythmia](#).

7) Probable Mechanism: induction of CYP3A4-mediated [aripiprazole](#) metabolism by [phenytoin](#); additive QT-interval prolongation

8) Literature Reports

a) During drug interaction studies, coadministration of [aripiprazole](#) 30 mg/day and [carbamazepine](#) 200 mg twice daily (a strong CYP3A4 inducer) resulted in a 70% decrease in the AUC and C<sub>max</sub> of both [aripiprazole](#) and its active metabolite [88].

### 3.5.1.BU] [Galantamine](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation [88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation [88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BV] [Gatifloxacin](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation [88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation [88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

**3.5.1.BW] Gemifloxacin**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.BX] Gonadorelin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[153][154][155]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[153][154][155].
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.BY] Goserelin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[153][154][155]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[153][154][155].
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.BZ] Granisetron**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.CA] [Halofantrine](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.CB] [Haloperidol](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.CC] [Histrelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT

interval and cause additive effects when administered with QT-interval prolonging drugs[153][154][155]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[153][154][155].

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CD] [Hydrocodone](#)

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: Use caution with the concomitant use of [hydrocodone](#) and a CNS depressant as this may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and consider using a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[113]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [110].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [hydrocodone](#) and a CNS depressant may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and use a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[113]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [110].

7) Probable Mechanism: additive CNS depression

### 3.5.1.CE] [Hydromorphone](#)

1) Interaction Effect: an increase in CNS or [respiratory depression](#)

2) Summary: The concomitant use of [HYDROmorphine](#) and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including [respiratory depression](#), hypotension, profound sedation, and coma. When administering [HYDROmorphine](#) and an antipsychotic together, dose reduction of one or both of the medications should be considered[127].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [HYDROmorphine](#) and other CNS depressants, such as antipsychotics, may result in [respiratory depression](#), hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered[127].

7) Probable Mechanism: additive CNS depression

### 3.5.1.CF] [Hydroquinidine](#)

1) Interaction Effect: increased risk of QT interval prolongation

2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7)) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CG| [Hydroxychloroquine](#)

1)) Interaction Effect: increased risk of QT-interval prolongation

2)) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation[95][96], [ventricular premature contractions](#), and [torsade de pointes](#) [96]. Therefore, use caution with coadministration of [hydroxychloroquine](#) and other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: [Hydroxychloroquine](#) has been associated with QT interval prolongation[95][96]. Therefore, use caution with coadministration of [hydroxychloroquine](#) and other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.

7)) Probable Mechanism: additive QT interval effects

8)) Literature Reports

a)) Hydroxychloroquine-associated QT interval prolongation was reported in a 41-year-old woman with [congestive heart failure](#) with [systolic left ventricular dysfunction](#). Her comorbidities included [hypertension](#), [systemic lupus erythematosus](#), and [stage 5 chronic kidney disease](#). One week after reinitiation of [hydroxychloroquine](#) therapy, a significant prolongation of the QT interval (QTc 614 msec) was observed during a routine ECG. Following treatment discontinuation of [hydroxychloroquine](#), serial ECGs demonstrated a shortening of the QTc interval. The patient's QTc was 473 msec at a follow up 1 year after discharge [95].

b)) QT prolongation and refractory [ventricular arrhythmia](#) were reported with chronic [hydroxychloroquine](#) use in a 67-year-old woman with [systemic lupus erythematosus](#). The patient had been receiving [prednisolone](#), [theophylline](#), and [hydroxychloroquine](#) 200 mg/day for 1 year. The patient had a medical history of [cirrhosis](#), [hepatitis B](#) virus related [hepatoma](#) with portal vein [thrombosis](#), and [asthma](#). The patient experienced a sudden episode of unconsciousness and generalized rigidity while at home. Although the patient regained consciousness within minutes and had no complaints of chest pain, palpitation, limb weakness, incontinence, or confusion, the episode recurred several times. Upon admission the ECG showed multiple [ventricular premature contractions](#), [torsade de pointes](#), and prolongation of the QT interval. Treatment with

[hydroxychloroquine](#) was discontinued. Following medical management, [ventricular arrhythmia](#) subsided after 4 days and the QT interval shortened [96].

### 3.5.1.CH| [Hydroxyzine](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Hydroxyzine](#) has been associated with QT interval prolongation and development of [Torsade de Pointes](#). Caution is advised if [hydroxyzine](#) is used concomitantly with this drug as additive effects on QT prolongation may occur[152]. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Hydroxyzine](#) has been associated with QT interval prolongation and development of [Torsade de Pointes](#). Caution is advised if [hydroxyzine](#) is used concomitantly with this drug as additive effects on QT prolongation may occur[152]. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CI| [Ibutilide](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CJ| [Idelalisib](#)

- 1) Interaction Effect: increased exposure of [aripiprazole](#)
- 2) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes. Coadministration with CYP3A4 inhibitors may inhibit [aripiprazole](#) elimination causing increased blood concentrations and increased risk for toxicity, including QT-interval prolongation. During drug interaction studies, coadministration of [aripiprazole](#) and [ketoconazole](#), a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of [aripiprazole](#) and its active metabolite. If [aripiprazole](#) is coadministered with a CYP3A4 inhibitor, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection is used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19].
- 3) Severity: major



- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor may result in increased [aripiprazole](#) plasma levels and increased risk for toxicity, including QT-interval prolongation. If coadministration of [aripiprazole](#) and a CYP3A4 inhibitor is required, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection is used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19].
- 7)) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [aripiprazole](#)
- 8)) Literature Reports
  - a)) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

### 3.5.1.CK] Iloperidone

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CL] Imipramine

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval



**3.5.1.CM] Indinavir**

1) Interaction Effect: increased exposure of [aripiprazole](#)

2) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes. Coadministration with CYP3A4 inhibitors may inhibit [aripiprazole](#) elimination causing increased blood concentrations and increased risk for toxicity, including QT-interval prolongation. During drug interaction studies, coadministration of [aripiprazole](#) and [ketoconazole](#), a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of [aripiprazole](#) and its active metabolite. If [aripiprazole](#) is coadministered with a CYP3A4 inhibitor, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection is used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor may result in increased [aripiprazole](#) plasma levels and increased risk for toxicity, including QT-interval prolongation. If coadministration of [aripiprazole](#) and a CYP3A4 inhibitor is required, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection is used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [aripiprazole](#)

8) Literature Reports

a) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

**3.5.1.CN] Itraconazole**

1) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes, and is also associated with QTc interval prolongation. Coadministration with CYP3A4 inhibitors that also prolong the QT interval may inhibit [aripiprazole](#) elimination and produce additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). During drug interaction studies, coadministration of [aripiprazole](#) and [ketoconazole](#), a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of [aripiprazole](#) and its active metabolite. If [aripiprazole](#) is coadministered with a CYP3A4 inhibitor, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19]

- 3j) Severity: major
- 4j) Onset: unspecified
- 5j) Substantiation: theoretical
- 6j) Clinical Management: Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor should be undertaken with caution, as this may result in increased [aripiprazole](#) plasma levels and additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). If coadministration of [aripiprazole](#) and a CYP3A4 inhibitor is required, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19]
- 7j) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [aripiprazole](#) and additive effects on the QT interval
- 8j) Literature Reports
  - a) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

### 3.5.1.CO| Ivabradine

- 1j) Interaction Effect: increased risk of QT interval prolongation
- 2j) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3j) Severity: major
- 4j) Onset: unspecified
- 5j) Substantiation: theoretical
- 6j) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7j) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CP| [Ketoconazole](#)

- 1j) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT-interval prolongation
- 2j) Summary: Use caution with concomitant administration of [aripiprazole](#) (CYP3A4 substrate) and [ketoconazole](#) (strong CYP3A4 inhibitor). During drug interaction studies, [aripiprazole](#) AUC increased 63% and the active metabolite AUC increased 77% after coadministration of a single dose of [aripiprazole](#) 15 mg during a 14 course of [ketoconazole](#) 200 mg/day. [Ketoconazole](#)[97] and [aripiprazole](#) are associated with QT-interval prolongation [88]. If coadministration of [aripiprazole](#) and [ketoconazole](#) is required, reduce the [aripiprazole](#) dose to one-half the normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. Closely monitor patients for signs or symptoms of increased or prolonged [aripiprazole](#) toxicity. If appropriate, plasma concentrations should be measured [97]. When [ketoconazole](#) is discontinued, the dose of [aripiprazole](#) should be increased [88]. Additionally, concurrent use of [aripiprazole](#) and QT-prolonging drugs, including

[paroxetine](#), may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution with concomitant administration of [aripiprazole](#) and [ketoconazole](#). Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor, such as [ketoconazole](#), increases exposure to [aripiprazole](#) and the active metabolite. [Ketoconazole](#)[97] and [aripiprazole](#) have been associated with QT-interval prolongation [88]. If coadministration of [aripiprazole](#) and [ketoconazole](#) is required, reduce the [aripiprazole](#) dose to one-half the normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. Closely monitor patients for signs or symptoms of increased or prolonged [aripiprazole](#) toxicity. If appropriate, plasma concentrations should be measured [97]. When [ketoconazole](#) is discontinued, the dose of [aripiprazole](#) should be increased [88]. Additionally, concurrent use of [aripiprazole](#) and QT-prolonging drugs, including [paroxetine](#), may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.

7J) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [aripiprazole](#); additive QT-interval prolongation

8J) Literature Reports

aJ) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

### 3.5.1.CQ] Lapatinib

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CR] Leuprolide

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[153][154][155]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3J) Severity: major

4J) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[153][154][155].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CS] **Levofloxacin**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: **Aripiprazole** has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including **torsade de pointes**.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: **Aripiprazole** has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including **torsade de pointes**.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CT] **Lopinavir**

- 1) Interaction Effect: increased exposure of **aripiprazole**
- 2) Summary: **Aripiprazole** is metabolized by CYP2D6 and CYP3A4 enzymes. Coadministration with CYP3A4 inhibitors may inhibit **aripiprazole** elimination causing increased blood concentrations and increased risk for toxicity, including QT-interval prolongation. During drug interaction studies, coadministration of **aripiprazole** and **ketoconazole**, a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of **aripiprazole** and its active metabolite. If **aripiprazole** is coadministered with a CYP3A4 inhibitor, reduce the **aripiprazole** dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the **aripiprazole** dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of **aripiprazole** should then be increased[88]. Dosage reductions are required if long-acting **aripiprazole** injection is used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If **aripiprazole** and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of **aripiprazole** is required.[19].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of **aripiprazole** and a CYP3A4 inhibitor may result in increased **aripiprazole** plasma levels and increased risk for toxicity, including QT-interval prolongation. If coadministration of **aripiprazole** and a CYP3A4 inhibitor is required, reduce the **aripiprazole** dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the **aripiprazole** dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of **aripiprazole** should then be increased[88]. Dosage reductions are required if long-acting **aripiprazole** injection is used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If **aripiprazole** and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of **aripiprazole** is required.[19].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of **aripiprazole**

**8) Literature Reports**

a) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

**3.5.1.CU] Lorcaserin**

1) Interaction Effect: increased [aripiprazole](#) plasma concentrations

2) Summary: The concomitant use of [aripiprazole](#), a CYP2D6 substrate[23], and lorcaserin, a CYP2D6 inhibitor, may increase [aripiprazole](#) plasma concentrations [90]. If administered concomitantly, reduce the [aripiprazole](#) dose by one-half. If therapy with lorcaserin is discontinued, the dose of [aripiprazole](#) should then be increased [23].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [aripiprazole](#), a CYP2D6 substrate[23], and lorcaserin, a CYP2D6 inhibitor, may result in increased [aripiprazole](#) plasma levels [90]. If administered concomitantly, reduce [aripiprazole](#) dose by one-half. If therapy with lorcaserin is discontinued, the dose of [aripiprazole](#) should then be increased [23].

7) Probable Mechanism: inhibition of CYP2D6-mediated [aripiprazole](#) metabolism by lorcaserin

**8) Literature Reports**

a) In a clinical trial in 21 CYP2D6 extensive metabolizers, coadministration of lorcaserin, a CYP2D6 inhibitor, 10 mg twice a day for 4 days increased [dextromethorphan](#), a CYP2D6 substrate, peak concentrations (C<sub>max</sub>) by approximately 76% and exposure (AUC) by approximately 2-fold [90].

b) Coadministration of [quinidine](#) 166 mg daily for 13 days with a single 10 mg dose of [aripiprazole](#) increased the AUC value of [aripiprazole](#) by 112% and decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. [Aripiprazole](#) is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministration with [quinidine](#), a potent CYP2D6 inhibitor, could inhibit [aripiprazole](#) elimination resulting in increased blood concentrations. Reduce the [aripiprazole](#) dose to one-half of its normal dose when these agents are coadministered [23].

**3.5.1.CV] Lumefantrine**

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

**3.5.1.CW] Mefloquine**

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

**3.5.1.CX] Meperidine**

- 1)) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2)) Summary: The concomitant use of [meperidine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Reserve concomitant use of [meperidine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 7)) Probable Mechanism: additive CNS depression

**3.5.1.CY] Mesoridazine**

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[122].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: established
- 6)) Clinical Management: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[122].
- 7)) Probable Mechanism: additive QT-interval prolongation

**3.5.1.CZ] Methadone**



- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.DA| [Metoclopramide](#)

- 1) Interaction Effect: an increased risk of extrapyramidal reactions or [neuroleptic malignant syndrome](#)
- 2) Summary: Concomitant use of [metoclopramide](#) with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated[125]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions. Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [126].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [metoclopramide](#) with antipsychotic agents is contraindicated[125]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#). Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [126].
- 7) Probable Mechanism: unknown

### 3.5.1.DB| [Metronidazole](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation and [arrhythmias](#)
- 2) Summary: Concurrent use of [metronidazole](#) with other QT-prolonging drugs was a probable cause of QT-interval prolongation in one study of cardiac ICU patients. Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs[104].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs[104].



**7J) Probable Mechanism: additive QT-interval prolongation****8J) Literature Reports**

aJ) In a retrospective study, 164 of 501 patients admitted in cardiac ICUs (87.7%) developed QT-interval prolongation potentially linked to inhibition of CYP450-mediated metabolism. Out of 1027 total interactions that were potentially associated with QT-interval prolonging effects, interactions with [metronidazole](#) (n=22) were some of the most common. No patients developed [torsades de pointes](#) during their ICU stays. Close [ECG monitoring](#) at baseline and during concurrent therapy with drugs known to cause QT-interval prolongation is recommended [104].

bJ) A 71-year-old woman with antibiotic-induced [pseudomembranous colitis](#) developed ECG QTc interval prolongation and [torsades de pointes](#) with concurrent [amiodarone](#) 450 mg bolus followed by 900 mg/day IV and [metronidazole](#) 1500 mg/day oral administration. Baseline QTc interval was 440 msec. [Amiodarone](#) was added after trial fibrillation developed with 3 days of [amiodarone](#) therapy. Conversion to sinus rhythm occurred 2 days later; however, the follow-up ECG revealed a QTc interval of 625 msec. Symptoms progressed to sustained torsades de pointes-variant [ventricular tachycardia](#) that required emergent [cardioversion/defibrillation](#) to restore normal sinus rhythm. [Amiodarone](#) and [metronidazole](#) were immediately withdrawn, and the QTc interval slowly returned to baseline values without further clinically significant [arrhythmia](#) events [105].

**3.5.1.DC] Mifepristone**

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

**3.5.1.DD] Milnacipran**

1J) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2J) Summary: Concomitant use of milnacipran and an antipsychotic may result in [hypertension](#), coronary artery vasoconstriction or [serotonin syndrome](#), which may be life-threatening. When concomitant use of milnacipran and an antipsychotic is required, caution should be used. If symptoms of [serotonin syndrome](#) develop (eg, restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea), treatment should be immediately discontinued and the appropriate supportive therapy initiated[148].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6) Clinical Management: Coadministration of milnacipran and an antipsychotic may result in [hypertension](#) and coronary artery vasoconstriction through additive serotonergic effects. Therefore, use caution when coadministering these agents. If symptoms of [serotonin syndrome](#) develop, discontinue treatment immediately and institute the appropriate supportive symptomatic treatment[148].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.DE] [Mitotane](#)

1) Interaction Effect: decreased exposure of [aripiprazole](#)

2) Summary: Coadministration of [aripiprazole](#) and this drug, a strong CYP3A4 inducer, may result in decreased [aripiprazole](#) plasma levels. Avoid coadministration of long-acting [aripiprazole](#) injection with strong CYP3A4 inducers for more than 14 days[19]. During drug interaction studies, coadministration of [aripiprazole](#) and [carbamazepine](#) (a strong CYP3A4 inducer) resulted in decreased AUC and Cmax concentrations of [aripiprazole](#) and its active metabolite. As a similar reaction cannot be ruled out, double the normal [aripiprazole](#) dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased over 1 to 2 weeks to the original level [4][3].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [aripiprazole](#) and this drug, a strong CYP3A4 inducer, may result in decreased [aripiprazole](#) plasma levels. Avoid coadministration of long-acting [aripiprazole](#) injection with strong CYP3A4 inducers for more than 14 days[19]. Double the normal [aripiprazole](#) dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased over 1 to 2 weeks to the original level [4][3].

7) Probable Mechanism: induction of CYP3A4-mediated metabolism of [aripiprazole](#)

8) Literature Reports

a) During drug interaction studies, coadministration of [aripiprazole](#) 30 mg/day and [carbamazepine](#) 200 mg twice daily resulted in a 70% decrease in the AUC and Cmax of both [aripiprazole](#) and its active metabolite [88].

b) Coadministration of [carbamazepine](#), a strong CYP3A4 inducer, twice daily with [aripiprazole](#) once daily decreased plasma concentrations of [aripiprazole](#) and its active metabolite, dehydro-aripiprazole by 64% and 68%, respectively. In this [pharmacokinetic study](#), 18 patients with [schizophrenia](#) (mean age 35.8 years) on a fixed dose of [aripiprazole](#) (12 mg (n=3) or 24 mg (n=18)) once daily for 3 to 5 weeks were started on [carbamazepine](#) 200 mg twice daily for 1 week. Blood samples were analyzed before [carbamazepine](#) initiation and 1 week after completion. The mean [carbamazepine](#) plasma concentration achieved was 9.3 mcg/mL. A review of CYP2D6 genotypes showed no association between genotypes and changes in [aripiprazole](#) and dehydro-aripiprazole plasma concentrations. The concentration ratio of [aripiprazole](#) to dehydro-aripiprazole did not change during the study. Because [carbamazepine](#) is a potent inducer of CYP3A4, the most likely mechanism for this interaction is CYP3A4 induction [102].

### 3.5.1.DF] [Mizolastine](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.DG| Morphine

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant [morphine](#) and other CNS depressants for hypotension, [respiratory depression](#) and sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[143][144][145].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, [respiratory depression](#) or sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[143][144][145].
- 7) Probable Mechanism: additive CNS depression effects

#### 3.5.1.DH| Morphine Sulfate Liposome

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant [morphine](#) and other CNS depressants for hypotension, [respiratory depression](#) and sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[143][144][145].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, [respiratory depression](#) or sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[143][144][145].
- 7) Probable Mechanism: additive CNS depression effects

#### 3.5.1.DI| Moxifloxacin

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.DJ] [Nafarelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[153][154][155]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[153][154][155].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.DK] [Nefazodone](#)

- 1) Interaction Effect: increased [aripiprazole](#) concentrations
- 2) Summary: [Aripiprazole](#) coadministered with [nefazodone](#) may result in increased [aripiprazole](#) levels. Coadministration of [ketoconazole](#) 200 mg per day for 14 days with a single 15 mg [aripiprazole](#) dose increased the AUC values of both [aripiprazole](#) and its active metabolite, dehydro-aripiprazole, by 63% and 77%, respectively. [Aripiprazole](#) is partly metabolized by CYP3A4 enzymes. [Ketoconazole](#), a potent CYP3A4 inhibitor, could inhibit [aripiprazole](#) elimination resulting in increased blood concentrations. Coadministration of [aripiprazole](#) with [nefazodone](#), also a strong CYP3A4 inhibitor, may result in a similar effect. If [aripiprazole](#) is coadministered with [nefazodone](#), reduce the [aripiprazole](#) dose to one-half of its normal dose. For concomitant use of [aripiprazole](#) and [nefazodone](#) in poor CYP2D6 metabolizers, the [aripiprazole](#) dose should be reduced to one-quarter of its normal dose. If coadministration includes a CYP3A4 and CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with [nefazodone](#) and/or the CYP2D6 inhibitor are discontinued, the dose of [aripiprazole](#) should then be increased[23][24].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor, such as [nefazodone](#), may result in increased [aripiprazole](#) plasma levels. Consider reducing [aripiprazole](#) dose by approximately

one-half when these agents are coadministered. For concomitant use of aripiprazole and nefazodone in poor CYP2D6 metabolizers, the aripiprazole dose should be reduced to one-quarter of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with nefazodone and/or the CYP2D6 inhibitor are discontinued, the dose of aripiprazole should then be increased[23][24].

7J) Probable Mechanism: inhibition of CYP3A4-mediated aripiprazole metabolism

### 3.5.1.DL] Nelfinavir

1J) Interaction Effect: increased exposure of aripiprazole and increased risk of QT interval prolongation

2J) Summary: Aripiprazole is metabolized by CYP2D6 and CYP3A4 enzymes, and is also associated with QTc interval prolongation. Coadministration with CYP3A4 inhibitors that also prolong the QT interval may inhibit aripiprazole elimination and produce additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes. During drug interaction studies, coadministration of aripiprazole and ketoconazole, a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of aripiprazole and its active metabolite. If aripiprazole is coadministered with a CYP3A4 inhibitor, reduce the aripiprazole dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of aripiprazole should then be increased[88]. Dosage reductions are required if long-acting aripiprazole injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If aripiprazole and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of aripiprazole is required.[19]

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of aripiprazole and a CYP3A4 inhibitor should be undertaken with caution, as this may result in increased aripiprazole plasma levels and additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes. If coadministration of aripiprazole and a CYP3A4 inhibitor is required, reduce the aripiprazole dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of aripiprazole should then be increased[88]. Dosage reductions are required if long-acting aripiprazole injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If aripiprazole and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of aripiprazole is required.[19]

7J) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of aripiprazole and additive effects on the QT interval

8J) Literature Reports

aJ) During drug interaction studies, coadministration of ketoconazole 200 mg/day for 14 days with single dose aripiprazole 15 mg resulted in a 63% and 77% increase in the AUC of aripiprazole and its active metabolite, respectively. Studies have not yet been conducted with higher ketoconazole doses (ie, 400 mg/day) [88].

### 3.5.1.DM] Nilotinib

1J) Interaction Effect: increased exposure of CYP3A4 substrate and increased risk of QT-interval prolongation

2J) Summary: Nilotinib is a moderate CYP3A4 inhibitor and is independently capable of prolonging the QT interval. Avoid use of nilotinib with CYP3A4 substrates that also prolong the QT interval as concomitant use may lead to increased exposure to the CYP3A4 substrate and an increased risk of QT-

interval prolongation and [torsade de pointes](#). If possible, treatment with nilotinib should be interrupted. If concurrent treatment is required, close monitoring for QT interval prolongation is recommended and dose adjustments of the CYP3A4 substrate may be necessary[163]. Monitoring for toxic effects should be considered.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Nilotinib is a moderate CYP3A4 inhibitor and is independently capable of prolonging the QT interval. Use of nilotinib with CYP3A4 substrates that also prolong the QT interval should be avoided, as concomitant use may lead to increased exposure to the CYP3A4 substrate and an increased risk of QT-interval prolongation and [torsade de pointes](#). If possible, treatment with nilotinib should be interrupted. If concurrent treatment is required, close monitoring for QT interval prolongation is recommended and dose adjustments of the CYP3A4 substrate may be necessary[163]. Monitoring for toxic effects should be considered.

7J) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of this drug by nilotinib; additive QT-interval prolongation

#### 3.5.1.DN| [Norfloxacin](#)

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.DO| [Octreotide](#)

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.DP| [Ofloxacin](#)



- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.DQ| [Olanzapine](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.DR| [Ondansetron](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.DS| [Oxycodone](#)

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Use caution with concomitant use of the CNS depressant [oxycodone](#) with another CNS depressant, as additive CNS depressant effects, such as [respiratory depression](#), hypotension, and profound



sedation, can progress to coma or death. Assess the duration of use and degree of tolerance to CNS depressants (including alcohol and illicit drugs) before concurrent use. If coadministration is clinically necessary, monitor the patient and decrease the dose of 1 or both drugs[136]. Initiate **oxycodone** controlled-release formulations at one-third to one-half of the usual dosage [137][138].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant use of **oxycodone** with another CNS depressant, as additive CNS depressant effects, such as **respiratory depression**, hypotension, and profound sedation, can progress to coma or death. Assess the duration of use and degree of tolerance to CNS depressants (including alcohol and illicit drugs) before concurrent use. If coadministration is clinically necessary, monitor the patient and decrease the dose of 1 or both drugs[136]. Initiate **oxycodone** controlled-release formulations at one-third to one-half of the usual dosage [137][138].

7) Probable Mechanism: additive CNS depression effects

### 3.5.1.DT] **Oxymorphone**

1) Interaction Effect: increased risk of **respiratory depression**, profound sedation, coma, and death

2) Summary: Coadministration of **oxymorphone** and a CNS depressant may result in additive respiratory and CNS depressant effects and an increased risk of **respiratory depression**, profound sedation, coma, and death. If concurrent use is clinically necessary, initiate **oxymorphone** at a dose of 5 mg every 12 hours. Monitor patients for sedation, hypotension, and **respiratory depression**, and consider reducing the CNS depressant dose[139].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of **oxymorphone** and a CNS depressant may result in additive respiratory and CNS depressant effects. If concurrent use is clinically necessary, initiate **oxymorphone** at a dose of 5 mg every 12 hours. Monitor patients for sedation and **respiratory depression**, sedation, and hypotension, and consider reducing the CNS depressant dose[139].

7) Probable Mechanism: additive respiratory and CNS depressant effects

### 3.5.1.DU] **Paliperidone**

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: **Aripiprazole** has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including **torsade de pointes**.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: **Aripiprazole** has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including **torsade de pointes**.

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.DV] **Panobinostat**

1) Interaction Effect: increased risk of QT-interval prolongation

2)) Summary: Concurrent use of panobinostat with QT-prolonging drugs is not recommended, as additive effects on the QT interval may develop. Conduct frequent [ECG monitoring](#) if concurrent use with antiemetics known to prolong the QT interval is warranted. Interrupt treatment if the Fridericia-corrected QT interval increases to 480 msec or more. Discontinue panobinostat if QT-interval prolongation does not resolve after any electrolyte abnormalities are corrected[159].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concurrent use of panobinostat with QT-prolonging drugs is not recommended, as additive effects on the QT interval may develop. Conduct frequent [ECG monitoring](#) if concurrent use with antiemetics known to prolong the QT interval is warranted. Interrupt treatment if the Fridericia-corrected QT interval increases to 480 msec or more. Discontinue panobinostat if QT-interval prolongation does not resolve after any electrolyte abnormalities are corrected[159].

7)) Probable Mechanism: additive QT effects

### 3.5.1.DW] [Paroxetine](#)

1)) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT-interval prolongation

2)) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes. Coadministration with CYP2D6 inhibitors, such as [paroxetine](#), may inhibit [aripiprazole](#) elimination causing increased blood concentrations. If [aripiprazole](#) is coadministered with [paroxetine](#), dose reduction of oral [aripiprazole](#) is required immediately, and dose reduction of [aripiprazole](#) long-acting injection is required when concurrent use exceeds 14 days. If [aripiprazole](#) and [paroxetine](#) are concurrently used with a strong CYP3A4 inhibitor, further dose reduction of [aripiprazole](#) is required. If concurrent [paroxetine](#) is discontinued, [aripiprazole](#) dose should then be increased[14][88]. Dosage adjustments with concomitant use are not recommended if low-dose [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [88]. Additionally, concurrent use of [aripiprazole](#) and QT-prolonging drugs, including [paroxetine](#), may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [aripiprazole](#) with [paroxetine](#) may result in increased [aripiprazole](#) plasma levels. Dose reduction of oral [aripiprazole](#) is required immediately during concurrent use of [paroxetine](#), and dose reduction of [aripiprazole](#) long-acting injection is required when concurrent use exceeds 14 days. If [aripiprazole](#) and [paroxetine](#) are concurrently used with a strong CYP3A4 inhibitor, further dose reduction of [aripiprazole](#) is required. If concurrent [paroxetine](#) is discontinued, the dose of [aripiprazole](#) should then be increased[14][88]. Specific dosage adjustments are not recommended if low-dose oral [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [88]. Additionally, coadministration may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.

7)) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [aripiprazole](#); additive QT-interval prolongation

### 3.5.1.DX] [Pasireotide](#)

1)) Interaction Effect: increased risk of QT interval prolongation

2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.DY] Pazopanib

- 1) Interaction Effect: increased [aripiprazole](#) exposure and increased risk for QT-interval prolongation
- 2) Summary: Pazopanib is a weak inhibitor of CYP2D6 and CYP3A4, [aripiprazole](#) is a substrate of CYP2D6 and CYP3A4, and both drugs are known to prolong the QTc interval[88][158]. Although this interaction has not been specifically studied, concurrent use should be approached with caution, as increased [aripiprazole](#) exposure and additive effects on the QT interval may occur. If coadministration is required, initially reduce the [aripiprazole](#) dose to one-quarter of the usual dose and adjust to achieve desirable clinical response [88]. Perform baseline and periodic [monitoring of ECG](#) and maintain electrolytes (eg, [calcium](#), magnesium, potassium) within the normal range during pazopanib therapy [158]. If concurrent pazopanib is discontinued, increase [aripiprazole](#) dose as clinically indicated [88].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Approach coadministration of [aripiprazole](#) and pazopanib with caution as increased [aripiprazole](#) exposure may occur. If concurrent use is required, initially reduce the [aripiprazole](#) dose to one-quarter of the usual dose and adjust to achieve desirable clinical response[88]. Additionally, both drugs are known to prolong QTc [88][158], and coadministration may increase risk of serious cardiac adverse effects. Perform baseline and periodic [monitoring of ECG](#) and maintain electrolytes (eg, [calcium](#), magnesium, potassium) within the normal range during pazopanib therapy [158]. If concurrent pazopanib is discontinued, increase [aripiprazole](#) dose as clinically indicated [88].
- 7) Probable Mechanism: inhibition CYP2D6- and CYP3A4-mediated [aripiprazole](#) metabolism by pazopanib; additive effects on QT interval
- 8) Literature Reports

a) During drug interaction studies, coadministration of [quinidine](#) 166 mg/day for 13 days (strong CYP2D6 inhibitor) with a single dose of [aripiprazole](#) 10 mg resulted in a 112% increase in [aripiprazole](#) AUC. The AUC of dehydro-aripiprazole, the active metabolite of [aripiprazole](#), was decreased by 35% [88].

b) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days (strong CYP3A4 inhibitor) with a single dose of [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively [88].

#### 3.5.1.DZ] Pentamidine

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.EA] [Pentazocine](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [pentazocine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [pentazocine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 7) Probable Mechanism: additive CNS depression

#### 3.5.1.EB] [Perflutren Lipid Microsphere](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.EC] [Periciazine](#)

- 1) Interaction Effect: risk of enhanced CNS depression
- 2) Summary: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[83][84].
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[83][84].
- 7) Probable Mechanism: additive CNS depression

### 3.5.1.ED] Perphenazine

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EE] Phenytoin

- 1) Interaction Effect: decreased exposure of aripiprazole
- 2) Summary: Coadministration of aripiprazole and this drug, a strong CYP3A4 inducer, may result in decreased aripiprazole plasma levels. Avoid coadministration of long-acting aripiprazole injection with strong CYP3A4 inducers for more than 14 days[19]. During drug interaction studies, coadministration of aripiprazole and carbamazepine (a strong CYP3A4 inducer) resulted in decreased AUC and Cmax concentrations of aripiprazole and its active metabolite. As a similar reaction cannot be ruled out, double the normal aripiprazole dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the aripiprazole dose should be decreased over 1 to 2 weeks to the original level [4][3].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of aripiprazole and this drug, a strong CYP3A4 inducer, may result in decreased aripiprazole plasma levels. Avoid coadministration of long-acting aripiprazole injection with strong CYP3A4 inducers for more than 14 days[19]. Double the normal aripiprazole dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the aripiprazole dose should be decreased over 1 to 2 weeks to the original level [4][3].
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism of aripiprazole
- 8) Literature Reports
  - a) During drug interaction studies, coadministration of aripiprazole 30 mg/day and carbamazepine 200 mg twice daily resulted in a 70% decrease in the AUC and Cmax of both aripiprazole and its active metabolite [88].
  - b) Coadministration of carbamazepine, a strong CYP3A4 inducer, twice daily with aripiprazole once daily decreased plasma concentrations of aripiprazole and its active metabolite, dehydro-

aripiprazole by 64% and 68%, respectively. In this [pharmacokinetic study](#), 18 patients with [schizophrenia](#) (mean age 35.8 years) on a fixed dose of [aripiprazole](#) (12 mg (n=3) or 24 mg (n=18)) once daily for 3 to 5 weeks were started on [carbamazepine](#) 200 mg twice daily for 1 week. Blood samples were analyzed before [carbamazepine](#) initiation and 1 week after completion. The mean [carbamazepine](#) plasma concentration achieved was 9.3 mcg/mL. A review of CYP2D6 genotypes showed no association between genotypes and changes in [aripiprazole](#) and dehydro-aripiprazole plasma concentrations. The concentration ratio of [aripiprazole](#) to dehydro-aripiprazole did not change during the study. Because [carbamazepine](#) is a potent inducer of CYP3A4, the most likely mechanism for this interaction is CYP3A4 induction [102].

### 3.5.1.EF] Pimavanserin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Clinically significant QT-interval prolongation has occurred at the usual pimavanserin dosage. Avoid concomitant use of pimavanserin with other agents that prolong the QT interval due to the potential for additive effects on the QT interval and an increased risk of [cardiac arrhythmia](#)[82].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of pimavanserin with other agents that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and an increased risk of [cardiac arrhythmia](#)[82].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EG] Pimozide

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[121].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[121].
- 7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.EH] Pipamperone

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution



because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EI] Piperaquine

1J) Interaction Effect: increased exposure of CYP3A4 substrates and increased risk of QT-interval prolongation

2J) Summary: Concomitant administration of piperaquine and QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperaquine administration, is contraindicated. Concurrent administration of piperaquine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperaquine, caution is advised when administering a CYP3A4 substrate for up to 3 months after discontinuation of piperaquine therapy[112].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of piperaquine (a QT-interval prolonging drug) with other QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperaquine administration, is contraindicated. Concurrent administration of piperaquine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperaquine, caution is advised when administering a CYP3A4 substrate for up to 3 months after discontinuation of piperaquine therapy[112].

7J) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of this drug by piperaquine; additive QT-interval prolongation

### 3.5.1.EJ] Pitolisant

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant administration of pitolisant and another drug that prolongs the QT interval should be done with careful monitoring[114].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant administration of pitolisant and another drug that prolongs the QT interval should be done with careful monitoring[114].

7J) Probable Mechanism: additive QT prolongation

### 3.5.1.EK] [Posaconazole](#)

1J) Interaction Effect: increased exposure of CYP3A4 substrate and increased risk of QT-interval prolongation

2J) Summary: [Posaconazole](#) is a strong CYP3A4 inhibitor and is independently capable of prolonging the QT interval. Cases of [torsade de pointes](#) have been reported with the use of [posaconazole](#). Use of [posaconazole](#) with CYP3A4 substrates that also prolong the QT interval is contraindicated, as concomitant use may lead to increased exposure to the CYP3A4 substrate and increased risk of QT-interval prolongation and [torsade de pointes](#)[124].

3J) Severity: contraindicated

4J) Onset: unspecified



- 5) Substantiation: theoretical
- 6) Clinical Management: [Posaconazole](#) is a strong CYP3A4 inhibitor and is independently capable of prolonging the QT interval. Use of [posaconazole](#) with CYP3A4 substrates that also prolong the QT interval is contraindicated, as concomitant use may lead to increased exposure to the CYP3A4 substrate and increased risk of QT-interval prolongation and [torsade de pointes](#)[124].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of this drug by [posaconazole](#); additive QT-interval prolongation

### 3.5.1.EL] [Probucol](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EM] [Procainamide](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EN] [Prochlorperazine](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.EO] [Promethazine](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.EP] [Propafenone](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.EQ] [Protriptyline](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution

because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.ER] [Quetiapine](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of [quetiapine](#) and a QT-prolonging drug should be avoided. [Quetiapine](#) is known to increase the QT interval and concurrent use with another drug known to prolong the QT interval may lead to an increased risk of serious cardiac adverse events[128].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The coadministration of [quetiapine](#) and a drug known to prolong the QT interval should be avoided, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events[128].

7J) Probable Mechanism: additive effects on QT interval

### 3.5.1.ES] [Quinidine](#)

1J) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT-interval prolongation

2J) Summary: [Aripiprazole](#) is partly metabolized by CYP2D6 enzymes. Coadministration with CYP2D6 inhibitors, such as [quinidine](#), may inhibit [aripiprazole](#) elimination causing increased blood concentrations. During drug interaction studies, coadministration of [aripiprazole](#) and [quinidine](#), a potent CYP2D6 inhibitor, resulted in a substantial increase in [aripiprazole](#) AUC. If [aripiprazole](#) is coadministered with [quinidine](#), reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with [quinidine](#) is discontinued, the dose of [aripiprazole](#) should then be increased. Specific dose adjustments with concomitant use are not recommended if low-dose [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#)[88]. Additionally, concurrent use of [aripiprazole](#) and QT-prolonging drugs, including [quinidine](#), may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Coadministration of [aripiprazole](#) and a CYP2D6 inhibitor, such as [quinidine](#), may result in increased [aripiprazole](#) plasma levels. Reduce the [aripiprazole](#) dose to one-half of its normal dose when these agents are coadministered. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with [quinidine](#) is discontinued, the dose of [aripiprazole](#) should then be increased. Specific dose adjustments with concomitant use are not recommended if low-dose [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#)[88]. Additionally, concurrent use of [aripiprazole](#) and QT-prolonging drugs, including [quinidine](#), may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.

7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [aripiprazole](#); additive QT-interval prolongation

8J) Literature Reports

aJ) During drug interaction studies, coadministration of [quinidine](#) 166 mg/day for 13 days with a single dose of [aripiprazole](#) 10 mg resulted in a 112% increase in [aripiprazole](#) AUC. The AUC of dehydro-aripiprazole, the active metabolite of [aripiprazole](#), was decreased by 35% [88]

**3.5.1.ET] Quinine**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.EU] Ranolazine**

- 1) Interaction Effect: increased exposure of aripiprazole and increased risk of QT-interval prolongation
- 2) Summary: Aripiprazole is partly metabolized by CYP2D6 enzymes. Coadministration with CYP2D6 inhibitors, such as ranolazine, may inhibit aripiprazole elimination causing increased blood concentrations. If aripiprazole is coadministered with ranolazine, reduce the aripiprazole dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with ranolazine is discontinued, the dose of aripiprazole should then be increased. Specific dose adjustments with concomitant use are not recommended if low-dose aripiprazole is being used adjunctively for the treatment of major depressive disorder[88]. Additionally, concurrent use of aripiprazole and QT-prolonging drugs, including ranolazine, may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of aripiprazole and a CYP2D6 inhibitor, such as ranolazine, may result in increased aripiprazole plasma levels. Reduce the aripiprazole dose to one-half of its normal dose when these agents are coadministered. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with ranolazine is discontinued, the dose of aripiprazole should then be increased. Specific dose adjustments with concomitant use are not recommended if low-dose aripiprazole is being used adjunctively for the treatment of major depressive disorder[88]. Additionally, concurrent use of aripiprazole and QT-prolonging drugs, including ranolazine, may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted.
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of aripiprazole; additive QT-interval prolongation

**3.5.1.EV] Remifentanyl**

- 1) Interaction Effect: increased risk of CNS depression (ie, respiratory depression, profound sedation, coma)
- 2) Summary: The concomitant use of remifentanyl with other CNS depressants may result in profound sedation, respiratory depression, coma, and/or death. Reserve concomitant use to clinical settings where

alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of [remifentanyl](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].

7J) Probable Mechanism: additive CNS depression

### 3.5.1.EW] [Rifampin](#)

1J) Interaction Effect: decreased exposure of [aripiprazole](#)

2J) Summary: Coadministration of [aripiprazole](#) and this drug, a strong CYP3A4 inducer, may result in decreased [aripiprazole](#) plasma levels. Avoid coadministration of long-acting [aripiprazole](#) injection with strong CYP3A4 inducers for more than 14 days[19]. During drug interaction studies, coadministration of [aripiprazole](#) and [carbamazepine](#) (a strong CYP3A4 inducer) resulted in decreased AUC and Cmax concentrations of [aripiprazole](#) and its active metabolite. As a similar reaction cannot be ruled out, double the normal [aripiprazole](#) dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased over 1 to 2 weeks to the original level [4][3].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [aripiprazole](#) and this drug, a strong CYP3A4 inducer, may result in decreased [aripiprazole](#) plasma levels. Avoid coadministration of long-acting [aripiprazole](#) injection with strong CYP3A4 inducers for more than 14 days[19]. Double the normal [aripiprazole](#) dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased over 1 to 2 weeks to the original level [4][3].

7J) Probable Mechanism: induction of CYP3A4-mediated metabolism of [aripiprazole](#)

8J) Literature Reports

aJ) During drug interaction studies, coadministration of [aripiprazole](#) 30 mg/day and [carbamazepine](#) 200 mg twice daily resulted in a 70% decrease in the AUC and Cmax of both [aripiprazole](#) and its active metabolite [88].

bJ) Coadministration of [carbamazepine](#), a strong CYP3A4 inducer, twice daily with [aripiprazole](#) once daily decreased plasma concentrations of [aripiprazole](#) and its active metabolite, dehydro-aripiprazole by 64% and 68%, respectively. In this [pharmacokinetic study](#), 18 patients with [schizophrenia](#) (mean age 35.8 years) on a fixed dose of [aripiprazole](#) (12 mg (n=3) or 24 mg (n=18)) once daily for 3 to 5 weeks were started on [carbamazepine](#) 200 mg twice daily for 1 week. Blood samples were analyzed before [carbamazepine](#) initiation and 1 week after completion. The mean [carbamazepine](#) plasma concentration achieved was 9.3 mcg/mL. A review of CYP2D6 genotypes showed no association between genotypes and changes in [aripiprazole](#) and dehydro-aripiprazole plasma concentrations. The concentration ratio of [aripiprazole](#) to dehydro-aripiprazole did not change during the study. Because [carbamazepine](#) is a potent inducer of CYP3A4, the most likely mechanism for this interaction is CYP3A4 induction [102].

**3.5.1.EX] Rilpivirine**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.EY] Risperidone**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.EZ] Ritonavir**

- 1) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes, and is also associated with QTc interval prolongation. Coadministration with CYP3A4 inhibitors that also prolong the QT interval may inhibit [aripiprazole](#) elimination and produce additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). During drug interaction studies, coadministration of [aripiprazole](#) and [ketoconazole](#), a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of [aripiprazole](#) and its active metabolite. If [aripiprazole](#) is coadministered with a CYP3A4 inhibitor, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19]
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical



6) Clinical Management: Coadministration of aripiprazole and a CYP3A4 inhibitor should be undertaken with caution, as this may result in increased aripiprazole plasma levels and additive effects on the QT interval that can lead to serious cardiac adverse effects, including *torsade de pointes*. If coadministration of aripiprazole and a CYP3A4 inhibitor is required, reduce the aripiprazole dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of aripiprazole should then be increased[88]. Dosage reductions are required if long-acting aripiprazole injection is used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If aripiprazole and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of aripiprazole is required.[19]

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of aripiprazole and additive effects on the QT interval

#### 8) Literature Reports

a) During drug interaction studies, coadministration of ketoconazole 200 mg/day for 14 days with single dose aripiprazole 15 mg resulted in a 63% and 77% increase in the AUC of aripiprazole and its active metabolite, respectively. Studies have not yet been conducted with higher ketoconazole doses (ie, 400 mg/day) [88].

### 3.5.1.FA] Saquinavir

1) Interaction Effect: increased exposure of aripiprazole and increased risk of QT-interval prolongation

2) Summary: Using saquinavir together with a CYP3A4 substrate known to prolong the QT interval, such as aripiprazole, is contraindicated[133]. Concomitant use may result in elevated plasma concentrations of aripiprazole, increasing the risk for QT prolongation. If coadministration is required, reduce the aripiprazole dose to one-half of its normal dose. For concomitant use of aripiprazole and saquinavir in poor CYP2D6 metabolizers, the aripiprazole dose should be reduced to one-quarter of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with saquinavir and/or the CYP2D6 inhibitor is discontinued, the dose of aripiprazole should then be increased [88].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Using saquinavir together with a CYP3A4 substrate known to prolong the QT interval, such as aripiprazole, is contraindicated[133]. Concomitant use may result in elevated plasma concentrations of aripiprazole, increasing the risk for QT prolongation. If coadministration is required, reduce the aripiprazole dose to one-half of its normal dose. For concomitant use of aripiprazole and saquinavir in poor CYP2D6 metabolizers, the aripiprazole dose should be reduced to one-quarter of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole dose to one-quarter of its normal dose. If therapy with saquinavir and/or the CYP2D6 inhibitor is discontinued, the dose of aripiprazole should then be increased [88].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of aripiprazole; additive QT-interval prolongation

### 3.5.1.FB] Sertindole

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including *torsade de pointes*.



- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.FC| [Sevoflurane](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.FD| [Sodium Phosphate](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.FE| [Sodium Phosphate, Dibasic](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.FF] [Sodium Phosphate, Monobasic](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.FG] [Solifenacin](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.FH] [Sorafenib](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution

because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.FI] Sotalol

1J) Interaction Effect: increased risk for [torsade de pointes](#)

2J) Summary: Avoid use of [sotalol](#) with agents that prolong the QT interval. If use is unavoidable, monitor the ECG for excessive increases in the QT interval[115][116]. There have been isolated reports of QTc prolongation and [torsade de pointes](#) temporally related to the concomitant administration of [ciprofloxacin](#) and [sotalol](#) [118][117].

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: Avoid use of [sotalol](#) with agents that prolong the QT interval. If use is unavoidable, monitor the ECG for excessive increases in the QT interval[115][116].

7J) Probable Mechanism: additive effects on the QT interval

8J) Literature Reports

aJ) A 70-year-old female receiving [sotalol](#) therapy experienced [torsade de pointes](#) following coadministration of [ciprofloxacin](#). The patient was admitted with new onset [atrial fibrillation](#) with rapid ventricular response and was given IV [amiodarone](#) (loading dose, 450 mg; followed by 24-hour infusion, 650 mg) and [digoxin](#) (0.25 mg/day). The patient converted to sinus rhythm within 48 hours of admission. Both [amiodarone](#) and [digoxin](#) were discontinued and [sotalol](#) (40 mg twice daily) was initiated. The next day the patient presented with [jaundice](#), fever, and [cholecystitis](#), and was treated with IV [ciprofloxacin](#) 400 mg twice daily. Within 12 hours of [ciprofloxacin](#) administration, the patient developed syncope with documented [torsade de pointes](#) that necessitated [defibrillation](#). Her QTc interval, which was 0.38 seconds prior to [ciprofloxacin](#) initiation, was significantly (0.62 seconds) increased following resuscitation. Within 3 days of [ciprofloxacin](#) and [sotalol](#) discontinuation, the QTc interval decreased to 0.42 seconds [117].

bJ) [Torsade de pointes](#) temporally related to [ciprofloxacin](#) administration was reported in a 44-year-old female who was stable on [sotalol](#) 160 mg twice a day for the treatment of [supraventricular arrhythmia](#). [Pyelonephritis](#) was treated with [ciprofloxacin](#) 1 g in the emergency room (ER). At that time, the QTc interval measured 405 milliseconds. The patient was discharged on [ciprofloxacin](#) 500 mg twice a day. Within hours of discharge, she experienced several presyncopal and syncopal episodes and returned to the ER. Torsade-induced syncope was diagnosed and [defibrillation](#) was required. The QTc interval following resuscitation was 590 milliseconds which was compared with previous normal or slightly increased intervals (maximum, 460 milliseconds) during [sotalol](#) maintenance therapy. Upon discontinuation of both medications, the QTc interval normalized within 2 days [118].

### 3.5.1.FJ] Sparfloxacin

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of [sparfloxacin](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[164].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6) Clinical Management: The concomitant use of [sparfloxacin](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[164].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.FK] St John's Wort

1) Interaction Effect: decreased exposure of [aripiprazole](#)

2) Summary: Coadministration of [aripiprazole](#) and this drug, a strong CYP3A4 inducer, may result in decreased [aripiprazole](#) plasma levels. Avoid coadministration of long-acting [aripiprazole](#) injection with strong CYP3A4 inducers for more than 14 days[19]. During drug interaction studies, coadministration of [aripiprazole](#) and [carbamazepine](#) (a strong CYP3A4 inducer) resulted in decreased AUC and Cmax concentrations of [aripiprazole](#) and its active metabolite. As a similar reaction cannot be ruled out, double the normal [aripiprazole](#) dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased over 1 to 2 weeks to the original level [4][3].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [aripiprazole](#) and this drug, a strong CYP3A4 inducer, may result in decreased [aripiprazole](#) plasma levels. Avoid coadministration of long-acting [aripiprazole](#) injection with strong CYP3A4 inducers for more than 14 days[19]. Double the normal [aripiprazole](#) dose over 1 to 2 weeks when these agents are coadministered. If the CYP3A4 inducer is discontinued, the [aripiprazole](#) dose should be decreased over 1 to 2 weeks to the original level [4][3].

7) Probable Mechanism: induction of CYP3A4-mediated metabolism of [aripiprazole](#)

8) Literature Reports

a) During drug interaction studies, coadministration of [aripiprazole](#) 30 mg/day and [carbamazepine](#) 200 mg twice daily resulted in a 70% decrease in the AUC and Cmax of both [aripiprazole](#) and its active metabolite [88].

b) Coadministration of [carbamazepine](#), a strong CYP3A4 inducer, twice daily with [aripiprazole](#) once daily decreased plasma concentrations of [aripiprazole](#) and its active metabolite, dehydro-aripiprazole by 64% and 68%, respectively. In this [pharmacokinetic study](#), 18 patients with [schizophrenia](#) (mean age 35.8 years) on a fixed dose of [aripiprazole](#) (12 mg (n=3) or 24 mg (n=18)) once daily for 3 to 5 weeks were started on [carbamazepine](#) 200 mg twice daily for 1 week. Blood samples were analyzed before [carbamazepine](#) initiation and 1 week after completion. The mean [carbamazepine](#) plasma concentration achieved was 9.3 mcg/mL. A review of CYP2D6 genotypes showed no association between genotypes and changes in [aripiprazole](#) and dehydro-aripiprazole plasma concentrations. The concentration ratio of [aripiprazole](#) to dehydro-aripiprazole did not change during the study. Because [carbamazepine](#) is a potent inducer of CYP3A4, the most likely mechanism for this interaction is CYP3A4 induction [102].

### 3.5.1.FL] Sufentanil

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [sufentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of

the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of [sufentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].

7J) Probable Mechanism: additive CNS depression

### 3.5.1.FM] Sulpiride

1J) Interaction Effect: increased risk of QT interval prolongation and [torsades de pointes](#)

2J) Summary: Use caution with the concomitant use of sulpiride with other agents that prolong the QT interval. Because sulpiride by itself prolongs the QT interval, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such [torsade de pointes](#) and is not recommended. If administration cannot be avoided, [monitoring of heart rate](#) and correction of any electrolyte disturbances is warranted[91].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with the concomitant use of sulpiride with other agents that prolong the QT interval. Because sulpiride by itself prolongs the QT interval, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such [torsade de pointes](#) and is not recommended. If administration cannot be avoided, [monitoring of heart rate](#) and correction of any electrolyte disturbances is warranted[91].

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.FN] Sunitinib

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.FO] Tacrolimus

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk

for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.FP] Tamoxifen

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.FQ] Tapentadol

1) Interaction Effect: increased risk of CNS depression

2) Summary: Concomitant use of tapentadol, which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patient's degree of tolerance to CNS depressants. If tapentadol is coadministered with a CNS depressant, initiate the dose of tapentadol ER at 50 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[129].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of tapentadol, which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patient's degree of tolerance to CNS depressants. If tapentadol is coadministered with a CNS depressant, initiate the dose of tapentadol ER at 50 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[129].

7) Probable Mechanism: additive CNS depression effects

### 3.5.1.FR] Telaprevir

1) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT interval prolongation



2j) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes, and is also associated with QTc interval prolongation. Coadministration with CYP3A4 inhibitors that also prolong the QT interval may inhibit [aripiprazole](#) elimination and produce additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). During drug interaction studies, coadministration of [aripiprazole](#) and [ketoconazole](#), a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of [aripiprazole](#) and its active metabolite. If [aripiprazole](#) is coadministered with a CYP3A4 inhibitor, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19]

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor should be undertaken with caution, as this may result in increased [aripiprazole](#) plasma levels and additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). If coadministration of [aripiprazole](#) and a CYP3A4 inhibitor is required, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19]

7j) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [aripiprazole](#) and additive effects on the QT interval

8j) Literature Reports

a) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

### 3.5.1.FS] Telavancin

1j) Interaction Effect: increased risk of QT interval prolongation

2j) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7j) Probable Mechanism: additive effects on the QT interval



**3.5.1.FT] Telithromycin**

- 1) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes, and is also associated with QTc interval prolongation. Coadministration with CYP3A4 inhibitors that also prolong the QT interval may inhibit [aripiprazole](#) elimination and produce additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). During drug interaction studies, coadministration of [aripiprazole](#) and [ketoconazole](#), a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of [aripiprazole](#) and its active metabolite. If [aripiprazole](#) is coadministered with a CYP3A4 inhibitor, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19]
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor should be undertaken with caution, as this may result in increased [aripiprazole](#) plasma levels and additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). If coadministration of [aripiprazole](#) and a CYP3A4 inhibitor is required, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19]
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [aripiprazole](#) and additive effects on the QT interval
- 8) Literature Reports

a) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

**3.5.1.FU] Terfenadine**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [terfenadine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[162].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [terfenadine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[162].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.FV] Tetrabenazine**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.FW] Thioridazine**

- 1) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT-interval prolongation
- 2) Summary: The concurrent administration of [thioridazine](#) and agents that prolong the QT interval, such as [aripiprazole](#), is contraindicated[101]. [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes. Coadministration with CYP2D6 inhibitors, like [thioridazine](#), may inhibit [aripiprazole](#) elimination causing increased blood concentrations. During drug interaction studies, coadministration of [aripiprazole](#) and [quinidine](#), a potent CYP2D6 inhibitor, resulted in a substantial increase in [aripiprazole](#) AUC. If [aripiprazole](#) is coadministered with a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to at least one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP2D6 inhibitor (and CYP3A4 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased. Specific dose adjustments are not recommended if low-dose [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [88].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [thioridazine](#) and agents that prolong the QT interval, such as [aripiprazole](#), is contraindicated[101]. If concomitant use of [aripiprazole](#) and [thioridazine](#), a CYP2D6 inhibitor, is required, reduce the [aripiprazole](#) dose to at least one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP2D6 inhibitor (and CYP3A4 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased. Specific dose adjustments are not recommended if low-dose [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [88].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [aripiprazole](#) by [thioridazine](#); additive QT-interval prolongation
- 8) Literature Reports

a) During drug interaction studies, coadministration of [quinidine](#) 166 mg/day (a potent inhibitor of CYP2D6) for 13 days with a single dose of [aripiprazole](#) 10 mg resulted in a 112% increase in [aripiprazole](#) AUC. The AUC of dehydro-aripiprazole, the active metabolite of [aripiprazole](#), was decreased by 35% [88]

**3.5.1.FX] Tizanidine**

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

**3.5.1.FY] Tolterodine**

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

**3.5.1.FZ] Toremifene**

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7)) Probable Mechanism: additive effects on the QT interval

**3.5.1.GA] Tramadol**

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [tramadol](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [tramadol](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[110].
- 7) Probable Mechanism: additive CNS depression

#### 3.5.1.GB| [Trazodone](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.GC| [Trimipramine](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.GD| [Triptorelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation

2)) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[153][154][155]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[153][154][155].

7)) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GE] Vandetanib

1)) Interaction Effect: increased risk of QT interval prolongation

2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7)) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GF] Vardenafil

1)) Interaction Effect: increased risk of QT interval prolongation

2)) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7)) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GG] Vemurafenib

1)) Interaction Effect: increased risk of QT-interval prolongation

2)) Summary: Do not start vemurafenib treatment in patients who are receiving another drug known to prolong the QT interval. Vemurafenib is known to increase the QT interval, which may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#). Coadministration of vemurafenib with

another drug that prolongs the QT interval may result in additive effects on the QT interval and further increase the risk of [torsade de pointes](#)[93].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Do not start vemurafenib treatment in patients who are receiving another drug known to prolong the QT interval, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#)[93].

7J) Probable Mechanism: additive effects on QT interval

### 3.5.1.GHJ Venlafaxine

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GIJ Vilanterol

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GJJ Vinflunine

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3J) Severity: major

4J) Onset: unspecified



5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GK] [Voriconazole](#)

1) Interaction Effect: increased exposure of [aripiprazole](#) and increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes, and is also associated with QTc interval prolongation. Coadministration with CYP3A4 inhibitors that also prolong the QT interval may inhibit [aripiprazole](#) elimination and produce additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). During drug interaction studies, coadministration of [aripiprazole](#) and [ketoconazole](#), a potent CYP3A4 inhibitor, resulted in a substantial increase in the AUC of [aripiprazole](#) and its active metabolite. If [aripiprazole](#) is coadministered with a CYP3A4 inhibitor, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19]

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor should be undertaken with caution, as this may result in increased [aripiprazole](#) plasma levels and additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). If coadministration of [aripiprazole](#) and a CYP3A4 inhibitor is required, reduce the [aripiprazole](#) dose to one-half of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with the CYP3A4 inhibitor (and CYP2D6 inhibitor) is discontinued, the dose of [aripiprazole](#) should then be increased[88]. Dosage reductions are required if long-acting [aripiprazole](#) injection if used with strong CYP3A4 inhibitor when concurrent use exceeds 14 days. If [aripiprazole](#) and a CYP3A4 inhibitor are concurrently used with a strong CYP2D6 inhibitor, further dose reduction of [aripiprazole](#) is required.[19]

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [aripiprazole](#) and additive effects on the QT interval

8) Literature Reports

a) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

### 3.5.1.GL] [Vorinostat](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).



- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Aripiprazole has been associated with QTc interval prolongation[88], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
- 7)) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.GM] Ziprasidone

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[99][100].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[99][100].
- 7)) Probable Mechanism: additive QT interval effects

#### 3.5.1.GN] Zuclopenthixol

- 1)) Interaction Effect: increased risk of QT prolongation
- 2)) Summary: Avoid the concomitant use of zuclopenthixol and other drugs known to significantly increase the QT interval. Additionally, drugs known to cause electrolyte disturbances (eg, hypokalemia) or drugs known to increase the plasma concentration of zuclopenthixol should be used cautiously. Cases of QT prolongation, ventricular arrhythmias and fibrillation, ventricular tachycardia, torsade de pointes, and sudden death have been reported with zuclopenthixol[119][120].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Avoid the concomitant use of zuclopenthixol and other drugs known to significantly increase the QT interval. Additionally, drugs known to cause electrolyte disturbances (eg, hypokalemia) or drugs known to increase the plasma concentration of zuclopenthixol should be used cautiously. Cases of QT prolongation, ventricular arrhythmias and fibrillation, ventricular tachycardia, torsade de pointes, and sudden death have been reported with zuclopenthixol[119][120].
- 7)) Probable Mechanism: additive QT prolongation

### 3.5.2] Drug-Food Combinations

#### 3.5.2.A] Grapefruit Juice

- 1)) Interaction Effect: increased aripiprazole exposure
- 2)) Summary: Coadministration of aripiprazole and a CYP3A4 inhibitor, such as grapefruit juice, may result in increased aripiprazole plasma levels. Reduce the aripiprazole dose to one-half of its normal dose when these substances are coadministered. For concomitant use of aripiprazole and grapefruit juice in poor CYP2D6 metabolizers, the aripiprazole dose should be reduced to one-quarter of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the aripiprazole

dose to one-quarter of its normal dose. If grapefruit juice use and/or the CYP2D6 inhibitor therapy is discontinued, the dose of [aripiprazole](#) should then be increased[88].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [aripiprazole](#) and a CYP3A4 inhibitor, such as grapefruit juice, may result in increased [aripiprazole](#) plasma levels. Reduce the [aripiprazole](#) dose to one-half of its normal dose when these substances are coadministered. For concomitant use of [aripiprazole](#) and grapefruit juice in poor CYP2D6 metabolizers, the [aripiprazole](#) dose should be reduced to one-quarter of its normal dose. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If grapefruit juice use and/or the CYP2D6 inhibitor therapy is discontinued, the dose of [aripiprazole](#) should then be increased[88].

7J) Probable Mechanism: inhibition of CYP3A4-mediated [aripiprazole](#) metabolism by grapefruit juice

8J) Literature Reports

aJ) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day (a strong CYP3A4 inhibitor) for 14 days with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively. Studies have not yet been conducted with higher [ketoconazole](#) doses (ie, 400 mg/day) [88].

## 4.0J Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

### 4.1J Monitoring Parameters

AJ) Therapeutic

1J) Physical Findings

aJ) Oral Route

1J) A reduction in the severity or resolution of signs and symptoms of schizophrenia, bipolar disorder (manic or mixed episodes), depression, agitation associated with bipolar mania or schizophrenia, Tourette disorder, or irritability associated with autistic disorder are indicative of efficacy.

2J) Periodically assess the need for continued treatment [3][4].

bJ) IM Route

1J) Establish tolerability to oral aripiprazole prior to initiating treatment with the extended-release IM injection; may take up to 2 weeks to establish tolerability [14].

BJ) Toxic

**1) Laboratory Parameters**

**a)** Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic [monitoring for obesity and diabetes](#), as listed below [179]:

**1)** Measure fasting plasma glucose at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of diabetes. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control [179].

**2)** Measure fasting lipid profile at baseline, at week 12, and then every 5 years thereafter. Repeat testing should be done more frequently as clinically indicated [179].

**b)** In patients with preexisting low WBC or a history of drug-induced [leukopenia](#) or [neutropenia](#), perform CBC with differential frequently during the first few months of therapy [14][3][4].

**2) Physical Findings**

**a)** Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic [monitoring for obesity and diabetes](#), as listed below [179]:

**1)** Obtain personal and family history of obesity, diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease, prior to treatment and review annually with patient [179].

**2)** Track weight and BMI at baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter [179].

**3)** Measure waist circumference at baseline, and annually thereafter [179].

**4)** Measure blood pressure at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of hypertension [179].

**b)** Monitor all patients for clinical symptoms of [hyperglycemia](#) (eg, polydipsia, polyuria, [polyphagia](#), weakness) [14][3][4].

**c)** Examine patient for [tardive dyskinesia](#) before initiation and then annually. Patients at higher risk for [tardive dyskinesia](#) (ie, elderly, patients who have experienced acute dystonic reactions, [akathisia](#), or other clinically significant extrapyramidal side effects) should be examined every 6 months throughout the duration of treatment [180].

**d)** Monitor patients for suicidality during therapy, especially during the initial months of treatment and with dose adjustments, and in patients younger than 24 years of age [3][4].

## 4.2] Patient Instructions

### A) Aripiprazole (By injection)

#### Aripiprazole

Treats [schizophrenia](#), and agitation caused by [schizophrenia](#) or [bipolar disorder](#).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. You should not receive it if you had an [allergic reaction](#) to [aripiprazole](#).

How to Use This Medicine:

Injectable

Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles.

A nurse or other health provider will give you this medicine.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: This medicine needs to be given on a fixed schedule. Call your doctor or pharmacist for instructions.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how [aripiprazole](#) works. Tell your doctor if you are using any of the following:

[Carbamazepine](#), [clarithromycin](#), [fluoxetine](#), [itraconazole](#), [ketoconazole](#), [paroxetine](#), [quinidine](#), [rifampin](#)

Benzodiazepine or sedative medicine (including [lorazepam](#))

Blood pressure medicine

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [diabetes](#), [heart failure](#), [heart](#) or [blood vessel disease](#), heart rhythm problems, high or low blood pressure, high cholesterol, or a history of seizures, [heart attack](#), or [stroke](#).

For some children, teenagers, and young adults, this medicine may increase mental or emotional problems. This may lead to thoughts of suicide and violence. Talk with your doctor right away if you have any thoughts or behavior changes that concern you. Tell your doctor if you or anyone in your family has a history of [bipolar disorder](#) or suicide attempts.

This medicine may cause the following problems:

[Neuroleptic malignant syndrome](#) (NMS), a [neurologic disorder](#) than can be life-threatening

[Tardive dyskinesia](#) (movement disorder that may become permanent)

Changes in blood sugar levels

Unusual changes in behavior, such as gambling urges, binge or compulsive eating, compulsive shopping, or sexual urges

This medicine may make you dizzy or drowsy. Do not drive or do anything that could be dangerous until you know how this medicine affects you. Stand or sit up slowly if you feel lightheaded or dizzy.

You may get overheated more easily while you are receiving this medicine. Be careful when you exercise or you are outside in hot or humid weather. Drink plenty of water to stay hydrated.

Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

**Allergic reaction:** Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Anxiety, irritability, nervousness, restlessness, trouble sleeping

Compulsive behavior or intense urges you cannot control

Confusion, unusual behavior, depressed mood, or thoughts of hurting yourself or others

Fever, chills, **cough**, sore throat, body aches

Increased hunger or thirst, change in how much or how often you urinate

Jerky muscle movements that you cannot control (often in your face, tongue, or jaw)

Lightheadedness, dizziness, fainting

Seizures

Sweating, uneven heartbeat, muscle stiffness

Unusual tiredness or sleepiness

If you notice these less serious side effects, talk with your doctor:

Headache

Nausea, vomiting

Redness, pain, swelling, or itching where the shot was given

Unusual weight gain

If you notice other side effects that you think are caused by this medicine, tell your doctor.

**B) Aripiprazole** (By mouth)

**Aripiprazole**

Treats **schizophrenia**, **bipolar disorder**, **depression**, and **Tourette syndrome**. Also treats irritability associated with **autism**.

**When This Medicine Should Not Be Used:**

This medicine is not right for everyone. Do not use it if you had an **allergic reaction** to **aripiprazole**.

**How to Use This Medicine:**

Liquid, Tablet, Dissolving Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

Tablet: Swallow whole. Do not break, crush, or chew it.

Disintegrating tablet: Make sure your hands are dry before you handle the disintegrating tablet. Peel back the foil from the blister pack, then remove the tablet. Do not push the tablet through the foil. Place the tablet in your mouth. After it has melted, swallow or take a drink of water.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

**Drugs and Foods to Avoid:**

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how **aripiprazole** works. Tell your doctor if you are using any of the following:

**Carbamazepine**, **clarithromycin**, **fluoxetine**, **itraconazole**, **ketoconazole**, **paroxetine**, **quinidine**, **rifampin**

Benzodiazepine or sedative medicine (including **lorazepam**)

## Blood pressure medicine

### Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [diabetes](#), [heart failure](#), [heart](#) or [blood vessel disease](#), heart rhythm problems, high or low blood pressure, high cholesterol, or a history of seizures, [heart attack](#) or [stroke](#).

For some children, teenagers, and young adults, this medicine may increase mental or emotional problems. This may lead to thoughts of suicide and violence. Talk with your doctor right away if you have any thoughts or behavior changes that concern you. Tell your doctor if you or anyone in your family has a history of [bipolar disorder](#) or suicide attempts.

This medicine may cause the following problems:

- [Neuroleptic malignant syndrome](#) (NMS), a [neurologic disorder](#) than can be life-threatening
- [Tardive dyskinesia](#) (muscle movements you cannot control)

- Changes in blood sugar levels

- Unusual changes in behavior, such as gambling urges, binge or compulsive eating, or compulsive shopping, or sexual urges

This medicine may make you dizzy or drowsy. Do not drive or do anything that could be dangerous until you know how this medicine affects you. Stand or sit up slowly if you feel lightheaded or dizzy.

You may get overheated more easily while you are using this medicine. Be careful when you exercise or you are outside in hot or humid weather. Drink plenty of water to stay hydrated.

Tell your doctor if you have [phenylketonuria](#) (PKU). The disintegrating tablet contains [phenylalanine](#).

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

### Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

- [Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

- Anxiety, irritability, nervousness, restlessness, or trouble sleeping

- Compulsive behavior or intense urges you cannot control

- Confusion, unusual behavior, depressed mood, or thoughts of hurting yourself or others

- Fever, chills, [cough](#), sore throat, body aches

- Increased hunger or thirst, change in how much or how often you urinate

- Jerky muscle movements you cannot control (often in your face, tongue, or jaw)

- Lightheadedness, dizziness, or fainting

- Seizures

- Sweating, uneven heartbeat, or muscle stiffness

- Unusual tiredness or sleepiness

If you notice these less serious side effects, talk with your doctor:

- Headache

- Nausea, vomiting, drooling

- Unusual weight gain

If you notice other side effects that you think are caused by this medicine, tell your doctor.

### 4.3] Place In Therapy

**A)** Current users of atypical antipsychotic drugs (including [aripiprazole](#)) and typical antipsychotic drugs had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular [tachyarrhythmia](#). Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of [chlorpromazine](#), and doses comparable to [chlorpromazine](#) 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis [181]. In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation [182].

**B)** Agitation Associated with [Schizophrenia](#) or Bipolar Mania

**1)** [Aripiprazole](#) as an [intramuscular injection](#) is approved for the treatment of agitation associated with [schizophrenia](#) and [bipolar disorder](#), manic or mixed [32].

[Aripiprazole](#) was more effective than placebo for the acute treatment of agitation in patients with [schizophrenia](#), [schizoaffective disorder](#), or [schizophreniform disorder](#) in a dose-ranging, multicenter, randomized, double-blind clinical trial [33].

A double-blind, placebo-controlled study demonstrated that intramuscular [aripiprazole](#) was noninferior to intramuscular [haloperidol](#) and superior to placebo in voluntarily hospitalized agitated patients with [schizophrenia](#) or [schizoaffective disorder](#) [34].

In one short-term (24-hour), placebo-controlled trial (n=291), intramuscular [aripiprazole](#) was statistically superior to placebo in improving symptoms of agitation in patients with Bipolar I Disorder (manic or mixed; using the Positive and Negative Syndrome Scale (PANSS) Excited Component scores and the Clinical Global Impression of Improvement (CGI-I) scale scores) [32].

**C)** [Autistic disorder](#)

**1)** [Aripiprazole](#) is indicated for the treatment of irritability associated with autistic disorder in pediatric patients aged 6 to 17 [12][11].

There was a significant improvement in Aberrant Behavior Checklist (ABC) subscale in aripiprazole-treated patients compared with placebo according to two 8-week studies in pediatric patients aged 6 to 17 with irritability associated with autistic disorder (study 1 [12][7], n=98; study 2 [12], n=218).



**D) Bipolar I Disorder, Acute Mixed or Manic Episodes**

1) **Aripiprazole** is indicated for the treatment of acute manic and mixed episodes associated with bipolar I disorder with or without psychotic features in adults and pediatric patients age 10 to 17 years, as monotherapy or as adjunct therapy with **lithium** or **valproate** [11][12].

In a multicenter, randomized, double-blind, placebo-controlled study, **aripiprazole** monotherapy was more effective than placebo in the treatment of acute manic or mixed episodes in patients (n=262) with **bipolar disorder** [27].

In a 6-week study of 384 bipolar I patients with an acute manic or mixed episode who had an inadequate initial response to **lithium** or **valproate**, randomization to adjunct **aripiprazole** 15 to 30 mg per day plus **lithium** or **valproate** resulted in greater reduction of mania symptoms compared with placebo plus **lithium** or **valproate**, as measured by Young Mania Rating Scale and the Clinical Global Impression of Improvement scale [11][12].

**E) Bipolar I Disorder, Maintenance Therapy**

1) **Aripiprazole** is indicated for the maintenance therapy of bipolar I disorder in adults and pediatric patients age 10 to 17 years, as monotherapy or as adjunct therapy with **lithium** or **valproate** [11][12].

In a randomized, double-blind, parallel-group trial (n=161), maintenance treatment with oral **aripiprazole** monotherapy, at doses of 15 to 30 mg per day for up to 26 weeks, resulted in a longer time to **relapse** compared to placebo in adults with a recent manic or mixed bipolar I episode who were recently stabilized on **aripiprazole** [28].

In a randomized, double-blind, placebo-controlled trial (n=337), patients previously stabilized on adjunct **aripiprazole** 15 to 30 mg per day plus **lithium** or **valproate** who were randomized to continue adjunct **aripiprazole** plus **lithium** or **valproate** experienced fewer hospitalizations and a longer time to **relapse** of any acute mood event over a 52-week period, compared with patients switched to placebo plus **lithium** or **valproate** [11][12].

**F) Major Depressive Disorder, Adjunctive Treatment in Patients Receiving Antidepressants**

1) **Aripiprazole** is indicated for use as an adjunctive treatment to antidepressants for **major depressive disorder** [11][12].

In two 6-week, placebo-controlled trials (n=743), treatment with **aripiprazole** was superior to placebo in reducing depressive symptoms in patients with **major depressive disorder** (MDD) and an inadequate response to prior antidepressant therapies; additionally, one of the studies also demonstrated improved patient functioning with **aripiprazole** compared to placebo [11][12].

**G) Schizophrenia**

1) **Aripiprazole** (oral and extended-release injection) is indicated for the treatment of **schizophrenia** in adults [36], and orally administered **aripiprazole** is also indicated in adolescent patients aged 13 to 17 [11][12].

Longer time to **relapse** was seen in adult patients with chronic, stable **schizophrenia** treated with **aripiprazole** oral therapy in a 26-week multicenter, randomized, double-blind, placebo-controlled study [15], and with **aripiprazole** extended-release IM monthly injection in a 52-week, multicenter, randomized, double-blind, placebo-controlled, phase 3 study (n=403) [17].

In a placebo-controlled, phase 3 study involving relapsed schizophrenic or schizoaffective patients (n=414), **aripiprazole** 15 or 30 mg daily and **haloperidol** 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in Positive and Negative Syndrome Scale

(PANSS) total and Brief Psychiatric Rating Scale (BPRS) total scores; based on responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit). Each dose of [aripiprazole](#) was significantly more effective than placebo, whereas [haloperidol](#) was not [20].

## H) Tourette's Disorder

1) Oral [aripiprazole](#) is indicated in pediatric patients aged 6 to 18 years for the treatment of [Tourette disorder](#). Efficacy of maintenance treatment has not been established [3][4].

[Aripiprazole](#) significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; 15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in a randomized, 10-week trial of patients aged 6 to 18 years with [Tourette disorder](#) (N=61). The response rate (score of 1 or 2 on the [Tourette's syndrome](#) CGI-Improvement scale) was 65.5% vs 44.8%, respectively [5]. The mean [aripiprazole](#) dose was 6.5 mg. In a similar 8-week trial in patients aged 7 to 17 years (N=133) who received weight-based [aripiprazole](#), significant improvements compared with placebo were seen on YGTSS-TTS (-13.4 and -16.9 with low- and high-dose [aripiprazole](#) compared with -7.1 in placebo) [3][4].

## 4.4] Mechanism of Action / Pharmacology

### A) Mechanism of Action

1) [Aripiprazole](#) is an atypical antipsychotic agent (quinolinone derivative). It exhibits relatively high affinity for [dopamine](#) D2 and D3 receptors and serotonin 5-HT1A and 5-HT2A receptors [172][173][174]. The efficacy of the drug in [schizophrenia](#) appears related to partial agonist activity at D2 and 5-HT1A receptors [173][172][174][175], and antagonist activity at 5-HT2A receptors has also been speculated [172].

2) However, other actions may be involved. In vitro data have indicated D2- agonist activity of [aripiprazole](#) at presynaptic autoreceptors, with antagonist activity at postsynaptic D2 receptors (regulating inhibition of cAMP synthesis) [176][174][175][173][177]. These dual effects are seen at the same dose level (concentration) [173], and are unlike those of conventional antipsychotic drugs (typical and atypical). Preclinical and clinical data suggest that these actions minimize extrapyramidal and endocrine (eg, prolactin increases) side effects [176][174][173].

3) Electrophysiological studies in animals suggest that [aripiprazole](#) acts as a dopamine-D2 agonist on dopaminergic neurons of the ventral tegmental area, and as a dopamine-D2 (and possibly D3) antagonist on striatal neurons and nucleus accumbens neurons [175].

4) In a small magnetoencephalographic study involving schizophrenic patients (n=5), treatment with [aripiprazole](#) for two months was associated with a decrease (normalizing effect) of abnormal delta and theta activity, loosely correlating with decreases in Positive and Negative Syndrome Scale (PANSS) scores [178].

## 4.5] Therapeutic Uses

### 4.5.1] FDA Uses

#### 4.5.1.A] Autistic disorder - Psychomotor agitation

FDA Labeled Indication

1) Overview

FDA Approval: Adult, no; [Pediatric, yes \(age 6 to 17 years; oral only\)](#)

Efficacy: Pediatric, Evidence favors efficacy

Recommendation: **Pediatric, Class IIb**

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**2) Summary:**

Evidence

In patients 6 to 17 years with [autistic disorder](#) (N=98), doses up to 15 mg/day (mean, 8.6 mg/day) improved Aberrant Behavior Checklist (ABC)-Irritability subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods [6]. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 for placebo. Clinical Global Impressions (CGI)-Improvement scores were significantly improved 2.6 points for 5 mg/day, 2.5 for 10 mg/day, and 2.5 for 15 mg/day compared with 3.3 for placebo. At the higher doses, ABC Stereotypy, Hyperactivity, CGI-S scores, and other secondary measures were also improved (N=218) [7].

**4.5.1.B) Bipolar disorder - Psychomotor agitation**

FDA Labeled Indication

**1) Overview**

FDA Approval: Adult, yes (immediate-release injectable only); **Pediatric, no**

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**2) Summary:**

Product Availability

The marketing and distribution of [Abilify\(R\)](#) immediate-release [injection for IM](#) use has been discontinued, with estimated product availability until 06/15/15. This decision is not related to product safety or efficacy [31].

Indication

[Aripiprazole](#) immediate-release injection is approved for the treatment of agitation associated with [schizophrenia](#) and [bipolar disorder](#), manic or mixed [35].

Evidence

In patients with mostly moderate levels of agitation associated with bipolar I disorder (manic or mixed), Positive and Negative Syndrome Scale-Excited Component and Clinical Global Impression of Improvement scale scores were significantly improved at 2 hours postinjection with both 9.75 and 15 mg of IM [aripiprazole](#) compared with placebo, but there was no additional benefit with 15 mg [32].

#### 4.5.1.C] Bipolar I disorder, Adjunctive therapy with lithium or valproate

##### FDA Labeled Indication

###### 1) Overview

FDA Approval: Adult, yes (oral only); [Pediatric, yes \(10 to 17 years; oral only\)](#)

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; [Pediatric, Class IIb](#)

Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

###### 2) Summary:

###### Indication

[Aripiprazole](#) is indicated for use in adults and children aged 10 years or older as adjunctive therapy with [lithium](#) or [valproate](#) for acute and maintenance treatment of bipolar I disorder [23][24].

###### Evidence (Adult)

In patients partially nonresponsive to monotherapy (N=384), addition of [aripiprazole](#) to [valproate](#) or [lithium](#) significantly decreased Young Mania Rating Scale (YMRS) total score a mean 13.3 compared with 10.7 for add-on placebo. Improvement was seen as early as week 1. Clinical Global Impression Bipolar Version (CGI-BP) severity of illness (mania) score was significantly reduced by 1.9 compared with 1.6 for placebo. Fewer patients experienced emergent depression with [aripiprazole](#) (7.7% vs 16.9%) [25].

Overall [relapse](#) risk was significantly reduced by 46% and manic [relapse](#) risk by 65% compared with placebo. Patients were in remission for 12 weeks with [aripiprazole](#) plus [valproate](#) or [lithium](#) and continued on [aripiprazole](#) or switched to placebo for 52 weeks or until [relapse](#) (N=337). There was no significant difference for depressive [relapse](#), but time to [relapse](#) of any mood event was longer with [aripiprazole](#) [26].

###### Evidence (Pediatric)

[Efficacy of adjunctive aripiprazole for maintenance therapy was extrapolated from adult data with additional pharmacokinetic comparisons in adult and pediatric patients \[11\]\[12\].](#)

#### 4.5.1.D] Bipolar I disorder, Monotherapy, manic or mixed episodes

##### FDA Labeled Indication

###### 1) Overview

FDA Approval: Adult, yes (oral only); **Pediatric, yes (age 10 to 17 years; oral only)**

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; **Pediatric, Class IIb**

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

## 2) Summary:

### Indication

[Aripiprazole](#) is indicated for the acute and maintenance treatment of manic and mixed episodes associated with bipolar I disorder in adults and pediatric patients aged 10 to 17 years [23][24].

### Evidence (Adult)

In the treatment of acute manic or mixed episodes in patients with [bipolar disorder](#) (N=262), Young Mania Rating Scale (YMRS) total score was reduced a mean 8.2 for patients receiving [aripiprazole](#) compared with 3.4 receiving placebo; 40% of patients receiving [aripiprazole](#) had at least a 50% reduction, significantly more than 19% receiving placebo. Significant improvement was observed as early as day 4 [27]. Patients who achieved stabilization during open-label oral [aripiprazole](#) 15 to 30 mg for 6 to 18 weeks continued on the same dose or were switched to placebo (N=161). Risk of [relapse](#) for a manic, depressive, or mixed mood episode was significantly reduced by 48%, and [relapse](#) rates were 25% with [aripiprazole](#) compared with 43% with placebo. Time to [relapse](#) of [manic episodes](#) was significantly delayed, but [depressive episodes](#) were not. The overall discontinuation rate was 58%; 19 [aripiprazole](#) patients stopped due to lack of efficacy [28].

### Evidence (Pediatric)

[Aripiprazole](#) improved manic symptomatology compared with placebo (N=296) in patients 10 to 17 years old [29]. Decreases in mean YMRS (23.8 to 8.5) and Clinical Global Impressions Scale-Severity (4 to 1.9) scores occurred in patients 4 to 9 years old with [bipolar disorder](#) (N=96) during an open-label, flexible dose (mean, 6.5 mg/day) study. Weight gain increased significantly from a mean 26.9 to 29.3 kg [30].

## **4.5.1.E| Gilles de la Tourette's syndrome**

### FDA Labeled Indication

#### 1) Overview

FDA Approval: Adult, no; **Pediatric, yes (6 to 18 years, oral only)**

Efficacy: Pediatric, Evidence favors efficacy

Recommendation: **Pediatric, Class IIb**

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

## 2) Summary:

### Evidence

[Aripiprazole](#) significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in a randomized, 10-week trial of patients aged 6 to 18 years with [Tourette disorder](#) (N=61). The response rate (score of 1 or 2 on the [Tourette's syndrome](#) CGI-Improvement scale) was 65.5% vs 44.8%, respectively [5]. The mean [aripiprazole](#) dose was 6.5 mg. In a similar 8-week trial in patients aged 7 to 17 years (N=133) who received weight-based [aripiprazole](#), significant improvements compared with placebo were seen on YGTSS-TTS (-13.4 and -16.9 with low- and high-dose [aripiprazole](#) compared with -7.1 in placebo) [3][4].

### Limitations of Use

The efficacy of maintenance treatment has not been established in pediatric patients [3][4].

#### 4.5.1.F] Major depressive disorder, Adjunctive treatment in patients receiving antidepressants

### FDA Labeled Indication

#### 1) Overview

FDA Approval: Adult, yes (oral only); [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

## 2) Summary:

### Evidence

Compared with placebo, [aripiprazole](#) added to current antidepressant therapy was superior in reducing mean Montgomery-Asberg Depression Rating Scale (MADRS) total scores (2 studies, N=381) and the mean Sheehan Disability Scale score (1 study, N=362). The mean reduction in total MADRS score was smaller in men than in women [11][12]. In a pooled analysis of 3 studies (N=409), add-on to current antidepressant therapy in adults 50 to 67 years decreased mean MADRS scores by 10 points compared with 6.4 points for placebo, and 39.7% had decreases of at least 50% compared with 24.4% for placebo. The discontinuation rate was 5.7% for [aripiprazole](#) compared with 2% for placebo [13].

### Limitations of Use

Long-term efficacy has not been established [6].

#### 4.5.1.G] Psychomotor agitation - Schizophrenia

## FDA Labeled Indication

### 1) Overview

FDA Approval: Adult, yes (immediate-release injectable only); **Pediatric, no**

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

### 2) Summary:

#### Product Availability

The marketing and distribution of [Abilify\(R\)](#) immediate-release [injection for IM](#) use has been discontinued, with estimated product availability until 06/15/15. This decision is not related to product safety or efficacy [31].

#### Indication

[Aripiprazole](#) immediate-release injection is approved for agitation associated with [schizophrenia](#) and [bipolar disorder](#), manic or mixed [32].

#### Evidence

The Positive and Negative Syndrome Scale-Excited Component (PEC) score from baseline to 2 hours was significantly improved with [aripiprazole](#) 5.25, 9.75, and 15 mg compared with placebo for treatment of acute agitation in patients with [schizophrenia](#), [schizoaffective disorder](#), or [schizophreniform disorder](#) (N=357); significant difference was observed as early as 45 minutes, and the Agitation-Calmness Evaluation Scale score was significantly improved at 2 hours with the 9.75-mg dose vs placebo [33]. The 9.75-mg dose was also noninferior to IM [haloperidol](#) and superior to placebo in voluntarily hospitalized agitated patients; a decrease in PEC score of 40% or greater at 2 hours after the first injection occurred in 55% receiving [aripiprazole](#), 58% receiving [haloperidol](#), and 36% receiving placebo. Second injections were required in 41% receiving [aripiprazole](#) compared with 57% receiving placebo [34].

### 4.5.1.H] Schizophrenia

## FDA Labeled Indication

### 1) Overview

FDA Approval: Adult, yes (Oral and extended-release [IM injection](#) only); **Pediatric, yes (13 to 17 years, oral only)**

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; **Pediatric, Class IIb**

Strength of Evidence: Adult, Category B; Pediatric, Category B



See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

## 2) Summary:

### Evidence (Adults)

Time to [relapse](#) was longer, and 33.8% of stable patients with [chronic schizophrenia](#) (N=310) relapsed with oral [aripiprazole](#) compared with 57% with placebo at 26 weeks, a significant 41% decrease in relative risk. Other measures improved, including Positive and Negative Syndrome Scale (PANSS) total and subscale scores, Clinical Global Impression-Improvement (CGI-I) score, and the CGI-Severity (CGI-S) score (Pigott et al, 2003) [15]. Previous studies found similar results [16]. Similar results occurred with maintenance therapy in patients initially stabilized on oral followed by extended-release IM [aripiprazole](#) (16 to 48 weeks total; N=403) then continued at the same IM dose or switched to placebo. Risk of [relapse](#) over the course of the study was 403% higher with placebo. Mean PANSS total scores were maintained with [aripiprazole](#) [17].

In adults with acute exacerbation of psychotic symptoms, monthly [IM injections](#) of long-acting [aripiprazole](#) plus 2 weeks of oral [aripiprazole](#) to establish blood levels significantly decreased the least squares mean change from baseline in PANSS total score compared with placebo at week 10 (-26.8 vs -11.7) in a 12-week, randomized trial (N=340). The change in CGI-S score at week 10 was also significant for [aripiprazole](#) (-1.4 vs -0.6). PANSS total score, CGI-I, and PANSS positive and negative subscale scores were all significantly improved with [aripiprazole](#) at all time points through week 12 compared with placebo [18].

### Evidence (Pediatric)

Improvement in PANSS total scores at both the 10- and 30-mg dose was significant in outpatients 13 to 17 years old compared with placebo, but 30 mg was not superior to 10 mg (6-week study; N=302) [11][12].

## 4.5.2] Non FDA Uses

### 4.5.2.A] Borderline personality disorder

#### 1) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

#### 2) Summary:

### Evidence (Monotherapy)

Short-term [aripiprazole](#) was more effective than placebo in reduction of symptoms, including affective dysregulation, aggressive impulsivity, and cognitive perceptual impairment in an 8-week, randomized and blinded trial (N=52). See results table 1 below, noting that relationship disruption was not evaluated [8]. During an 18-month open-label extension of all original subjects, efficacy persisted. See results table 2 below. Self injury occurred in 4 patients treated only with [aripiprazole](#) and in 11 patients who were ex-placebo. Two ex-placebo attempted suicide [10].

### Evidence (Combination Therapy)

In an open-label study (N=21), [aripiprazole](#) added to [sertraline](#) significantly improved Clinical Global Impression Scale-Severity and Brief Psychiatric Rating Scale scores, but not the Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Social Occupational Functioning Assessment Scale, or other items of the [Borderline Personality Disorder](#) Severity Index [9].

### 3) Adult:

Table 1: Mean Outcome Scores for the [Symptom Checklist](#), HAM-D, HAM-A and STAXI at Week 8

| Outcome                      | Mean Score*    |                  |                   |              |
|------------------------------|----------------|------------------|-------------------|--------------|
|                              | Som SCL-90-R   | OCD SCL-90-R     | ISC SCL-90-R      | DEP SCL-90-R |
| <a href="#">Aripiprazole</a> | 62.5*          | 55.2             | 59.7              | 56.8         |
| Placebo                      | 65.4           | 58.6             | 64.2              | 73.2         |
|                              | ANX SCL-90-R   | AGG/HOS SCL-90-R | PHOB/ANX SCL-90-R | PAR SCL-90-R |
| <a href="#">Aripiprazole</a> | 61.1           | 64.6             | 61.4              | 60.2         |
| Placebo                      | 70.2           | 73.1             | 67.1              | 68.3         |
|                              | PSYCH SCL-90-R | HAM-D            | HAM-A             | State Anger  |
| <a href="#">Aripiprazole</a> | 54.3           | 13.9             | 16.3              | 18.5         |
| Placebo                      | 60.5           | 18.8             | 19.5              | 26.2         |
|                              | Trait Anger    | Anger In         | Anger Out         | Anger Cont   |
| <a href="#">Aripiprazole</a> | 18.1           | 16.3             | 14.3              | 22.1         |
| Placebo                      | 24             | 20.5             | 20.7              | 19.4         |

KEY: Som = somatization; OCD = obsessiveness/compulsiveness; ISC = insecurity in social contacts; DEP = depression; ANX = anxiety; AGG/HOS = aggression/hostility; PHOB/ANX = phobic anxiety; PAR = paranoid thinking; PSYCH = [psychoticism](#); HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; STAXI = [State-Trait Anger Expression Inventory](#)  
 \* Only the Som SCL-90-R score difference from placebo was not significant.

Table 2: Mean Outcome Scores For [Symptom Checklist](#), HAM-D, HAM-A, and STAXI at 18 months

| Marker                                 | <a href="#">Aripiprazole</a> * | Ex-placebo** |
|--|--------------------------------|--------------|
| SCL-90-R, somatization                 | 59                             | 69.1         |
| SCL-90-R, obsessive/compulsiveness     | 53.1                           | 61.4         |
| SCL-90-R, insecurity in social contact | 57.2                           | 67           |
| SCL-90-R, depression                   | 45                             | 77           |
| SCL-90-R, anxiety                      | 58                             | 73.1         |
| SCL-90-R, hostility/aggression         | 61.7                           | 75.2         |
| SCL-90-R, phobic anxiety               | 60                             | 70.2         |
| SCL-90-R, paranoid thinking            | 58.8                           | 70.3         |
| SCL-90-R, <a href="#">psychoticism</a> | 52.5                           | 64           |
| HAM-A                                  | 13.9                           | 20.6         |
| HAM-D                                  | 12                             | 19.1         |
| STAXI                                  | all scales                     | all scales   |

KEY: (SCL-90-R) = [symptom checklist](#) 90-R, (HAM-A) = Hamilton Anxiety Rating

Scale, (HAM-D) Hamilton Depression Rating Scale; (STAXI) = [State-Trait Anger Expression Inventory](#).

\* All measures were significantly different from placebo.

\*\* Ex-placebo patients were on placebo during the original 8-week study; they received no study drug or placebo during the open-label extension study.

#### 4.5.2.B| [Dementia](#)

See Drug Consult reference: Behavioral and Psychological Symptoms of [Dementia](#)

#### 4.5.2.C| [Drug-induced hyperprolactinemia, Caused by antipsychotics](#)

##### 1| Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### 2| Summary:

##### Evidence

In a meta-analysis of 5 randomized trials including 639 patients, treatment with adjunctive [aripiprazole](#) resulted in 125 prolactin level normalization events compared with 7 with placebo (a significant 24% reduction in the risk of [hyperprolactinemia](#)) without significantly increasing adverse events or discontinuation rates. When data was analyzed excluding [aripiprazole](#) doses greater than 5 mg/day, the prolactin normalization events were 103 compared with 6 events with placebo. [Aripiprazole](#) did not improve psychiatric symptoms [2].

### 4.6| Comparative Efficacy / Evaluation With Other Therapies

#### 4.6.A| [Chlorpromazine](#)

##### 4.6.A.1| [Schizophrenia](#)

a) Based upon comparisons of minimum effective dosages identified in placebo-controlled, fixed-dose and fixed-dose-ranging drug development trials, the minimum effective dose of [aripiprazole](#) was 15 milligrams/day (equivalent to [chlorpromazine](#) 200 milligrams/day) (Woods SW, 2003).

#### 4.6.B| [Haloperidol](#)

##### 4.6.B.1| [Delirium](#)

a) In a study of adults with [cancer](#) who developed [delirium](#) while hospitalized (N=84; mean age, 64 years; 26% with concurrent [dementia](#)) that compared [haloperidol](#) with atypical antipsychotics, [aripiprazole](#), [olanzapine](#), or [risperidone](#), all treatments significantly reduced the Memorial [Delirium](#) Assessment Scale

score from baseline, with no difference between treatments. There were also no between-group differences in [delirium](#) resolution rates at 2 to 3 days (42.9% to 52.4%) or 4 to 7 days (61.9% to 85.7%) following diagnosis. Mean daily doses were [haloperidol](#) 5.5 mg, [risperidone](#) 1.3 mg, [aripiprazole](#) 18.3 mg, and [olanzapine](#) 7.1 mg. Significant increases in side effects included [parkinsonism](#) (19% with [haloperidol](#) and 4.8% with [risperidone](#)) and sedation (28.6% with [olanzapine](#)) [185].

#### 4.6.B.2] Schizophrenia

a) SUMMARY: [Aripiprazole](#) (up to 30 mg daily) and [haloperidol](#) (up to 20 mg daily) appear similarly effective in patients with acutely relapsed [schizophrenia](#) or [schizoaffective disorder](#); adverse effects may be less with [aripiprazole](#).

b) [Haloperidol](#) 5 to 20 mg daily, but not [aripiprazole](#) (5 to 30 mg daily), was superior to placebo with respect to improvement in BPRS scores in a 4-week study involving acutely relapsed inpatients with DSM-III/IV [schizophrenia](#) (n=103). Both [haloperidol](#) and [aripiprazole](#) were more effective than placebo in responder analysis based on CGI-severity scores (Prod Info [Abilify](#)(TM), 2002).

c) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (n=414), [aripiprazole](#) 15 or 30 mg daily and [haloperidol](#) 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in PANSS-total and BPRS-total scores; based on responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit), each dose of [aripiprazole](#) was significantly more effective than placebo, whereas [haloperidol](#) was not. There was evidence of better tolerability with [aripiprazole](#) compared to [haloperidol](#) (eg, [benztropine](#) requirements for extrapyramidal effects, prolactin increases, weight increase). Extrapyramidal symptoms were reportedly similar with [aripiprazole](#) and placebo, and fewer patients receiving [aripiprazole](#) discontinued treatment due to adverse events compared to [haloperidol](#) and placebo [186]. However, this study did not report statistical comparisons of [aripiprazole](#) and [haloperidol](#) for any parameter (efficacy versus baseline or adverse effects); responder-analysis data revealed only a small difference between the two drugs. Overall, this study does not provide evidence that [aripiprazole](#) is significantly more efficacious than [haloperidol](#).

d) Results of phase II studies also suggested fewer adverse effects with [aripiprazole](#) compared to [haloperidol](#) [187][188]. In these studies, lower changes from baseline in Simpson-Angus Scale scores (parkinsonian symptoms) and less requirement for [benztropine](#) were observed with all doses of [aripiprazole](#) (2, 10, or 30 mg daily) than with [haloperidol](#) 10 mg daily; prolactin levels were not increased by [aripiprazole](#), compared to significant increases with [haloperidol](#), and significantly less weight gain was evident in the [aripiprazole](#) groups (all doses). Comparative efficacy data were not presented.

#### 4.6.C] Olanzapine

##### 4.6.C.1] Delirium

a) In a study of adults with [cancer](#) who developed [delirium](#) while hospitalized (N=84; mean age, 64 years; 26% with concurrent [dementia](#)) that compared [haloperidol](#) with atypical antipsychotics, [aripiprazole](#), [olanzapine](#), or [risperidone](#), all treatments significantly reduced the Memorial [Delirium](#) Assessment Scale score from baseline, with no difference between treatments. There were also no between-group differences in [delirium](#) resolution rates at 2 to 3 days (42.9% to 52.4%) or 4 to 7 days (61.9% to 85.7%) following diagnosis. Mean daily doses were [haloperidol](#) 5.5 mg, [risperidone](#) 1.3 mg, [aripiprazole](#) 18.3 mg, and [olanzapine](#) 7.1 mg. Significant increases in side effects included [parkinsonism](#) (19% with [haloperidol](#) and 4.8% with [risperidone](#)) and sedation (28.6% with [olanzapine](#)) [185].

#### 4.6.D] Paliperidone

##### 1) Adverse Effects

a) In a 52-week, randomized study of outpatient adults with first-episode [schizophrenia](#) (N=254; mean age 26.4 years), [metabolic syndrome](#) occurred in 15.5% treated with [aripiprazole](#), 9% treated with [ziprasidone](#), and 8% treated with [paliperidone](#) extended-release. Mean daily treatment doses at week 52 were [aripiprazole](#) 14.5 mg, [paliperidone](#) 6.4 mg, and [ziprasidone](#) 28.4 mg. [Aripiprazole](#) significantly increased body weight (+3.1 kg), fasting blood glucose, and [HbA1c](#) compared with baseline values, and significantly more so than the other 2 treatment groups. [LDL](#) and [triglycerides](#) were significantly increased from baseline in both the [paliperidone](#) and [aripiprazole](#) groups and were significantly increased compared with [ziprasidone](#). There were no changes in the [ziprasidone](#) group in glucose or lipid parameters, and no difference in waist circumference in any treatment group [189].

#### 4.6.E] [Paliperidone](#) Palmitate

##### 4.6.E.1] [Schizophrenia](#)

a) In the 28-week randomized QUALIFY trial in adults with [schizophrenia](#) (N=295), once-monthly injections of [aripiprazole](#) compared with [paliperidone](#) palmitate met non-inferiority criteria and demonstrated significant improvement on the Heinrichs-Carpenter Quality-of-Life Scale (QLS; mean change from baseline, 7.47 vs 2.8), the Clinical Global Impression-Severity Scale (CGI-S), and the Investigator's Assessment Questionnaire (IAQ). The between-group difference in QLS total score change from baseline (4.67) may not be a clinically meaningful difference. In predefined subgroup analysis, [aripiprazole](#) significantly improved CGI-S and IAQ in patients aged 35 years or less, while patients aged over 35 years had no significant improvements on QLS, CGI-S, or IAQ. [Paliperidone](#) was associated with a higher incidence of treatment-emergent adverse events leading to discontinuation (11.9% vs 5) [183].

#### 4.6.F] [Perphenazine](#)

##### 4.6.F.1] [Schizophrenia](#), Treatment resistant

a) Both [aripiprazole](#) and [perphenazine](#) improved symptoms associated with treatment-resistant [schizophrenia](#) in a randomized, double-blind, multicenter study. Patients (n=416) with treatment-resistant [schizophrenia](#) (ie, failure of at least 2 trials of antipsychotic therapy of at least 6 weeks in duration in the last 2 years) with a Positive and Negative Syndrome Scale (PANSS) total score of at least a 75, a score greater than or equal to 4 on at least 2 of the items of conceptual disorganization, suspiciousness, hallucinatory behavior, or delusions, and a Clinical Global Impressions-Severity of Illness (CGI-S) score of 4 or greater. After a 2-day washout period, patients entered a 4 to 6 week open-label treatment phase receiving [olanzapine](#) 10 to 20 milligrams/day (mg/day) or [risperidone](#) 2 to 8 mg/day to confirm treatment resistance. At the end of this open-label screening period, 300 patients entered a 2 to 10 day placebo washout period then were randomized to 6 weeks of treatment with [aripiprazole](#) 15 to 30 mg/day or [perphenazine](#) 8 to 64 mg/day. The primary endpoint was mean change in PANSS score during the 6-week double-blind treatment period. In the [aripiprazole](#) group, the mean decrease in PANSS score was 9.8 points (95% confidence interval (CI), -13.2 to -6.3) from a mean total baseline score of 97.5 (95% CI, 95 to 100). In the [perphenazine](#) group, the mean decrease in PANSS total score was 10.5 points (95% CI, -14 to -7) from a mean total baseline score of 99.5 (95% CI, 97 to 102.1). The difference between groups was not statistically significant (p-value not reported). At the end of 6 weeks, 27% (40/150) of patients responded to [aripiprazole](#) and 25% (36/144) of patients responded to [perphenazine](#) treatment, with response defined as at least a 30% decrease in PANSS total score or a CGI-S score of 1 or 2. Extrapyramidal symptoms were reported in 13.7% (n=21) of patients in the [aripiprazole](#) group and 19.4% (n=28) of patients in the [perphenazine](#) group. Serious adverse events were reported in 21% (n=32) and 17% (n=24) of patients treated with [aripiprazole](#) and [perphenazine](#), respectively, with the most common being [psychosis](#) (9.8% and 6.3%, respectively) [184].

## 4.6.G] Risperidone

### 4.6.G.1] Autistic disorder - Psychomotor agitation

a) There were no significant differences between aripiprazole and risperidone treatment at 2 months when evaluated by Aberrant Behavior Checklist subscale scores (irritability and agitation, lethargy and social withdrawal, stereotypic behavior, hyperactivity and noncompliance, and inappropriate speech) in a randomized trial of pediatric patients 4 to 18 years old (N=59; mean age about 9.5 years) with autism spectrum disorder. Additionally, there were no significant between-group differences seen on the Clinical Global Impression-Improvement scale or in adverse events, including weight gain. Mean doses during the first and second months of treatment were 4.6 and 5.5 mg of aripiprazole, and 1.09 and 1.12 mg of risperidone. Treatment discontinuations occurred due to exacerbated epilepsy in 1 patient receiving aripiprazole and severe crying and agitation in 1 patient receiving risperidone [190].

### 4.6.G.2] Delirium

a) In a study of adults with cancer who developed delirium while hospitalized (N=84; mean age, 64 years; 26% with concurrent dementia) that compared haloperidol with atypical antipsychotics, aripiprazole, olanzapine, or risperidone, all treatments significantly reduced the Memorial Delirium Assessment Scale score from baseline, with no difference between treatments. There were also no between-group differences in delirium resolution rates at 2 to 3 days (42.9% to 52.4%) or 4 to 7 days (61.9% to 85.7%) following diagnosis. Mean daily doses were haloperidol 5.5 mg, risperidone 1.3 mg, aripiprazole 18.3 mg, and olanzapine 7.1 mg. Significant increases in side effects included parkinsonism (19% with haloperidol and 4.8% with risperidone) and sedation (28.6% with olanzapine) [185].

## 4.6.H] Ziprasidone Hydrochloride

### 1) Adverse Effects

a) In a 52-week, randomized study of outpatient adults with first-episode schizophrenia (N=254; mean age 26.4 years), metabolic syndrome occurred in 15.5% treated with aripiprazole, 9% treated with ziprasidone, and 8% treated with paliperidone extended-release. Mean daily treatment doses at week 52 were aripiprazole 14.5 mg, paliperidone 6.4 mg, and ziprasidone 28.4 mg. Aripiprazole significantly increased body weight (+3.1 kg), fasting blood glucose, and HbA1c compared with baseline values, and significantly more so than the other 2 treatment groups. LDL and triglycerides were significantly increased from baseline in both the paliperidone and aripiprazole groups and were significantly increased compared with ziprasidone. There were no changes in the ziprasidone group in glucose or lipid parameters, and no difference in waist circumference in any treatment group [189].

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