

DRUGDEX-EV 2413

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QUETIAPINE

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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)] [Quetiapine](#) Fumarate

1] Adult

a)] [quetiapine](#) regular-release may be switched to [quetiapine](#) extended-release at the equivalent total daily dose taken once daily; individual dosage adjustments may be required [2]

b)] reinitiation of therapy: if less than 1 week off of [quetiapine](#), titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of [quetiapine](#), initial titration schedule should be followed [2] [6]

1] Bipolar disorder, depressed phase, Monotherapy in acute management

a)] regular-release tablets, 50 mg ORALLY once daily on day 1, 100 mg once daily on day 2, 200 mg once daily on day 3, and then 300 mg once daily on day 4, with all doses given at bedtime; usual recommended and MAX dose is 300 mg/day [6]

b)] extended-release tablets, 50 mg ORALLY once daily on day 1, 100 mg once daily on day 2, 200 mg once daily on day 3, and then 300 mg once daily on day 4, with doses given in the evening; usual recommended and MAX dose is 300 mg/day [2]

2] Bipolar disorder, Maintenance, in combination with lithium or divalproex; Adjunct

a) regular-release tablets, 400 mg to 800 mg per day ORALLY divided twice daily, generally continuation of stabilization dose; MAX 800 mg/day; periodically reassess for need and appropriate dose for maintenance treatment [6]

b) extended-release tablets, 400 mg to 800 mg ORALLY once daily in the evening; MAX 800 mg/day; periodically reassess for need and appropriate dose for maintenance treatment [6]

3) Major depressive disorder; Adjunct

a) extended-release tablets, initial 50 mg ORALLY once daily in the evening; increase to 150 mg once daily in the evening on day 3; recommended dosage range is 150 to 300 mg/day; MAX 300 mg/day [2]

4) Manic bipolar I disorder, Acute management; Adjunct

a) regular-release tablets, 100 mg ORALLY divided twice daily on day 1; 200 mg divided twice daily on day 2; 300 mg divided twice daily on day 3; 400 mg divided twice daily on day 4; with further dosage adjustments in increments of not more than 200 mg/day up to MAX 800 mg/day by day 6; usual effective dose is 400 to 800 mg/day [6]

b) extended-release tablets, 300 mg ORALLY in the evening on day 1; 600 mg in the evening on day 2; with further dosage adjustment to usual maintenance dose between 400 and 800 mg once daily beginning on day 3, depending on patient response and tolerance; MAX dose 800 mg/day [2]

5) Manic bipolar I disorder, Monotherapy in acute management

a) regular-release tablets, 100 mg ORALLY divided twice daily on day 1; 200 mg divided twice daily on day 2; 300 mg divided twice daily on day 3; 400 mg divided twice daily on day 4; with further dosage adjustments in increments of not more than 200 mg/day up to MAX 800 mg/day by day 6; usual effective dose is 400 to 800 mg/day [6]

b) extended-release tablets, 300 mg ORALLY in the evening on day 1; 600 mg in the evening on day 2; with further dosage adjustment to usual maintenance dose between 400 and 800 mg once daily beginning on day 3, depending on patient response and tolerance; MAX dose 800 mg/day [2]

6) Schizophrenia

a) regular-release tablets, 25 mg ORALLY twice daily on day 1 and increase total daily dosage by 25 to 50 mg divided into 2 to 3 doses on days 2 and 3, to achieve a target dose of 300 to 400 mg by day 4; further dosage adjustment should generally occur in increments of 25 to 50 mg twice daily at intervals of

no less than 2 days, up to a MAX 750 mg/day; usual effective dose is 150 to 750 mg/day [6]

b) extended-release tablets, 300 mg ORALLY in the evening on day 1 and titrate to usual maintenance dose between 400 to 800 mg once daily; dose increases may occur at intervals of at least 1 day in increments of up to 300 mg/day; MAX dose 800 mg/day [2]

7) Schizophrenia, Maintenance

a) regular-release tablets (unapproved use), 400 mg to 800 mg per day ORALLY divided twice daily has been recommended [6]

b) extended-release tablets, 400 to 800 mg ORALLY once daily in the evening; generally continuation of stabilization dose; MAX 800 mg/day; periodically reassess for need and appropriate dose for maintenance treatment [2]

2) Pediatric

a) [quetiapine](#) regular-release may be switched to [quetiapine](#) extended-release at the equivalent total daily dose taken once daily; individual dosage adjustments may be required [2]

b) reinitiation of therapy: if less than 1 week off of [quetiapine](#), titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of [quetiapine](#), initial titration schedule should be followed [2] [6]

c) safety and efficacy of [quetiapine](#) not established in pediatric patients younger than 10 years [2] [6]

1) Manic bipolar I disorder, Monotherapy in acute management

a) initiate medication therapy only after thorough diagnostic evaluation; total treatment program includes medication and psychological, educational, and social interventions [6] [2]

b) 10 to 17 years of age, regular-release tablets, 25 mg ORALLY twice daily on day 1, 100 mg divided twice daily on day 2; 200 mg divided twice daily on day 3; 300 mg divided twice daily on day 4; 400 mg divided twice daily on day 5; with further dosage adjustments in increments of not more than 100 mg/day up to MAX 600 mg/day; usual effective dose is 400 to 600 mg/day; depending upon tolerability, may be administered 3 times daily [6]

c) 10 to 17 years, extended-release tablets, 50 mg ORALLY in the evening on day 1; 100 mg on day 2; 200 mg on day 3; 300 mg on day 4; 400 mg on day 5; with further dosage adjustment to usual maintenance dose between 400 and 600 mg once daily depending on patient response and tolerance; MAX dose 600 mg/day [2]

2) Schizophrenia

a) initiate medication therapy only after thorough diagnostic evaluation; total treatment program includes medication and psychological, educational and social interventions [6] [2]

b) 13 to 17 years, regular-release tablets, 25 mg ORALLY twice daily on day 1, 100 mg divided twice daily on day 2; 200 mg divided twice daily on day 3; 300 mg divided twice daily on day 4; 400 mg divided twice daily on day 5; with further dosage adjustments in increments of not more than 100 mg/day up to MAX 800 mg/day; usual effective dose is 400 to 800 mg/day; depending upon tolerability, may be administered 3 times daily [6]

c) 13 to 17 years, extended-release tablets, 50 mg ORALLY in the evening on day 1; 100 mg on day 2; 200 mg on day 3; 300 mg on day 4; 400 mg on day 5; with further dosage adjustment to usual maintenance dose between 400 and 800 mg once daily depending on patient response and tolerance; MAX dose 800 mg/day [2]

3) Contraindications

a) Quetiapine Fumarate

1) hypersensitivity to [quetiapine](#) or any component of the product [6] [2]

2) [anaphylactic reactions](#) have been reported [6] [2]

4) Serious Adverse Effects

a) Quetiapine Fumarate

1) [Agranulocytosis](#)

2) [Anaphylaxis](#)

3) [Diabetic ketoacidosis](#)

4) [Leukopenia](#)

5) [Neuroleptic malignant syndrome](#)

6) [Neutropenia](#)

7) [Pancreatitis](#)

8) [Priapism](#)

9) Prolonged QT interval

10) Seizure

11) Sudden cardiac death

12) Suicidal thoughts

13) Syncope

14) Tardive dyskinesia

5) Clinical Applications

a) Quetiapine Fumarate

1) FDA Approved Indications

- a) Bipolar disorder, depressed phase, Monotherapy in acute management
- b) Bipolar disorder, Maintenance, in combination with lithium or divalproex; Adjunct
- c) Major depressive disorder; Adjunct
- d) Manic bipolar I disorder, Acute management; Adjunct
- e) Manic bipolar I disorder, Monotherapy in acute management
- f) Schizophrenia
- g) Schizophrenia, Maintenance

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

Quetiapine

Quetiapine Fum

Quetiapine Fumarate

C) Physicochemical Properties

1) Molecular Weight

a) Quetiapine fumarate: 883.11 [29]

2) Solubility

a) Quetiapine fumarate is moderately soluble in water [29].

1.2] Storage and Stability

A) Quetiapine Fumarate

1) Preparation

a) Oral route

1) Administration

a) Quetiapine extended-release tablets should not be chewed, crushed, or split and should be swallowed whole [2].

b) The absorption of extended-release quetiapine tablets is affected by food; give without food or with a light meal of approximately 300 Calories [2]. Regular-release tablets are only marginally affected by food, and may be given without regard to food [6].

B) Quetiapine Fumarate

1) Oral route

a) Tablet/Tablet, Extended Release

1) Store at 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [185] [186].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Quetiapine Fumarate

1.3.1.A.1] Oral route

1.3.1.A.1.a] Bipolar disorder, depressed phase, Monotherapy in acute management

1) Regular-Release

a) The recommended dose titration is 50 mg, 100 mg, 200 mg, and 300 mg given once a day at bedtime on days 1 through 4, respectively. The usual recommended and maximum dose is 300 mg/day. In clinical trials, both 300 mg and 600 mg doses demonstrated antidepressant efficacy; however, no greater benefit was seen in the 600 mg group [6].

b) When restarting treatment in patients who have had an interval of less than 1 week off of quetiapine, titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule should be followed when reinitiating therapy in patients who have not taken quetiapine for more than 1 week [6].

2) Extended-Release

a) The recommended dose titration is 50 mg, 100 mg, 200 mg, and 300 mg given once a day in the evening on days 1 through 4, respectively. The usual recommended and maximum dose is 300 mg/day [2].

b) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule for acute treatment should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [2].

1.3.1.A.1.b) Bipolar disorder, Maintenance, in combination with lithium or divalproex; Adjunct

1) Regular-Release

a) The recommended dosage is 400 to 800 mg/day orally, divided, and given twice daily. Maximum dose is 800 mg/day. Generally, patients should be continued on their stabilization dose with periodic reassessment for need and appropriate dose for maintenance treatment [6].

b) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule for acute treatment should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [6].

2) Extended-Release

a) The recommended dosage is 400 to 800 mg orally once daily, given in the evening. Maximum dose is 800 mg/day. Generally, patients should be continued on the stabilization dose with reassessment for need and appropriate dose for maintenance treatment [2].

b) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule for acute treatment should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [2].

1.3.1.A.1.c) Major depressive disorder; Adjunct

1) Extended-Release

a) The recommended dosage is 150 to 300 mg/day. Initiate therapy with 50 mg once daily in the evening and increase the dose to 150 mg once daily in the evening on day 3. Doses above 300 mg/day were not evaluated [2].

b) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule for acute treatment should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [2].

1.3.1.A.1.d) Manic bipolar I disorder, Acute management; Adjunct

1) Regular-Release

a) The recommended initial dose is 100 mg/day (in 2 divided doses) on day 1, increased to 400 mg/day on day 4 in increments of up to 100 mg/day (in 2 divided doses). Additional dosage adjustments up to 800 mg/day by day 6 should be made in increments of no more than 200 mg/day. Most patients respond to doses between 400 to 800 mg/day. The maximum dose is 800 mg/day [6].

b) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [6].

2) Extended-Release

a) The recommended initial dose is 300 mg in the evening on day 1 and 600 mg on day 2. Adjust the dose between 400 and 800 mg daily beginning on day 3, depending on patient response and tolerance. The maximum dose is 800 mg/day [2].

b) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule for acute treatment should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [2].

1.3.1.A.1.e] Manic bipolar I disorder, Monotherapy in acute management

1) Regular-Release

a) The recommended initial dose of [quetiapine](#) is 100 mg/day (in 2 divided doses) on day 1, increased to 400 mg/day on day 4 in increments of up to 100 mg/day (in 2 divided doses). Additional dosage adjustments up to 800 mg/day by day 6 should be made in increments of no more than 200 mg/day. Most patients respond to doses between 400 to 800 mg/day. The maximum dose is 800 mg/day [6].

b) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [6].

2) Extended-Release

a) The recommended initial dose is 300 mg in the evening on day 1 and 600 mg on day 2. Adjust the dose between 400 and 800 mg daily beginning on day 3, depending on patient response and tolerance. The maximum dose is 800 mg/day [2].

b) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule for acute treatment should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [2].

1.3.1.A.1.f] Schizophrenia

1) Regular-Release

a) The recommended initial dose is 25 mg orally twice daily. On the second and third day, the dose may be increased in increments of 25 to 50 mg divided into 2 or 3 doses.

By the fourth day, a target dose of 300 to 400 mg daily divided in 2 or 3 doses is recommended. Further dosage adjustments can be made in increments/decrements of 25 to 50 mg divided twice daily at intervals of not less than 2 days. Antipsychotic efficacy has been demonstrated in the range of 150 to 750 mg. The maximum recommended dose is 750 mg/day [6].

b)) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [6].

2)) Extended-Release

a)) The recommended initial dose is 300 mg orally once daily, preferably given in the evening. Titrate the dose based upon patient response and tolerance within a range of 400 to 800 mg/day. Doses may be increased in increments of up to 300 mg/day and in intervals as short as 1 day. The maximum recommended dose is 800 mg/day [2].

b)) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [2].

1.3.1.A.1.g) Schizophrenia, Maintenance

1)) Regular-Release

a)) [Quetiapine](#) 400 to 800 mg/day, given twice daily with a maximum dose of 800 mg/day has been recommended [6].

b)) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule for acute treatment should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [6].

2)) Extended-Release

a)) The recommended dosage is 400 to 800 mg orally once daily, given in the evening. Maximum dose is 800 mg/day. Generally, patients should be continued on the stabilization dose with reassessment for need and appropriate dose for maintenance treatment [2].

b)) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule for acute treatment should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [2].

1.3.1.A.2)) Important Note

a)) The US Food and Drug Administration (FDA) Safety Information and Adverse Event Reporting Program has reported that there have been dispensing errors due to the similarity of the [names](#), dosage forms, strengths, and dosing intervals for [Seroquel\(R\)](#) and [Serzone\(R\)](#) [28].

1.3.1.A.3)) Patients currently being treated with [quetiapine](#) regular-release may be switched to [quetiapine](#) extended-release at the equivalent total daily dose taken once daily. Individual dosage adjustments may be required [2].

1.3.3] Dosage in Hepatic Insufficiency**A) Quetiapine Fumarate****1) Regular-Release**

a) Initiate therapy at a dose of 25 mg/day then increase daily in increments of 25 to 50 mg/day to an effective and tolerable dose. In these patients [6].

2) Extended-Release

a) Initiate therapy with 50 mg/day. The dose may be increased in increments of 50 mg/day depending on patient response and tolerance [2].

1.3.4] Dosage in Geriatric Patients**A) Quetiapine Fumarate**

1) Initiate therapy with 50 mg/day. The dose may be increased in increments of 50 mg/day depending on patient response and tolerance. Perform dose escalation with caution and consider a slower rate of dose titration and a lower target dose [6] [2].

1.3.6] Dosage in Other Disease States**A) Quetiapine Fumarate****1) Concomitant Use with Strong CYP3A4 Inducers**

a) Increase quetiapine dose by as much as 5-fold during chronic (greater than 7 to 14 days) coadministration with a strong CYP3A4 inducer (eg, phenytoin, carbamazepine, rifampin, avasimibe, St John's wort), titrating dose based on clinical response and tolerability. When the CYP3A4 inducer is discontinued, reduce quetiapine to the original dose within 7 to 14 days [6] [2].

2) Concomitant Use with Strong CYP3A4 Inhibitors

a) Reduce quetiapine dose to one-sixth the original dose when using concurrently with a strong CYP3A4 inhibitor (eg, ketoconazole, itraconazole, indinavir, ritonavir, nefazodone). When the CYP3A4 inhibitor is discontinued, increase quetiapine dose by 6-fold [6] [2].

3) Debilitated Patients

a) Perform dose escalation with caution and consider a slower rate of dose titration and a lower target dose [6] [2].

4) Patients Predisposed to Hypotension

a) Perform dose escalation with caution and consider a slower rate of dose titration and a lower target dose [6] [2].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Quetiapine Fumarate

1.4.1.A.1] Oral route

1.4.1.A.1.a] Manic bipolar I disorder, Monotherapy in acute management

1) Regular-Release

a) Medication therapy for pediatric bipolar I disorder should be initiated only after thorough diagnostic evaluation and careful consideration has been given to the risks associated with medication treatment. A total treatment program for bipolar I disorder includes medication as well as psychological, educational and social interventions [6].

b) The recommended dose titration in pediatric patients age 10 to 17 years is 50 mg/day orally on day 1, 100 mg/day on day 2, 200 mg/day on day 3, 300 mg/day on day 4, and 400 mg/day on day 5. The doses should be divided and given 2 or 3 times daily depending upon tolerability. Further dosage adjustments in increments of not more than 100 mg/day, up to the recommended dosage range of 400 to 600 mg/day, may occur based upon patient response and tolerability. The maximum dose is 600 mg/day [6].

c) When restarting treatment in patients who have had an interval of less than 1 week off of quetiapine, titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule should be followed when reinitiating therapy in patients who have not taken quetiapine for more than 1 week [6].

2) Extended-Release

a) Medication therapy for pediatric bipolar I disorder should be initiated only after thorough diagnostic evaluation and careful consideration has been given to the risks associated with medication treatment. A total treatment program for bipolar I disorder includes medication as well as psychological, educational and social interventions [2].

b) The recommended dose titration in pediatric patients age 10 to 17 years is 50 mg in the evening on day 1, 100 mg on day 2, 200 mg on day 3, 300 mg on day 4, and 400 mg on day 5. Further dosage adjustments to the recommended dosage range of 400 to 600 mg once daily may occur based upon patient response and tolerability. The maximum dose is 600 mg/day [2].

c) When restarting treatment in patients who have had an interval of less than 1 week off of quetiapine, titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule should be followed when reinitiating therapy in patients who have not taken quetiapine for more than 1 week [2].

1.4.1.A.1.b] Schizophrenia

1) Regular-Release

a) Medication therapy for pediatric schizophrenia should be initiated only after thorough diagnostic evaluation and careful consideration has been given to the risks

associated with medication treatment. A total treatment program for [schizophrenia](#) includes medication as well as psychological, educational and social interventions [6].

b) The recommended dose titration in patients 13 to 17 years of age, is 50 mg/day orally on day 1, 100 mg/day on day 2, 200 mg/day on day 3, 300 mg/day on day 4, and 400 mg/day on day 5. The doses should be divided and administered 2 to 3 times daily depending upon patient response and tolerability. Further dosage adjustments in increments of not more than 100 mg/day, up to the recommended dosage range of 400 to 800 mg/day, may occur based upon patient response and tolerability. The maximum dose is 800 mg/day [6].

c) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [6].

2) Extended-Release

a) Medication therapy for pediatric [schizophrenia](#) should be initiated only after thorough diagnostic evaluation and careful consideration has been given to the risks associated with medication treatment. A total treatment program for [schizophrenia](#) includes medication as well as psychological, educational and social interventions [2].

b) The recommended dose titration in pediatric patients age 13 to 17 years is 50 mg in the evening on day 1, 100 mg on day 2, 200 mg on day 3, 300 mg on day 4, and 400 mg on day 5. Further dosage adjustments to the recommended dosage range of 400 to 800 mg once daily may occur based upon patient response and tolerability. The maximum dose is 800 mg/day [2].

c) When restarting treatment in patients who have had an interval of less than 1 week off of [quetiapine](#), titration of the dose is not required and the maintenance dose may be reinitiated. The initial titration schedule should be followed when reinitiating therapy in patients who have not taken [quetiapine](#) for more than 1 week [2].

1.4.1.A.2) Important Note

a) The US Food and Drug Administration (FDA) Safety Information and Adverse Event Reporting Program has reported that there have been dispensing errors due to the similarity of the [names](#), dosage forms, strengths, and dosing intervals for [Seroquel\(R\)](#) and [Serzone\(R\)](#) [28].

1.4.1.A.3) Patients currently being treated with [quetiapine](#) regular-release may be switched to [quetiapine](#) extended-release at the equivalent total daily dose taken once daily. Individual dosage adjustments may be required [2].

1.4.1.A.4) The safety and efficacy of [quetiapine](#) have not been established in pediatric patients younger than 10 years old [2] [6].

2.0) Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

2.1) Onset and Duration

A) Onset

1) Quetiapine Fumarate**a) Initial Response****1) Schizophrenia, oral: 7 to 14 days [172] [173]**

a) The initial onset of improvement in schizophrenia symptomatology occurs within 7 to 14 days [172] [173].

2.2] Drug Concentration Levels**A) Quetiapine Fumarate****1) Peak Concentration****a) Adult****1) Oral, multiple-dose, 250 mg/day: 278 nanograms/milliliter [174]**

a) A mean quetiapine C_{max} of 278 nanograms/milliliter (ng/mL; range, 140 to 365 ng/mL) was observed after a 75 mg oral midday dose on day 23 of quetiapine therapy; at this time, patients were receiving total daily doses of up to 250 mg [174].

b) The steady-state mean C_{max} of norquetiapine, the major active metabolite, was 21% to 27% of that observed for quetiapine [2].

2) Oral, single-dose, 25 mg: 60 nanograms/milliliter [174]

a) After a single oral dose of 25 mg quetiapine in schizophrenic patients, peak serum levels ranged from 18 to 136 nanograms/milliliter (ng/mL; mean, 60 ng/mL) [174].

3) The plasma concentration of quetiapine and its active metabolite, norquetiapine, were proportional to the total daily dose with predictable accumulation upon multiple dosing [6] [2].

b) Pediatric**1) Oral, extended-release, multiple-dose, 150 to 300 mg/day: 39% lower than adults [2]**

a) The mean dose- and weight-adjusted quetiapine C_{max} was 39% lower than in adults during a randomized clinical trial of children and adolescents, aged 10 to 17 years, receiving quetiapine extended-release 150 to 300 mg/day in the treatment of bipolar disorder. The mean dose-and weight-adjusted C_{max} of norquetiapine, the major active metabolite, was similar to that in adults [2].

c) Quetiapine pharmacokinetics are unchanged by gender and race [6] [2].

2)) Time to Peak Concentration**a)) Oral, regular-release tablet: 1.5 hours [6]**

1)) Peak plasma concentrations of quetiapine are reached in 1.5 hours following oral administration of a quetiapine fumarate regular-release tablet. Steady-state concentrations occur within 2 days of dosing [6].

b)) Oral, extended-release tablet: 6 hours [2]

1)) Peak plasma concentrations of quetiapine are reached in 6 hours following oral administration of a quetiapine fumarate extended-release tablet. Steady-state concentrations of quetiapine fumarate extended-release tablets occur within 2 days of dosing [2].

c)) Quetiapine pharmacokinetics are unchanged by gender and race [6] [2].**3)) Area Under the Curve****a)) Adult**

1)) The plasma concentration of quetiapine and its active metabolite, norquetiapine, were proportional to the total daily dose with predictable accumulation upon multiple dosing [6] [2].

2)) The steady-state mean AUC of norquetiapine, the major active metabolite, was 46% to 56% of that observed for quetiapine [2].

b)) Pediatric

1)) Oral, extended-release, multiple-dose, 150 to 300 mg/day: 41% lower than adults [2]

a)) The mean dose- and weight-adjusted quetiapine AUC was 41% lower than in adults during a randomized clinical trial of children and adolescents, aged 10 to 17 years, receiving quetiapine extended-release 150 to 300 mg/day in the treatment of bipolar disorder. The mean dose- and weight-adjusted AUC of norquetiapine, the major active metabolite, was similar to that in adults [2].

c)) Quetiapine pharmacokinetics are unchanged by gender and race [6] [2].**2.3] ADME****2.3.1] Absorption****A)) Quetiapine** Fumarate**1)) Bioavailability**

a) Oral: rapid [6]

1) Following oral administration, quetiapine fumarate is rapidly absorbed. The bioavailability of the regular-release tablets is 100% relative to solution [6].

2) The steady-state bioavailability of the extended-release quetiapine fumarate tablets, dosed once daily, is comparable to an equivalent dose of the regular-release tablets, dosed twice daily [2].

3) Quetiapine pharmacokinetics are unchanged by gender and race [6] [2].

2) Effects of Food**a) Regular-release tablet: marginally affected [6]**

1) When regular-release quetiapine fumarate tablets were administered with food, the C_{max} and AUC increased by 25% and 15%, respectively [6].

2) Food increases the absorption of quetiapine [175]. In healthy volunteers, administration of quetiapine with food resulted in an increase in C_{max} and AUC (each by approximately 1.5-fold) compared to the fasting state [176].

b) Extended-release tablets: significant with high-fat meal (800 to 1000 calories); no effect with light meal (300 calories) [2]

1) Statistically significant increases in the C_{max} and AUC of 44% to 52% and 20% to 22%, respectively, were seen for the 50 mg and 300 mg quetiapine fumarate extended-release tablets when given with a high-fat meal (approximately 800 to 1000 calories). There was no significant effect on the C_{max} or AUC when given with a light meal (approximately 300 calories) [2].

2.3.2] Distribution**A) Distribution Sites****1) Quetiapine Fumarate****a) Protein Binding**

1) 83% [6] [2]

a) Quetiapine is 83% bound to plasma proteins at therapeutic concentrations [6] [2].

B) Distribution Kinetics**1) Quetiapine Fumarate**

a) Volume of Distribution**1) 10 L/kg [6] [2]**

a) Quetiapine is widely distributed in the body and has a Vd of 10 +/- 4 L/kg [6] [2].

b) Quetiapine pharmacokinetics are unchanged by gender and race [6] [2].

2.3.3] Metabolism**A) Metabolism Sites and Kinetics****1) Quetiapine Fumarate****a) Liver: extensive [6] [2]**

1) Quetiapine fumarate is primarily metabolized by sulfoxidation and oxidation via the CYP3A4 isoenzyme [6] [2].

2) Extensive first-pass metabolism occurs with quetiapine [177].

3) After a single oral dose, less than 1% of quetiapine is excreted unchanged in the urine [6] [2].

B) Metabolites**1) Quetiapine Fumarate****a) Quetiapine sulfoxide: inactive [6] [2]**

1) The major inactive metabolite of quetiapine is quetiapine sulfoxide [6] [2].

b) Norquetiapine and 7-hydroxyquetiapine: active [6] [2] [175]

1) Twenty metabolites of quetiapine have been identified; the 7-hydroxylated metabolite [175] and the N-dealkylated metabolite are pharmacologically active [6] [2] [175].

C) Other**1) Quetiapine Fumarate****a) Metabolic Enzymes and Transporters****1) Substrate of CYP3A4**

a) Quetiapine is a substrate of CYP3A4 [6] [2].

2.3.4] Excretion**A) Kidney****1) Quetiapine Fumarate****a) Renal Excretion (%)****1) 73% [6] [2]**

a) Following administration of a single oral dose of carbon-labeled quetiapine, approximately 73% of the dose was recovered in the urine [6] [2].

b) Less than 5% of the average dose fraction of free quetiapine and norquetiapine is excreted in the urine [2].

B) Feces**1) Quetiapine Fumarate****a) 20% [6] [2]**

1) Following administration of a single oral dose of carbon-labeled quetiapine, approximately 20% of the dose was recovered in the feces [6] [2].

C) Total Body Clearance**1) Quetiapine Fumarate****a) Age****1) 40% reduction [6] [2]**

a) In a pharmacokinetic study, quetiapine clearance was reduced by 40% in patients 65 years or older (n=9) compared with young patients (n=12) [6] [2].

b) Gender**1) no effect [6] [2]**

a) Gender did not effect pharmacokinetics of quetiapine [6] [2].

c) Hepatic Impairment**1) 30% reduction [6] [2]**

a) Patients with hepatic impairment (n=8) experienced a 30% reduction in mean oral clearance of quetiapine compared with normal patients. Two of 8

patients with hepatic impairment experienced a 3-fold increase in AUC and C_{max} compared with healthy patients [6] [2].

d) Race

1) no effect [6] [2]

a) Race did not effect pharmacokinetics of quetiapine [6] [2].

e) Renal Impairment

1) 25% reduction [6] [2]

a) In a pharmacokinetic study, quetiapine clearance was reduced by 25% in patients with severe renal impairment (CrCl 10 to 30 mL/min/1.73 m²; n=8) compared with patients with normal renal function (CrCl greater than 80 mL/min/1.73 m²; n=8); however, plasma concentrations did not significantly differ between the two groups [6] [2].

f) Smoking status

1) no effect [6] [2]

a) Smoking status does not effect quetiapine clearance [6] [2].

2.3.5] Elimination Half-life

A) Parent Compound

1) Quetiapine Fumarate

a) 6 to 7 hours [6] [2]

1) Quetiapine has a mean t_{1/2} of approximately 6 to 7 hours [6] [2].

2) Quetiapine pharmacokinetics are unchanged by gender and race [6] [2].

B) Metabolites

1) Quetiapine Fumarate

a) Norquetiapine: 12 hours [2]

1) Norquetiapine has a mean t_{1/2} of approximately 12 hours [2].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.0.A] Black Box WARNING

Quetiapine Fumarate

Oral (Tablet; Tablet, Extended Release)

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Quetiapine fumarate and quetiapine fumarate XR are not approved for the treatment of patients with dementia-related psychosis or for patients under 10 years of age. There is an increased risk of suicidal thoughts and behavior in children, adolescents and young adults taking antidepressants. Monitor patients closely for clinical worsening and emergence of suicidal thoughts and behaviors [6] [2].

3.1] Contraindications

A) [Quetiapine](#) Fumarate

- 1) hypersensitivity to [quetiapine](#) or any component of the product [6] [2]
- 2) [anaphylactic reactions](#) have been reported [6] [2]

3.2] Precautions

A) [Quetiapine](#) Fumarate

- 1) Black Box Warning:
- 2) -- elderly patients with dementia-related [psychosis](#) (unapproved use) are at increased risk of death [6] [2]
- 3) -- [suicidal ideation](#) and behavior or worsening depression may occur, especially in children, adolescents, and young adults, ages 18 to 24, particularly during first few months of therapy or during dosing changes [29] [30]
- 4) Cardiovascular:
- 5) -- avoid use in patients with history of [cardiac arrhythmias](#), including bradycardia, due to increased risk of [torsades de pointes](#) or sudden death [29] [30]
- 6) -- [congestive heart failure](#) and [cardiac hypertrophy](#) may increase risk of QT prolongation [6] [2]
- 7) -- avoid use in patients with history of congenital [long QT syndrome](#) due to increased risk of [torsades de pointes](#) or sudden death [29] [30]
- 8) -- QT prolongation has been reported, especially in patients with a family history or older age [6] [2]

9)) -- patients with known [cardiovascular disease](#) are at risk for orthostatic hypotension and QT prolongation [29] [30]

10)) -- orthostatic hypotension, with or without syncope, may occur, especially during initial dose-titration period; return to previous dose if develops during titration [29] [30]

11)) -- [hypovolemia](#) increases risk of orthostatic hypotension [29] [30]

12)) -- [hypertension](#) has been reported in children and adolescents; monitoring recommended [6] [2]

13)) Endocrine and Metabolic:

14)) -- use caution in patients with or who are at risk for [diabetes mellitus](#) due to occurrence of [hyperglycemia](#), with some cases associated with [ketoacidosis](#), [hyperosmolar coma](#) or death; monitoring recommended [6] [2]

15)) -- metabolic changes, including [hyperglycemia](#), [dyslipidemia](#), and weight gain, and clinical worsening of multiple metabolic parameters have been reported; monitoring recommended [6] [2]

16)) -- avoid use in patients with hypokalemia or hypomagnesemia due to increased risk of [torsades de pointes](#) or sudden death [29] [30]

17)) -- elevated cholesterol and [triglyceride](#) levels have been reported; monitoring recommended [6] [2]

18)) -- [hyperprolactinemia](#) has been reported [6] [2]

19)) -- [hypothyroidism](#) has been reported; monitoring recommended [6] [2]

20)) Hematologic:

21)) -- [leukopenia](#) and [neutropenia](#) have been reported, especially with history of drug-induced [leukopenia](#) and [neutropenia](#) or preexisting low WBC; monitoring recommended and discontinue if develops [29] [30]

22)) -- [agranulocytosis](#), including fatal cases, has been reported [29] [30]

23)) Hepatic:

24)) -- dose adjustment may be required in patients with [hepatic impairment](#) [6] [2]

25)) -- asymptomatic, transient and reversible elevations in serum transaminases have been reported [29] [30]

26)) Musculoskeletal:

27)) -- [tardive dyskinesia](#) may occur, especially with increased duration of treatment and increased total cumulative dose, with greater prevalence among elderly female patients; consider discontinuation if condition develops [6] [2]

28)) Neurologic:

29)) -- use caution in patients with history of or predisposing factors for developing seizures [29] [30]

30)) -- patients with [cerebrovascular disease](#) are at risk for orthostatic hypotension [29] [30]

31)) Ophthalmic:

32)) -- cataracts or lens changes have been reported; monitoring recommended [29] [30]

33)) Respiratory:

34)) -- patients at risk for [aspiration pneumonia](#) may experience [esophageal dysmotility](#) and aspiration [29] [30]

35)) Other:

36)) -- [neuroleptic malignant syndrome](#) (NMS) has occurred; immediately discontinue if suspected [29] [30]

37)) -- elderly patients with dementia-related [psychosis](#) (unapproved use) are at increased risk for potentially fatal cerebrovascular adverse effects, including [stroke](#) and TIA [6] [2]

38)) -- elderly patients, especially elderly women, are at increased risk for [tardive dyskinesia](#) and QT prolongation [6] [2]

39)) -- abrupt withdrawal may result in acute withdrawal symptoms; gradual withdrawal recommended [29] [30]

40)) -- dehydration increases risk of orthostatic hypotension [29] [30]

41)) Concomitant use:

42)) -- avoid drugs that prolong QT interval [29] [30]

43)) -- antihypertensive medications increase risk of orthostatic hypotension [29] [30]

44)) -- avoid alcohol use [29] [30]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] [Quetiapine Fumarate](#)

3.3.1.A.1] [Bradyarrhythmia](#)

a)) Incidence: 0.1% to less than 1% [6]

b)) Bradycardia has been reported in 0.1% to less than 1% of approximately 2200 patients administered [quetiapine](#) for [schizophrenia](#) during clinical trials [6].

c)) A 63-year-old woman experienced bradycardia following treatment with [quetiapine](#) for [paranoid schizophrenia](#). At the time of admission, she was receiving [quetiapine](#) 1000 mg/day, but her [psychosis](#) remained. Physical examination found a slow irregular pulse rate of 52 beats per minute and a blood pressure of 115/77 mmHg without orthostasis. In the days that followed, bradycardia remained with varying pulse rates (40 to 55 beats per minute). An ECG revealed [sinus bradycardia](#) with normal conduction times and some [ventricular extrasystoles](#). Laboratory results showed [quetiapine](#) levels within normal limits. Since both bradycardia and [psychosis](#) persisted, the [quetiapine](#) dose was reduced. Bradycardia continued during the 6-week taper, but completely resolved after full cessation of therapy. Her pulse rate increase to over 60 beats per minute. The patient was administered [clozapine](#), with no further issues [37].

3.3.1.A.2] [Cardiomyopathy](#)

a) **Cardiomyopathy**, temporally related to **quetiapine** therapy, has been reported during postmarketing surveillance [2] [6].

3.3.1.A.3] Hypertension

a) Incidence: adults, 2% [2] [6]

b) **Hypertension** was reported in 2% of adults administered adjunctive **quetiapine** 100 to 800 mg/day (n=196) compared with 1% of patients administered placebo (n=203) during 3-week clinical trials in the treatment of bipolar mania [6].

3.3.1.A.4] Increased diastolic arterial pressure

a) Incidence: pediatrics, 40.6% [2] [6]

b) Increases at any time in diastolic blood pressure (10 mmHg or greater) occurred in 40.6% (136 of 335) of children and adolescents treated with **quetiapine** compared with 24.5% (40 of 163) of those treated with placebo in clinical trials of 3 to 6 weeks duration in the treatment of bipolar mania and **schizophrenia**. In a 26-week open-label clinical trial, 1 child who had a history of **hypertension** experienced a **hypertensive crisis**. Therefore, blood pressure should be monitored at baseline and periodically thereafter during **quetiapine** therapy in pediatric patients [2] [6].

3.3.1.A.5] Increased systolic arterial pressure

a) Incidence: pediatrics, 15.2% [2] [6]

b) Increases at any time in systolic blood pressure (20 mmHg or greater) occurred in 15.2% (51 of 335) of children and adolescents treated with **quetiapine** compared with 5.5% (9 of 163) of those treated with placebo in clinical trials of 3 to 6 weeks duration in the treatment of bipolar mania or **schizophrenia**. In a 26-week open-label clinical trial, 1 child who had a history of **hypertension** experienced a **hypertensive crisis**. Therefore, blood pressure should be monitored at baseline and periodically thereafter during **quetiapine** therapy in pediatric patients [2] [6].

3.3.1.A.6] Myocarditis

a) **Myocarditis**, temporally related to **quetiapine** therapy, has been reported during postmarketing surveillance [2] [6].

3.3.1.A.7] Orthostatic hypotension

a) Summary

1) The risk of hypotension is greater during dose-titration periods. Use **quetiapine** cautiously in patients with **cerebrovascular disease**, **cardiovascular disease**, or conditions that predispose them to hypotension (ie, **hypovolemia**, dehydration, and concomitant **antihypertensive therapy**). Should hypotension develop during titration, returning to the pre-titration dose is appropriate [2] [6].

b) Incidence: up to 7% [2] [6]

c) Adults

1) Orthostatic hypotension was reported in 2% of patients administered **quetiapine** extended-release 300 mg/day (n=137) compared with 1% of patients administered placebo (n=140) during an 8-week placebo-controlled clinical trial for the treatment of **bipolar depression** [2].

2) Orthostatic hypotension was reported in 3% of patients administered **quetiapine** extended-release 400 to 800 mg/day (n=151) compared with 0% of patients administered placebo

(n=160) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [2].

3j) Postural hypotension was reported in 4% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 1% of patients administered placebo (n=404) during monotherapy clinical trials of 3 to 12 weeks duration for the treatment of [schizophrenia](#) or bipolar mania [6].

4j) Orthostatic hypotension was reported in 4% of patients administered [quetiapine](#) 300 and 600 mg/day (n=698) compared with 3% of patients administered placebo (n=347) during 8-week, clinical trials for the treatment of [bipolar depression](#) [6].

5j) Postural hypotension was reported in 7% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 2% of patients administered placebo (n=203) during 3-week clinical trial for the treatment of bipolar mania [6].

6j) Orthostatic hypotension was reported in 7% of patients administered [quetiapine](#) extended-release 300 to 800 mg/day (n=951) compared with 5% of patients administered placebo (n=319) during 6-week clinical trials for the treatment of [schizophrenia](#) [2].

dj) Pediatrics

1j) Orthostatic hypotension was reported in less than 1% of pediatric patients [2].

3.3.1.A.8] Prolonged QT interval

a) Incidence: 0.1% to less than 1% [6]

b) QT prolongation has been reported in 0.1% to less than 1% of approximately 2200 patients who received [quetiapine](#) for [schizophrenia](#) during clinical trials [6] and during postmarketing use with [quetiapine](#) in patients with concomitant illness and in patients taking concomitant medications known to cause [electrolyte imbalance](#) or increase the QT interval [2] [6].

c) The use of [quetiapine](#) should be avoided in combination with drugs known to increase QT interval and other circumstances that may increase the risk of occurrence of [torsade de pointes](#) and/or sudden death (eg, history of [cardiac arrhythmias](#) such as bradycardia, hypokalemia or hypomagnesemia, presence of congenital prolongation of the QT interval). Caution should be exercised when [quetiapine](#) is used in combination with drugs known to cause [electrolyte imbalance](#) and when prescribed to patients with increased risk of QT prolongation (eg, [cardiovascular disease](#), [congestive heart failure](#), [cardiac hypertrophy](#), elderly, family history of QT prolongation) [29] [30].

3.3.1.A.9] Sudden cardiac death

a) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic drugs and 186,600 nonusers of antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participants 30 to 74 years of age (mean age, 45.7 years) who were using [quetiapine](#) compared with those who were not using antipsychotic drugs (incidence-rate ratio, 1.88; 95% CI, 1.3 to 2.71; p less than 0.001). In participants being treated with atypical antidepressants (eg, [clozapine](#), [olanzapine](#), [quetiapine](#), [risperidone](#)), the incidence-rate ratio for sudden cardiac death increased from 1.59 (95% CI, 1.03 to 2.46) for those using low doses to 2.86 (95% CI, 2.25 to 3.65) for those using high doses (p=0.01) [38].

3.3.1.A.10] Syncope

a) Incidence: 0.3% to 1% [32] [33]

- b) Syncope was reported in 0.3% (5 of 1866) of patients treated with [quetiapine](#) extended-release across all indications and 1% (28 of 3265) of patients treated with [quetiapine](#) compared with 0.2% on placebo in multiple clinical trials [32] [33].
- c) Syncope was reported in 2% of children and adolescents (10 to 17 years of age) treated for [schizophrenia](#) (up to 6 weeks) and bipolar mania (up to 3 weeks) with [quetiapine](#) at doses of 400, 600, or 800 mg/day (n=340) compared with 0% of those treated with placebo (n=165) in short-term, placebo-controlled clinical trials [32].
- d) The risk of syncope is greater during dose-titration periods. Use [quetiapine](#) cautiously in patients with [cerebrovascular disease](#), [cardiovascular disease](#), or conditions that predispose them to hypotension (ie, [hypovolemia](#), dehydration, and concomitant [antihypertensive therapy](#)) . The risk of syncope may be minimized by limiting the starting dose of [quetiapine](#) [32] [33].

3.3.1.A.11] [Tachycardia](#)

a) Incidence: up to 6% [2] [6]

b) Adults

- 1) [Tachycardia](#) was reported in 2% of patients administered [quetiapine](#) extended-release 400 to 800 mg/day (n=151) compared with 1% of patients administered placebo (n=160) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [2].
- 2) [Tachycardia](#) was reported in 2% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 1% of patients administered placebo (n=203) during a 3-week, placebo-controlled adjunctive therapy clinical trial for the treatment of bipolar mania [6].
- 3) [Tachycardia](#) was reported in 3% of patients administered [quetiapine](#) extended-release 300 to 800 mg/day (n=951) compared with 1% of patients administered placebo (n=319) during 6-week clinical trials for the treatment of [schizophrenia](#) [2].
- 4) [Tachycardia](#) was reported in 6% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 4% of patients administered placebo (n=404) during monotherapy clinical trials of 3 to 12 weeks duration in the treatment of [schizophrenia](#) or bipolar mania [6].
- 5) [Tachycardia](#) (greater than 120 beats/min) at any time was reported in 2.5% of patients administered extended-release [quetiapine](#) compared with 2.3% of patients administered placebo during clinical trials. ECG measurements showed a mean increase in heart rate of 6.3 beats/min and 0.4 beats/min for [quetiapine](#)- and placebo-treated patients, respectively [2].
- 6) [Tachycardia](#) (greater than 120 beats/min) was reported in 1.9% of patients administered [quetiapine](#) compared with 0.9% of patients administered placebo during clinical trials [2]. ECG measurements showed a mean increase in heart rate of 7 beats/min and 1 beats/min for [quetiapine](#)- and placebo-treated patients, respectively [2] [6].

c) Pediatrics

- 1) [Tachycardia](#) was reported in 6% of pediatric patients (10 to 17 years) administered [quetiapine](#) 400 mg/day (n=95) and 9% of patients administered [quetiapine](#) 600 mg/day (n=98) compared with 0% of patients administered placebo (n=90) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [6].
- 2) [Tachycardia](#) was reported in 6% of pediatric patients (13 to 17 years) administered [quetiapine](#) 400 mg/day (n=73) and 11% of patients administered [quetiapine](#) 800 mg/day

(n=74) compared with 0% of patients administered placebo (n=75) during a 6-week placebo-controlled clinical trial for the treatment of [schizophrenia](#) [6].

3J) Increases in heart rate to greater than 110 beats/min occurred in 1.1% of pediatric patients (10 to 17 years) administered [quetiapine](#) 400 mg (n=89) and 4.7% of patients receiving [quetiapine](#) 600 mg (n=85) compared with 0% of patients receiving placebo (n=98) during an acute, 3-week clinical trial for the treatment of bipolar mania. Mean increases in heart rate were 12.8 beats/min and 13.4 beats/min for the [quetiapine](#) 400-mg and 600-mg groups, respectively, compared with a decrease of 1.7 beats/min in placebo-treated patients [2] [6].

4J) Increases in heart rate to greater than 110 beats/min occurred in 5.2% of pediatric patients (aged 13 to 17 years) receiving [quetiapine](#) 400 mg (n=73) and 8.5% of patients receiving [quetiapine](#) 800 mg (n=74) compared with 0% of placebo-treated patients (n=75) during an acute, 6-week clinical trial for the treatment of [schizophrenia](#). Mean increases in heart rate were 3.8 beats/min and 11.2 beats/min for the 400-mg and 800-mg groups, respectively, compared with a decrease of 3.3 beats/min in placebo-treated patients [2] [6].

3.3.1.A.12] [Ventricular premature beats](#)

aJ) A 17-year-old girl treated with [lithium](#) 600 mg/day for newly diagnosed bipolar II disorder developed uniform frequent [premature ventricular contractions](#) (PVCs) with slight palpitations 2 days after concomitant [quetiapine](#) 25 mg/day therapy was added to her regimen to treat emotional lability. [Quetiapine](#) was discontinued twice; palpitations resolved and Holter [ECG monitoring](#) administered 6 days after each treatment discontinuation revealed 0.6% and 1.1%, respectively, of total beats per day as uniform frequent PVCs. When [quetiapine](#) was restarted between treatment discontinuations, PVCs rose to 7.1% of total beats per day (with no palpitations). [Lithium](#) therapy was maintained throughout the monitoring process [36].

3.3.2] Dermatologic Effects

3.3.2.A] [Quetiapine Fumarate](#)

3.3.2.A.1] [Rash](#)

aJ) Incidence: up to 5% [32]; [33]

bJ) Rash was reported in up to 5% of adult patients treated with [quetiapine](#) or [quetiapine](#) extended-release in multiple, placebo-controlled clinical trials [32] [33].

3.3.2.A.2] [Stevens-Johnson syndrome](#)

aJ) [Stevens-Johnson syndrome](#), temporally related to [quetiapine](#) therapy, has been reported during postmarketing surveillance [2] [6].

3.3.2.A.3] [Toxic epidermal necrolysis due to drug](#)

aJ) [Toxic epidermal necrolysis](#), temporally related to [quetiapine](#) therapy, has been reported during postmarketing surveillance [2] [6].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] [Quetiapine Fumarate](#)

3.3.3.A.1] [Diabetic ketoacidosis](#)

a) A case report described [pancreatitis](#) and life-threatening [diabetic ketoacidosis](#) in a 30-year-old woman following [quetiapine](#) use. The patient, who was mildly obese and had a history of [polycystic ovary disease](#), was being treated with oral [ziprasidone](#) 80 mg twice daily for [schizophrenia](#). Two months later, oral [quetiapine](#) 20 mg/day was initiated for augmentation and titrated up to 200 mg/day. Seven months after [quetiapine](#) was initiated, she presented to the emergency department with a 2-day history of acute stomach pain along with vomiting and excessive thirst and urination. Her family and personal histories were negative for hypertriglyceridemia, alcohol abuse, and [diabetes mellitus](#). Laboratory results showed elevated blood glucose (1081 mg/dL) with 4+ acetone and elevated [triglyceride](#) level of 537 mg/dL. Following ICU admittance for [diabetic ketoacidosis](#), further lab results revealed elevated [amylase](#) and lipase levels of 550 and 982 international units/L, respectively. In addition, abdominal [CT scan](#) and ultrasound revealed moderate acute [pancreatitis](#) and gallbladder sludge. Subsequently, IV fluids and pain medications were administered. [Quetiapine](#) and [ziprasidone](#) were withdrawn and [haloperidol](#) was initiated. After 3 days, [amylase](#) and lipase levels normalized (114 and 126 international units/L, respectively). She was discharged from the hospital with no further [sequelae](#). Despite the patient's risk factors for developing [glucose intolerance](#), the authors concluded that the case of [pancreatitis](#) was attributable to the use of low-dose [quetiapine](#) in associated with [ziprasidone](#) [50].

3.3.3.A.2] [Hyperglycemia](#)

a) Summary

1) [Hyperglycemia](#), including cases associated with [ketoacidosis](#), [hyperosmolar coma](#), or death, has been reported in patients receiving atypical antipsychotics, including [quetiapine](#). Monitoring is recommended for all patients receiving antipsychotic therapy and especially in patients with risk factors (ie, [obesity](#), family history) for or an established diagnosis of [diabetes mellitus](#). [Hyperglycemia](#) has resolved in some cases after discontinuation of the drug, while in other cases, continuation of antidiabetic treatment was required after drug discontinuation [2] [6].

b) Adults

1) The mean change in glucose from baseline was 5 mg/dL in patients administered [quetiapine](#) (n=646) compared with -0.05 mg/dL in patients administered placebo (n=680) during 2 long-term, placebo-controlled, randomized withdrawal trials in the maintenance treatment of bipolar I disorder [2] [6].

2) A shift in blood glucose 126 mg/dL or greater was reported in 7% of patients administered extended-release [quetiapine](#) 150 mg (n=280) and 12% of patients administered extended-release [quetiapine](#) 300 mg (n=269) compared with 6% of patients administered placebo (n=277) during an adjunct therapy trial in patients with [major depressive disorder](#) [2].

3) During short-term (less than or equal to 12 weeks), placebo-controlled clinical trials, a shift in fasting-glucose from borderline (greater than 100 mg/dL but less than 126 mg/dL) to high (greater than or equal to 126 mg/dL) was reported in 11.7% of patients administered [quetiapine](#) (n=572) compared with 11.8% of patients administered placebo (n=279). Similarly, a shift in fasting-glucose from normal (less than 100 mg/dL) to high (greater than or equal to 126 mg/dL) was reported in 2.4% of patients administered [quetiapine](#) (n=2907) compared with 1.4% of patients administered placebo (n=1346) [2] [6].

4) In a 24-week, active-controlled trial designed to evaluate glycemic status with oral glucose tolerance testing, the incidence of treatment-emergent post-glucose challenge glucose levels

of 200 mg/dL or greater was 1.7%, and the incidence of a fasting treatment-emergent blood glucose level of 126 mg/dL or higher was 2.6% in adult patients receiving [quetiapine](#) fumarate (n=115). The mean change in fasting glucose from baseline was 3.2 mg/dL, and the mean change in 2-hour glucose from baseline was -1.8 mg/dL [2] [6].

5j) A 42-year-old man was diagnosed with new-onset [diabetes mellitus](#) after 1 month of [quetiapine](#) use. The patient was admitted to the hospital after several days of nausea, vomiting, polyuria, and confusion. His blood glucose concentration upon admission was 607 mg/dL. Random blood glucose concentrations 4 months prior to the patient's admission were 126 and 107 mg/dL. He had no prior history of [glucose intolerance](#), [hyperglycemia](#), and no familial history of [diabetes](#). The patient's history of [bipolar disorder](#) was concurrently treated with [lithium](#) carbonate, [gabapentin](#), [clonazepam](#), and [venlafaxine](#) in addition to his [quetiapine](#) titration of 200 mg at night. He was eventually discharged on an [insulin](#) regimen, and [quetiapine](#) was discontinued over the course of 9 days. The patient's [insulin](#) dose was weaned over a course of 5 months after hospital discharge [52].

c) Pediatrics

1j) In a 6-week, placebo-controlled study in adolescents (13 to 17 years old) with [schizophrenia](#), the mean change in fasting glucose level for patients treated with [quetiapine](#) was -0.75 mg/dL (n=138) compared with -1.70 mg/dL in the placebo group (n=67). In a 3-week, placebo-controlled study in pediatric patients (aged 10 to 17 years) with bipolar mania, the mean change in fasting blood glucose level for patients treated with [quetiapine](#) was 3.62 mg/dL (n=170) compared with -1.17 mg/dL in the placebo group (n=81). No patient in either study with a baseline fasting glucose level less than 126 mg/dL had a treatment-emergent blood glucose level of 126 mg/dL or greater [2] [6].

3.3.3.A.3] Hyperlipidemia

a) Undesirable changes in total cholesterol, [triglycerides](#), LDL-C, and HDL-C have been reported with [quetiapine](#) fumarate use during clinical trials. Therefore, lipid evaluations at baseline and periodically during [quetiapine](#) therapy are recommended [32] [33].

3.3.3.A.4] Hyperprolactinemia

a) Incidence: 3.6% to 13.4% [2] [6]

b) Shifts in prolactin levels to a clinically significant value were reported in 3.6% of adult patients treated with [quetiapine](#) fumarate (n=4416) compared with 2.6% of those treated with placebo (n=1968) [2] [6].

c) In acute, placebo-controlled trials of children and adolescents being treated for bipolar mania (3 weeks) or [schizophrenia](#) (6 weeks), shifts in prolactin levels to a clinically significant value, greater than 20 mcg/L at any time, were reported in 13.4% of male patients treated with [quetiapine](#) (n=134) compared with 4% of those treated with placebo (n=75). In female patients, prolactin levels of greater than 26 mcg/L at any time were reported in 8.7% of those treated with [quetiapine](#) (n=104) compared with 0% of those treated with placebo (n=39) [2] [6].

d) Elevated prolactin levels may persist in some patients during chronic [quetiapine](#) administration. [Hyperprolactinemia](#) may result in reduced pituitary gonadotrophin secretion which could potentially lead to inhibited reproductive function. Long-standing [hyperprolactinemia](#) when associated with [hypogonadism](#) may result in [bone mineral density](#) loss in female and male patients [2] [6].

e) A 14-year-old boy developed hyperprolactinemic [galactorrhea](#) following treatment with [quetiapine](#). At age 9, the adolescent was diagnosed with conduct disorder and had previously been treated with [sulpiride](#) and [risperidone](#). His aggressive and disruptive behavior became increasingly

hard to manage, requiring hospitalization. His baseline prolactin serum level was 175 milliunits/L (normal range, 53 milliunits/L to 360 milliunits/L). Quetiapine was initiated at 25 mg/day and gradually titrated up over a 2-month period to 600 mg/day. He showed significant improvements in all behavioral areas and was discharged. Three months later, the adolescent reported spontaneous nipple discharge, and galactorrhea was confirmed. His prolactin serum level at this time was 760 milliunits/L, a probable cause of galactorrhea. When quetiapine dose was gradually decreased over a 2-week period to 400 mg/day, his galactorrhea resolved along with normalization of prolactin serum levels to 200 milliunits/L. The lower dose (400 mg/day) of quetiapine and psychosocial therapy was effective in controlling his behavior. The Naranjo score of 7 indicated a probable relationship between quetiapine, hyperprolactinemia, and galactorrhea [51].

3.3.3.A.5] Hyponatremia

a) Hyponatremia, temporally related to quetiapine therapy, has been reported during postmarketing surveillance [2] [6].

3.3.3.A.6] Hypothyroidism

a) Summary

1) Cases of dose-related hypothyroidism have been reported with quetiapine use. Thyroid monitoring, including both TSH and free thyroxine (T4), is recommended with quetiapine therapy [2] [6].

b) Adults

1) In clinical trials, decreases in total and free thyroxine (T4) appeared to be dose-related, with levels dropping approximately 20% at the higher end of the therapeutic dose range; maximal decreases were seen during the first 6 weeks of therapy. In many patients, these changes were of no clinical significance; however about 0.7% (26 of 3489) of patients in monotherapy trials did experience TSH increases and some patients required thyroid replacement therapy [2] [6].

2) In clinical trials of extended-release quetiapine across all indications, decreased free thyroxine (T4) was reported in 1.8% of patients administered extended-release quetiapine (n=1336) compared with 0.6% of patients administered placebo (n=1346). Similarly, 1.6% of quetiapine patients (n=1346) reported increased TSH levels compared with 3.4% of placebo patients (n=534) [2].

3) Increased TSH was reported in 0.7% to 12% of adult patients treated with quetiapine or quetiapine extended-release in multiple, placebo-controlled clinical trials. In mania adjunct studies, where quetiapine was added to lithium or divalproex, 12% (24 of 196) of the quetiapine patients had elevated TSH levels compared with 7% (15 of 203) of the placebo patients. In short-term clinical trials, decreased free thyroxine was reported in 0.7% of adult patients treated with quetiapine (n=7218) compared with 0.1% of those treated with placebo (n=3668) [2] [6].

c) Pediatrics

1) In acute placebo-controlled studies in pediatric patients with schizophrenia or bipolar mania, the shift to elevated TSH levels was 2.9% (8 of 280) compared with 0.7% (1 of 138) in quetiapine- and placebo-treated patients, respectively. Additionally, the shift to decreases of total thyroxine levels was 2.8% (8 of 289) and 0% (0 of 145) in quetiapine- and placebo-treated patients, respectively [2] [6].

3.3.3.A.7] Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - [METABOLIC SYNDROME](#)

3.3.3.A.8] Serum cholesterol raised**a) Summary**

1) Undesirable changes in total cholesterol, [triglycerides](#), LDL-C, and HDL-C have been reported with [quetiapine](#) fumarate use during clinical trials. Therefore, lipid evaluations at baseline and periodically during [quetiapine](#) therapy are recommended [32] [33].

b) Incidence: 7% to 18% [2] [6]

c) Elevations in total cholesterol to levels of 240 mg/dL or greater were reported in 7% to 18% of adult patients treated with [quetiapine](#) or [quetiapine](#) extended-release compared with 3% to 9% of patients administered placebo during multiple, placebo-controlled clinical trials [2] [6].

d) Elevations in total cholesterol to levels of 200 mg/dL or greater were reported in 10% to 12% of pediatric patients treated with [quetiapine](#) in clinical trials compared with 2% to 3% in placebo-treated patients [2] [6].

3.3.3.A.9] Serum triglycerides raised**a) Summary**

1) Undesirable changes in total cholesterol, [triglycerides](#), LDL-C, and HDL-C have been reported with [quetiapine](#) fumarate use during clinical trials. Therefore, lipid evaluations at baseline and periodically during [quetiapine](#) therapy are recommended [32] [33].

b) Incidence: 8% to 28% [2] [6]

c) Elevations in serum [triglyceride](#) levels of 200 mg/dL or greater were reported in 8% to 22% of adult patients treated with [quetiapine](#) or [quetiapine](#) extended-release compared with 5% to 16% of patients administered placebo during multiple, placebo-controlled clinical trials [2] [6].

d) Elevations in serum [triglycerides](#) of 150 mg/dL or greater were reported in 17% to 28% of children and adolescents treated with [quetiapine](#) in clinical trials compared with 8% to 13% in placebo-treated patients [2] [6]

e) A 54-year-old man experienced increases in serum [triglycerides](#) and total cholesterol after 16 weeks of treatment with [quetiapine](#) for [paranoid schizophrenia](#) (DSM IV). After previous trials of [olanzapine](#), zuclopenthixol, and [risperidone](#) had each failed to control his psychiatric symptoms, [quetiapine](#) was initiated and titrated to 800 mg daily. Within 16 weeks of starting [quetiapine](#), his fasting [triglyceride](#) (TG) level rose from 165 mg/dL to 1011 mg/dL, his fasting total cholesterol (TC) level rose from 207 mg/dL to 313 mg/dL, and his body weight increased from 72.5 kg to 78.5 kg (BMI 23.2 to 25.3 kg/m²). With no other identifiable causes for these changes, [quetiapine](#) was switched to amisulpride 800 mg daily, and his TG and TC levels decreased to 187 mg/dL and 218 mg/dL, respectively. While continuing amisulpride, he experienced a postpsychotic [depressive syndrome](#), and [venlafaxine](#) was added to his regimen without significant changes in his [triglyceride](#) levels. Due to a [relapse](#) of his psychiatric illness 15 weeks after stopping [quetiapine](#), the patient was reintroduced to a lower dose of [quetiapine](#) 400 mg per day. However, his fasting TG increased to 716 mg/dL and fasting TC increased to 306 mg/dL, requiring discontinuation of [quetiapine](#) again. He was then switched to [clozapine](#) 300 mg daily and pregabalin 300 mg daily, and the amisulpride dose was increased to 1200 mg daily with good response. Although his weight continued increasing to 86.9 kg (BMI 28.1 kg/m²), his blood sugar level remained stable throughout this time period (HbA1c of 5.9%). [Fluvastatin](#)

40 mg daily was added to his regimen, and his fasting lipid levels improved to TG 459 mg/dL and TC 228 mg/dL [53].

3.3.3.A.10] Syndrome of inappropriate antidiuretic hormone secretion

a) SIADH, temporally related to [quetiapine](#) therapy, has been reported during postmarketing surveillance [2] [6].

3.3.3.A.11] Weight gain

a) Summary

1) Significant weight gain of 7% or greater of body weight has occurred in 3% to 23% of adults and in 12% to 28% of pediatric patients treated with [quetiapine](#) or [quetiapine](#) extended-release in multiple, placebo-controlled clinical trials. Logistic regression analysis of a placebo-controlled clinical study in adult patients with [schizophrenia](#) revealed a positive correlation between dose and the occurrence of weight gain (p less than 0.05). Regularly monitor weight during [quetiapine](#) use [2] [6].

b) Incidence: 3% to 28% [2] [6]

c) Adults

1) Weight increase was reported in 3% of patients administered adjunctive [quetiapine](#) extended-release 150 mg/day (n=315) and 5% of patients administered [quetiapine](#) extended-release 300 mg/day (n=312) compared with 0% of patients administered placebo (n=309) during a 6-week placebo-controlled, fixed-dose clinical trial for [major depressive disorder](#) [2].

2) Weight increase was reported in 4% of patients administered [quetiapine](#) 300 and 600 mg/day (n=698) compared with 1% of patients administered placebo (n=347) during an 8-week placebo-controlled clinical trial for the treatment of [bipolar depression](#) [6].

3) Weight gain was reported in 5% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 1% of patients administered placebo (n=404) during monotherapy clinical trials of 3 to 12 weeks duration in the treatment of [schizophrenia](#) or bipolar mania [6].

4) Weight gain was reported in 6% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 3% of patients administered placebo (n=203) during a 3-week, placebo-controlled clinical trial for the treatment of bipolar mania [6].

5) Weight gain was reported in 7% of patients administered [quetiapine](#) extended-release 300 mg/day (n=137) compared with 1% of patients administered placebo (n=140) during an 8-week placebo-controlled clinical trial for the treatment of [bipolar depression](#) [2].

6) Weight gain was reported in 7% of patients administered [quetiapine](#) extended-release 400 to 800 mg/day (n=151) compared with 1% of patients administered placebo (n=160) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [2].

7) A weight gain of 7% or greater of body weight was reported in 3% to 23% of adult patients treated with [quetiapine](#) or [quetiapine](#) extended-release in multiple, placebo-controlled clinical trials [2] [6]. A logistic regression analysis of a placebo-controlled clinical study of 5 fixed-doses of [quetiapine](#) in adult patients with [schizophrenia](#) revealed a positive correlation between dose and the occurrence of weight gain (p less than 0.05). In these studies, daily doses included 75 mg, 150 mg, 300 mg, 600 mg, and 750 mg [6].

d) Pediatrics

1J) Weight increase was reported in 6% of pediatric patients (aged 10 to 17 years) administered [quetiapine](#) 400 mg/day (n=95) and 6% of patients administered [quetiapine](#) 800 mg/day (n=98) compared with 0% of patients administered placebo (n=90) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [6].

2J) A weight gain of 7% or greater was reported in 12% to 28% of children and adolescents treated with [quetiapine](#) in multiple clinical trials. Mean change in body weight was 2 kg, 1.4 kg, and 1.7 kg in the [quetiapine](#) fumarate-treated patients and -0.4 kg, 0.6 kg, and 0.4 kg in the placebo-treated patients in the [schizophrenia](#), [bipolar depression](#), and bipolar mania trials, respectively. In a 26-week open-label continuation study, the mean increase in body weight for patients completing the study (241 of 380) was 4.4 kg with 45% gaining 7% or greater of their body weight. Adjusted for normal growth (an increase of at least 0.5 standard deviation from baseline in BMI was considered a clinically significant change), 18.3% experienced a clinically significant change in weight [2] [6].

3J) Adolescent patients taking [olanzapine](#) experienced greater weight gain and increases in BMI than patients taking [quetiapine](#) in a retrospective study involving 103 patients younger than 18 years. Patients received [olanzapine](#) (n=50; mean daily dose, 13.9 mg) or [quetiapine](#) (n=53; mean daily dose, 510.9 mg) for at least 2 weeks. Weight and height were measured at baseline and 14 or more days after baseline. Average weight gain from baseline in the [olanzapine](#) group was 3.8 kg (p less than 0.001) compared with 0.03 kg in the [quetiapine](#) group. Both the [olanzapine](#) and [quetiapine](#) groups showed slight, but significant, increases in height from baseline (0.006 meters, p=0.042 and 0.006 meters, p less than 0.001, respectively). After controlling for baseline differences, the mean weight change between groups was significant (3.4 kg, p less than 0.001). BMI increased by an average of 1.3 kg/m(2) in the [olanzapine](#) group (p less than 0.001) compared with a decrease of 0.2 kg/m(2) in the [quetiapine](#) group. After controlling for baseline differences, the mean difference in change in BMI was significant (0.9 kg/m(2); p=0.008) [54].

3.3.4] Gastrointestinal Effects

3.3.4.A] [Quetiapine Fumarate](#)

3.3.4.A.1] Abdominal pain

aJ) Incidence: 3% to 7% [6]

bJ) Adults

1J) Abdominal pain was reported in 4% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 1% of patients administered placebo (n=404) during monotherapy clinical trials of 3 to 12 weeks duration in the treatment of [schizophrenia](#) or bipolar mania [6].

2J) Abdominal pain was reported in 7% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 3% of patients administered placebo (n=203) during 3-week clinical trial in the treatment of bipolar mania [6].

3J) A logistic regression analysis of a placebo-controlled clinical study of 5 fixed-doses of [quetiapine](#) in adult patients with [schizophrenia](#) revealed a positive correlation between dose and the occurrence of abdominal pain (p less than 0.05). Doses included in these studies were 75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day, and 750 mg/day [6].

cJ) Pediatrics

1j) Abdominal pain was reported in 3% of pediatric patients (aged 13 to 17 years) administered [quetiapine](#) 400 mg/day (n=73) and 1% of patients administered [quetiapine](#) 800 mg/day (n=74) compared with 0% of patients administered placebo (n=75) during a 6-week clinical trial in the treatment of [schizophrenia](#) [6].

3.3.4.A.2] Constipation

a) Incidence: 2% to 11% [2] [6]

b) Adults

1j) Constipation was reported in 6% of patients administered [quetiapine](#) extended-release 300 to 800 mg/day (n=951) compared with 5% of patients administered placebo (n=319) during 6-week placebo-controlled clinical trials in the treatment of [schizophrenia](#) [2].

2j) Constipation was reported in 6% of patients administered adjunctive [quetiapine](#) extended-release 150 mg/day (n=315), 11% of patients administered [quetiapine](#) extended-release 300 mg/day (n=312), and 4% of patients administered placebo (n=309) during a 6-week clinical trial for [major depressive disorder](#) [2].

3j) Constipation was reported in 8% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 3% of patients administered placebo (n=404) during monotherapy trials of 3 to 12 weeks duration in the treatment of [schizophrenia](#) or bipolar mania [6].

4j) Constipation was reported in 8% of patients administered [quetiapine](#) extended-release 300 mg/day (n=137) compared with 6% of patients administered placebo (n=140) during an 8-week clinical trial for the treatment of [bipolar depression](#) [2].

5j) Constipation was reported in 10% of patients administered [quetiapine](#) extended-release 400 to 800 mg/day (n=151) compared with 3% of patients administered placebo (n=160) during a 3-week clinical trial for the treatment of bipolar mania [2].

6j) Constipation was reported in 10% of patients administered [quetiapine](#) 75 to 800 mg/day (n=698) compared with 4% of patients administered placebo (n=347) during 8-week clinical trials for the treatment of [bipolar depression](#) [6].

7j) Constipation was reported in 10% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 5% of patients administered placebo (n=203) during a 3-week, clinical trial for the treatment of bipolar mania [6].

c) Pediatrics

1j) In a study of children and adolescents (10 to 17 years old) with bipolar mania, constipation was reported in 4% of patients administered [quetiapine](#) 400 mg/day (n=95), 2% of patients administered [quetiapine](#) 600 mg/day (n=98), and 0% of patients administered placebo (n=90) during a 3-week a clinical trial [2] [6].

3.3.4.A.3] Increased appetite

a) Incidence: 2% to 12% [2] [6]

b) Adults

1j) Increased appetite was reported in 2% of patients administered [quetiapine](#) extended-release 300 to 800 mg/day (n=951) compared with 0% of patients administered placebo

(n=319) during a 6-week placebo-controlled clinical trial for the treatment of [schizophrenia](#) [2].

2) Increased appetite was reported in 2% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 1% of patients administered placebo (n=203) during 3-week clinical trials in the treatment of bipolar mania [6].

3) Increased appetite was reported in 3% of patients administered adjunctive [quetiapine](#) extended-release 150 mg/day (n=315) and 5% of patients administered [quetiapine](#) extended-release 300 mg/day (n=312) compared with 3% of patients administered placebo (n=309) during a 6-week, fixed-dose clinical trial for [major depressive disorder](#) [2].

4) Increased appetite was reported in 4% of patients administered [quetiapine](#) extended-release 400 to 800 mg/day (n=151) compared with 2% of patients administered placebo (n=160) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [2].

5) Increased appetite was reported in 5% of patients administered [quetiapine](#) 300 and 600 mg/day (n=698) compared with 3% of patients administered placebo (n=347) during 8-week placebo-controlled clinical trials for the treatment of [bipolar depression](#) [6].

6) Increased appetite was reported in 12% of patients administered [quetiapine](#) extended-release 300 mg/day (n=137) compared with 6% of patients administered placebo (n=140) during an 8-week placebo-controlled clinical trial for the treatment of [bipolar depression](#) [2].

c) Pediatrics

1) Increased appetite was reported in 10% of pediatric patients (aged 10 to 17 years) administered [quetiapine](#) 400 mg/day (n=95) and 9% of patients administered [quetiapine](#) 800 mg/day (n=98) compared with 1% of patients administered placebo (n=90) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [6].

3.3.4.A.4) Indigestion

a) Incidence: 2% to 7% [2] [6]

b) Adults

1) [Dyspepsia](#) was reported in 2% of patients administered adjunctive [quetiapine](#) extended-release 150 mg/day (n=315), 3% of patients administered [quetiapine](#) extended-release 300 mg/day (n=312), and 2% of patients administered placebo (n=309) during 6-week clinical trials in the treatment of [major depressive disorder](#) [2].

2) [Dyspepsia](#) was reported in 4% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 3% of patients administered placebo (n=203) during a 3-week clinical trial in the treatment of bipolar mania [6].

3) [Dyspepsia](#) was reported in 5% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 1% of patients administered placebo (n=404) during monotherapy trials of 3 to 12 weeks duration in the treatment of [schizophrenia](#) or bipolar mania [6].

4) [Dyspepsia](#) was reported in 5% of patients administered [quetiapine](#) extended-release 300 to 800 mg/day (n=951) compared with 2% of patients administered placebo (n=319) during 6-week clinical trials in the treatment of [schizophrenia](#) [2].

5j) **Dyspepsia** was reported in 7% of patients administered **quetiapine** extended-release 400 to 800 mg/day (n=151) compared with 4% of patients administered placebo (n=160) during a 3-week clinical trial in the treatment of bipolar mania [2].

6j) **Dyspepsia** was reported in 7% of patients administered **quetiapine** 300 and 600 mg/day (n=698) compared with 4% of patients administered placebo (n=347) during an 8-week clinical trial for the treatment of **bipolar depression** [6].

7j) **Dyspepsia** was reported in 7% of patients administered **quetiapine** extended-release 300 mg/day (n=137) compared with 1% of patients administered placebo (n=140) during an 8-week clinical trial for the treatment of **bipolar depression** [2].

8j) A logistic regression analysis of a placebo-controlled clinical study of 5 fixed-doses of **quetiapine** in adult patients with **schizophrenia** revealed a positive correlation between dose and the occurrence of **dyspepsia** (p less than 0.05). Doses included in these studies were 75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day, and 750 mg/day [6].

3.3.4.A.5] Nausea

a) Incidence: pediatrics, 6% to 10% [2] [6]

b) Pediatrics

1j) In a study of children and adolescents (10 to 17 years old) with bipolar mania, nausea was reported in 6% of patients administered **quetiapine** 400 mg/day (n=95), 10% of patients administered **quetiapine** 600 mg/day (n=98), and 4% of patients administered placebo (n=90) during a 3-week clinical trial [6].

3.3.4.A.6] Pancreatitis

a) **Pancreatitis**, temporally related to **quetiapine** therapy, has been reported during postmarketing surveillance [2] [6].

b) A case report described **pancreatitis** and life-threatening **diabetic ketoacidosis** in a 30-year-old woman following **quetiapine** use. The patient, who was mildly obese and had a history of **polycystic ovary disease**, was being treated with oral **ziprasidone** 80 mg twice daily for **schizophrenia**. Two months later, oral **quetiapine** 20 mg/day was initiated for augmentation and titrated up to 200 mg/day. Seven months after **quetiapine** was initiated, she presented to the emergency department with a 2-day history of acute stomach pain along with vomiting and excessive thirst and urination. Her family and personal histories were negative for hypertriglyceridemia, alcohol abuse, and **diabetes mellitus**. Laboratory results showed elevated blood glucose (1081 mg/dL) with 4+ acetone and elevated **triglyceride** level of 537 mg/dL. Following ICU admittance for **diabetic ketoacidosis**, further lab results revealed elevated **amylase** and lipase levels of 550 and 982 international units/L, respectively. In addition, abdominal **CT scan** and ultrasound revealed moderate acute **pancreatitis** and gallbladder sludge. Subsequently, IV fluids and pain medications were administered. **Quetiapine** and **ziprasidone** were withdrawn and **haloperidol** was initiated. After 3 days, **amylase** and lipase levels normalized (114 and 126 international units/L, respectively). She was discharged from the hospital with no further **sequelae**. Despite the patient's risk factors for developing **glucose intolerance**, the authors concluded that the case of **pancreatitis** was attributable to the use of low-dose **quetiapine** in associated with **ziprasidone** [50].

c) Three cases of acute **pancreatitis**, 1 of which fatal, were reported in 3 women (aged 35, 58, and 45 years) following **quetiapine** use. Although 2 cases involved coadministration of **valproic acid**, acute **pancreatitis** appeared to occur shortly after initiation of **quetiapine** therapy [55].

1J) A 35-year-old woman, who had a history of bipolar effective disorder, was admitted for psychiatric care for agitation, hallucination, and delusional thinking. She was reinitiated on [quetiapine](#) (titrated to 100 mg in the morning and 300 mg at bedtime) and [valproic acid](#) (1000 mg twice daily) due to noncompliance on an outpatient basis. Nine days later, her [valproic acid](#) trough blood level was suboptimal to warrant a dose increase to a daily dose of 2250 mg. Her concomitant regimen also included oral [haloperidol](#) and IM [haloperidol](#) decanoate. She was discharged with psychiatric follow-up while maintaining on [valproic acid](#) 2250 mg/day, [quetiapine](#) 400 mg/day, and IM [haloperidol](#) decanoate. Three weeks after discharge, lab results showed normal levels and the patient was not experiencing any abdominal pain. However, 1 week later, she died suddenly. An autopsy showed acute [pancreatitis](#) with severe hydration as cause of death that was possibly associated with either [quetiapine](#) or [valproic acid](#) [55].

2J) A 58-year-old woman was presented with 24-hour history of abdominal and back pain and 3-week history of unresolved nausea. The patient reported taking [quetiapine](#) 50 mg initiated within the previous month for [bipolar disorder](#), [valproic acid](#) 750 mg twice daily, [bupropion](#) sustained-release 150 mg once daily, [gabapentin](#) 100 mg 3 times daily, [warfarin](#), [clonidine](#), and [docusate](#). Laboratory results showed elevated [amylase](#) and lipase values of 232 and 1335 international units/L, respectively. A diagnosis of acute [pancreatitis](#) of unknown origin was made based on [magnetic resonance cholangiopancreatography](#). She was treated with narcotics and IV fluids, and then discharged. Seventeen months later, the patient again presented with abdominal pain. Upon admission, her [quetiapine](#) dose was 50 mg/day. Laboratory results showed elevated [amylase](#) and lipase values of 881 and 7440 international units/L. She was diagnosed with acute exacerbation of [chronic pancreatitis](#). Eleven days later, she was discharged with oral [pancrelipase](#). The Naranjo probability scale score of 6 suggested that [quetiapine](#) was a probable cause of the [pancreatitis](#) [55].

3J) The last case involved a 45-year-old woman on [quetiapine](#) therapy (dose not specified) who was hospitalized with abdominal pain, decreased appetite, nausea, and vomiting. An abdominal [CT scan](#) showed colon [diverticulosis](#). Laboratory results revealed an elevated lipase level of 323 international units/L and a normal [amylase](#) level. She was treated and discharged home after 4 days. Six months later, she was admitted for left lower quadrant abdominal pain. Laboratory results showed elevated lipase, [amylase](#), and WBC counts. The pancreatic tract showed inflammatory change on abdominal [CT scan](#). An MRI revealed [chronic pancreatitis](#) with multiple [pseudocysts](#) and acute in chronic [pancreatitis](#) in the pancreatic tail. She was treated with supportive care (IV fluids and pain medication) before being discharged with [pancrelipase](#) powder and [quetiapine](#) 200 mg/day. The Naranjo probability scale score of 4 suggested that [quetiapine](#) was a possible cause of the [pancreatitis](#) [55].

3.3.4.A.7] Summary

aJ) Anticholinergic adverse effects of [quetiapine](#) therapy are dose-related. Dry mouth occurred in 8% to 17% of schizophrenic patients in clinical trials. Constipation was also reported. Abdominal pain, [dyspepsia](#), and anorexia occurred less commonly [45] [56] [15]. In addition, 4 cases of acute [pancreatitis](#), 1 of which was fatal, were reported in 4 women following [quetiapine](#) use [50] [55].

3.3.4.A.8] Vomiting

aJ) Incidence: pediatrics, 7% to 8% [2] [6]

b) Pediatrics

1j) In a study of children and adolescents (10 to 17 years old) with bipolar mania, vomiting was reported in 8% of patients administered [quetiapine](#) 400 mg/day (n=95), 7% of patients administered [quetiapine](#) 600 mg/day (n=98), and 3% of patients administered placebo (n=90) during a 3-week clinical trial [6].

3.3.4.A.9j Xerostomia

a) Incidence: adults, 9% to 44%; pediatrics, 4% to 10% [2] [6]

b) Adults

1j) Dry mouth was reported in 9% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 3% of patients administered placebo (n=404) during monotherapy clinical trials of 3 to 12 weeks duration for the treatment of [schizophrenia](#) or bipolar mania [6].

2j) Dry mouth was reported in 12% of patients administered [quetiapine](#) extended-release 300 to 800 mg/day (n=951) compared with 1% of patients administered placebo (n=319) during 6-week placebo-controlled clinical trials for the treatment of [schizophrenia](#) [2].

3j) Dry mouth was reported in 19% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 3% of patients administered placebo (n=203) during a 3-week, clinical trial for the treatment of bipolar mania [6].

4j) Dry mouth was reported in 27% of patients administered adjunctive [quetiapine](#) extended-release 150 mg/day (n=315) and 40% of patients administered [quetiapine](#) extended release 300 mg/day (n=312) compared with 8% of patients administered placebo (n=309) during a 6-week, fixed-dose clinical trial for [major depressive disorder](#) [2].

5j) Dry mouth was reported in 34% of patients administered [quetiapine](#) extended-release 400 to 800 mg/day (n=151) compared with 7% of patients administered placebo (n=160) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [2].

6j) Dry mouth was reported in 37% of patients administered [quetiapine](#) extended-release 300 mg/day (n=137) compared with 7% of patients administered placebo (n=140) during an 8-week placebo-controlled clinical trial for the treatment of [bipolar depression](#) [2].

7j) Dry mouth was reported in 44% of patients administered [quetiapine](#) 300 and 600 mg/day (n=698) compared with 13% of patients administered placebo (n=347) during an 8-week, placebo-controlled clinical trial for the treatment of [bipolar depression](#) [6].

c) Pediatrics

1j) Dry mouth was reported in 4% of pediatric patients (aged 13 to 17 years) administered [quetiapine](#) 400 mg/day (n=73) and 10% of patients administered [quetiapine](#) extended release 800 mg/day (n=74) compared with 1% of patients administered placebo (n=75) during a 6-week placebo-controlled clinical trial for the treatment of [schizophrenia](#) [6].

2j) Dry mouth was reported in 7% of pediatric patients (aged 10 to 17 years) administered [quetiapine](#) 400 mg/day (n=95) and 7% of patients administered [quetiapine](#) extended release 600 mg/day (n=98) compared with 0% of patients administered placebo (n=90) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [2].

3.3.5] Hematologic Effects

3.3.5.A] Quetiapine Fumarate

3.3.5.A.1] Agranulocytosis

a)] **Agranulocytosis**, including fatal incidences, has been reported during clinical trials and postmarketing use of **quetiapine** [32] [33].

3.3.5.A.2] Decreased hemoglobin

a)] Incidence: 8.3% [2] [6]

b)] Decreases in **hemoglobin** (less than or equal to 13 g/dL for males and less than or equal to 12 g/dL for females) occurring at least once were reported in 8.3% of patients administered **quetiapine** (n=7155) compared with 6.2% of patients administered placebo (n=3536) during short-term, placebo-controlled clinical trials. In a pooled analysis of controlled and uncontrolled clinical trials, decreased **hemoglobin** was reported in 11% of patients administered **quetiapine** (n=20,279) [2] [6].

3.3.5.A.3] Leukopenia

a)] **Leukopenia** has been reported during clinical trials and postmarketing use of **quetiapine** fumarate. Patients possibly at risk for developing **leukopenia** include those with a preexisting low WBC or a history of drug-induced **leukopenia**. Should **leukopenia** develop during **quetiapine** therapy, discontinue therapy [32] [33].

b)] A 38-year-old man with **paranoid schizophrenia** experienced **leukopenia** while taking **quetiapine**. The patient was started on **quetiapine** after experiencing side effects to numerous other antipsychotic agents, including clozapine-induced **neutropenia**. Over a 4-year period of **quetiapine** 400 mg daily, the patient complained of frequent and severe **upper respiratory infections**, requiring 4 hospitalizations. Throughout that time, the WBC count was often 2 to 3 x10(9)/L; the lowest value noted was 1.07 x 10(9)/L with an absolute neutrophil count of 0.89 x 10(9)/L. During each hospitalization, other possible causes were investigated and ruled out via abdominal CT and testing for HIV, **hepatitis**, cytomegalovirus, and Epstein-Barr virus. After discontinuing **quetiapine**, the WBC increased to 4.83 x 10(9)/L and the patient noted significantly fewer respiratory infections [34].

3.3.5.A.4] Neutropenia

a)] Incidence: 0.3% to 1.5% [2] [6]

b)] **Neutropenia** has also been reported during postmarketing use of **quetiapine** fumarate. Patients possibly at risk for developing **neutropenia** include those with a preexisting low WBC or a history of drug-induced **neutropenia**. Should severe **neutropenia** develop, discontinue therapy [2] [6]

c)] **Neutropenia** (neutrophil count less than 1.5 x 10(9)/L) was reported in 1.5% of patients administered extended-release **quetiapine** monotherapy compared with 0.8% of patients administered placebo during clinical trials in adults with **bipolar disorder** [2].

d)] **Neutropenia** (neutrophil count less than 1 x 10(9)/L) was reported in 0.3% of patients treated with **quetiapine** monotherapy (n=2967) compared with 0.1% for placebo (n=1349) during placebo-controlled clinical trials [6].

e)] A 38-year old man with **paranoid schizophrenia** experienced **neutropenia** while taking **quetiapine**. The patient was started on **quetiapine** after experiencing side effects to numerous other antipsychotic agents, including clozapine-induced **neutropenia**. Over a 4-year period of **quetiapine** 400 mg daily, the patient complained of frequent and severe **upper respiratory infections**, requiring 4 hospitalizations. Throughout that time, the WBC count was often 2 to 3 x10(9)/L; the lowest value noted was 1.07

x 10(9)/L with an absolute neutrophil count of 0.89 x 10(9)/L. During each hospitalization other possible causes were investigated and ruled out via abdominal CT, and testing for HIV, hepatitis, cytomegalovirus and Epstein-Barr virus. After discontinuing quetiapine, the WBC increased to 4.83 x 10(9)/L and the patient noted significantly fewer respiratory infections [34].

3.3.5.A.5] Pancytopenia

a) Pancytopenia developed in a 71-year-old Caucasian male with a history of Parkinson disease 3 weeks after beginning quetiapine therapy at a dose of 25 mg twice daily for the treatment of drug-induced hallucinations. The patient's blood counts improved within 48 hours of withdrawal of the drug and returned to normal in 7 days [35].

3.3.5.A.6] Thrombocytopenia

a) Incidence: less than 1% [6]

b) Thrombocytopenia has been reported in less than 1% of approximately 2200 patients who received quetiapine for schizophrenia during clinical trials [6].

c) Within 9 months of starting quetiapine, a 16-year-old girl developed thrombocytopenia, which resolved after discontinuation of quetiapine. She started on quetiapine 25 mg/day for insomnia in combination with sertraline, valproic acid, and buspirone for depression, anxiety, and 2 failed suicide attempts. Her baseline platelet count was within normal limits (233,000/mcL). Her mood stabilized. After approximately 9 months of treatment, the patient returned with manic symptoms including agitation, paranoia, suspicion, disorganization, and hypersexual tendencies and was diagnosed with bipolar I disorder. Sertraline and buspirone were discontinued and valproic acid was started at 500 mg twice daily. Quetiapine was increased to 50 mg/day. At the time of hospitalization for bipolar disorder symptoms, her platelet count was 183,000/mcL and valproic acid level was 99 mcg/mL. The patient's condition continued to deteriorate and she was readmitted to the hospital 1 week later with worsening symptoms. On admission her platelet count was 149,000/mcL and valproic acid level was 118 mcg/mL. Valproic acid was discontinued and the dose of quetiapine was gradually increased to 600 mg/day. One week after readmission the platelet count was 61,000/mcL and the valproic acid level was less than 10 mcg/mL. This confirmed that valproic acid was not the causative factor for the lowered platelet counts and further observation revealed that the patient's platelet count lowered with each dose increase of quetiapine. Quetiapine was discontinued and lithium was started at 150 mg twice daily. The platelet count 24 hours after discontinuation of quetiapine was 122,000/mcL. The patient had a platelet count within normal limits (183,000/mcL) 1 week after discontinuation and reported a significant mood improvement and resolution of manic and psychotic symptoms [31].

3.3.6] Hepatic Effects

3.3.6.A] Quetiapine Fumarate

3.3.6.A.1] Increased liver enzymes

a) Incidence: 1% to 6% [2] [6]

b) Transient, asymptomatic, and reversible elevations in serum transaminases, primarily ALT, have been reported. Peak elevations are usually seen within the first 3 weeks of treatment and most return to baseline values with continued therapy [2] [6].

c) Elevated serum transaminase levels (greater than 3 times the ULN) was reported in 1% to 6% of adult patients treated with quetiapine or quetiapine extended-release in multiple, placebo-controlled clinical trials [2] [6].

3.3.7] Immunologic Effects

3.3.7.A] Quetiapine Fumarate

3.3.7.A.1] Anaphylaxis

a) **Anaphylactic reactions**, temporally related to **quetiapine** therapy, have been reported during postmarketing surveillance [2] [6].

3.3.8] Musculoskeletal Effects

3.3.8.A] Quetiapine Fumarate

3.3.8.A.1] Backache

a) Incidence: 3% to 5% [32] [33]

b) Back pain was reported in 3% to 5% of adult patients treated with **quetiapine** or **quetiapine** extended-release in multiple, placebo-controlled clinical trials [32] [33].

c) Back pain was reported in 2% of children and adolescents (10 to 17 years of age) treated for **schizophrenia** (up to 6 weeks) and bipolar mania (up to 3 weeks) with **quetiapine** at doses of 400, 600, or 800 mg/day (n=340) compared with 1% of those treated with placebo (n=165) in short-term, placebo-controlled clinical trials [32].

3.3.8.A.2] Rhabdomyolysis

a) **Rhabdomyolysis**, temporally related to **quetiapine** therapy, has been reported during postmarketing surveillance [2] [6].

3.3.9] Neurologic Effects

3.3.9.A] Quetiapine Fumarate

3.3.9.A.1] Akathisia

a) Incidence: 1% to 4.8% [32] [33]

b) **Akathisia** was reported in 1% to 4.8% of adult, adolescent, and pediatric patients treated with **quetiapine** or **quetiapine** extended-release in multiple clinical trials [32] [33].

c) **Akathisia** developed in a male patient with **Parkinson disease** following the administration of **quetiapine** for the treatment of dopaminergic **psychosis**. The 62-year-old man was taking **levodopa** at a daily dose of 400 mg and **quetiapine** at a dose of 12.5 to 25 mg daily for approximately 5 days when he developed severe motor restlessness and an inability to stop pacing. His score on the Barnes **Akathisia** Scale reached 14 (range, 0=no symptoms to 14=severe **akathisia**). **Quetiapine** was withdrawn and symptoms of **akathisia** completely resolved within 2 days [41].

3.3.9.A.2] Altered mental status

a) A 62-year-old man experienced acute mental status changes within 3 days of increasing his **quetiapine** dose to 300 mg daily and symptoms resolved within 48 hours of discontinuing **quetiapine**. There was no clinical evidence of **stroke**, **serotonin syndrome**, or alcohol intoxication or withdrawal. **Quetiapine** is believed to be associated with the mental status changes due to the close temporal relationship between the onset and resolution of symptoms [48].

3.3.9.A.3] Asthenia

a) Incidence: up to 10% [6]

b) Adults

1) Asthenia was reported in 2% of patients administered [quetiapine](#) 300 and 600 mg/day (n=698) compared with 1% of patients administered placebo (n=347) during an 8-week clinical trial for the treatment of [bipolar depression](#) [6].

2) Asthenia was reported in 5% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 3% of patients administered placebo (n=404) during monotherapy trials of 3 to 12 weeks duration in the treatment of [schizophrenia](#) or bipolar mania [6].

3) Asthenia was reported in 10% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 4% of patients administered placebo (n=203) during a 3-week clinical trial for bipolar mania [6].

c) Pediatrics

1) In a study of adolescents (13 to 17 years) with [schizophrenia](#), asthenia was reported in 1% of pediatric patients administered [quetiapine](#) 400 mg/day (n=73), 3% of patients administered [quetiapine](#) 800 mg/day (n=74), and 1% of patients administered placebo (n=75) during a 6-week, placebo-controlled clinical trial [6].

3.3.9.A.4] Cerebrovascular accident

a) Cerebrovascular adverse reactions, including cerebrovascular accident and [transient ischemic attack](#), were reported more frequently in elderly patients with dementia-related [psychosis](#) administered an atypical antipsychotic (eg, [risperidone](#), [aripiprazole](#), [olanzapine](#)) compared with patients administered placebo during clinical trials [2] [6].

3.3.9.A.5] Dizziness

a) Incidence: 8% to 19% [2] [6]

b) Adults

1) Dizziness was reported in 9% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 6% of patients administered placebo (n=203) during a 3-week clinical trial in the treatment of bipolar mania [6].

2) Dizziness was reported in 10% of patients administered [quetiapine](#) extended-release 300 to 800 mg/day (n=951) compared with 4% of patients administered placebo (n=319) during 6-week clinical trials in the treatment of [schizophrenia](#) [2].

3) Dizziness was reported in 10% of patients administered [quetiapine](#) extended-release 400 to 800 mg/day (n=151) compared with 4% of patients administered placebo (n=160) during a 3-week clinical trial in the treatment of bipolar mania [2].

4) Dizziness was reported in 11% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 5% of patients administered placebo (n=404) during monotherapy trials of 3 to 12 weeks duration in the treatment of [schizophrenia](#) or bipolar mania [6].

5j) Dizziness was reported in 11% of patients administered adjunctive [quetiapine](#) extended-release 150 mg/day (n=315), 12% of patients administered [quetiapine](#) extended-release 300 mg/day (n=312), and 7% of patients administered placebo (n=309) during a 6-week clinical trial in the treatment of [major depressive disorder](#) [2].

6j) Dizziness was reported in 13% of patients administered [quetiapine](#) extended-release 300 mg/day (n=137) compared with 11% of patients administered placebo (n=140) during an 8-week clinical trial in the treatment of [bipolar depression](#) [2].

7j) Dizziness was reported in 18% of patients administered [quetiapine](#) 300 or 600 mg/day (n=698) compared with 7% of patients administered placebo (n=347) during an 8-week clinical trial for the treatment of [bipolar depression](#) [6].

c) Pediatrics

1j) In a study of adolescents (13 to 17 years old) with [schizophrenia](#), dizziness was reported in 8% of patients administered [quetiapine](#) 400 mg/day (n=73), 15% of patients administered [quetiapine](#) 800 mg/day (n=74), and 5% of patients administered placebo (n=75) during a 6-week clinical trial [6].

2j) In a study of children and adolescents (10 to 17 years old) with bipolar mania, dizziness was reported in 19% of patients administered [quetiapine](#) 400 mg/day (n=95), 17% of patients administered [quetiapine](#) 600 mg/day (n=98), and 2% of patients administered placebo (n=90) during a 3-week clinical trial [6].

3.3.9.A.6] [Dystonia](#)

a) Incidence: 1% to less than 5% [33] [32]

b) During the first few days after initiating treatment with an antipsychotic medication, symptoms of [dystonia](#) may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of the throat, swallowing difficulty, breathing difficulty, or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with a greater severity) with high potency and at higher doses of first generation antipsychotic medications. Men and younger age groups appear to be at greater risk for developing acute [dystonia](#) [32].

c) [Dystonia](#) was reported in 1% of adult patients receiving [quetiapine](#) at doses of 300 to 600 mg/day (n=698) compared with 0% of those receiving placebo (n=347) in placebo-controlled clinical trials for the treatment of [bipolar depression](#) (up to 8 weeks) [32].

d) [Dystonia](#) was reported in less than 5% of adult patients taking [quetiapine](#) extended-release during clinical trials for the treatment of [schizophrenia](#) [33].

e) A 43-year-old Caucasian woman developed acute [dystonia](#) after receiving 4 weeks of [quetiapine](#) at a stable dose of 400 mg daily. The woman experienced slow movement of her head to the right side, neck stiffness, and an increased incidence of involuntary movement when under stress. Dystonic movement of her head to the right was also observed. The patient was cross-tapered to [ziprasidone](#) (80 mg/day) and symptoms of [dystonia](#) resolved once the [quetiapine](#) dose was reduced to 100 mg/day [42].

3.3.9.A.7] [Extrapyramidal disease](#)

a) Incidence: 1.1% to 12.9% [2] [6]

b) Adults

1J) Extrapyramidal symptoms were reported in 3% of patients administered [quetiapine](#) 300 or 600 mg/day (n=698) compared with 1% of patients administered placebo (n=347) during an 8-week clinical trial for the treatment of [bipolar depression](#) [6].

2J) Extrapyramidal symptoms (ie, [akathisia](#), muscle spasm, [dystonia](#), tremor) were reported in 4% of patients administered [quetiapine](#) extended-release 300 mg/day (n=137) compared with 1% of patients administered placebo (n=140) during an 8-week placebo-controlled clinical trial for the treatment of [bipolar depression](#) [2].

3J) Extrapyramidal symptoms (ie, [akathisia](#), [dyskinesia](#), muscle spasm, tremor) were reported in 4% of patients administered adjunctive [quetiapine](#) extended-release 150 mg/day (n=315), 6% of patients administered [quetiapine](#) extended-release 300 mg/day (n=312), and 4% of patients administered placebo (n=309) during a 6-week clinical trial for [major depressive disorder](#) [2].

4J) Extrapyramidal symptoms (ie, [akathisia](#), muscle spasm, [dystonia](#)) were reported in 7% of patients administered [quetiapine](#) extended-release 400 to 800 mg/day (n=151) compared with 4% of patients administered placebo (n=160) during a 3-week clinical trial for the treatment of bipolar mania [2].

5J) In placebo-controlled clinical trials for the treatment of [schizophrenia](#) utilizing [quetiapine](#) doses between 300 mg and 800 mg/day, the incidence of any adverse reaction potentially related to extrapyramidal symptoms was 8% for both [quetiapine](#) and [quetiapine](#) extended-release compared with 5% in placebo. In these studies, the incidence of the individual adverse reactions (eg, [akathisia](#), [extrapyramidal disorder](#), tremor, [dyskinesia](#), [dystonia](#), restlessness, and muscle rigidity) did not exceed 3% for any treatment group [2].

cJ) Pediatrics

1J) The aggregated incidence of extrapyramidal symptoms was 1.1% in pediatric patients (aged 10 to 17 years) administered [quetiapine](#) extended-release monotherapy (n=92) compared with 0% of patients administered placebo (n=100) during an 8-week clinical trial for the treatment of [bipolar depression](#) [2].

2J) The aggregated incidence of extrapyramidal symptoms was 3.6% in pediatric patients (aged 10 to 17 years) administered [quetiapine](#) monotherapy (n=193) compared with 1.1% of patients administered placebo (n=90) during a 3-week clinical trial for the treatment of bipolar mania [6].

3J) The aggregated incidence of extrapyramidal symptoms was 12.9% in pediatric patients (aged 13 to 17 years) administered [quetiapine](#) monotherapy (n=147) compared with 5.3% of patients administered placebo (n=75) during a 6-week clinical trial for the treatment of [schizophrenia](#). The incidence of individual adverse events (ie, [akathisia](#), tremor, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, [dyskinesia](#)) did not exceed 4.1% in any treatment group [6].

3.3.9.A.8J Extrapyramidal sign

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.A.9J Headache

aJ) Incidence: 17% to 21% [6]

b) Headache was reported in 17% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 13% of patients administered placebo (n=203) during a 3-week clinical trial for the treatment of bipolar mania [6].

c) Headache was reported in 21% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 14% of patients administered placebo (n=404) during monotherapy clinical trials of 3 to 12 weeks duration for the treatment of [schizophrenia](#) or bipolar mania [6].

3.3.9.A.10] Insomnia

a) Incidence: 8% to 12% [32] [33] [43] [44] [45] [46] [15] [47]

b) Insomnia was reported in 8.5% of adult schizophrenic patients taking [quetiapine](#) extended-release (n=94) in a randomized, placebo-controlled, long-term trial (up to 12 months) [33].

c) Insomnia was reported in 8% of children and adolescent patients treated with [quetiapine](#) tablets for [schizophrenia](#) or bipolar mania in a 26-week, open-label trial [32].

d) The adverse effect of insomnia has a 12% frequency with [quetiapine](#) use [43] [44] [45] [46] [15] [47].

3.3.9.A.11] Lethargy

a) Incidence: 1% to 5% [32] [33]

b) Lethargy was reported in 5% of adult patients receiving [quetiapine](#) at doses ranging from 300 to 600 mg/day (n=698) compared with 2% of patients receiving placebo (n=347) in controlled clinical trials for the treatment of [bipolar depression](#) (up to 8 weeks) [32].

c) Lethargy was reported in 1% to 2% of adult patients receiving [quetiapine](#) extended-release at doses ranging from 150 to 800 mg/day in multiple, placebo-controlled clinical trials for the treatment of bipolar mania (3 weeks) and for the adjunctive treatment of [major depressive disorder](#) (up to 6 weeks) [33].

d) Lethargy was reported in 1% of children and adolescents (aged 10 to 17 years) receiving [quetiapine](#) at doses of 400, 600, or 800 mg/day (n=340) compared with 0% of patients receiving placebo (n=165) in short-term, placebo-controlled clinical trials for the treatment of [schizophrenia](#) (up to 6 weeks) and bipolar mania (up to 3 weeks) [32].

3.3.9.A.12] [Parkinsonism](#)

a) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk for the development of [parkinsonism](#) as does typical antipsychotic therapy. In a population-based, retrospective, cohort study, adults (aged 66 years or older) with evidence of [dementia](#) were followed for up to 1 year for the development of [parkinsonism](#) symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, [olanzapine](#), [risperidone](#), [quetiapine](#)), incident [parkinsonism](#) was 30% more likely to occur in those taking typical antipsychotics (ie, [chlorpromazine](#), [haloperidol](#), [perphenazine](#); adjusted hazard ratio [HR], 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patients who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing [parkinsonism](#) compared with patients prescribed atypical antipsychotics (all were considered lower potency; HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing [parkinsonism](#) was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95% CI, 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incident [parkinsonism](#) and the use of atypical antipsychotics. The risk for developing [parkinsonism](#) was more than twice as great in patients using a high-dose atypical antipsychotic agent compared with those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the development of

[parkinsonism](#) as patients receiving high-dose atypical antipsychotic therapy (p=nonsignificant). The authors concluded that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered [40].

3.3.9.A.13] [Pleurothotonus](#)

a) A 69-year-old woman experienced Pisa syndrome following treatment with [quetiapine](#) for anxious-depressive condition and slight [dementia](#). [Quetiapine](#) (200 mg/day) and [olanzapine](#) (10 mg/day) stabilized her condition during her 2.5-month hospital stay, but were discontinued during her outpatient follow-up care. Alzheimer-type [dementia](#) returned and [galantamine](#) therapy was initiated (up to 16 mg/day), but was discontinued after rapid deterioration 1.5 years later. The patient was again hospitalized for severe [dementia](#). One week before hospitalization, the patient received [trazodone](#) (50 mg/day), [lorazepam](#) (2 mg/day), and [olanzapine](#) (5 mg/day). Five days prior to hospitalization, [quetiapine](#) was reinitiated due to increased agitation with dose titration up to 300 mg/day. Although [quetiapine](#) reduced her aggressive impulses, the appearance of [dystonia](#) on her trunk was apparent during the first days of admittance, fulfilling the criteria of a Pisa Syndrome with a rotation to the right side. [Quetiapine](#) was immediately reduced to 75 mg/day, and [olanzapine](#) was discontinued. All other medications remained unchanged. The severity of the Pisa syndrome reduced significantly following [quetiapine](#) dose reduction and [olanzapine](#) discontinuation. On day 3, [quetiapine](#) was discontinued; however, her confusion increased. Again [quetiapine](#) was introduced at 50 mg/day which led to a slight rotation of her trunk to the right side. [Quetiapine](#) was discontinued within 3 days, and within 2 days, [dystonia](#) decreased and disappeared [39].

3.3.9.A.14] [Restless legs syndrome](#)

a) Incidence: 1% to 2% [32] [33].
b) [Restless legs](#) were reported in 1% to 2% of adult patients receiving [quetiapine](#) fumarate during multiple clinical trials. [Restless leg](#) has also been reported in postmarketing use [32] [33].

3.3.9.A.15] [Retrograde amnesia](#)

a) [Retrograde amnesia](#), temporally related to [quetiapine](#) therapy, has been reported during postmarketing surveillance [2] [6].

3.3.9.A.16] [Seizure](#)

a) Incidence: 0.05% to 0.5% [32] [33]
b) Seizures were reported in 0.5% of patients treated with [quetiapine](#) (n=3490) compared with 0.7% treated with active control drugs (n=527) and 0.2% treated with placebo (n=954) in clinical trials [32].
c) Seizures were reported in 0.05% of patients treated with [quetiapine](#) extended-release (1 of 1866) compared with 0.3% for placebo (3 of 928) in clinical trials across all indications [33].
d) [Quetiapine](#) fumarate should be used cautiously in patients with a history of seizures or with conditions that may lower seizure threshold. These conditions may be more prevalent in patients older than 65 years [32] [33].

3.3.9.A.17] [Somnolence](#)

a) Summary

1) Somnolence was commonly reported during [quetiapine](#) fumarate clinical trials, especially during the initial dose titration periods [6] [2].

b) Incidence: 18% to 57% [2] [6]

c) Adults

- 1)** Somnolence was reported in 18% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 8% of patients administered placebo (n=404) during monotherapy clinical trials of 3 to 12 weeks duration for the treatment of [schizophrenia](#) or bipolar mania. Somnolence was the primary reason for study discontinuation in 0.8% of patients administered [quetiapine](#) for [schizophrenia](#) compared with 0% of patients administered placebo [6].
- 2)** Somnolence was reported in 25% of patients administered [quetiapine](#) extended-release 300 to 800 mg/day (n=951) compared with 10% of patients administered placebo (n=319) during a 6-week placebo-controlled clinical trial for the treatment of [schizophrenia](#) [2].
- 3)** Somnolence was reported in 34% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 9% of patients administered placebo (n=203) during a 3-week clinical trial for the treatment of bipolar mania [6].
- 4)** Somnolence was reported in 37% of patients administered adjunctive [quetiapine](#) extended-release 150 mg/day (n=315), 43% of patients administered [quetiapine](#) extended-release 300 mg/day (n=312), and 9% of patients administered placebo (n=309) during a 6-week clinical trial for [major depressive disorder](#). Somnolence was the primary reason for study discontinuation in greater than or equal to 2% of patients administered [quetiapine](#) [2].
- 5)** Somnolence was reported in 50% of patients administered [quetiapine](#) extended-release 400 to 800 mg/day (n=151) compared with 12% of patients administered placebo (n=160) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania [2].
- 6)** Somnolence was reported in 52% of patients administered [quetiapine](#) extended-release 300 mg/day (n=137) compared with 13% of patients administered placebo (n=140) during an 8-week placebo-controlled clinical trial for the treatment of [bipolar depression](#). Somnolence was the primary reason for study discontinuation in greater than or equal to 2% of patients administered [quetiapine](#) [2].
- 7)** Somnolence was reported in 57% of patients administered [quetiapine](#) 300 or 600 mg/day (n=698) compared with 15% of patients administered placebo (n=347) during an 8-week clinical trial for the treatment of [bipolar depression](#) [6].

d) Pediatrics

- 1)** In adolescents, 13 to 17 years old, somnolence was reported in 33% of patients administered [quetiapine](#) 400 mg/day (n=73), 35% of patients administered [quetiapine](#) 800 mg/day (n=74), and 11% of patients administered placebo (n=75) during a 6-week, placebo-controlled clinical trial for the treatment of [schizophrenia](#). Somnolence was the primary reason for study discontinuation in 2.7% of patients administered [quetiapine](#) compared with 0% of patients administered placebo [2] [6].
- 2)** In pediatric patients age 10 to 17 years, somnolence was reported in 50% of patients administered [quetiapine](#) 400 mg/day (n=95), 57% of patients administered [quetiapine](#) 600 mg/day (n=98), and 14% of patients administered placebo (n=90) during a 3-week placebo-controlled clinical trial for the treatment of bipolar mania. Somnolence was the primary reason for study discontinuation in 4.1% of patients administered [quetiapine](#) compared with 1.1% of patients administered placebo [2] [6].

3.3.9.A.18] Tardive dyskinesia

a) A potentially irreversible **tardive dyskinesia** may develop in patients receiving antipsychotic drugs; this may be related to the duration of treatment and the cumulative dose. Less commonly, the syndrome can develop after brief treatment periods at low doses. Antipsychotics may mask the underlying process by suppressing the signs and symptoms of the syndrome. The prevalence of the syndrome appears to be highest among the elderly, especially elderly women; however, it is impossible to rely upon prevalence to estimate which patients are likely to develop the syndrome. The syndrome may remit partially or completely upon discontinuation of the antipsychotic medication [32] [33].

b) During clinical trials for the treatment of **schizophrenia** in approximately 2200 adults, **tardive dyskinesia** was reported 0.1% to 1% of patients taking **quetiapine** [32].

c) A 44-year-old woman, who had **schizophrenia** that was resistant to typical neuroleptic agents, developed **tardive dyskinesia** after 6 months of **quetiapine** therapy. While receiving 150 mg of **quetiapine** daily, she developed involuntary **choreiform movements** of the tongue and jaw. Later, she also developed finger involvement. **Quetiapine** was discontinued and she began **clozapine** therapy, which improved the **tardive dyskinesia** symptoms [49].

3.3.9.A.19] Transient ischemic attack

a) Cerebrovascular adverse reactions, including cerebrovascular accident and **transient ischemic attack**, were reported more frequently in elderly patients with dementia-related **psychosis** administered an atypical antipsychotic (eg, **risperidone**, **aripiprazole**, **olanzapine**) compared with patients administered placebo during clinical trials [2] [6].

3.3.9.A.20] Tremor

a) Incidence: 2% to 8% [2] [6]

b) Tremor was reported in 2% of patients administered **quetiapine** 300 and 600 mg/day (n=698) compared with 1% of patients administered placebo (n=347) during 8-week clinical trials for the treatment of **bipolar depression** [6].

c) Tremor was reported in 2% of patients administered **quetiapine** extended-release 300 to 800 mg/day (n=951) compared with 1% of patients administered placebo (n=319) during 6-week clinical trials for the treatment of **schizophrenia** [2].

d) Tremor was reported in 8% of patients administered adjunctive **quetiapine** 100 to 800 mg/day (n=196) compared with 7% of patients administered placebo (n=203) during 3-week clinical trials for the treatment of bipolar mania [6].

3.3.10] Ophthalmic Effects

3.3.10.A] Quetiapine Fumarate

3.3.10.A.1] Amblyopia

a) Incidence: 2% to 3% [32]

b) **Amblyopia** was reported in 2% of patients receiving **quetiapine** at doses ranging from 75 to 800 mg/day (n=719) compared with 1% for patients receiving placebo (n=404) in controlled clinical trials for the treatment (monotherapy) of **schizophrenia** (up to 6 weeks) and bipolar mania (up to 12 weeks) in adults [32].

c) **Amblyopia** was reported in 3% of patients receiving **quetiapine** (n=203) compared with 2% for patients receiving placebo (n=196) in 3-week, placebo-controlled clinical trials for the adjunct treatment of acute mania in adult patients [32].

3.3.10.A.2] Disorder of lens

a)] Although a causal relationship has not been substantiated, lens changes in patients during long-term use of [quetiapine](#) fumarate have been reported. Examination to detect cataract formation is recommended at initiation of treatment or shortly after beginning treatment and every 6 months during the course of treatment [32] [33].

3.3.12] Psychiatric Effects

3.3.12.A] [Quetiapine](#) Fumarate

3.3.12.A.1] Agitation

a)] Incidence: 6% to 20% [6]

b)] Agitation was reported in 6% of patients administered adjunctive [quetiapine](#) 100 to 800 mg/day (n=196) compared with 4% of patients administered placebo (n=203) during 3-week, clinical trials in the acute management of bipolar mania [6].

c)] Agitation was reported in 20% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 17% of patients administered placebo (n=404) during monotherapy clinical trials of 3 to 12 weeks duration for the treatment of [schizophrenia](#) or bipolar mania [6].

3.3.12.A.2] Anxiety

a)] Incidence: 2% to 4% [32] [33]

b)] Anxiety was reported in 2% to 4% of adult patients treated with [quetiapine](#) or [quetiapine](#) extended-release in multiple, placebo-controlled clinical trials [32] [33].

3.3.12.A.3] Suicidal thoughts

a)] Adult and pediatric patients being treated with antidepressants for [major depressive disorder](#) or other psychiatric disorders who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), or mania may be at risk of [suicidal ideation](#) and behavior (suicidality). If these symptoms are observed, therapy should be reevaluated, and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. The dose should be tapered off, avoiding abrupt discontinuation whenever possible. Patients and their caregivers should be provided with the Medication Guide that is available for this drug [32] [33].

b)] A causal role for antidepressants in inducing suicidality has been established in children, adolescents, and young adults (up to 24 years old). Anyone considering the use of [quetiapine](#) fumarate or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Families and caregivers should be encouraged to observe the patient carefully for emerging symptoms and unexpected behavior. This causal role in children and adolescents was determined from pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressants (SSRIs and others) which included over 4400 patients with [major depressive disorder](#), [obsessive-compulsive disorder](#) (OCD), or other psychiatric disorders. The causal role in adults was determined from pooled analyses of 295 short-term, placebo-controlled trials of 11 antidepressants which included over 77,000 patients with [major depressive disorder](#) or other psychiatric disorders. The risk of suicidal thinking and behavior was increased in children, adolescents, and young adults up to 24 years old. This increased risk did not exist in adults older than 24 years, and the risk was lower in adults older than 65 years. The risk was highest in patients with [major depressive disorder](#), but there were signs of risk emerging from trials in other psychiatric indications, such as OCD and [social anxiety](#)

disorder. No suicides occurred in the pediatric trials. The risk of suicidality during longer-term use (ie, beyond several months) is not known [32] [33].

c) The incidence of treatment emergent suicidal ideation or attempt during 8 weeks of treatment was 1.7% and 2.6% in patients treated with quetiapine 300 mg/day (n=350) and 600 mg/day (n=348), respectively, compared with 2% of patients treated with placebo in 2 clinical studies involving patients with bipolar depression [32].

3.3.14] Reproductive Effects

3.3.14.A] Quetiapine Fumarate

3.3.14.A.1] Priapism

a) Priapism was reported in 1 patient taking quetiapine; a causal relationship has not been established [32] [33].

3.3.15] Respiratory Effects

3.3.15.A] Quetiapine Fumarate

3.3.15.A.1] Cough

a) Incidence: 3% [32]

b) Cough was reported in 3% of patients receiving quetiapine (n=698) compared with 1% for placebo (n=347); doses ranged from 300 to 600 mg/day [32].

3.3.15.A.2] Hyperventilation

a) A 69-year-old African-American woman, admitted for major depression with psychotic features, developed tachypnea and acute respiratory alkalosis 3 days after being discharged from the hospital. At the time of the occurrence, her maintenance dose of quetiapine was 50 mg twice daily with concurrent treatments with metronidazole and miconazole. Possible etiologies include a comorbid hypersensitivity to quetiapine or to the concomitant administration of metronidazole, which may inhibit metabolism of quetiapine. Symptoms improved after discontinuation of quetiapine [57].

3.3.15.A.3] Nasal congestion

a) Incidence: 3% to 5% [32] [33]

b) Nasal congestion was reported in 3% to 5% of adult patients treated with quetiapine or quetiapine extended-release in multiple, placebo-controlled clinical trials [32] [33].

c) Nasal congestion was reported in 3% of children and adolescents (10 to 17 years of age) treated for schizophrenia (up to 6 weeks) and bipolar mania (up to 3 weeks) with quetiapine at doses of 400, 600, or 800 mg/day (n=340) compared with 2% of those treated with placebo (n=165) in short-term, placebo-controlled clinical trials [32].

3.3.15.A.4] Pharyngitis

a) Incidence: 4% to 6% [6]

b) Pharyngitis was reported in 4% of patients administered quetiapine 75 to 800 mg/day (n=719) compared with 3% of patients administered placebo (n=404) during monotherapy trials of 3 to 12 weeks duration in the treatment of schizophrenia or bipolar mania [6].

c) **Pharyngitis** was reported in 6% of patients administered adjunctive **quetiapine** 100 to 800 mg/day (n=196) compared with 3% of patients administered placebo (n=203) during a 3-week, clinical trial for the treatment of bipolar mania [6].

3.3.15.A.5] **Rhinitis**

a) Incidence: 3% to 4% [32]

b) **Rhinitis** was reported in 3% to 4% of adult patients treated with **quetiapine** in multiple, placebo-controlled clinical trials [32]. **Rhinitis** has also been reported in patients treated with **quetiapine** extended-release in clinical trials [33].

3.3.16] **Other**

3.3.16.A] **Quetiapine Fumarate**

3.3.16.A.1] **Death**

a) Mortality in Elderly Patients with **Bipolar Disorder**

1) Among elderly patients newly treated with atypical antipsychotic monotherapy for **bipolar disorder**, the highest death rates were in patients treated with **risperidone** and **olanzapine**, followed by **quetiapine** and **valproic acid** and its derivatives (sodium **valproate** and **divalproex**), according to a retrospective study of US Department of Veterans Affairs registries (n=4717). Patients were 65 years of age or older and had a 12-month period without exposure to any antipsychotics or mood stabilizers prior to the initial prescription fill date. In an intent-to-treat analysis of deaths within 180 days from the initial fill date, patients treated with **risperidone** (n=1027; mean initial dose, 1.082 mg/day) had the highest death rate (11.8 (95% CI, 9 to 15.3) per 100 person-years). Compared with **risperidone**, patients treated with **olanzapine** (n=868; mean initial dose, 6.615 mg/day) did not have a significantly reduced death rate (10.3; 95% CI, 7.5 to 13.1) per 100 person-years (hazard ratio [HR], 0.98; 95% CI, 0.62 to 1.55; p=0.9371), but a significantly lower death rate was reported in patients who received **quetiapine** (n=1119; mean initial dose, 72.691 mg/day; death rate, 5.3; 95% CI, 3.6 to 7.7) per 100 person-years (HR, 0.46; 95% CI, 0.28 to 0.76; p=0.0027) and **valproic acid** and derivatives (n=1703; mean initial dose, 776.8 mg/day; death rate, 4.6; 95% CI, 3.2 to 6.3) per 100 person-years (HR, 0.48; 95% CI, 0.29 to 0.8; p=0.0046) [62].

b) Mortality in Elderly Patients with **Dementia** Compared with Placebo or Nonuse

1) An increased risk of death has been reported in elderly patients with dementia-related **psychosis** treated with antipsychotic drugs. Analysis of 17 placebo-controlled trials (modal duration of 10 weeks) revealed a 1.6 to 1.7-fold increased risk of death in patients administered an atypical antipsychotic compared with patients administered placebo. Similarly, death was reported in 4.5% of patients administered **quetiapine** compared with 2.6% of patients administered placebo over the course of a typical 10-week controlled clinical trial. The causes of death were typically varied; however, deaths that were cardiovascular (ie, **heart failure**, sudden death) or infectious (ie, **pneumonia**) in nature were the most common [2] [6].

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 or 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 vs long-term

care facilities). In order to adjust for differences 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% CI, 1.02 to 1.7; 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, 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 [63].

3J) 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 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 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 [64].

cJ) Mortality in Elderly Patients Compared with Conventional Antipsychotics

1J) 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 or 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% CI, 1.39 to 1.56). In the multivariable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional compared with 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 with [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 compared with atypical drug therapy was greatest when 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 multivariable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study [65].

2j) 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 9142 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 (RR) of death was associated with the use of conventional antipsychotics 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, 1.3 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 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 [66].

3.3.16.A.2] Fatigue

a) Incidence: 3% to 14% [2] [6]

b) Fatigue was reported in 3% of patients administered [quetiapine](#) extended-release 300 to 800 mg/day (n=951) compared with 2% of patients administered placebo (n=319) during 6-week clinical trial for the treatment of [schizophrenia](#) [2].

c) Fatigue was reported in 6% of patients administered [quetiapine](#) extended-release 300 mg/day (n=137) compared with 2% of patients administered placebo (n=140) during an 8-week placebo-controlled clinical trial for the treatment of [bipolar depression](#) [2].

d) Fatigue was reported in 7% of patients administered [quetiapine](#) extended-release 400 to 800 mg/day (n=151) compared with 4% of patients administered placebo (n=160) during a 3-week clinical trial for the treatment of bipolar mania [2].

e) Fatigue was reported in 10% of patients administered [quetiapine](#) 300 and 600 mg/day (n=698) compared with 8% of patients administered placebo (n=347) during an 8-week clinical trial for the treatment of [bipolar depression](#) [6].

f) Fatigue was reported in 14% of patients administered adjunctive [quetiapine](#) extended-release 150 mg/day (n=315), 11% of patients administered [quetiapine](#) extended-release 300 mg/day (n=312), and 4% of patients administered placebo (n=309) during a 6-week clinical trial for [major depressive disorder](#) [2].

g) Pediatrics

1j) In a study of children and adolescents (10 to 17 years old) with bipolar mania, fatigue was reported in 14% of patients administered [quetiapine](#) 400 mg/day (n=95), 9% of patients administered [quetiapine](#) 600 mg/day (n=98), and 4% of patients administered placebo (n=90) during a 3-week clinical trial. Fatigue was the primary reason for study discontinuation in

2.1% of patients administered [quetiapine](#) compared to 0% of patients administered placebo [2] [6].

3.3.16.A.3] Fever

a) Incidence: 2% [32]

b) Fever was reported in 2% of adult patients treated with [quetiapine](#) in multiple, placebo-controlled clinical trials [32].

c) Persistent pyrexia attributed to [quetiapine](#) was described in a 45-year-old man with [schizophrenia](#). The patient had fevers of 38 to 40 degrees C and drenching sweats after initiation of [quetiapine](#). Despite good control of psychotic symptoms, the patient discontinued therapy as an outpatient due to the intolerable, persistent fevers. The patient presented to the hospital with symptoms of overt [psychosis](#) with auditory hallucinations, delusions of grandeur, and paranoia. [Quetiapine](#) was prescribed a second time due to the previous positive clinical response. Past medical history included an episode of fever after a single dose of [olanzapine](#) during an [acute psychotic episode](#). Pyrexia recurred after [quetiapine](#) was resumed, but features of [neuroleptic malignant syndrome](#) were absent. Laboratory studies (full blood examination, [blood cultures](#), viral serology, [autoimmune screening](#)) and imaging studies (abdominal ultrasound; [CT of chest](#), abdomen, and pelvis; and [echocardiography](#)) were normal, excluding an infectious cause. [Quetiapine](#) was discontinued, and the fever abated. [Risperidone](#) was initiated, and the patient had no further episodes of pyrexia [61].

3.3.16.A.4] Neuroleptic malignant syndrome

a) [Neuroleptic malignant syndrome](#) (NMS), which can manifest clinically with [hyperpyrexia](#), muscle rigidity, autonomic instability, altered mental status, elevated CPK levels, myoglobinuria, and [acute renal failure](#), has been reported with the use of antipsychotic substances, including [quetiapine](#) fumarate. If NMS does occur, all antipsychotic medications and other drugs not essential to concurrent therapy should be discontinued, intensive symptomatic and medical monitoring should be initiated, and treatment of any concomitant serious medical problems should occur. Careful consideration of reintroduction of antipsychotics after a patient has experienced NMS should be taken; recurrences have been reported [32] [33].

b) A 20-year-old man developed [neuroleptic malignant syndrome](#) (NMS) within 8 to 9 weeks of starting [quetiapine](#) for the treatment of unprovoked aggression. The patient's medical history included severe [mental retardation](#) (IQ=27), a 2-year history of frequent unprovoked episodes of aggression, and treatment with [haloperidol](#) 5 mg/day for 14 months with partial control of symptoms. [Quetiapine](#) (100 mg/day) was added to the [haloperidol](#) therapy to help control the aggression. The patient developed increased salivation, profuse perspiration, daytime drowsiness, and decreased psychomotor activity with decreased emotional reactivity within 4 to 5 days of starting the [quetiapine](#). The symptoms persisted for 5 weeks and the dose of [haloperidol](#) was decreased to 2.5 mg/day and the [quetiapine](#) was increased to 200 mg/day. Additionally, the patient was started on [lorazepam](#) up to 5 mg/day. Within 3 weeks, the symptoms worsened and the patient developed intermittent low-grade fever and later developed difficulty in walking with stiffness of the entire body, coarse tremors, high-grade fever, altered sensorium, and difficulty in swallowing with regurgitation of both liquids and solids. Upon physical examination, the patient had muscular rigidity, profuse perspiration, and elevated blood pressure. Laboratory analyses revealed [leukocytosis](#), elevated [creatinine](#) phosphokinase (greater than 10-fold increase), myoglobinuria, and mild [renal impairment](#). The patient did not have a recent history of strenuous physical exercise, exposure to high ambient temperatures, or any concomitant use of over-the-counter medications. CT of the brain and cerebrospinal fluid analysis did not reveal any abnormalities. The patient was diagnosed with NMS and all psychotropic medications were discontinued. [Bromocriptine](#) 7.5 mg/day was consequently

started along with supportive management. Within 48 hours, the patient experienced a decrease in rigidity, perspiration, and his blood pressure stabilized. By day 4 of treatment with [bromocriptine](#), his muscular rigidity resolved; however, he developed patchy [pneumonitis](#) and was treated with antibiotics. Despite the treatment with antibiotics, his respiratory status continued to decline and he died on day 10. Authors concluded a temporal relationship between the initiation of [quetiapine](#) and the onset of NMS symptoms [58].

c) Based on a retrospective medication review, [quetiapine](#) was a probable cause of [neuroleptic malignant syndrome](#) (NMS) in a 34-year-old man. His past medical history included a childhood accident resulting in severe brain damage that progressed to [mental retardation](#), and seizures. He was hospitalized for mental status changes, tremors, temperature of 39.9 degrees C, and was subsequently diagnosed with NMS accompanied by extrapyramidal effects (EPS). During hospitalization, the patient experienced lead pipe rigidity, [tachycardia](#), and a high [creatinine kinase](#) (CK) level. His medications included [quetiapine](#) 200 mg 3 times per day, [guanfacine](#) 2 mg/day, [carbamazepine](#) 400 mg every 12 hours, [valproic acid](#) 500 mg twice daily, and [lorazepam](#) 2 mg (frequency unknown). [Quetiapine](#) was discontinued on hospital day 2, and the patient was started on a traditional treatment for NMS, which included [bromocriptine](#) 2.5 mg via a [gastric feeding tube](#) every 8 hours as needed and IV [dantrolene](#) 1 mg/kg. On day 3, the patient continued to have a high fever (41 degrees C), became hypoxic and acidotic, and was intubated. A [midazolam](#) drip was started and titrated per hospital protocol to sedate the patient, [bromocriptine](#) was increased to 5 mg every 8 hours, and an infusion of 0.45% NaCl with [sodium bicarbonate](#) was started due to a high CK level of 12,654 international units/L and serum creatine levels up to 1.4 mcg/mL. Further, IV [norepinephrine](#) drip was started because the patient was not hemodynamically stable. On day 6, his blood cell counts remained stable, the infusion of 0.45% NaCl with [sodium bicarbonate](#) was discontinued, and [bromocriptine](#) was decreased to 2.5 mg every 6 hours because the CK level and temperature had decreased (4450 international units/L and 39.3 degrees C, respectively). On day 7, the symptoms of NMS had resolved. The Naranjo probability scale suggested that [quetiapine](#) was the probable cause of NMS. Even though it is not common for atypical antipsychotic drugs to cause NMS with associated EPS as reported in this case, there have been 13 cases of NMS due to [quetiapine](#) identified in the literature and 75% of these cases had reactions that included EPS [59].

d) A 44-year-old woman with a history of [schizoaffective disorder](#) and 3 earlier episodes of [neuroleptic malignant syndrome](#) (NMS) presented with fever, decreased level of consciousness, rigidity, and [urinary incontinence](#). Her medications were [quetiapine](#) 200 mg/day, [clozapine](#) 400 mg/day, [divalproex sodium](#) 750 mg/day, [lamotrigine](#) 200 mg/day, and [clonazepam](#) 4 mg/day. She was found to have [bilateral pneumonia](#) and highly elevated creatine phosphokinase (CPK). Antibiotics and oral [bromocriptine](#) 1.25 mg twice daily were started; antipsychotics were withheld. When she was extubated on day 3, she showed [paranoid delusions](#). [Clozapine](#), [divalproex sodium](#), [lamotrigine](#), and [clonazepam](#) were restarted. On hospital day 4, her temperature was normal and her CPK level reduced. Ten days later, her CPK level was normal and she had returned to her baseline mental status. Although some of the findings could be attributable to [pneumonia](#), the collection of symptoms and the previous history of NMS supported the diagnosis of NMS in this instance [60].

3.3.16.A.5] Pain

a) Incidence: 7% [6]

b) Pain was reported in 7% of patients administered [quetiapine](#) 75 to 800 mg/day (n=719) compared with 5% of patients administered placebo (n=404) during monotherapy trials of 3 to 12 weeks duration in the treatment of [schizophrenia](#) or bipolar mania [6].

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](#).

2) Australian Drug Evaluation Committee's (ADEC) Category: C

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown**4) Clinical Management**

a) There are no adequate and well-controlled studies of [quetiapine](#) in pregnant women; however, third-trimester antipsychotic drug exposure has been associated with extrapyramidal and/or withdrawal symptoms in neonates [6] [2]. Limited published data on [quetiapine](#) use during pregnancy showed no major abnormalities in the infants [169] [170]. Until more information is available, administer [quetiapine](#) during pregnancy only if the potential benefit to the mother justifies the potential [risk to the fetus](#) [6] [2].

5) Literature Reports

a) 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 has ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care [6] [2].

b) No major malformations were reported in infants who were born to 21 women exposed to [quetiapine](#) and other psychoactive medications during pregnancy in a prospective, observational study, or in 42 other infants (from 1 study in 36 women and 6 case reports) born to women who used [quetiapine](#) during pregnancy. However, with the limited published data on [quetiapine](#) exposure during pregnancy, the frequency or absence of adverse outcomes cannot be reliably established [6] [2].

c) A prospective, observational study of 54 women (mean age, 30.7 years) exposed to antipsychotic medication during pregnancy showed permeability of the placental barrier. Outcomes were determined by maternal and umbilical cord blood samples taken at delivery and through data collected from maternal reports and medical records. Placental passage showed a significant difference between antipsychotic medications, [olanzapine](#) 72.1% (95% confidence interval (CI), 46.8% to 97.5%) being the highest, followed by [haloperidol](#) 65.5% (95% CI, 40.3% to 90.7%) and [risperidone](#) 49.2% (95% CI, 13.6% to 84.8%), with [quetiapine](#) 24.1% (95% CI, 18.7% to 29.5%) showing the lowest placental passage. In the [quetiapine](#) group (n=21), there was one case of [preterm labor](#) (less than 37 weeks gestation) and 2 infants that required neonatal intensive care admission.

Seven neonates developed respiratory complications and 2 developed cardiovascular events. Low birth weight (less than 2500 g) occurred in 1 infant [168].

d) Treatment of a 33-year-old woman with [fluvoxamine](#) 200 mg/day and [quetiapine](#) 400 mg/day during her second pregnancy resulted in an uneventful pregnancy and the birth of a healthy female infant. The patient was being treated with [fluvoxamine](#) and [quetiapine](#) when she was diagnosed with a severe postpartum [psychotic depression](#) after the birth of her first child; multiple attempts at reducing her medication led to [relapse](#). After being informed of the risk-benefit of [fluvoxamine/quetiapine](#) exposure during pregnancy, the patient decided to go forward with a second pregnancy while maintaining her drug regimen of [fluvoxamine](#) and [quetiapine](#) with the addition of folate 5 mg/day throughout the pregnancy. The patient gained 9 kg with no symptoms of psychiatric instability. Routine biochemical tests were within the normal range and 5 echographic reports found no fetal abnormalities. The presence of an intrauterine myoma led to an elective [caesarean-section](#). A healthy female infant weighing 2600 g and measuring 49 cm in length was delivered, with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively [169].

e) One case report describes the maternal use of [quetiapine](#) 300 to 400 mg throughout gestation, and the subsequent birth of a healthy male infant without abnormality. At 6 months of age, the infant was developing normally [170].

f) In pregnant rats and rabbits treated with [quetiapine](#) up to 2.4 times the maximum recommended human dose (MRHD) of 800 mg/day for [schizophrenia](#), no [teratogenicity](#) was observed. However, embryo/fetal toxicity, including delays in skeletal ossification, was observed in both rats and rabbits at doses approximately 1 and 2 times the MRHD, and an increased incidence of carpal/tarsal flexure, a minor soft tissue anomaly, occurred in rabbit fetuses at approximately 2 times the MRHD. In both rats and rabbits, reduced fetal body weight was observed. The high [quetiapine](#) dose (2 times the MRHD) in rats and all doses (1 to 2 times the MRHD) in rabbits produced maternal toxicity, including decreased body weights and death. In a perio/postnatal reproductive study in rats, no [quetiapine](#)-related effects were observed at 0.01, 0.12, and 0.2 the MRHD. There were, however, increased fetal and pup death and decreased mean litter weights at 3 times the MRHD [6] [2].

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) Limited data on the safety of [quetiapine](#) in nursing infants demonstrates no evidence of toxicity [171] [169]. However, [quetiapine](#) is excreted in human breast milk. In published case reports, the level of [quetiapine](#) in breast milk was undetectable up to 170 mcg/L, with an estimated infant dose ranging from 0.09% to 0.43% of the maternal dose after adjusting for weight. The calculated infant daily doses based on a limited number of mother-infant pairs (n=8) range from less than 0.01 mg/kg (for a maternal dose up to 100 mg/day) to 0.1 mg/kg for a maternal dose of 400 mg/day. Because potential harm to the nursing infant exists, either breastfeeding or [quetiapine](#) should be discontinued considering the need for treatment of the mother [6] [2]. If [quetiapine](#) treatment is required in a

nursing mother, monitor infant progress and periodically measure [quetiapine](#) in the infant's plasma [171].

3) Literature Reports

a) A case report of a 26-year-old woman prescribed [quetiapine](#) while breastfeeding her 3-month-old infant demonstrated a milk to plasma (M:P) ratio of 0.29 (an estimated relative infant dose of 0.09% of the maternal weight-adjusted dose) suggesting a low level of exposure generally acceptable for breastfeeding. The woman was prescribed [quetiapine](#) 400 mg at night for the off-label treatment of nonresponsive depression with concomitant chronic pain. At 16 months prior to the study, she was started on [quetiapine](#) 300 mg with an increase to 400 mg during month 4 of her pregnancy and continuing to the study day. She was also treated with [oxycodone](#) 20 mg 3 times daily and [fluoxetine](#) 40 mg daily during gestation and up to the study day. A male infant weighing 3.4 kg (50th percentile) was delivered at week 37. On the study day, the 3-month-old infant weighed 5.6 kg (25th percentile). During the study, the infant was receiving oral [morphine](#) 120 mcg 3 times daily for opioid dependency and was breastfed 6 to 7 times daily. Blood samples were collected immediately prior to the mother's [quetiapine](#) dose and 5 times during the elimination phase (between 12.8 and 23.1 hours after the dose). Due to limited plasma concentration measurements early after [quetiapine](#) dosing, the M:P ratio, calculated using the milk and average plasma concentration during the elimination phase, was 0.29 (0.09% of the maternal weight-adjusted dose). The infant's plasma contained [quetiapine](#) 1.4 mcg/L equivalent to 6% of the maternal plasma concentration. Upon clinical examination, the infant was healthy and his Denver age was the same as his chronological age [171].

b) Treatment with [fluvoxamine](#) 200 mg/day and [quetiapine](#) 400 mg/day in a 33-year-old woman during her second pregnancy resulted in an uneventful pregnancy and the birth of a healthy female infant weighing 2600 g and measuring 49 cm in length with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively. The patient chose to breastfeed; however, formula was required to supplement her breast milk due to insufficient milk production. In the 3 months that the infant received breast milk supplemented with formula, no adverse effects were detected and the infant continues to develop normally [169].

4) Drug Levels in Breastmilk

a) [Quetiapine](#) Fumarate

1) Parent Drug

a) Percent Adult Dose in Breastmilk

1) The estimated infant dose ranged from 0.09% to 0.43% of the weight-adjusted maternal dose [6] [2].

b) Concentration in Breastmilk at Therapeutic Dose

1) Based on case reports, the level of [quetiapine](#) ranges from undetectable to 170 mcg/L [6] [2].

c) Peak Concentration in Infant

1)) Calculated infant doses ranged from less than 0.01 mg/kg/day (maternal dose 100 mg/day) to 0.1 mg/kg/day (maternal dose 400 mg/day) based on limited data from 8 mother/infant pairs [6] [2].

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] [Acarbose](#)

- 1)) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2)) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7)) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.B] [Albiglutide](#)

- 1)) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2)) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7)) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.C] [Alfuzosin](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.D) Alogliptin

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.E) 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](#) [103].
- 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](#) [103].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.F) [Amiodarone](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.G] Amitriptyline

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.H] Anagrelide

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.I] Apomorphine

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.J] [Aprepitant](#)

1J) Interaction Effect: increased [quetiapine](#) serum concentrations

2J) Summary: [Quetiapine](#) is primarily metabolized by the CYP3A4 isozyme and [aprepitant](#) is a CYP3A4 inhibitor. Coadministration of [aprepitant](#) with [quetiapine](#) in one patient resulted in an 11-fold increase in [quetiapine](#) plasma concentrations and deep somnolence, which recurred upon rechallenge. A 50% reduction in [quetiapine](#) dose coadministered with [aprepitant](#) resulted in [quetiapine](#) levels below quantification and no somnolence. Therefore, caution is recommended when [quetiapine](#) is administered to patients receiving [aprepitant](#) concomitantly, and a dose reduction of [quetiapine](#) may be necessary [113].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution with the concomitant use of [aprepitant](#) and [quetiapine](#) due to a risk of increased [quetiapine](#) plasma concentrations and adverse events [113].

7J) Probable Mechanism: inhibition of CYP3A4-mediated [quetiapine](#) metabolism by [aprepitant](#)

8J) Literature Reports

aJ) A 44-year-old man with [laryngeal carcinoma](#) experienced extreme somnolence with the concomitant use of [quetiapine](#) 50 mg/day for anxiety and [aprepitant](#) for nausea. Other medical history included depression treated with [citalopram](#). Following a laryngeal resection, [chemoprophylaxis](#) was initiated with cisplatin 100 mg/m² every 3 weeks and a prophylactic antiemetic regimen containing [aprepitant](#) (3-day course: 125 mg, 80 mg, and 80 mg), [dexamethasone](#), and [ondansetron](#) was administered. After receiving the first course of cisplatin, the patient was hospitalized for deep somnolence and dehydration. Suspecting a drug interaction, laboratory tests completed before and after [aprepitant](#) administration during the second course of cisplatin revealed an 11-fold increase in [quetiapine](#) plasma concentration (from 5 mcg/L to 55 mcg/L). Deep somnolence was again noted. A 50% dose reduction of [quetiapine](#) administered during the third 3-day course of [aprepitant](#) resulted in [quetiapine](#) plasma concentrations below the limit of quantification. No somnolence was evident at the reduced [quetiapine](#) dose [113].

3.5.1.K] [Aripiprazole](#)

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

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation [143], 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 [143], 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.L] Armodafinil

- 1) Interaction Effect: decreased [quetiapine](#) exposure and effectiveness
- 2) Summary: Coadministration of armodafinil, a moderate CYP3A4 inducer [68], and [quetiapine](#), a CYP3A4 substrate [30], may lead to reduced [quetiapine](#) exposure. In a study of 37 patients with [schizophrenia](#), coadministration of armodafinil 250 mg with [quetiapine](#) in doses of 300 mg daily or greater resulted in decreased systemic exposure of [quetiapine](#), with decreases in AUC and Cmax of 42% and 45%, respectively. Despite the decreased exposure, there were no observed changes in [schizophrenia](#) symptoms or disease status [67]. If armodafinil and [quetiapine](#) are coadministered, dosage adjustments of [quetiapine](#) may be needed [68].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Coadministration of armodafinil and [quetiapine](#) may lead to reduced [quetiapine](#) exposure [67]. If armodafinil and [quetiapine](#) are coadministered, dosage adjustments of [quetiapine](#) may be needed [68].
- 7) Probable Mechanism: induction of CYP3A4-mediated [quetiapine](#) metabolism by armodafinil
- 8) Literature Reports

a) Coadministration of armodafinil with [quetiapine](#) significantly decreased the systemic exposure of [quetiapine](#) (AUC and Cmax decreased by 42% and 45%, respectively) compared with [quetiapine](#) alone in patients with [schizophrenia](#) (n=37) in an open-label, multiple-dose, [pharmacokinetic study](#). Patients received escalating doses of armodafinil of 100 mg on day 7, 150 mg on days 8 and 9, 200 mg on days 10 and 11, and 250 mg on days 12 through 39. Maintenance doses of [quetiapine](#) 300 mg or greater were administered in the evening. The AUC(0 to 24 hours) after steady-state dosing with armodafinil plus [quetiapine](#) vs [quetiapine](#) alone was 2395.3 +/- 1212.15 nanograms x hour/milliliter (ng x hr/mL) vs 3659.3 +/- 1568.1 ng x hr/mL, respectively. The Cmax at steady state for armodafinil plus [quetiapine](#) vs [quetiapine](#) alone was 595.6 +/- 391.23 ng/mL vs 720.9 +/- 320.77 ng/mL, respectively. Despite the decreased exposure of [quetiapine](#), there were no observed changes in symptoms of [schizophrenia](#) or disease status [67].

3.5.1.M] Arsenic Trioxide

- 1) Interaction Effect: prolongation of the QTc interval and/or [torsades de pointes](#)
- 2) Summary: [Arsenic trioxide](#) can prolong the QT interval in some patients, which may result in [ventricular tachycardia](#), [ventricular fibrillation](#), and [torsades de pointes](#) and should not be administered with other drugs that may prolong the QT interval [154]. Several antipsychotic agents have demonstrated QT prolongation including amisulpride [155], [haloperidol](#) [156], [paliperidone](#) [157], [risperidone](#) [158], [sertindole](#) [159], [quetiapine](#) [160], [sultopride](#) [161], , and [zotepine](#) [162].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [arsenic trioxide](#) and antipsychotics is not recommended.
- 7) Probable Mechanism: additive effects on QTc prolongation
- 8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with [arsenic trioxide](#) and [torsade de pointes](#) as well as [complete heart block](#) has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with [arsenic trioxide](#) were evaluated for QTc

prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after [arsenic trioxide](#) infusion, and then returned towards baseline by the end of 8 weeks after [arsenic trioxide](#) infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age [153].

3.5.1.N] Asenapine

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7)) Probable Mechanism: additive effects on QT interval

3.5.1.O] Astemizole

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7)) Probable Mechanism: additive effects on QT interval

3.5.1.P] Atazanavir

- 1)) Interaction Effect: increased exposure of [quetiapine](#) and increased risk of QT-interval prolongation
- 2)) Summary: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and a strong CYP3A4 inhibitor that prolongs the QT interval may increase the exposure of [quetiapine](#). Coadministration may also result in additive effects on the QT interval. Concomitant administration is contraindicated [145] [146].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6) Clinical Management: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and a strong CYP3A4 inhibitor that prolongs the QT interval may increase the exposure of [quetiapine](#) and result in additive effects on the QT interval. Concomitant administration is contraindicated [145] [146].

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

3.5.1.Q] [Azithromycin](#)

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.R] [Bedaquiline](#)

1) Interaction Effect: increased risk of QT prolongation

2) Summary: Bedaquiline is associated with QT-interval prolongation. Concomitant use of bedaquiline with other drugs that prolong the QT interval, including fluoroquinolones, macrolide antibacterial drugs, and the antimycobacterial drug, [clofazimine](#), may result in additive prolonging effects on the QT interval. Close monitoring of baseline and on-treatment ECGs are recommended when bedaquiline is coadministered with other QT-prolonging agents [148].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of bedaquiline and other QT-prolonging drugs may result in additive prolongation effects on the QT interval. Baseline and on-treatment ECGs should be monitored closely when bedaquiline is coadministered with other QT-prolonging agents, including fluoroquinolones, macrolide antibacterial drugs, and the antimycobacterial drug, [clofazimine](#) [148].

7) Probable Mechanism: additive QT-interval prolongation

8) Literature Reports

a) The mean increase in QTc interval at week 24 was greater in patients who received concomitant bedaquiline and [clofazimine](#), compared with patients who received bedaquiline without [clofazimine](#) (mean change from reference, 31.9 msec vs 12.3 msec, respectively) in an open-label, noncomparative study in previously treated patients with multidrug-resistant pulmonary *Mycobacterium tuberculosis* [148].

3.5.1.S] [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 [150], 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 [150], as coadministration may increase the risk of [ventricular arrhythmias](#).
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.T] Boceprevir

- 1) Interaction Effect: increased [quetiapine](#) exposure
- 2) Summary: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of [quetiapine](#)
- 8) Literature Reports
 - a) During in-vivo drug interaction studies, coadministration of [ketoconazole](#) 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in clearance of [quetiapine](#) and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

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 [138] [139] [140]. 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 [138] [139] [140].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.V] Canagliflozin

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.W] Carbamazepine

- 1) Interaction Effect: increased [carbamazepine](#) exposure and risk for toxicity and decreased [quetiapine](#) efficacy
- 2) Summary: Concomitant use of [carbamazepine](#) (CYP3A4 substrate) and [quetiapine](#) (CYP3A4 inhibitor) may cause elevated [carbamazepine](#) levels. Closely monitor [carbamazepine](#) levels and adjust the dose as necessary [107]. Coadministration of [carbamazepine](#) (CYP3A4 inducer) and [quetiapine](#) (CYP3A4 substrate) may also result in decreased [quetiapine](#) exposure. Increase the dose of [quetiapine](#) up to 5 times the original dose when [carbamazepine](#) is used for more than 1 to 2 weeks and then titrate based on the individual patient's needs. If [carbamazepine](#) is stopped, reduce the dose of [quetiapine](#) to the original level within 1 to 2 weeks [6].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [carbamazepine](#) (CYP3A4 substrate) and [quetiapine](#) (CYP3A4 inhibitor) may cause elevated [carbamazepine](#) levels. Closely monitor [carbamazepine](#) levels and adjust the dosage, if required [107]. Coadministration of [carbamazepine](#) (CYP3A4 inducer) and [quetiapine](#) (CYP3A4 substrate) may also result in decreased [quetiapine](#) exposure. Increase the dose of [quetiapine](#) up to 5 times the original dose when used in combination with [carbamazepine](#) for more than 1 to 2 weeks and then titrate based on the individual patient's needs. If [carbamazepine](#) is stopped, reduce the dose of [quetiapine](#) to the original level within 1 to 2 weeks [6].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [carbamazepine](#) metabolism by [quetiapine](#); induction of CYP3A4-mediated [quetiapine](#) metabolism by [carbamazepine](#)

3.5.1.X] Ceritinib

- 1) Interaction Effect: increased exposure of CYP3A substrate
- 2) 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 [120].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6)) 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 [120].

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

3.5.1.Y] Chloroquine

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.Z] Chlorpromazine

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.AA] Chlorpropamide

1)) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2)) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using

antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.AB| [Ciprofloxacin](#)

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.AC| [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](#) [94].

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](#) [94].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AD| [Citalopram](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [80] and [quetiapine](#) has also been associated with QT interval prolongation [30]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) and [quetiapine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [80].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) and [quetiapine](#) is not recommended as concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and

discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [80].

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

3.5.1.AE] [Clarithromycin](#)

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

2J) Summary: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects on the QT interval prolongation. During drug interaction studies, coadministration of [ketoconazole](#) and [quetiapine](#) resulted in a 6.2-fold increase in [quetiapine](#) AUC. Avoid concomitant use. If coadministration cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects on the QT interval prolongation. Avoid concomitant use. If coadministration cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

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

8J) Literature Reports

aJ) During drug interaction studies, coadministration of a potent CYP3A4 inhibitor [ketoconazole](#) 200 mg once daily for 4 days and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in [quetiapine](#) clearance and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

bJ) A 32-year-old male with [schizoaffective disorder](#) and [metabolic syndrome](#) experienced a significant increase in plasma concentration following administration of [quetiapine](#). The patient, hospitalized for acute psychotic symptoms was treated with 50 mg [quetiapine](#) daily, with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg [clarithromycin](#) along with his evening dose of [quetiapine](#) 400 mg. The following morning, 750 mg sultamicillin, 500 mg [clarithromycin](#), and the morning 300-mg [quetiapine](#) dose were given. Within hours the patient became somnolent, and plasma sample testing resulted in 826.8 mcg/L (normal range, 70 to 170 mcg/L). The patient developed severe impaired consciousness and [respiratory depression](#). [Quetiapine](#) overdose was suspected and treatment was discontinued. Plasma levels were continually measured over the course of a week until complete recovery was achieved [144].

3.5.1.AF] [Clomipramine](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de](#)

[pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.AG] [Clonidine](#)

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

2) Summary: [Quetiapine](#) is a neuroleptic agent which may enhance the effects of certain antihypertensive medications, which may induce hypotension [30]. As the concomitant use of [clonidine](#) with [quetiapine](#) may result in orthostatic regulation disturbance induction or exacerbation [81] [82], coadministration 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 [quetiapine](#) [30], may induce or exacerbate orthostatic regulation disturbances (eg, dizziness, fatigue, orthostatic hypotension) [81] [82] and should be approached with caution.

7) Probable Mechanism: unknown

3.5.1.AH] [Clozapine](#)

1) Interaction Effect: increased risk of QT prolongation

2) Summary: [Clozapine](#) is associated with QT-interval prolongation. Concomitant administration of [clozapine](#) with other drugs that prolong the QT interval may result in additive prolongation effects on the QT interval and increase the risk of serious cardiac events, including [ventricular arrhythmias](#) and [torsade de pointes](#). If concomitant therapy is required, use caution and monitor the patient closely for QT-interval prolongation. Discontinue [clozapine](#) if the corrected QT interval exceeds 500 milliseconds. Cardiac evaluation and treatment discontinuation are warranted if the patient develops symptoms of [torsade de pointes](#) or other [arrhythmias](#) [97].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of [clozapine](#) and QT-prolonging drugs may result in additive prolongation effects on the QT interval. If concomitant therapy is required, use caution and monitor the patient closely for QT-interval prolongation. Discontinue [clozapine](#) if the corrected QT interval exceeds 500 milliseconds. Cardiac evaluation and treatment discontinuation are warranted if the patient develops symptoms of [torsade de pointes](#) or other [arrhythmias](#) [97].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AI] [Cobicistat](#)

1) Interaction Effect: increased [quetiapine](#) exposure

2) Summary: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated

with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].

7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of [quetiapine](#)

8) Literature Reports

a) During in-vivo drug interaction studies, coadministration of [ketoconazole](#) 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in clearance of [quetiapine](#) and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

3.5.1.AJ] [Conivaptan](#)

1) Interaction Effect: increased [quetiapine](#) exposure

2) Summary: Use caution when coadministering [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor as this may increase the exposure of [quetiapine](#) and increase the risk of adverse events. In a drug-interaction study, concomitant use of single dose [quetiapine](#) 25 mg with the strong CYP3A4 inhibitor, [ketoconazole](#), increased [quetiapine](#) exposure. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth, and when the strong CYP3A4 is discontinued, subsequently reduce the [quetiapine](#) dose 6-fold [6] [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects and should therefore be undertaken with caution. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth, and when the strong CYP3A4 is discontinued, subsequently reduce the [quetiapine](#) dose 6-fold [6] [2].

7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of [quetiapine](#)

8) Literature Reports

a) During in-vivo drug interaction studies, coadministration of [ketoconazole](#) 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in [ketoconazole](#) clearance and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

3.5.1.AK] [Crizotinib](#)

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

2) Summary: QT-interval prolongation has occurred during crizotinib therapy. Risk of additive QT-interval prolongation increases during coadministration with other drugs associated with QT prolongation. If concomitant use is clinically indicated, use caution and consider periodic ECG and [electrolyte monitoring](#) during therapy [125]. Dose reduction of crizotinib may be warranted.

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution in coadministering crizotinib with a drug known to prolong the QT interval, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events. If concomitant use is clinically indicated, consider periodic ECG and [electrolyte monitoring](#) during therapy [125]. Dose reduction of crizotinib may be warranted.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.AL] [Cyclobenzaprine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.AM] [Dabrafenib](#)

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates; increased risk of QT-interval prolongation
- 2) Summary: Dabrafenib is a CYP3A4 inducer known to prolong the QT interval. Use of dabrafenib with CYP3A4 substrates that also prolong the QT interval may lead to decreased exposure of the CYP3A4 substrate and an increased risk of QT-interval prolongation. Alternative therapy is recommended whenever possible. If concomitant use is required, monitor patients for loss of efficacy [132] and consider assessment and periodic monitoring for [ventricular arrhythmia](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Dabrafenib is a CYP3A4 inducer capable of prolonging the QT interval. Use of dabrafenib with a CYP3A4 substrate that also prolongs the QT interval may lead to decreased exposure of the CYP3A4 substrate and an increased risk of QT-interval prolongation. Alternative therapy is recommended whenever possible. If concomitant use is required, monitor patients for loss of efficacy and [132] consider assessment and periodic monitoring for [ventricular arrhythmia](#).
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism by dabrafenib; additive QT-interval prolongation
- 8) Literature Reports

- a) Administration of dabrafenib 150 mg twice daily for 15 days with a single 3 mg [midazolam](#) dose, decreased [midazolam](#) AUC by 74%. Dabrafenib is a CYP3A4 inducer, while [midazolam](#) is a CYP3A4 substrate [133].

3.5.1.AN] Dapagliflozin

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.AO] Darunavir

- 1) Interaction Effect: increased CYP3A substrate exposure
- 2) Summary: Use caution with coadministration of [darunavir](#) (a CYP3A inhibitor) with CYP3A substrates. Coadministration may increase CYP3A substrate exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. If coadministered, monitor for adverse reactions associated with concomitant drugs [93].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [darunavir](#) (a CYP3A inhibitor) with CYP3A substrates. Coadministration may increase CYP3A substrate exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. Monitor for adverse reactions associated with concomitant drugs if coadministered [93].
- 7) Probable Mechanism: inhibition of CYP3A substrate metabolism

3.5.1.AP] Dasatinib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.AQ| Deferasirox

- 1) Interaction Effect: reduced plasma concentrations of CYP3A4 substrate
- 2) Summary: Concomitant use of [deferasirox](#), a CYP3A4 inducer, and drugs that are metabolized by CYP3A4 may lead to decreased CYP3A4 substrate concentrations. Concomitant use [midazolam](#), a CYP3A4 substrate, and [deferasirox](#) resulted in decreases in the [midazolam](#) Cmax and AUC by 23% and 17%, respectively, in healthy volunteers. In the clinical setting, this effect may be more pronounced. Therefore, caution should be used when [deferasirox](#) is coadministered with other CYP3A4 substrates. If concomitant use is required, monitor patients for reduced effectiveness [131].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [deferasirox](#) and a CYP3A4 substrate such as escitalopram, [imatinib](#), and [tacrolimus](#), may result in decreased CYP3A4 substrate plasma concentrations. Therefore, caution is advised when [deferasirox](#) and drugs metabolized by CYP3A4 are coadministered and monitoring of patients for reduced effectiveness is recommended [131].
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism by [deferasirox](#)

3.5.1.AR| 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 [138] [139] [140]. 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 [138] [139] [140].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.AS| Dehydroepiandrosterone

- 1) Interaction Effect: reduced effectiveness of [quetiapine](#)
- 2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive for optimal treatment of patients with [psychosis](#) [137]. In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated [137]. Patients being treated with [quetiapine](#) should avoid DHEA supplementation.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and [quetiapine](#). If DHEA is elevated, treatment with [dexamethasone](#) 1 mg orally per day may be used to normalize DHEA levels.
- 7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to [quetiapine](#)
- 8) Literature Reports

a)) A 24-year-old female diagnosed with [schizophrenia](#) was resistant to daily doses of [haloperidol](#) 20 milligrams (mg), [fluphenazine](#) 40 mg, [lithium](#) carbonate 1200 mg, and [lithium](#) carbonate 900 mg plus [thioridazine](#) 300 mg. The patient appeared Cushingoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). [Dexamethasone](#) 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe [psychosis](#) resistant to conventional antipsychotic therapy [136].

b)) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with [chronic paranoid schizophrenia](#); [schizophrenia](#), chronic undifferentiated type, and [schizoaffective disorder](#), excited type. He was resistant to daily doses of [trifluoperazine](#) 40 mg, [chlorpromazine](#) 400 mg, and [imipramine](#) 100 mg. He was also resistant to combination therapy with [chlorpromazine](#) 400 mg with [thiothixene](#) 80 mg, [thioridazine](#) 1000 mg, [perphenazine](#) 48 mg with [lithium](#) carbonate 1200 mg, [clonazepam](#) 4 mg, and [carbamazepine](#) 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with [dexamethasone](#) 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, [psychosis](#) improved and the patient was well-oriented, conversational, and was making good eye contact. Once [dexamethasone](#) was discontinued, rapid decompensation and florid [psychosis](#) ensued despite "substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid [psychosis](#) resistant to conventional antipsychotic therapy [136].

3.5.1.AT] Delamanid

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg, more than once a month) during the full course of delamanid therapy [116].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg, more than once a month) during the full course of delamanid therapy [116].
- 7)) Probable Mechanism: additive QT- interval prolongation

3.5.1.AU] [Desipramine](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de](#)

[pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.AV] 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 [138] [139] [140]. 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 [138] [139] [140].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AW] Disopyramide

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.AX] Dofetilide

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de](#)

[pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.AY] [Dolasetron](#)

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.AZ] [Domperidone](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Avoid coadministration of [quetiapine](#), a potential QT prolonging drug [29], and domperidone, a drug that has been associated with an increased risk of sudden cardiac death. In case control studies, an increased risk of sudden cardiac death was observed with the use of oral domperidone, particularly at doses greater than 30 mg/day and in patients older than 60 years of age. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [87].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of domperidone and [quetiapine](#) should be avoided as this may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#), [torsades de pointes](#), and sudden cardiac death [29], particularly at domperidone doses greater than 30 mg/day, and in patients older than 60 years. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [87].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BA] [Doxepin](#)

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

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](#) [112].

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](#) [112].

7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.BC] Droperidol

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.BD] Dulaglutide

1)) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2)) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor

glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7J) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.BE] Ebastine

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.BF] Empagliflozin

1J) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2J) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7J) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.BG] Enzalutamide

1J) Interaction Effect: decreased [quetiapine](#) exposure

2J) Summary: Use caution when coadministering [quetiapine](#) with strong CYP3A4 inducers, as this may reduce [quetiapine](#) exposure. Coadministration of [phenytoin](#) (a strong CYP3A4 inducer) with [quetiapine](#) resulted in a 5-fold increase in the clearance of [quetiapine](#). When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original

quetiapine dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the quetiapine dose to the original level within 7 to 14 days [6] [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of quetiapine with strong CYP3A4 inducers may reduce quetiapine exposure. When quetiapine is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original quetiapine dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the quetiapine dose to the original level within 7 to 14 days [6] [2].

7) Probable Mechanism: induction of CYP3A4-mediated metabolism of quetiapine

8) Literature Reports

a) During in-vivo drug interaction studies, coadministration of phenytoin 100 mg 3 times daily (a strong CYP3A4 inducer) with quetiapine 250 mg 3 times daily resulted in a 5-fold increase in the clearance of quetiapine [6] [2].

3.5.1.BH] Eribulin

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

2) Summary: The concomitant use of quetiapine with 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, including torsade de pointes [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of quetiapine with 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, including torsade de pointes [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.BI] Erythromycin

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

2) Summary: The concomitant use of quetiapine with 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, including torsade de pointes [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of quetiapine with 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, including torsade de pointes [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.BJ] Escitalopram

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.BK] Eslicarbazepine Acetate

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates
- 2) Summary: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer) and a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If used concomitantly [73], use caution and monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer) and a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If used concomitantly [73], use caution and monitor the patient closely.
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism by eslicarbazepine acetate

3.5.1.BL] Exenatide

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.BM] Famotidine

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.BN| [Felbamate](#)

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.BO| [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 [98]. 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](#) [99]. 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 [98].

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 [98].

7)) Probable Mechanism: additive CNS depression

3.5.1.BP] Fingolimod

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.BQ] Flecainide

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.BR] Fluconazole

- 1) Interaction Effect: increased [quetiapine](#) serum concentrations and an increased risk of QT prolongation
- 2) Summary: The concomitant use of [fluconazole](#) with drugs known to prolong the QT interval and which are metabolized via the CYP3A4 isoenzyme, such as [quetiapine](#) [30] [29], is contraindicated due to a risk of additive QT prolongation. [Fluconazole](#) is a moderate CYP3A4 inhibitor and may increase plasma concentrations of [quetiapine](#) when these drugs are coadministered [134].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [fluconazole](#) with other drugs known to prolong the QT interval and which are CYP3A4 substrates, such as [quetiapine](#) [30] [29], is contraindicated [134].
- 7) Probable Mechanism: inhibition of CYP3A-mediated [quetiapine](#) metabolism by [fluconazole](#) and additive effects on QT prolongation

3.5.1.BS] Fluoxetine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.BT] Formoterol

- 1) Interaction Effect: increased risk of [ventricular arrhythmias](#)
- 2) Summary: [Formoterol](#) may prolong the QT interval, therefore concomitant use with other drugs that prolong the QT interval should be approached with caution due to additive effects on the QT interval and the potential for increased risk of [ventricular arrhythmias](#) [135]. Monitoring for QT interval prolongation may be warranted if [formoterol](#) and QT prolonging drugs are used concurrently.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution with concomitant administration of [formoterol](#) and QT prolonging drugs as this may result in additive effects on the QT interval and may increase the risk of [ventricular arrhythmias](#) [135]. If coadministration is required, QT interval monitoring may be warranted.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.BU] Foscarnet

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.BV] Fosphenytoin

- 1) Interaction Effect: decreased [quetiapine](#) efficacy
- 2) Summary: Coadministration of [phenytoin](#) or [fosphenytoin](#), CYP3A4 inducers, and [quetiapine](#), a CYP3A4 substrate, may result in decreased [quetiapine](#) exposure [6] [2]. During drug interaction studies, coadministration of [phenytoin](#) and [quetiapine](#) resulted in a 5-fold increase in [quetiapine](#) clearance [122]. If coadministering [quetiapine](#) with chronic treatment of [phenytoin](#) or [fosphenytoin](#) for more than 7 to 14 days, the original [quetiapine](#) dose may need to be increased up to 5-fold based on clinical response and tolerance. If [phenytoin](#) or [fosphenytoin](#) is discontinued, return to the original [quetiapine](#) dose within 7 to 14 days [6] [2].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Coadministration of [phenytoin](#) or [fosphenytoin](#), CYP3A4 inducers, and [quetiapine](#), a CYP3A4 substrate, may result in decreased [quetiapine](#) exposure. If coadministering [quetiapine](#) with chronic treatment of [phenytoin](#) or [fosphenytoin](#) for more than 7 to 14 days, the original [quetiapine](#) dose may need to be increased up to 5-fold based on clinical response and tolerance. If [phenytoin](#) or [fosphenytoin](#) is discontinued, return to the original [quetiapine](#) dose within 7 to 14 days [6] [2].
- 7) Probable Mechanism: induction of CYP3A4-mediated [quetiapine](#) metabolism by [phenytoin](#) or [fosphenytoin](#)
- 8) Literature Reports

a) Coadministration of [phenytoin](#) with [quetiapine](#) significantly decreased the plasma concentration-time profile for [quetiapine](#), resulting in a 5-fold increase in oral clearance in patients with DSM-IV-diagnosed [schizophrenia](#), [schizoaffective disorder](#), or [bipolar disorder](#). Seventeen patients participated in an open-label, nonrandomized, multiple-dose study that compared the pharmacokinetics and tolerability of [quetiapine](#) when administered alone or in combination with [phenytoin](#). Patients received escalating doses of [quetiapine](#) from 25 to 250 mg 3 times daily on days 3 to 10. Maintenance doses of [quetiapine](#) were administered on days 11 to 22. [Phenytoin](#) 100 mg 3 times daily was administered between days 13 and 22. The AUC from 0 to 8 hours after dosing at steady-state with [quetiapine](#) versus [quetiapine](#) plus [phenytoin](#) was 3642 nanograms x hr/mL and 728 nanograms x hr/mL, respectively (p=0.0001). The steady-state C_{max} for [quetiapine](#) versus [quetiapine](#) plus [phenytoin](#) was 1048 nanograms/mL and 359 nanograms/mL, respectively. Clearance over bioavailability (CL/F) for [quetiapine](#) alone versus [quetiapine](#) plus [phenytoin](#) was 80.3 L/hr and 440 L/hr, respectively. The induction of CYP3A4 by [phenytoin](#) is the most likely mechanism for the apparent increase in [quetiapine](#) metabolism [122].

3.5.1.BW] Galantamine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.BX] [Gatifloxacin](#)

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.BY] [Gemifloxacin](#)

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.BZ] [Glimepiride](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using

antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CA] [Glipizide](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CB] [Glyburide](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CC] [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 [138] [139] [140]. 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 [138] [139] [140].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.CD] 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 [138] [139] [140]. 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 [138] [139] [140].
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.CE] Granisetron

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7)) Probable Mechanism: additive effects on QT interval

3.5.1.CF] Halofantrine

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7)) Probable Mechanism: additive effects on QT interval

3.5.1.CG| Haloperidol

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.CH| 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 [138] [139] [140]. 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 [138] [139] [140].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.CI| Hydromorphone

- 1) Interaction Effect: an increase in CNS or [respiratory depression](#)
- 2) Summary: The concomitant use of [HYDROmorphone](#) and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including [respiratory depression](#), hypotension, profound sedation, and coma. When administering [HYDROmorphone](#) and an antipsychotic together, dose reduction of one or both of the medications should be considered [117].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [HYDROmorphone](#) 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 [117].
- 7) Probable Mechanism: additive effects

3.5.1.CJ| Hydroquinidine

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7)) Probable Mechanism: additive effects on QT interval

3.5.1.CK] [Hydroxychloroquine](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation [84] [85], [ventricular premature contractions](#), and [torsade de pointes](#) [85]. 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 [84] [85]. 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 [84].

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 [85].

3.5.1.CL] Ibutilide

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of quetiapine with 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, including torsade de pointes [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of quetiapine with 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, including torsade de pointes [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.CM] Idelalisib

- 1) Interaction Effect: increased exposure of CYP3A substrate
- 2) Summary: Avoid coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects. During a drug interaction study, coadministration of idelalisib and midazolam (CYP3A substrate) resulted in a 5.4-fold increase in midazolam AUC and a 2.4 fold increase in midazolam Cmax [147].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate should be avoided, as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects [147].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism by idelalisib
- 8) Literature Reports

a) During a drug interaction study, administration of idelalisib 150 mg for 15 doses followed by a single dose of midazolam 5 mg (a CYP3A substrate) in healthy volunteers, resulted in a 5.4-fold increase in midazolam AUC and a 2.4 fold increase in midazolam Cmax [147].

3.5.1.CN] Iloperidone

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of quetiapine with 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, including torsade de pointes [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.
- 3) Severity: major
- 4) Onset: unspecified

- 5J) Substantiation: theoretical
- 6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7J) Probable Mechanism: additive effects on QT interval

3.5.1.COJ [Imipramine](#)

- 1J) Interaction Effect: increased risk of QT-interval prolongation
- 2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7J) Probable Mechanism: additive effects on QT interval

3.5.1.CPJ [Indinavir](#)

- 1J) Interaction Effect: increased [quetiapine](#) exposure
- 2J) Summary: Use caution when coadministering [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor as this may increase the exposure of [quetiapine](#) and increase the risk of adverse events. In a drug-interaction study, concomitant use of single dose [quetiapine](#) 25 mg with the strong CYP3A4 inhibitor, [ketoconazole](#), increased [quetiapine](#) exposure. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth, and when the strong CYP3A4 is discontinued, subsequently reduce the [quetiapine](#) dose 6-fold [6] [2].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects and should therefore be undertaken with caution. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth, and when the strong CYP3A4 is discontinued, subsequently reduce the [quetiapine](#) dose 6-fold [6] [2].
- 7J) Probable Mechanism: inhibition of CYP3A-mediated metabolism of [quetiapine](#)
- 8J) Literature Reports

aJ) During in-vivo drug interaction studies, coadministration of [ketoconazole](#) 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in [ketoconazole](#) clearance and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

3.5.1.CQJ [Insulin](#)

- 1J) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CR| [Insulin Aspart, Recombinant](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CS| [Insulin Bovine](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CT| [Insulin Degludec](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor

glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CU] [Insulin Detemir](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CV] [Insulin Glulisine](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CW] [Insulin Lispro, Recombinant](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.CX] Itraconazole

- 1) Interaction Effect: increased exposure of [quetiapine](#) and increased risk of QT-interval prolongation
- 2) Summary: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects on the QT interval prolongation. During drug interaction studies, coadministration of [ketoconazole](#) and [quetiapine](#) resulted in a 6.2-fold increase in [quetiapine](#) AUC. Avoid concomitant use. If coadministration cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects on the QT interval prolongation. Avoid concomitant use. If coadministration cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [quetiapine](#); additive QT-interval prolongation
- 8) Literature Reports

a) During drug interaction studies, coadministration of a potent CYP3A4 inhibitor [ketoconazole](#) 200 mg once daily for 4 days and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in [quetiapine](#) clearance and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

b) A 32-year-old male with [schizoaffective disorder](#) and [metabolic syndrome](#) experienced a significant increase in plasma concentration following administration of [quetiapine](#). The patient, hospitalized for acute psychotic symptoms was treated with 50 mg [quetiapine](#) daily, with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg [clarithromycin](#) along with his evening dose of [quetiapine](#) 400 mg. The following morning, 750 mg sultamicillin, 500 mg [clarithromycin](#), and the morning 300-mg [quetiapine](#) dose were given. Within hours the patient became somnolent, and plasma sample testing resulted in 826.8 mcg/L (normal range, 70 to 170 mcg/L). The patient developed severe impaired consciousness and [respiratory depression](#). [Quetiapine](#) overdose was suspected and treatment was discontinued. Plasma levels were continually measured over the course of a week until complete recovery was achieved [144].

3.5.1.CY] Ivabradine

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.CZ] Ivacaftor

1)) Interaction Effect: increased exposure of the CYP3A or P-gp substrate

2)) Summary: Concomitant use of ivacaftor with a CYP3A or P-gp substrate has the potential to increase the exposure of the CYP3A and/or P-gp substrate. Coadministration of ivacaftor with the sensitive CYP3A substrate [midazolam](#) increased the [midazolam](#) exposure by 1.5-fold. Coadministration of ivacaftor with the sensitive P-gp substrate [digoxin](#) increased the [digoxin](#) exposure by 1.3-fold. Use caution and monitor for adverse effects if coadministration is required [119].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of ivacaftor with a CYP3A and/or P-gp substrate has the potential to increase the exposure of the CYP3A and/or P-gp substrate. Use caution and monitor for adverse effects if coadministration is required [119].

7)) Probable Mechanism: inhibition of CYP3A or P-gp metabolism

8)) Literature Reports

a)) Coadministration of ivacaftor with the sensitive CYP3A substrate [midazolam](#) increased the [midazolam](#) exposure by 1.5-fold. Coadministration of ivacaftor with the sensitive P-gp substrate [digoxin](#) increased the [digoxin](#) exposure by 1.3-fold [119].

3.5.1.DA] Ketoconazole

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

2)) Summary: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects on the QT interval prolongation. During drug interaction studies, coadministration of [ketoconazole](#) and [quetiapine](#) resulted in a 6.2-fold increase in [quetiapine](#) AUC. Avoid concomitant use. If coadministration cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects on the QT interval prolongation. Avoid concomitant use. If coadministration

cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

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

8J) Literature Reports

aJ) During drug interaction studies, coadministration of a potent CYP3A4 inhibitor [ketoconazole](#) 200 mg once daily for 4 days and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in [quetiapine](#) clearance and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

bJ) A 32-year-old male with [schizoaffective disorder](#) and [metabolic syndrome](#) experienced a significant increase in plasma concentration following administration of [quetiapine](#). The patient, hospitalized for acute psychotic symptoms was treated with 50 mg [quetiapine](#) daily, with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg [clarithromycin](#) along with his evening dose of [quetiapine](#) 400 mg. The following morning, 750 mg sultamicillin, 500 mg [clarithromycin](#), and the morning 300-mg [quetiapine](#) dose were given. Within hours the patient became somnolent, and plasma sample testing resulted in 826.8 mcg/L (normal range, 70 to 170 mcg/L). The patient developed severe impaired consciousness and [respiratory depression](#). [Quetiapine](#) overdose was suspected and treatment was discontinued. Plasma levels were continually measured over the course of a week until complete recovery was achieved [144].

3.5.1.DB| Lapatinib

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.DC| 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 [138] [139] [140]. 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 [138] [139] [140].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.DD] Levofloxacin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.DE] Linagliptin

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.DF] Liraglutide

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using

antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.DG] Lixisenatide

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.DH] Lopinavir

1) Interaction Effect: increased [quetiapine](#) exposure

2) Summary: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].

7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of [quetiapine](#)

8) Literature Reports

a) During in-vivo drug interaction studies, coadministration of [ketoconazole](#) 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in clearance of [quetiapine](#) and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

3.5.1.DI] Lumefantrine

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

2) Summary: Avoid coadministration of artemether/lumefantrine and [quetiapine](#), due to the potential for additive effects on QT-interval prolongation [141] [29]. If concomitant administration of artemether/lumefantrine and [quetiapine](#) is medically required, use caution and monitor the ECG. Additionally,

caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [141].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid coadministration of artemether/lumefantrine and [quetiapine](#), due to the potential for additive effects on QT-interval prolongation [141] [29]. If concomitant administration of artemether/lumefantrine and [quetiapine](#) is medically required, use caution and monitor the ECG. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [141].

7J) Probable Mechanism: additive effects on QT interval

3.5.1.DJ] [Mefloquine](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.DK] [Mesoridazine](#)

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

2J) 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](#) [111].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: established

6J) 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](#) [111].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.DL] [Metformin](#)

1J) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2J) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3J) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.DM] [Methadone](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.DN] [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 [114]. 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 [115].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [metoclopramide](#) with antipsychotic agents is contraindicated [114]. 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 [115].
- 7) Probable Mechanism: unknown

3.5.1.DO] [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 [95].

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 [95].

7) Probable Mechanism: additive QT-interval prolongation

8) Literature Reports

a) 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 [95].

b) 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 [96].

3.5.1.DP] [Mifepristone](#)

1) Interaction Effect: increased [quetiapine](#) plasma concentrations and an increased risk of QT interval prolongation

2) Summary: [Quetiapine](#) (a CYP3A4 substrate) has been associated with QT interval prolongation [29] and [mifepristone](#) (a CYP3A substrate and inhibitor) can also prolong the QT interval in a dose-dependent manner. Concomitant use of [mifepristone](#) (Korlym(TM)) and [quetiapine](#) should be avoided due to the potential for increased [quetiapine](#) plasma concentrations and additive QT interval prolongation. Due to the long half-life of [mifepristone](#), wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [quetiapine](#). However, if concomitant use is necessary, use the lowest effective dose possible and monitor closely for QT interval prolongation; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing the [quetiapine](#) dose [106].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid the concomitant use of [mifepristone](#) (Korlym(TM)) and [quetiapine](#) as it may result in increased [quetiapine](#) plasma concentrations [29] and increase the risk of additive QT interval prolongation. Due to the long half-life of [mifepristone](#), wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [quetiapine](#). However, if concomitant use is necessary, use the lowest

effective dose possible and monitor closely for QT interval prolongation; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing the [quetiapine](#) dose [106].

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

3.5.1.DQJ [Miglitol](#)

1J) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2J) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7J) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.DRJ [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 [130].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [130].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.DSJ [Mitotane](#)

1J) Interaction Effect: decreased exposure of CYP3A4 substrates

2J) Summary: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [108] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6) Clinical Management: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [108] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.

7) Probable Mechanism: induction of CYP3A4-mediated metabolism by [mitotane](#)

3.5.1.DT] Mizolastine

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.DU] 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 [127] [128] [129].

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 [127] [128] [129].

7) Probable Mechanism: additive CNS depression effects

3.5.1.DV] 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 [127] [128] [129].

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 [127] [128] [129].

7) Probable Mechanism: additive CNS depression effects

3.5.1.DW] Moxifloxacin

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

2) Summary: The concomitant use of quetiapine with 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, including torsade de pointes [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of quetiapine with 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, including torsade de pointes [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.DX] 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 [138] [139] [140]. 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 [138] [139] [140].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DY] Nateglinide

1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia

2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor

glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7J) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.DZ] Nefazodone

1J) Interaction Effect: increased [quetiapine](#) exposure

2J) Summary: Use caution when coadministering [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor as this may increase the exposure of [quetiapine](#) and increase the risk of adverse events. In a drug-interaction study, concomitant use of single dose [quetiapine](#) 25 mg with the strong CYP3A4 inhibitor, [ketoconazole](#), increased [quetiapine](#) exposure. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth, and when the strong CYP3A4 is discontinued, subsequently reduce the [quetiapine](#) dose 6-fold [6] [2].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects and should therefore be undertaken with caution. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth, and when the strong CYP3A4 is discontinued, subsequently reduce the [quetiapine](#) dose 6-fold [6] [2].

7J) Probable Mechanism: inhibition of CYP3A-mediated metabolism of [quetiapine](#)

8J) Literature Reports

aJ) During in-vivo drug interaction studies, coadministration of [ketoconazole](#) 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in [ketoconazole](#) clearance and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

3.5.1.EA] Nelfinavir

1J) Interaction Effect: increased [quetiapine](#) exposure

2J) Summary: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of

quetiapine should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of quetiapine clinical response and adverse reactions [72].

7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of quetiapine

8) Literature Reports

- a) During in-vivo drug interaction studies, coadministration of ketoconazole 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of quetiapine 25 mg resulted in an 84% decrease in clearance of quetiapine and a 6.2-fold increase in quetiapine AUC [6] [2].

3.5.1.EB| Netupitant

1) Interaction Effect: increased exposure of CYP3A4 substrate

2) Summary: Caution is advised with the coadministration of netupitant (a CYP3A inhibitor) and a CYP3A substrate, as this may increase plasma concentrations of the CYP3A substrate due to inhibition of CYP3A4-mediated metabolism by netupitant and increase the risk of adverse effects that may persist for days. Examples of CYP3A substrates include IV administered chemotherapeutic agents and benzodiazepines; close monitoring is recommended of the increased adverse effects of these agents [69].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised with the coadministration of netupitant (a CYP3A inhibitor) and a CYP3A substrate, as this may increase plasma concentrations of the CYP3A substrate and increase the risk of adverse effects that may persist for days. Examples of CYP3A substrates include IV administered chemotherapeutic agents and benzodiazepines; close monitoring is recommended of the increased adverse effects of these agents [69].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by netupitant

8) Literature Reports

- a) Pharmacokinetic studies demonstrated that coadministration of netupitant 300 mg/palonosetron 0.5 mg and docetaxel, a chemotherapeutic agents metabolized by CYP3A4, increased docetaxel Cmax by 49% and AUC by 35%, compared with coadministration with palonosetron alone. Additionally, coadministration with another chemotherapeutic agent, etoposide, increased etoposide Cmax and AUC by 10% and 28%, respectively. After a single oral dose of the benzodiazepine midazolam 7.5 mg was coadministered with netupitant 300 mg, mean Cmax and AUC of midazolam was 36% and 126% higher, respectively [69].

3.5.1.EC| Nilotinib

1) Interaction Effect: increased exposure of CYP3A4 substrate and increased risk of QT-interval prolongation

2) 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 [151]. Monitoring for toxic effects should be considered.

3) Severity: major

4) Onset: unspecified

5) 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 [151]. 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.EDJ [Norfloxacin](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.EEJ [Octreotide](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.EFJ [Ofloxacin](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de](#)

[pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.EG] [Olanzapine](#)

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.EH] [Ondansetron](#)

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.EI] [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, decrease the dose of 1 or both drugs. Monitor patients for sedation, [respiratory depression](#), and hypotension, especially with therapy initiation and dose changes [123].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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, decrease the dose of 1 or both drugs. Monitor patients for sedation, [respiratory depression](#), and hypotension, especially with therapy initiation and dose changes [123].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.EJ] [Oxymorphone](#)

1J) Interaction Effect: increased risk of [respiratory depression](#), profound sedation, coma, and death

2J) 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 [124].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [124].

7J) Probable Mechanism: additive respiratory and CNS depressant effects

3.5.1.EK] [Paliperidone](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.EL] [Panobinostat](#)

1J) 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 [142].

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 [142].

7)) Probable Mechanism: additive QT effects

3.5.1.EM] [Paroxetine](#)

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.EN] [Pasireotide](#)

1)) Interaction Effect: increased risk of QT prolongation

2)) Summary: Pasireotide is associated with QT-interval prolongation. In 2 studies, QT prolongation occurred at both therapeutic and supratherapeutic doses of pasireotide. Concomitant administration of pasireotide with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval. ECGs at baseline and at 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents [90].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant administration of pasireotide and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation of the QT interval. ECGs at baseline and 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents [90].

7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.EO] [Pazopanib](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7)) Probable Mechanism: additive effects on QT interval

3.5.1.EP] [Pentamidine](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7)) Probable Mechanism: additive effects on QT interval

3.5.1.EQ] [Perflutren Lipid Microsphere](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7)) Probable Mechanism: additive effects on QT interval

3.5.1.ER] [Perphenazine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.ES] [Phenobarbital](#)

- 1) Interaction Effect: decreased [quetiapine](#) exposure
- 2) Summary: Use caution when coadministering [quetiapine](#) with strong CYP3A4 inducers, as this may reduce [quetiapine](#) exposure. Coadministration of [phenytoin](#) (a strong CYP3A4 inducer) with [quetiapine](#) resulted in a 5-fold increase in the clearance of [quetiapine](#). When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [quetiapine](#) with strong CYP3A4 inducers may reduce [quetiapine](#) exposure. When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism of [quetiapine](#)
- 8) Literature Reports

- a) During in-vivo drug interaction studies, coadministration of [phenytoin](#) 100 mg 3 times daily (a strong CYP3A4 inducer) with [quetiapine](#) 250 mg 3 times daily resulted in a 5-fold increase in the clearance of [quetiapine](#) [6] [2].

3.5.1.ET] [Phenylalanine](#)

- 1) Interaction Effect: increased incidence of [tardive dyskinesia](#)
- 2) Summary: Taking [phenylalanine](#) concomitantly with certain neuroleptic drugs may exacerbate [tardive dyskinesia](#) [92]. Abnormal [phenylalanine](#) metabolism in certain patients may lead to [phenylalanine](#) accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines [92].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised if [phenylalanine](#) is administered with a neuroleptic agent. Monitor the patient closely for signs of [tardive dyskinesia](#).

7J) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis

8J) Literature Reports

aJ) **Phenylalanine** tended to increase the incidence of **tardive dyskinesia** in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with **unipolar depression** with **tardive dyskinesia** (n=11), (2) patients with no **tardive dyskinesia** with current or past exposure to greater than or equal to 100 milligrams (mg) of a **chlorpromazine** equivalent for at least 3 months (n=10), and (3) patients with no **tardive dyskinesia** not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered **phenylalanine** 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to **phenylalanine** administration and 2 hours after administration. Three patients in group 1 (with **tardive dyskinesia**) had the highest postloading **phenylalanine** plasma levels, this group as a whole had higher (though nonsignificant) mean **phenylalanine** levels than the other groups. **Tardive dyskinesia** score (measured using the **Abnormal Involuntary Movements Scale (AIMS)**) nonsignificantly increased in group 1. Postloading **phenylalanine** level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading **phenylalanine** level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, **phenylalanine** loading increased plasma **phenylalanine** levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of **phenylalanine** to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly [91].

3.5.1.EU] **Phenytoin**

1J) Interaction Effect: decreased **quetiapine** efficacy

2J) Summary: Coadministration of **phenytoin** or **fosphenytoin**, CYP3A4 inducers, and **quetiapine**, a CYP3A4 substrate, may result in decreased **quetiapine** exposure [6] [2]. During drug interaction studies, coadministration of **phenytoin** and **quetiapine** resulted in a 5-fold increase in **quetiapine** clearance [122]. If coadministering **quetiapine** with chronic treatment of **phenytoin** or **fosphenytoin** for more than 7 to 14 days, the original **quetiapine** dose may need to be increased up to 5-fold based on clinical response and tolerance. If **phenytoin** or **fosphenytoin** is discontinued, return to the original **quetiapine** dose within 7 to 14 days [6] [2].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Coadministration of **phenytoin** or **fosphenytoin**, CYP3A4 inducers, and **quetiapine**, a CYP3A4 substrate, may result in decreased **quetiapine** exposure. If coadministering **quetiapine** with chronic treatment of **phenytoin** or **fosphenytoin** for more than 7 to 14 days, the original **quetiapine** dose may need to be increased up to 5-fold based on clinical response and tolerance. If **phenytoin** or **fosphenytoin** is discontinued, return to the original **quetiapine** dose within 7 to 14 days [6] [2].

7J) Probable Mechanism: induction of CYP3A4-mediated **quetiapine** metabolism by **phenytoin** or **fosphenytoin**

8J) Literature Reports

aJ) Coadministration of **phenytoin** with **quetiapine** significantly decreased the plasma concentration-time profile for **quetiapine**, resulting in a 5-fold increase in oral clearance in patients with DSM-IV-diagnosed **schizophrenia**, **schizoaffective disorder**, or **bipolar disorder**. Seventeen

patients participated in an open-label, nonrandomized, multiple-dose study that compared the pharmacokinetics and tolerability of [quetiapine](#) when administered alone or in combination with [phenytoin](#). Patients received escalating doses of [quetiapine](#) from 25 to 250 mg 3 times daily on days 3 to 10. Maintenance doses of [quetiapine](#) were administered on days 11 to 22. [Phenytoin](#) 100 mg 3 times daily was administered between days 13 and 22. The AUC from 0 to 8 hours after dosing at steady-state with [quetiapine](#) versus [quetiapine](#) plus [phenytoin](#) was 3642 nanograms x hr/mL and 728 nanograms x hr/mL, respectively ($p=0.0001$). The steady-state Cmax for [quetiapine](#) versus [quetiapine](#) plus [phenytoin](#) was 1048 nanograms/mL and 359 nanograms/mL, respectively. Clearance over bioavailability (CL/F) for [quetiapine](#) alone versus [quetiapine](#) plus [phenytoin](#) was 80.3 L/hr and 440 L/hr, respectively. The induction of CYP3A4 by [phenytoin](#) is the most likely mechanism for the apparent increase in [quetiapine](#) metabolism [122].

3.5.1.EV] [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](#) [110].
- 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](#) [110].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.EW] [Pioglitazone](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.EX] [Piperaquine](#)

- 1) Interaction Effect: increased exposure of CYP3A4 substrates and increased risk of QT-interval prolongation
- 2) 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 piperazine therapy [105].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of piperazine (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 piperazine administration, is contraindicated. Concurrent administration of piperazine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperazine, caution is advised when administering a CYP3A4 substrate for up to 3 months after discontinuation of piperazine therapy [105].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of this drug by piperazine; additive QT-interval prolongation

3.5.1.EY] Posaconazole

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

2) 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 quetiapine, a CYP3A4 substrate that also prolongs the QT interval, is contraindicated as concomitant use may lead to increased quetiapine exposure and increased risk of QT interval prolongation and torsade de pointes [83].

3) Severity: contraindicated

4) 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, such as quetiapine, is contraindicated as concomitant use may lead to increased exposure to quetiapine and increased risk of QT interval prolongation and torsade de pointes [83].

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

3.5.1.EZ] Pramlintide

1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia

2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [78].

7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

3.5.1.FA] Primidone

- 1) Interaction Effect: decreased [quetiapine](#) exposure
- 2) Summary: Use caution when coadministering [quetiapine](#) with strong CYP3A4 inducers, as this may reduce [quetiapine](#) exposure. Coadministration of [phenytoin](#) (a strong CYP3A4 inducer) with [quetiapine](#) resulted in a 5-fold increase in the clearance of [quetiapine](#). When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [quetiapine](#) with strong CYP3A4 inducers may reduce [quetiapine](#) exposure. When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism of [quetiapine](#)
- 8) Literature Reports
 - a) During in-vivo drug interaction studies, coadministration of [phenytoin](#) 100 mg 3 times daily (a strong CYP3A4 inducer) with [quetiapine](#) 250 mg 3 times daily resulted in a 5-fold increase in the clearance of [quetiapine](#) [6] [2].

3.5.1.FB| [Probucol](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.FC| [Procainamide](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.FD] [Prochlorperazine](#)

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.FE] [Promethazine](#)

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.FF] [Propafenone](#)

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.FG] [Protriptyline](#)

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.FH] [Quinidine](#)

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.FI] [Quinine](#)

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

2)) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.FJ] [Ranolazine](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.FK] [Repaglinide](#)

1J) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2J) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].

7J) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.FL] [Rifabutin](#)

1J) Interaction Effect: decreased [quetiapine](#) exposure

2J) Summary: Use caution when coadministering [quetiapine](#) with strong CYP3A4 inducers, as this may reduce [quetiapine](#) exposure. Coadministration of [phenytoin](#) (a strong CYP3A4 inducer) with [quetiapine](#) resulted in a 5-fold increase in the clearance of [quetiapine](#). When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6) Clinical Management: Concomitant use of [quetiapine](#) with strong CYP3A4 inducers may reduce [quetiapine](#) exposure. When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].

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

8) Literature Reports

a) During in-vivo drug interaction studies, coadministration of [phenytoin](#) 100 mg 3 times daily (a strong CYP3A4 inducer) with [quetiapine](#) 250 mg 3 times daily resulted in a 5-fold increase in the clearance of [quetiapine](#) [6] [2].

3.5.1.FM] Rifampin

1) Interaction Effect: decreased [quetiapine](#) exposure

2) Summary: Use caution when coadministering [quetiapine](#) with strong CYP3A4 inducers, as this may reduce [quetiapine](#) exposure. Coadministration of [phenytoin](#) (a strong CYP3A4 inducer) with [quetiapine](#) resulted in a 5-fold increase in the clearance of [quetiapine](#). When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [quetiapine](#) with strong CYP3A4 inducers may reduce [quetiapine](#) exposure. When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].

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

8) Literature Reports

a) During in-vivo drug interaction studies, coadministration of [phenytoin](#) 100 mg 3 times daily (a strong CYP3A4 inducer) with [quetiapine](#) 250 mg 3 times daily resulted in a 5-fold increase in the clearance of [quetiapine](#) [6] [2].

3.5.1.FN] Rifapentine

1) Interaction Effect: decreased [quetiapine](#) exposure

2) Summary: Use caution when coadministering [quetiapine](#) with strong CYP3A4 inducers, as this may reduce [quetiapine](#) exposure. Coadministration of [phenytoin](#) (a strong CYP3A4 inducer) with [quetiapine](#) resulted in a 5-fold increase in the clearance of [quetiapine](#). When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [quetiapine](#) with strong CYP3A4 inducers may reduce [quetiapine](#) exposure. When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When

the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].

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

8J) Literature Reports

aJ) During in-vivo drug interaction studies, coadministration of [phenytoin](#) 100 mg 3 times daily (a strong CYP3A4 inducer) with [quetiapine](#) 250 mg 3 times daily resulted in a 5-fold increase in the clearance of [quetiapine](#) [6] [2].

3.5.1.FO] [Rilpivirine](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.FP] [Risperidone](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.FQ] [Ritonavir](#)

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

2J) Summary: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and a strong CYP3A4 inhibitor that prolongs the QT interval may increase the exposure of [quetiapine](#). Coadministration may also result in additive effects on the QT interval. Concomitant administration is contraindicated [145] [146].

3J) Severity: contraindicated

4J) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and a strong CYP3A4 inhibitor that prolongs the QT interval may increase the exposure of [quetiapine](#) and result in additive effects on the QT interval. Concomitant administration is contraindicated [145] [146].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [quetiapine](#); additive QT-interval prolongation

3.5.1.FR] [Rosiglitazone](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.FS] [Saquinavir](#)

- 1) Interaction Effect: increased exposure of [quetiapine](#) and increased risk of QT-interval prolongation
- 2) Summary: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and [saquinavir](#) (a strong CYP3A4 inhibitor) may increase the exposure of [quetiapine](#). Additionally, concomitant administration of [quetiapine](#) and [saquinavir](#) may result in additive effects on the QT interval. Concomitant administration is contraindicated [104].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and [saquinavir](#) (a strong CYP3A4 inhibitor) may increase the exposure of [quetiapine](#). Additionally, concomitant administration of [quetiapine](#) and [saquinavir](#) may result in additive effects on the QT interval. Concomitant administration is contraindicated [104].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [quetiapine](#); additive QT-interval prolongation

3.5.1.FT] [Saxagliptin](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.FU] Sertindole

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.FV] Sevoflurane

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.FW] Siltuximab

- 1) Interaction Effect: decreased effectiveness of CYP3A4 substrate
- 2) Summary: Coadministration of siltuximab and a CYP3A4 substrate may result in increased metabolism and decreased effectiveness of the substrate. Approach concurrent use with caution. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation [100]. If coadministration is required, monitoring and dose adjustments may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6J) Clinical Management: Coadministration of siltuximab and a CYP3A4 substrate may increase the metabolism of the substrate and decrease its effectiveness. Use caution when coadministering siltuximab and a CYP3A4 substrate. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation [100]. If coadministration is required, monitoring and dose adjustments may be warranted.

7J) Probable Mechanism: inhibition of interleukin-6 by siltuximab increases CYP450 levels leading to increased metabolism of CYP450 substrates

3.5.1.FX| Sitagliptin

1J) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2J) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [78].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [78].

7J) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.FY| Sodium Phosphate

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.FZ| Sodium Phosphate, Dibasic

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.GA] [Sodium Phosphate, Monobasic](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.GB] [Solifenacin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.GC] [Sorafenib](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.GD] [Sotalol](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.GE] [Sparfloxacin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) 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](#) [152].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) 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](#) [152].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.GF] [St John's Wort](#)

- 1) Interaction Effect: decreased [quetiapine](#) exposure
- 2) Summary: Use caution when coadministering [quetiapine](#) with strong CYP3A4 inducers, as this may reduce [quetiapine](#) exposure. Coadministration of [phenytoin](#) (a strong CYP3A4 inducer) with [quetiapine](#) resulted in a 5-fold increase in the clearance of [quetiapine](#). When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [quetiapine](#) with strong CYP3A4 inducers may reduce [quetiapine](#) exposure. When [quetiapine](#) is used concomitantly with chronic treatment with a strong CYP3A4 inducer (for more than 7 to 14 days), increase the original [quetiapine](#) dose up to 5-fold. When the strong CYP3A4 inducer is discontinued, decrease the [quetiapine](#) dose to the original level within 7 to 14 days [6] [2].

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

8) Literature Reports

a) During in-vivo drug interaction studies, coadministration of [phenytoin](#) 100 mg 3 times daily (a strong CYP3A4 inducer) with [quetiapine](#) 250 mg 3 times daily resulted in a 5-fold increase in the clearance of [quetiapine](#) [6] [2].

3.5.1.GG| [Sunitinib](#)

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

2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

3.5.1.GH| [Suvorexant](#)

1) Interaction Effect: CNS depression

2) Summary: Use caution with coadministration of suvorexant with other CNS depressants due to the risk of additive CNS depressant effects. Cognitive and behavioral changes (eg, hallucinations, anxiety, amnesia, other neuropsychiatric symptoms) and complex sleep behaviors (eg, sleep-driving, preparing and eating food) may also be potentiated. Also alcohol should be avoided during treatment. If coadministration with another CNS depressant is required, dose adjustments of both drugs may be necessary. Concurrent use with other medications that treat insomnia is not recommended, and suvorexant discontinuation may be required if complex sleep behaviors develop [126].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of suvorexant with other CNS depressants due to the risk of additive CNS depressant effects. Cognitive and behavioral changes (eg, hallucinations, anxiety, amnesia, other neuropsychiatric symptoms) and complex sleep behaviors (eg, sleep-driving, preparing and eating food) may also be potentiated. Also alcohol should be avoided during treatment. If coadministration with another CNS depressant is required, dose adjustments of both drugs may be necessary. Concurrent use with other medications that treat insomnia is not recommended, and suvorexant discontinuation may be required if complex sleep behaviors develop [126].

7) Probable Mechanism: additive CNS depression

3.5.1.GI] Tacrolimus

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.GJ] Tamoxifen

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.GK] 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 [respiratory depression](#), hypotension, and sedation [118].
- 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 [118].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.GL] Telaprevir

1J) Interaction Effect: increased [quetiapine](#) exposure

2J) Summary: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].

7J) Probable Mechanism: inhibition of CYP3A-mediated metabolism of [quetiapine](#)

8J) Literature Reports

aJ) During in-vivo drug interaction studies, coadministration of [ketoconazole](#) 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in clearance of [quetiapine](#) and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

3.5.1.GM] Telavancin

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.GN] Telithromycin

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

2J) Summary: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects

on the QT interval prolongation. During drug interaction studies, coadministration of [ketoconazole](#) and [quetiapine](#) resulted in a 6.2-fold increase in [quetiapine](#) AUC. Avoid concomitant use. If coadministration cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects on the QT interval prolongation. Avoid concomitant use. If coadministration cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

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

8) Literature Reports

a) During drug interaction studies, coadministration of a potent CYP3A4 inhibitor [ketoconazole](#) 200 mg once daily for 4 days and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in [quetiapine](#) clearance and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

b) A 32-year-old male with [schizoaffective disorder](#) and [metabolic syndrome](#) experienced a significant increase in plasma concentration following administration of [quetiapine](#). The patient, hospitalized for acute psychotic symptoms was treated with 50 mg [quetiapine](#) daily, with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg [clarithromycin](#) along with his evening dose of [quetiapine](#) 400 mg. The following morning, 750 mg sultamicillin, 500 mg [clarithromycin](#), and the morning 300-mg [quetiapine](#) dose were given. Within hours the patient became somnolent, and plasma sample testing resulted in 826.8 mcg/L (normal range, 70 to 170 mcg/L). The patient developed severe impaired consciousness and [respiratory depression](#). [Quetiapine](#) overdose was suspected and treatment was discontinued. Plasma levels were continually measured over the course of a week until complete recovery was achieved [144].

3.5.1.GO] [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](#) [149].

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](#) [149].

7) Probable Mechanism: additive QT interval effects

3.5.1.GP] [Tetrabenazine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.GQ| [Thioridazine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [thioridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [86].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [thioridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [86].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.GR| [Tipranavir](#)

- 1) Interaction Effect: increased [quetiapine](#) exposure
- 2) Summary: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [quetiapine](#) (a CYP3A4 substrate) with a strong CYP3A4 inhibitor may increase the exposure of [quetiapine](#) and increase the risk of adverse effects [6] [2] and is contraindicated with certain strong CYP3A4 inhibitors [70] [71]. If concomitant use is required, reduce the [quetiapine](#) dose by one-sixth and when the strong CYP3A4 inhibitor is discontinued, the dose of [quetiapine](#) should subsequently be increased 6-fold [6] [2]. More frequent monitoring is also recommended of [quetiapine](#) clinical response and adverse reactions [72].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of [quetiapine](#)
- 8) Literature Reports

a)) During in-vivo drug interaction studies, coadministration of [ketoconazole](#) 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in clearance of [quetiapine](#) and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

3.5.1.GS| [Tizanidine](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: [Tizanidine](#) has the potential to cause QT-interval prolongation [101] [102]. Concomitant administration of [tizanidine](#) with other drugs that prolong the QT interval, including antiarrhythmic medications, may increase the risk of QT-interval prolongation. Consider a baseline ECG and on-treatment monitoring when [tizanidine](#) is coadministered with other QT interval-prolonging agents.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant administration of [tizanidine](#) and QT interval-prolonging drugs, including antiarrhythmic medications, may result in an increased risk of QT-interval prolongation. Consider a baseline ECG and on-treatment monitoring when [tizanidine](#) is coadministered with other QT interval-prolonging agents.
- 7)) Probable Mechanism: additive QT interval effects

3.5.1.GT| [Tolazamide](#)

- 1)) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2)) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [78].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [78].
- 7)) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.GU| [Tolbutamide](#)

- 1)) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2)) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [78].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [78].

7J) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.GV] [Tolterodine](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.GW] [Toremifene](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.GX] [Trazodone](#)

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.GY] Trimipramine

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.GZ] Triptorelin

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 [138] [139] [140]. 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

5J) Substantiation: theoretical

6J) 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 [138] [139] [140].

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

3.5.1.HA] Vandetanib

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

2J) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.HB| Vardenafil

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.HC| Vemurafenib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.HD| Venlafaxine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.HE] Vilanterol

- 1) Interaction Effect: increased risk of [ventricular arrhythmias](#)
- 2) Summary: Vilanterol (a beta-agonist) has potential to prolong the QT interval; therefore, concomitant use with other drugs that can prolong the QT interval may cause an increased risk of [ventricular arrhythmias](#). [Electrocardiograph](#) changes, such as QT-interval prolongation, have been reported with beta-agonists. Use extreme caution during coadministration of vilanterol with a QT-interval prolonging drug or when using vilanterol within 2 weeks of discontinuation of a QT-interval prolonging drug [121]. [ECG monitoring](#) may be warranted if vilanterol and QT-interval prolonging drugs are used concurrently.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of vilanterol and QT-interval prolonging drugs may potentiate cardiovascular effects, such as QT-interval prolongation, and increase the risk of [ventricular arrhythmias](#). Use extreme caution when coadministering vilanterol and QT-interval prolonging drugs, or if using vilanterol within 2 weeks of discontinuation of a QT interval-prolonging drug [121]. If coadministration is required, [ECG monitoring](#) may be warranted.
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.HF] Vildagliptin

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [77]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [78] and adjust antidiabetic agent doses as necessary [79]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [78].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

3.5.1.HG] Vinflunine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Vinflunine is associated with QT-interval prolongation. Concomitant administration of vinflunine with other drugs that prolong the QT interval may have additive prolonging effects on the QT interval and is not recommended [109]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring when vinflunine is coadministered with other QT-prolonging agents.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of vinflunine and QT-prolonging drugs may result in additive QT-interval prolongation effects and is therefore not recommended [109]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.
- 7) Probable Mechanism: additive QT interval effects

3.5.1.HH] Voriconazole

- 1) Interaction Effect: increased exposure of [quetiapine](#) and increased risk of QT-interval prolongation
- 2) Summary: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects on the QT interval prolongation. During drug interaction studies, coadministration of [ketoconazole](#) and [quetiapine](#) resulted in a 6.2-fold increase in [quetiapine](#) AUC. Avoid concomitant use. If coadministration cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [quetiapine](#) (a CYP3A4 substrate) and QT interval prolonging, potent CYP3A4 inhibitors may increase the exposure of [quetiapine](#) and additionally may result in additive effects on the QT interval prolongation. Avoid concomitant use. If coadministration cannot be avoided, the dose of [quetiapine](#) may need to be reduced to one-sixth of the original dose. When the potent CYP3A4 inhibitor is discontinued, the [quetiapine](#) dose should be subsequently increased 6-fold [6] [2]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [quetiapine](#); additive QT-interval prolongation
- 8) Literature Reports

a) During drug interaction studies, coadministration of a potent CYP3A4 inhibitor [ketoconazole](#) 200 mg once daily for 4 days and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in [quetiapine](#) clearance and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

b) A 32-year-old male with [schizoaffective disorder](#) and [metabolic syndrome](#) experienced a significant increase in plasma concentration following administration of [quetiapine](#). The patient, hospitalized for acute psychotic symptoms was treated with 50 mg [quetiapine](#) daily, with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg [clarithromycin](#) along with his evening dose of [quetiapine](#) 400 mg. The following morning, 750 mg sultamicillin, 500 mg [clarithromycin](#), and the morning 300-mg [quetiapine](#) dose were given. Within hours the patient became somnolent, and plasma sample testing resulted in 826.8 mcg/L (normal range, 70 to 170 mcg/L). The patient developed severe impaired consciousness and [respiratory depression](#). [Quetiapine](#) overdose was suspected and treatment was discontinued. Plasma levels were continually measured over the course of a week until complete recovery was achieved [144].

3.5.1.HI] Vorinostat

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [6] [2]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.HJ] [Warfarin](#)

- 1) Interaction Effect: increased INR and risk for bleeding
- 2) Summary: Concomitant use of [quetiapine](#) together with [warfarin](#) may result in increased INR and risk of bleeding. Two case reports have described elevations in INR following addition of [quetiapine](#) in patients previously stable on [warfarin](#), one of which included a patient who was diagnosed with warfarin-associated multiple [intracerebral hemorrhages](#) (ICH) [74] [76]. Monitor INR when starting, stopping, or changing the dose of the concomitant drug in patients receiving [warfarin](#) therapy [75].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [quetiapine](#) together with [warfarin](#) may result in increased INR and risk of bleeding [74]. Monitor INR when starting, stopping, or changing the dose of the concomitant drug in patients receiving [warfarin](#) therapy [75].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Increased INR and multiple [intracerebral hemorrhages](#) (ICH) was reported approximately 3 days after initiation of [quetiapine](#) in a 78-year-old man who had a stable INR for 1 year prior with [warfarin](#). The patient, who had a history of [coronary artery disease](#), [hypertension](#), and [dementia](#), was started on [quetiapine](#) 12.5 mg/day for agitation and delusions in the prior 2 months. Concomitant medications included [atenolol](#) 50 mg/day, [lacidipine](#) 4 mg/day, and [donepezil](#) 5 mg/day. Approximately 3 days after [quetiapine](#) initiation, the patient presented with an abrupt onset of varying levels of consciousness, dizziness, and headache. Laboratory evaluation revealed INR of 3.54, and a head CT revealed foci at the left posterolateral temporal lobe (34 mm), right lateral temporal (17.3 mm), left high parietal (14 mm) and deep left cerebellar hemisphere (25 mm); leading to a diagnosis of warfarin-associated multiple ICH. [Quetiapine](#) and [warfarin](#) were discontinued, and the INR fell to 1.04. No changes were identified in the recent dietary or bowel habits of the patient. Drug Interaction Probability Scale of 6 (0- to 11-point scale) indicated a probable interaction between [quetiapine](#) and [warfarin](#) [74].

b) A 71-year-old woman experienced enhanced anticoagulant effects from [warfarin](#) when [quetiapine](#) was added to her drug regimen. Her medications included [phenytoin](#) 300 mg daily with a serum concentration of 9.87 mg/L, [warfarin](#) 19.5 mg weekly with an INR of 2.6, [benztropine](#) 0.5 mg daily, and [olanzapine](#) 20 mg daily. [Olanzapine](#) was discontinued, and [quetiapine](#) therapy was initiated at 200 mg daily. Five days later, the INR was 2.7. After two weeks of [quetiapine](#) treatment, the INR increased to 9.2. [Quetiapine](#) was discontinued and two doses of vitamin K 10 mg were administered. The only clinical signs observed in the patient were a small amount of bleeding at the site of the vitamin K injection and a bruise on the hand. The INR decreased back to baseline with the discontinuation of [quetiapine](#) [76].

3.5.1.HK] [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](#) [88] [89].
- 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](#) [88] [89].
- 7)) Probable Mechanism: additive QT interval effects

3.5.2] Drug-Food Combinations

3.5.2.A] Ethanol

- 1)) Interaction Effect: potentiation of the cognitive and motor effects of alcohol
- 2)) Summary: [Quetiapine](#) potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected [psychotic disorders](#). Alcoholic beverages should be avoided while taking [quetiapine](#) [163].
- 3)) Severity: moderate
- 4)) Onset: rapid
- 5)) Substantiation: probable
- 6)) Clinical Management: Patients should be instructed to avoid ethanol ingestion while taking [quetiapine](#).
- 7)) Probable Mechanism: additive CNS depression

3.5.2.B] Grapefruit Juice

- 1)) Interaction Effect: increased [quetiapine](#) exposure
- 2)) Summary: The concomitant use of [quetiapine](#), a CYP3A4 substrate, and a strong CYP3A4 inhibitor, such as grapefruit juice may result in increased [quetiapine](#) concentrations. In a drug-interaction study, concomitant use of single dose [quetiapine](#) 25 mg with the strong CYP3A4 inhibitor, [ketoconazole](#), increased [quetiapine](#) exposure [6] [2]. Depending on the quantity of grapefruit juice consumed, the dose of [quetiapine](#) may need to be reduced. Monitor patients closely for adverse events associated with [quetiapine](#).
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Patients should be advised to use caution when consuming grapefruit juice during [quetiapine](#) administration, as grapefruit juice may increase [quetiapine](#) plasma concentrations [6] [2]. Depending on the quantity of grapefruit juice consumed, the dose of [quetiapine](#) may need to be reduced. Monitor patients closely for adverse events associated with [quetiapine](#).
- 7)) Probable Mechanism: inhibition of CYP3A4-mediated [quetiapine](#) metabolism by grapefruit
- 8)) Literature Reports

- a)) During in-vivo drug interaction studies, coadministration of [ketoconazole](#) 200 mg once daily for 4 days (a potent CYP3A4 inhibitor) and a single dose of [quetiapine](#) 25 mg resulted in an 84% decrease in clearance of [quetiapine](#) and a 6.2-fold increase in [quetiapine](#) AUC [6] [2].

3.5.3] Drug-Lab Modifications

3.5.3.A] [Methadone measurement](#), urine

- 1)) Interaction Effect: false-positive urine drug screen for [methadone](#)

2j) Summary: There have been cases of false-positive [methadone](#) urine drug screens with the use of assays such as the [Methadone II](#) testkit(R) in patients treated with [quetiapine](#). Clinicians should consider confirming positive [methadone](#) tests with more specific methods, such as [chromatography](#) [29] [30], [mass spectrometry](#), or other quantitative methods particularly in patients whose results do not coincide with medical history, or current behaviors and observations [165] [166].

3j) Severity: moderate

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: Clinicians should be aware that there have been cases of false-positive urine [methadone](#) drug screens in patients receiving [quetiapine](#). Consider confirming a positive urine methadone screen with more specific methods, such as [chromatography](#) [29] [30], [mass spectrometry](#), or other quantitative methods, particularly in patients whose results do not coincide with medical history, or current behaviors and observations [165] [166].

7j) Probable Mechanism: mechanism unknown

8j) Literature Reports

a) In a retrospective chart review, 12 pediatric patients (mean age of 15.5 years) admitted to a behavioral health program and treated with [quetiapine](#) from 125 to 160 mg daily had false methadone-positive urine drug screens with the [Methadone II](#) assay(R) by Roche. Although 5 of these patients had positive substance abuse history, none were admitted for substance-related issues. All patients denied current [methadone](#) use, and final clinical impressions were that they had not used any controlled substances. Results of confirmatory testing using [gas chromatography/mass spectroscopy](#), performed in 2 of the patients, were negative for [methadone](#) [165].

b) Three schizophrenic patients, being treated with [quetiapine](#) monotherapy, had false-positive urinalysis results for [methadone](#) using the Cobas Integra [Methadone II](#) testkit(R) by Roche. This method, used for semiquantitative and qualitative detection of [methadone](#) in urine, has a threshold of 300 ng/mL for [methadone](#) positivity. Blood samples that were taken on the day after [quetiapine](#) administration ended also tested positive for [methadone](#) with [mass spectrometry](#). However, given the medical histories of the patients, these results were unexpected. Further screening of the patient's plasma with a specific quantitative assay did not reveal [methadone](#) positivity [166].

3.5.3.B] Tricyclic antidepressant measurement

1j) Interaction Effect: a false-positive urine tricyclic antidepressant assay

2j) Summary: There have been cases of false-positive urine tricyclic antidepressant assays in patients treated with [quetiapine](#) [164]. Positive urine tricyclic antidepressant assays should be confirmed with more specific methods, such as [chromatography](#) [29] [30].

3j) Severity: moderate

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: Clinicians should be aware that [quetiapine](#) may cause false-positive test results in assays for urine tricyclic antidepressants. Positive urine tricyclic antidepressant assays should be confirmed with specific analytical techniques, such as [chromatography](#) [29] [30].

7j) Probable Mechanism: mechanism unknown

8j) Literature Reports

a) A 34-year-old man receiving [quetiapine](#) 600 mg daily showed a positive [toxicology screening](#) for tricyclic antidepressants despite his denial of tricyclic use. [Quetiapine](#) is structurally similar to tricyclic antidepressants and was suspected as the cause of this assay abnormality. A laboratory

test confirmed that [quetiapine](#) is capable of causing a false-positive urine screen for tricyclic antidepressants [164].

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

4.1] Monitoring Parameters

A) [Quetiapine](#) Fumarate

1) Therapeutic

a) Physical Findings

1) A reduction in the severity or resolution of signs and symptoms of schizophrenia, bipolar disorder (manic, depressed, or mixed episodes), or depression are indicative of efficacy.

2) Toxic

a) Laboratory Parameters

1) 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 [181]:

a) 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 [181].

b) 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 [181].

2) Perform CBC [182] [183] with differential frequently during the first few months of therapy in patients with preexisting low WBC or a history of drug-induced leukopenia or neutropenia.

b) Physical Findings

1) 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 [181]:

- a) Obtain personal and family history of obesity, diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease, prior to treatment and review annually with patient [181].
 - b) Track weight and BMI at baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter [181].
 - c) Measure waist circumference at baseline, and annually thereafter [181].
 - d) 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 [181].
- 2) 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 [184].
- 3) Monitor patients for suicidality during therapy due to the increased risk of suicide attempts in patients with schizophrenia, bipolar disorder, and depression [182] [183].
- 4) Ocular examination (eg, slit lamp exam) to detect cataract formation is recommended at treatment initiation and every 6 months during chronic quetiapine treatment [182] [183].

4.2] Patient Instructions

A) Quetiapine (By mouth)

Quetiapine Fumarate

Treats [schizophrenia](#), [bipolar disorder](#), or [depression](#).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use if you had an [allergic reaction](#) to [quetiapine](#).

How to Use This Medicine:

Tablet, Long Acting Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you. You need to start with a low dose, even if you have used this medicine before.

Your doctor may tell you to take the medicine at bedtime, because [quetiapine](#) can make you sleepy.

Extended-release tablets: Take this medicine either without food or with a light snack (approximately 300 calories).

Swallow the extended-release tablet whole. Do not crush, break, or chew it.

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 foods and medicines can affect how [quetiapine](#) works. Tell your doctor if you are using St John's wort, [levodopa](#), [methadone](#), [nefazodone](#), [rifampin](#), blood pressure medicine, medicine for heart rhythm problems (such as [amiodarone](#), [procainamide](#), [quinidine](#), [sotalol](#)), medicine to treat HIV/AIDS (such as [indinavir](#), [ritonavir](#)), medicine for seizures (such as [carbamazepine](#), [phenobarbital](#), [phenytoin](#)), medicine to treat an infection (such as [gatifloxacin](#), [itraconazole](#), [ketoconazole](#), [moxifloxacin](#), [pentamidine](#)), or other antipsychotic medicine (such as [chlorpromazine](#), [thioridazine](#), [ziprasidone](#)).

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 liver disease, [breast cancer](#), [diabetes](#), underactive thyroid, or a history of seizures or [neuroleptic malignant syndrome](#) (NMS). Tell your doctor if you have any kind of blood vessel or heart problems, including low or [high blood pressure](#), [heart failure](#), heart rhythm problems (such as QT prolongation, slow heartbeat), high cholesterol, or a history of [heart attack](#) or [stroke](#).

This medicine may cause the following problems:

[Neuroleptic malignant syndrome](#) (NMS)

High blood sugar levels

High cholesterol or [triglyceride](#) levels in your blood

[Tardive dyskinesia](#) (a movement disorder)

Changes in blood pressure, especially in children

Heart rhythm changes

Changes in body temperature

This medicine may cause depression or thoughts of suicide. Make sure family members know about this. Always tell your doctor about any behavior changes, depression, intense feelings, or thoughts of hurting yourself or others.

This medicine may make you dizzy, lightheaded, or drowsy. Do not drive or do anything else that could be dangerous until you know how this medicine affects you. Stand or sit up slowly if you feel dizzy.

This medicine may cause you to get infections easily because it can lower the number of white blood cells. Take precautions to prevent illness. Avoid people who are ill, and wash your hands often.

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.

You may also need to have your eyes tested on a regular basis.

Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results.

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

Changes in mood or behavior, agitation, anxiety, restlessness, or thoughts of hurting yourself or others

Constant muscle movement that you cannot control (often in your lips, tongue, jaw, arms, or legs)

Fast, slow, pounding, or uneven heartbeat

Fever, chills, cough, sore throat, and body aches
Fever, sweating, confusion, uneven heartbeat, muscle stiffness
Increase in how much or how often you urinate, increased thirst, increased hunger, or weakness
Lightheadedness, dizziness, fainting, or clumsiness
Seizures
Vision changes

If you notice these less serious side effects, talk with your doctor:

Constipation, vomiting, nausea, dry mouth
Headache
Tiredness, dizziness, or sleepiness
Trouble swallowing
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) Quetiapine Fumarate

1) Schizophrenia

a) Immediate-release and extended-release quetiapine tablets are indicated for the treatment of schizophrenia in adults and adolescents 13 years or older; although, the effectiveness of quetiapine monotherapy maintenance treatment has not been studied in controlled clinical trials [6] [2].

2) Bipolar I Disorder

a) Acute Treatment of Manic or Mixed Episodes

1) Immediate-release and extended-release quetiapine tablets are indicated as monotherapy and as an adjunct to lithium or divalproex in adults and pediatric patients 10 years or older [6] [2].

b) Maintenance Treatment of Manic and Mixed Episodes

1) Immediate-release and extended-release quetiapine tablets are indicated as monotherapy and as an adjunct to lithium or divalproex in adults; although, the effectiveness of quetiapine monotherapy maintenance treatment has not been studied in controlled clinical trials [6] [2].

c) Acute Treatment of Depressive Episodes

1) Immediate-release and extended-release quetiapine tablets are indicated for the acute treatment of depressive episodes associated with bipolar disorder in adults [6] [2].

3) Major Depressive Disorder

a) Extended-release quetiapine is indicated for use as adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults [2].

4.4] Mechanism of Action / Pharmacology

A) Quetiapine Fumarate

1) Mechanism of Action

a) Quetiapine is a dibenzothiazepine antipsychotic agent [6] [2] bearing structural similarity to clozapine and olanzapine [179] [175] [174] [180]. The precise mechanism of action of quetiapine fumarate is unknown; although, it is believed that efficacy in schizophrenia and its mood stabilization properties are due to the combined antagonism of D(2) and 5HT(2) receptors [6] [2], and the efficacy in major depression may be partially explained by norepinephrine antagonism [2]. It antagonizes multiple neurotransmitter receptors, including serotonin 5HT(1A) and 5HT(2), dopamine D(1) and D(2), histamine H(1), and adrenergic alpha(1) and alpha(2) receptors [6] [2]. The active metabolite, norquetiapine, has similar activity as quetiapine at D(2) receptors, greater activity at 5HT(2A) receptors, and uniquely antagonizes muscarinic M(1) and norepinephrine receptors [2].

4.5] Therapeutic Uses

4.5.A] Quetiapine Fumarate

4.5.A.1] Bipolar disorder, depressed phase, Monotherapy in acute management

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; 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

b) Summary:

Regular- and extended-release quetiapine is indicated for the acute treatment of depressive episodes associated with bipolar disorder [6] [2].

Quetiapine monotherapy was well tolerated and more effective than placebo in the treatment of bipolar I or II depression [20] [21] [22].

c) Adult:

1) In an 8-week, phase 3 study, extended-release (XR) quetiapine was more effective than placebo in the treatment of depressive episodes associated with bipolar disorder. The randomized, double-blind, placebo-controlled study enrolled patients with bipolar I or II disorder, with or without a rapid cycling course, to placebo (n=140) or quetiapine XR (n=140) titrated to 300 mg once daily. The primary endpoint was the change in Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to week 8, analyzed on a modified intent to treat (MITT) basis, described as patients who took at least one dose of assigned medication, and contributed a minimum of baseline plus one post-dose assessment. All participants (174 women, 96 men) were in an acute depressive phase, with a current episode within 4 to 52 weeks in duration, and were not resistant to more than 2 classes of antidepressants. Completion rates were 62.1% in the quetiapine and 68.6%

in the placebo arms; sufficient data was available for MITT analysis in 133 [quetiapine](#) and 137 placebo patients. The MADRS scores were by 17.4 (baseline, 29.8) in the [quetiapine](#) arm and by 11.9 (baseline, 30.1) in the placebo arm at week 8 (p less than 0.001 vs placebo). The treatment effect with [quetiapine](#) emerged at week 2 (p less than 0.01) and remained significant throughout the study. Adverse effects were common, reported by 88.3% of [quetiapine](#) and 68.8% of placebo patients, leading to withdrawal of 12.14% and 1.7%, respectively. Dry mouth (37.2%), somnolence (29.2%), sedation (23.4%), increased appetite (12.4%) and extrapyramidal effects (4.4%) were the most frequently reported events by [quetiapine](#) patients [20].

2j) [Quetiapine](#) monotherapy was well tolerated and more effective than placebo in the treatment of bipolar I or II depression. In a double-blind, randomized, fixed-dose, placebo-controlled, parallel-group study, patients with bipolar I (n=360) or II (n=182) with DSM-IV [major depressive episode](#) were assigned to 8 weeks of [quetiapine](#) 600 mg/day (n=180) or 300 mg/day (n=181) or placebo (n=181). An initial dose of 50 mg was given on day 1 and titrated up to 300 mg by day 4 or 600 mg by day 8, and all doses were given at bedtime. In this study, effects of treatment were evaluated by Montgomery-Asberg Depression Rating Scale (MADRS) total score (primary endpoint, mean change from baseline to week 8), Clinical Global Impression of severity and improvement, Hamilton Anxiety Rating Scale, Pittsburgh Sleep Quality Index, and Quality of Life Enjoyment and Satisfaction Questionnaire. Statistically significant improvement in MADRS total score from week 1 onward was observed in both [quetiapine](#) groups compared with placebo. The mean change in MADRS total score from baseline score of 30.4 to last assessment (intent-to-treat) was -16.73, -16.39, and -10.26 for the 600 mg, 300 mg, and placebo groups, respectively (p less than 0.001 for both [quetiapine](#) doses vs placebo). At the final assessment, both [quetiapine](#) groups had significantly higher response rates (defined as at least 50% MADRS score improvement) when compared with placebo (58.2% in 600 mg/day group and 57.6% in 300 mg/day group vs 36.1% in placebo; p less than 0.001). In addition, 52.9% of patients in both [quetiapine](#) groups met the remission criteria (MADRS score of 12 or less) compared with 28.4% of patients in the placebo group (p less than 0.001). Significant improvements from baseline were observed in 9 of 10 and 8 of 10 MADRS items in the [quetiapine](#) 600 and 300 mg/day groups, respectively, compared with placebo (p less than 0.05). [Quetiapine](#) and placebo groups had low and similar rates of treatment-emergent mania (3.2% and 3.9%, respectively). The rates of serious adverse events were not significantly different across treatment groups, and none were treatment related (5% in the 600-mg/day group and 3.4% in the 300-mg/day group compared with 8.9% in the placebo group). The overall rates of study discontinuation due to adverse events were 26.1% (n=47), 16% (n=29), and 8.8% (n=16) for the 600 mg/day group, 300 mg/day group, and placebo group, respectively [21].

a) [Quetiapine](#) was more effective than placebo for [depressive episodes](#) of rapid cycling [bipolar disorder](#) I or II in an 8-week, randomized, double-blind, placebo-controlled study [22]. Patients with rapid cycling disease (defined as 4 or more affective episodes in the previous 12 months) were identified for this a priori sub-analysis from a larger study [21] of 542 bipolar patients who had been randomized to [quetiapine](#) 300 mg or 600 mg once daily, or placebo for 8 weeks. Of the 119 patients initially identified as rapid cyclers, only 108 had sufficient data for inclusion in this analysis (n=31, n=42, n=35 in the [quetiapine](#) 600 mg, 300 mg and placebo groups, respectively). The changes from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score at week 8 (primary endpoint) were -21.1 (baseline, 31.8) for [quetiapine](#) 600 mg, -20.7 (baseline, 29.8) for [quetiapine](#) 300 mg, and -11.6 (baseline, 30.7) for placebo; both [quetiapine](#) doses were superior to placebo (p less than 0.001). Symptom benefits emerged with [quetiapine](#) at week 2 and persisted throughout the study. The Quality of Life Satisfaction Scale Questionnaire measurement also demonstrated statistically significant improvements in overall quality of life and

satisfaction for both [quetiapine](#) doses over placebo. Treatment-emergent mania occurred in 5 patients: 2 in the [quetiapine](#) 300 mg arm, 2 in the [quetiapine](#) 600 mg arm and 1 in the placebo arm. Other side effects were mild and generally consistent with those observed with [quetiapine](#) (somnolence, sedation, dry mouth) [22].

4.5.A.2] [Bipolar disorder](#), Maintenance, in combination with [lithium](#) or [divalproex](#); Adjunct

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; [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](#)

b) Summary:

[Quetiapine](#) regular- and extended-release tablets are indicated for the maintenance treatment of bipolar I disorder as adjunctive therapy to [lithium](#) or [divalproex](#) in adults [2] [6].

As adjunct therapy to [lithium](#) or [divalproex](#), [quetiapine](#) regular-release was more effective than placebo in maintenance treatment of bipolar I disorder in 2 double-blind, randomized, placebo-controlled, adult studies (n=1326) [6]; the efficacy of extended-release [quetiapine](#) for this indication was extrapolated from the 2 studies of [quetiapine](#) regular-release [2].

c) Adult:

1) As adjunct therapy to either [lithium](#) or [divalproex](#), [quetiapine](#) regular-release was more effective than placebo in maintenance treatment of bipolar I disorder. Two identical, randomized, double-blind studies evaluated patients (n=1326), with DSM-IV bipolar I disorder. Patients most recent episode could be manic, depressed, or mixed, with or without psychotic characteristics. During the open-label phase, patients were required to be stabilized on [quetiapine](#) plus [lithium](#) or [divalproex](#) for a minimum of 12 weeks (mean was 15 weeks). Patients were to continue either [lithium](#) or [divalproex](#), and were randomized to [quetiapine](#) twice daily for a total daily dose of 400 mg to 800 mg or to placebo. The primary outcome was time to recurrence of a mood event. A mood event was defined as medication intervention, or requirement of hospitalization for a mood occurrence, a Young Mania Rating Scale (YMRS) score, or a Montgomery-Asberg Depression Rating Scale (MADRS) score greater than or equal to 20, or discontinuation of study due to a mood event. During the double-blind phase, by day 280, approximately 50% of patients in the [quetiapine](#) group discontinued, and by day 117, approximately 50% of patients in the placebo group discontinued. Both studies revealed [quetiapine](#) as superior to placebo at improving length of time before recurrence of any mood event, and improvement was independent of subgroup specifics, such as concomitant mood stabilizers, gender, age, race, or most recent bipolar episode, or rapid cycling episode [2] [6].

4.5.A.3] [Bipolar disorder](#), Maintenance, monotherapy

a) 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](#)

b) Summary:

Maintenance monotherapy with [quetiapine](#) in patients with stable bipolar I disorder was associated with a longer time to recurrence of any mood event compared with placebo in a randomized, double-blind trial (n=1226) [5].

c) Adult:

1) Maintenance monotherapy with [quetiapine](#) in patients with stable bipolar I disorder was associated with a longer time to recurrence of any mood event compared with placebo in a randomized, double-blind trial (n=1226). Patients with bipolar I disorder with a current or recent manic, depressive, or mixed episode were entered into a 24-week prandomization phase, during which they received open-label [quetiapine](#) 300 to 800 mg/day; patients stabilized by week 20 and maintaining stabilization for 4 weeks (defined as a Young Mania Rating Scale (YMRS) score of 12 or less and a Montgomery-Asberg Depression Rating Scale (MADRS) score of 12 or less) moved to the double-blind randomized phase. In the randomized phase, patients continued to receive [quetiapine](#) (mean median dose, 546 +/- 173 mg; median treatment duration, 158 days), were switched to [lithium](#) that was dose adjusted to a serum concentration of 0.6 to 1.2 mEq/L (mean median serum concentration, 0.63 +/- 0.45 mEq/L; median treatment duration, 83 days), or received placebo (median treatment duration, 74 days). The study was initially to be terminated after 600 mood events, but an interim analysis was added after 150 manic and 150 depressive events; due to a statistically significant positive effect found at the interim analysis, the study was terminated early. [Quetiapine](#) was associated with a significantly longer time to recurrence of any mood event (hazard ratio (HR), 0.29; 95% CI, 0.23 to 0.38; p less than 0.0001), any manic event (HR, 0.29; 95% CI, 0.21 to 0.4; p less than 0.0001), and any depressive event (HR 0.3; 95% CI, 0.2 to 0.44; p less than 0.0001) compared with placebo. [Lithium](#) was also associated with a significantly longer time to recurrence of any mood event (HR, 0.46; 95% CI, 0.36 to 0.59; p less than 0.0001), any manic event (HR, 0.37; 95% CI, 0.27 to 0.53; p less than 0.0001), and any depressive event (HR, 0.59; 95% CI, 0.42 to 0.84; p less than 0.004) compared with placebo [5].

4.5.A.4] Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF [DEMENTIA](#)

4.5.A.5] Major depressive disorder, Monotherapy

a) 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](#)

b) Summary:

In a double-blind, multicenter, randomized withdrawal, placebo-controlled study (n=776) of adult patients with [major depressive disorder](#) (MDD), maintenance monotherapy treatment with extended-release [quetiapine](#) significantly decreased the risk of recurrence of a [depressive episode](#) compared with placebo [1].

c) Adult:

1j) In a double-blind, multicenter, randomized withdrawal, placebo-controlled study (n=776) of adult patients with [major depressive disorder](#) (MDD), maintenance monotherapy treatment with extended-release [quetiapine](#) significantly decreased the risk of recurrence of a [depressive episode](#) compared with placebo. Patients with single-episode or recurrent MDD (a Hamilton Rating Scale for Depression (HAM-D) 17-item total score of 20 or more, a HAM-D item 1 score of 2 or more, Montgomery-Asberg Depression Rating Scale (MADRS) of 12 or more, and a Clinical Global Impression-Severity of Illness (CGI-S) score of 3 or more) were eligible and received extended-release [quetiapine](#) in doses of 50, 150, or 300 mg/day in the open-label run-in (4 to 8 weeks) and stabilization phases (12 to 18 weeks), and were then randomized (if stable for at least 12 weeks) to receive the same dose of extended-release [quetiapine](#) (n=391) or placebo (n=385) for up to 52 weeks. The study was terminated when at least 101 [depressive episodes](#) occurred and when greater than 88 [depressive episodes](#) occurred 30 days or more after randomization. At study termination, 45.1% of randomized patients were discontinued from treatment. During the randomization period, the mean daily dose of extended-release [quetiapine](#) was 177.1 mg/day which was similar to the mean dose at randomization. The risk of recurrence of a [depressive episode](#) (primary outcome) was significantly reduced by 66% with extended-release [quetiapine](#) compared with placebo (hazard ratio (HR), 0.34; 95% CI, 0.25 to 0.46; p less than 0.001). [Relapse](#) rate was 14.2% (55 of 387) and 34.4% (132 of 384) in the extended-release [quetiapine](#) and placebo groups, respectively. Of these relapsed patients, 89 experienced a [depressive episode](#) within the first 30 days after randomization (extended-release [quetiapine](#), n=16; placebo, n=73). When analyzed according to the last open-label dose, extended-release [quetiapine](#) at doses of 50 mg, 150 mg, and 300 mg reduced the risk of [relapse](#) by 54% (HR, 0.46; 95% CI, 0.23 to 0.91; p less than 0.05), 64% (HR, 0.36; 95% CI, 0.22 to 0.57; p less than 0.001), and 74% (HR, 0.26; 95% CI, 0.15 to 0.45; p less than 0.001), respectively, compared with placebo. The time to [depressive episode](#) recurrence (events excluded that occurred within initial 30 days) was significantly longer with extended-release [quetiapine](#) compared with placebo (HR, 0.49; 95% CI, 0.32 to 0.73; p less than 0.001) [1].

4.5.A.6] Major depressive disorder; Adjunct

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release tablets); [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](#)

b) Summary:

Extended-release [quetiapine](#) is indicated as an adjunct to antidepressants for the treatment of [major depressive disorder](#) among adults [2].

Efficacy of [quetiapine](#) as an adjunct to antidepressants for the treatment of [major depressive disorder](#) (MDD) was established in two 6-week trials in adult patients (n=936) with MDD who had an inadequate response to antidepressant therapy [2].

In an 8-week, randomized, double-blind, parallel-group, phase 3 study (n=446), adjunctive treatment with [quetiapine](#) extended-release (XR) 300 mg resulted in a significant improvement on the Montgomery-Asberg Depression Rating Scale total score in adults with treatment-resistant [major depressive disorder](#) compared with placebo, but [quetiapine](#) 150 mg XR failed to show significant improvement compared with placebo [3].

In a 6-week, double-blind, double-dummy, randomized, placebo-controlled, multicenter trial (n=487), adjunctive treatment with extended-release [quetiapine](#) 150 or 300 mg/day provided modest clinical benefit in patients with [major depressive disorder](#) who had an inadequate response to antidepressant treatment [4].

c) Adult:

1) In a 6-week, double-blind, double-dummy, randomized, placebo-controlled, multicenter trial (n=487), adjunctive treatment with extended-release [quetiapine](#) 150 or 300 mg/day provided modest clinical benefit in patients with [major depressive disorder](#) (MDD) who had an inadequate response to their current antidepressant treatment. Patients with a single-episode or recurrent MDD of current duration of more than 4 weeks but less than 12 months were included if they met the following criteria: a Hamilton Rating Scale for Depression (HAM-D) 17-item total score of 20 or more, a HAM-D item 1 score of 2 or more, and an inadequate response during the current episode to an antidepressant at adequate doses for 6 or more weeks (antidepressants were [amitriptyline](#), [bupropion](#), [citalopram](#), [duloxetine](#), escitalopram, [fluoxetine](#), [paroxetine](#), [sertraline](#), or [venlafaxine](#) at the minimum effective dose and at least 1 dose increase per the manufacturer's labeling). Patients were randomized to receive either [quetiapine](#) extended-release (XR) 150 mg/day (n=167), [quetiapine](#) XR 300 mg/day (n=163), or placebo (n=163) for 6 weeks. [Quetiapine](#) XR was initiated at 50 mg/day for 2 days, then 150 mg/day for 2 days, and, for those in the group, 300 mg/day thereafter. The dose of the current antidepressant was continued throughout the study. The primary efficacy endpoint was the change from baseline to week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score and was assessed in the modified intent-to-treat population (all randomized patients who took study medication, and had baseline and at least 1 valid MADRS evaluation after randomization). Mean baseline MADRS total scores were 28.6 +/- 5.4, 28.4 +/- 5.5, and 28.2 +/- 5.6 in the 150 mg/day, 300 mg/day, and placebo groups, respectively. From baseline to week 6, MADRS total scores decreased by 12.21 in the placebo group (n=160) compared with decreases of 15.26 and 14.94 in the [quetiapine](#) XR 150-mg/day (n=166) and 300-mg/day groups (n=161), respectively (p less than 0.01 for both). A significant reduction in the MADRS score was evident within 1 week in the 150-mg/day dose group (6.52, p less than 0.001) and the 300-mg/day dose group (6.38, p less than 0.001) compared with placebo (4.16). At week 6, a 50% or greater reduction in the MADRS score occurred in 55.4% of patients in the 150-mg/day dose group (p=0.107) and 57.8% of patients in the 300-mg/day dose group (p less than 0.05) compared with 46.3% of patients in the placebo group. Remission (MADRS score of 8 or less) rates were 36.1%, 31.1%, and 23.8% in the 150-mg/day (p less than 0.05 vs placebo), 300-mg/day (p=0.126 vs placebo), and placebo groups, respectively. To achieve a 50% or greater reduction in MADRS score at week 6, the number needed to treat was 10.9 in the 150-mg/day dose group and 8.7 in the 300-mg/day dose group. Both [quetiapine](#) regimens were well tolerated, with similar incidences of extrapyramidal symptoms reported in the 150-mg/day (4.2%) and 300-mg/day (4.9%) groups [4].

2J) Adjunctive treatment with [quetiapine](#) extended-release (XR) 300 mg resulted in a significant improvement on the Montgomery-Asberg Depression Rating Scale (MADRS) total score in adults with treatment-resistant [major depressive disorder](#) (MDD) compared with placebo according to an 8-week, randomized, double-blind, parallel-group, phase 3 study (n=446); however, [quetiapine](#) XR 150 mg failed to show significant improvement compared with placebo. Outpatients (age 18 to 65 years) with single episode or recurrent MDD following at least 6 weeks of antidepressant therapy ([amitriptyline](#), [bupropion](#), [citalopram](#), [duloxetine](#), [escitalopram](#), [fluoxetine](#), [paroxetine](#), [sertraline](#), or [venlafaxine](#)), had a Hamilton Depression Rating Scale (HAMD) total score of at least 20, and depressed mood score of at least 2 were included in the trial. Patients were randomized to receive a once-daily dose of either placebo (n=148), [quetiapine](#) extended-release (XR) 150 mg (n=148), or [quetiapine](#) XR 300 mg (n=150) in addition to their ongoing antidepressant therapy, followed by a 2-week drug-discontinuation period. At baseline, patients had a mean MADRS total score of 27.5 +/- 5.5, 27.2 +/- 5.2, and 27.6 +/- 5 in the placebo, [quetiapine](#) XR-150, and [quetiapine](#) XR-300 groups, respectively. In a modified intent-to-treat analysis (n=432), the mean change at week 6 from baseline in MADRS total score (primary endpoint) was significantly greater in the [quetiapine](#) XR-300 group compared with placebo (-14.7 vs -11.7; p less than 0.01), but was not significant in the [quetiapine](#) XR-150 group compared with placebo (-13.6 vs -11.7; p=0.067). [Quetiapine](#) XR-300 also demonstrated significant improvements compared with placebo in the secondary MADRS endpoints of inner tension (p less than 0.05), reduced sleep (p less than 0.001), pessimistic thought (p less than 0.01), and suicidal thoughts (p less than 0.01). [Quetiapine](#) XR-150 had significant changes compared with placebo on reduced sleep (p less than 0.001). At week 6, a MADRS remission rate (defined a priori at a total score of 8 or less) was achieved by 42.5% in the [quetiapine](#) XR-300 group (p less than 0.01 vs placebo), and 35% in the [quetiapine](#) XR-150 group (p=0.059 vs placebo) compared with 24.5% in placebo. [Quetiapine](#) XR-300 also demonstrated significant improvements from baseline compared with placebo on the HAMD total score (-13.53 vs -10.8; p less than 0.01), and the Hamilton Anxiety Rating Scale total score (-8.5 vs -6.67; p less than 0.05). The rate of discontinuation from the study due to adverse events was 19.5% with [quetiapine](#) XR-300, 11.5% with [quetiapine](#) XR-150, and 0.7% with placebo; of which sedation and somnolence were leading causes among [quetiapine](#)-treated patients. Somnolence-related events (including sedation, lethargy, and sluggishness) occurred in 50.3% and 46.6% in the [quetiapine](#) XR-300 and [quetiapine](#) XR-150 groups, and extrapyramidal signs occurred in 8.1% and 3.4%, respectively. Weight gain of 7% or greater occurred in 7.6%, 1.4%, and 2.1% of patients receiving [quetiapine](#) XR 300 mg, [quetiapine](#) XR 150 mg, and placebo [3].

4.5.A.7] [Manic bipolar I disorder](#), Acute management; Adjunct

FDA Labeled Indication

aJ) Overview

FDA Approval: Adult, yes; [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](#)

bJ) Summary:

Regular- and extended-release [quetiapine](#) is indicated as adjunct to [lithium](#) or [divalproex](#) in the treatment of acute manic or mixed episodes associated with bipolar I disorder in adults [2] [6].

As adjunct therapy, [quetiapine](#) was more effective than placebo in the treatment of acute manic symptoms in adults with bipolar I mania [10] [11].

c) Adult:

1) Adjunct Therapy

a) [Quetiapine](#) with [lithium](#) or [divalproex](#) was more effective than [lithium](#) or [divalproex](#) monotherapy for the treatment of acute mania in patients with bipolar I disorder. This 3-week, double-blind, placebo-controlled, parallel study randomized patients to receive [quetiapine](#) (n=81) as add-on therapy to [lithium](#) or [divalproex](#) compared with placebo (n=89) plus [lithium](#) or [divalproex](#). Inclusion criteria allowed for adult patients, average age of 39.6 years, 49 patients were male, with DSM-IV bipolar I disorder. Patients required hospitalization for less than 3 weeks for a current [manic episode](#) and treatment with [lithium](#) or [divalproex](#) for at least 7 days of the immediately preceding 28 days prior to randomization. Patients were also required to have at least 1 previous, well-documented manic or mixed episode prior to the current episode, and a score of at least 4, on 2 of the core YMRS items of irritability, speech, content, and disruptive/aggressive behavior. Patients with rapidly cycling episodes were excluded. Eligible patients either began or continued [lithium](#) or [divalproex](#) on day 1 of study. [Quetiapine](#) was administered twice daily, morning and evening, starting at 100 mg on day 1, 200 mg on day 2, 300 mg on day 3, and 400 mg on day 4. By day 5, the patients' dose could range from 200 mg/day to 600 mg/day based on efficacy and tolerability, and up to 800 mg/day on days 6 to 21. Study guidelines encouraged clinicians to titrate [quetiapine](#) dosage to at least 600 mg/day prior to patients withdrawing from the study due to lack of efficacy. The average last-week [quetiapine](#) dose among the responders was 584 mg/day. The primary outcome was the change from baseline of the YMRS score at final assessment. Mean baseline YMRS scores for the [quetiapine](#) with [lithium](#) or [divalproex](#) group was 31.5 and 31.1 for the placebo group. Outcomes were analyzed on the intent-to-treat (ITT) groups. At day 21, change in YMRS score from baseline was statistically significant in the [quetiapine](#) group versus placebo (-13.76 vs -9.93; p=0.021). Secondary outcomes, also statistically significant, were YMRS response rates, defined as 50% or greater reduction in YMRS score from baseline at day 21, (54.3% vs 32.6%; p=0.005), and YMRS remission rates, defined as a YMRS score of 12 or less at day 21, (45.7% vs 25.8%; p=0.007). The most common adverse effects, occurring at 10% or greater, were somnolence, headache, dry mouth, asthenia, postural hypotension, and dizziness [10].

b) [Quetiapine](#) with [lithium](#) or [divalproex](#) was more effective than [lithium](#) or [divalproex](#) monotherapy for the treatment of acute mania in patients with bipolar I disorder. This double-blind, placebo-controlled study randomized patients to receive [quetiapine](#) (n=185) as add-on therapy to [lithium](#) or [divalproex](#) compared with placebo (n=185) plus [lithium](#) or [divalproex](#) for either 3 weeks or 6 weeks. Eligible patients were adults, average age of 39.2 years, 54.1% were male, with DSM-IV diagnosis of bipolar I disorder, with or without psychotic features. Patients required hospitalization for less than 3 weeks for a current [manic episode](#), treatment with [lithium](#) or [divalproex](#) for at least 7 days prior to randomization, and a history of at least 1 manic or mixed episode in the last 5 years. Patients with rapidly cycling or mixed episodes were excluded. Patients required a score of 4 or greater, on 2 of the core Young Mania Rating Scale (YMRS) items

of irritability, speech, content, and disruptive/aggressive behavior, and a score of 4 or greater on the Clinical Global Impression-Bipolar (CGI-BP) Severity of Illness (SI) score. At randomization, patients were to continue [lithium](#) or [divalproex](#) treatment. Clinicians could adjust [lithium](#) or [divalproex](#) doses for efficacy, for reduction of adverse effects, and for established, therapeutic range (0.7 to 1 mEq/L [lithium](#), or 50 to 100 mcg/mL [divalproex](#)). [Quetiapine](#) was administered twice daily, starting at 100 mg/day on day 1, 200 mg/day on day 2, 300 mg/day on day 3, and 400 mg/day on day 4. By day 5, [quetiapine](#) could be administered up to 600 mg/day, and up to 800 mg/day from day 6 to the end of treatment. By day 21, the average dose of [quetiapine](#) in the responders was 492 mg/day. The primary outcome was the change from baseline of the YMRS score at day 21. Because the protocol was identical for the 3-week and 6-week treatment group, the results were combined for analysis to increase the power of the study to identify other clinically important effects. Mean baseline YMRS scores for the [quetiapine](#) with [lithium](#) or [divalproex](#) group was 32 and 31.9 for the placebo group. Outcomes were analyzed on the intent to treat (ITT) groups. At day 21, change in YMRS score from baseline was statistically significant in the [quetiapine](#) group versus placebo (-15.29 vs -12.19; p less than 0.05). Other statistically significant secondary outcomes were change in response rate, defined as 50% or greater reduction in YMRS score from baseline at day 21, (55.7% vs 41.6%; p less than 0.01). YMRS remission rates, defined as a YMRS score of 12 or less at day 21, was statistically significant (48.7% vs 33%; p less than 0.01). Common adverse effects, occurring at 5% or greater and at least twice that of placebo, were somnolence, dry mouth, asthenia, postural hypotension, weight gain, and [pharyngitis](#) [11].

4.5.A.8] Manic bipolar I disorder, Monotherapy in acute management

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(10 to 17 years of age\)](#)

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Regular- and extended-release [quetiapine](#) is indicated as monotherapy in treatment of acute manic or mixed episodes associated with bipolar I disorder in adults and pediatric patients 10 to 17 years old [2] [6].

In pediatric patients (10 to 17 years old) with mania associated with [bipolar disorder](#), [quetiapine](#) treatment significantly improved manic symptoms compared with placebo in a 3-week, randomized, double-blind study (n=284) [7].

As monotherapy, 2 studies revealed that [quetiapine](#) was more effective than placebo in the treatment of acute mania in adults with bipolar I disorder [8] [9].

As adjunct therapy, [quetiapine](#) was more effective than placebo in the treatment of acute manic symptoms in adults with bipolar I mania [10] [11].

c) Adult:

1j) Monotherapy

a) **Quetiapine** monotherapy was more effective than placebo in the treatment of acute mania in patients with bipolar I disorder. This international, 12-week, multicenter, double-blind, parallel-group study randomized patients to receive **quetiapine** (n=107), **lithium** (n=98), or placebo (n=95). Primary inclusion criteria allowed for adult patients, who were hospitalized for less than 3 weeks, with DSM-IV bipolar I disorder, and who were presently experiencing an acute **manic episode**. Patients were required to have at least 1 previous, well-documented manic or mixed episode; however, patients with rapid cycling and mixed episodes were excluded. Patients required a score of at least 4, on 2 of the core Young Mania Rating Scale (YMRS), items of irritability, speech, content, and disruptive/aggressive behavior. **Quetiapine** was administered as a flexible, twice-daily dose, starting at 100 mg on day 1, 200 mg on day 2, 300 mg on day 3, and 400 mg on day 4. By day 5, the patients' dose could be increased to 600 mg/day, and up to 800 mg/day from treatment days 6 to 84. The average dose of **quetiapine** in the responders was 586 mg/day in the week prior to day 21. The primary outcome was the change from baseline of the YMRS score at day 21. The parallel group evaluated **lithium** versus placebo. Primary and secondary outcomes were analyzed on the intent-to-treat (ITT) groups and included all randomized patients who took at least 1 dose of study treatment and who had at least 1 set of postbaseline YMRS scores. The average age of patients was 38 years and 56.1% of them were male. Mean baseline YMRS scores for the **quetiapine** group was 32.7 and 34 for the placebo group. At day 21, change in YMRS score from baseline was statistically significant in the **quetiapine** groups versus placebo (-14.62 vs -6.71; p less than 0.001). Change in YMRS scores for the **lithium** versus placebo group was also statistically significant (-15.2 vs -6.71; p less than 0.001); however, the difference between **quetiapine** and **lithium** groups was not significant. Secondary outcomes of note include significant improvement in the change in YMRS score from baseline through treatment day 84 (-20.28 vs -9; p less than 0.001). Response rates, defined as 50% or greater reduction in YMRS score from baseline at day 21 were significant (53.3% vs 27.4%; p less than 0.001). YMRS remission rates, defined as a YMRS score of 12 or less at day 21 were also significant (46.7% vs 22.1%; p less than 0.001). Adverse effects were considered mild to moderate. The most common, occurring at 5% or greater, included dry mouth, somnolence, weight gain, dizziness, insomnia, headache, asthenia, depression, tremor, and diarrhea [9].

b) **Quetiapine** monotherapy was more effective than placebo in the treatment of acute mania in patients with bipolar I disorder. This international, 12-week, multicenter, double-blind, parallel-group study randomized patients to receive **quetiapine** (n=101), **haloperidol** (n=98), or placebo (n=100). Primary inclusion criteria allowed for adult patients, average age of 42.8 years, 36.6% male, who were hospitalized for less than 3 weeks, with DSM-IV bipolar I disorder with or without psychotic characteristics, and who were presently experiencing an acute **manic episode**. Patients were required to have at least 1 previous, well-documented manic or mixed episode; however, patients with rapid cycling and mixed episodes were excluded. Patients required a score of at least 4, on 2 of the core Young Mania Rating Scale (YMRS), items of irritability, speech, content, and disruptive/aggressive behavior. **Quetiapine** was administered twice daily, starting at 100 mg on day 1, 200 mg on day 2, 300 mg on day 3, and 400 mg on day 4. By day 5, the patients' dose could be increased to 600 mg/day based on efficacy and tolerability, and up to 800 mg/day thereafter from treatment days 6 to 84. The recommended target dose was 600 mg/day. The average dose of **quetiapine** in the responders was 559 mg/day. The primary outcome

was the change from baseline of the YMRS score at day 21. The parallel group evaluated [haloperidol](#) versus placebo. Primary and secondary outcomes were analyzed on the intent to treat (ITT) groups and included all randomized patients who took at least 1 dose of study treatment and who had at least 1 set of postbaseline YMRS scores. Mean baseline YMRS scores for the [quetiapine](#) group was 34 and 33.1 for the placebo group. At day 21, change in YMRS score from baseline was statistically significant in the [quetiapine](#) groups versus placebo (-12.29 vs -8.32; p less than 0.01). Change in YMRS scores for the [haloperidol](#) versus placebo group was also statistically significant (-15.71 vs -8.32; p less than 0.001). Secondary outcome of change from baseline in YMRS score at day 84 revealed [quetiapine](#)- and haloperidol-treated patients continued to experience statistically significant improvement (-17.52 and -18.92 vs -9.48, respectively; p less than 0.001 for both comparisons to placebo). The most common adverse effects, occurring in greater than 10% of patients, included insomnia, somnolence, and extrapyramidal-related effects. Tremor, [akathisia](#), and extrapyramidal syndromes were significantly more frequent with [haloperidol](#) compared with [quetiapine](#) or placebo (p less than 0.001) [8].

d) Pediatric:

1) [Quetiapine](#) treatment significantly improved manic symptoms compared with placebo in adolescents aged 10 to 17 years with mania associated with [bipolar disorder](#) in a 3-week, multicenter, randomized, double-blind study ($n=284$). Following a screening phase of up to 28 days including a washout period, outpatients or inpatients with a Young Mania Rating Scale (YMRS) total score of at least 20 were randomized to receive [quetiapine](#) 400 mg/day ($n=95$; 52.7% comorbid ADHD), [quetiapine](#) 600 mg/day ($n=98$; 42.1% comorbid ADHD), or placebo ($n=91$; 39.3% comorbid ADHD) in 2 or 3 divided doses. Quetiapine-treated patients were initiated on 50 mg/day and titrated over 5 days (400-mg group) or 7 days (600-mg group). Permitted concomitant medications included stable-dose psychostimulants, [diphenhydramine](#), [hydroxyzine](#), [lorazepam](#), and [benztropine](#) (only for treatment-emergent extrapyramidal symptoms). After 3 weeks, the least squares mean change from baseline to day 21 in YMRS total score (primary endpoint) in the intent-to-treat population ($n=277$) was -14.25 (standard error [SE], 0.96; 95% CI, -16.15 to -12.35; p less than 0.001) in the [quetiapine](#) 400-mg group, -15.6 (SE, 0.97; 95% CI, -17.51 to -13.7; p less than 0.001) in the [quetiapine](#) 600-mg group, compared with -9.04 (SE, 1.12; 95% CI, -11.24 to -6.84) in placebo. Significant improvements in YMRS were noted at day 4 in the [quetiapine](#) 400-mg group and on day 7 in the [quetiapine](#) 600-mg group. In a subgroup analysis, [quetiapine](#) was equally effective in patients categorized by age (10 to 12 years vs 13 to 17 years), gender, ADHD status, and psychostimulant use. Response (50% or greater reduction in YMRS from baseline) rates at day 21 (secondary endpoint) in patients treated with [quetiapine](#) 400 mg/day (55%) and [quetiapine](#) 600 mg/day (56%) were significantly less than placebo (28%; p less than 0.001 for both). Remission (YMRS score of 12 or less) rates at day 21 (secondary endpoint) in the [quetiapine](#) 400-mg/day group, [quetiapine](#) 600-mg/day group, and placebo group were 45%, 52%, and 23%, respectively, significant improvement seen with both [quetiapine](#) doses (p less than 0.01 and p less than 0.001, respectively) compared with placebo. Clinically significant increases in body weight, shifts in lipid parameters, pulse rate, [tachycardia](#), and extrapyramidal symptoms were noted in quetiapine-treated patients. In younger quetiapine-treated patients (10 to 12 years), there was a higher incidence of increased appetite, pulse rate, suicidal behavior/ideation, and syncope compared with patients aged 13 to 17 years [7].

4.5.A.9] [Obsessive-compulsive disorder](#), Refractory

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category A

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

A meta-analysis of 3 randomized, double-blind, placebo-controlled trials found a slight benefit in [obsessive-compulsive disorder](#) (OCD) symptoms when [quetiapine](#) was added to serotonin reuptake inhibitor (SRI) treatment; however, the validity of the findings for clinical response rates among refractory OCD patients were affected by differences among studies [23].

Published studies have found conflicting results [24] [25] [26] [27].

c) Adult:

1) A meta-analysis of 3 randomized, double-blind, placebo-controlled trials found a slight benefit in [obsessive-compulsive disorder](#) (OCD) symptoms when [quetiapine](#) was added to serotonin reuptake inhibitor (SRI) treatment. The number of responders to [quetiapine](#) therapy were not different than the number of responders to placebo, nor were there significant benefits with [quetiapine](#) in Sheehan Disability Scores; however, the validity of the findings for clinical response rates among refractory OCD patients were affected by differences among studies [23].

2) In a 12-week, randomized, placebo-controlled trial, the addition of [clomipramine](#) or placebo to [fluoxetine](#) was more effective than the addition of [quetiapine](#) to [fluoxetine](#) in reducing symptoms of [obsessive-compulsive disorder](#) (OCD; DSM-IV TR criteria) in adult patients refractory to [fluoxetine](#) monotherapy (n=54). For study inclusion, all patients had a Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores of at least 16, which was also a decrease of less than 35% from baseline, despite at least 8 weeks of [fluoxetine](#) (maximum dose, 80 mg/day). Enrolled patients were randomized to receive [clomipramine](#) (n=18; initial dose, 25 mg/day; weekly titration up to 75 mg/day; mean dose, 55 mg/day) plus [fluoxetine](#) (maximum dose, 40 mg/day), [quetiapine](#) (n=18, initial dose, 50 mg/day; weekly titration up to 200 mg/day; mean dose, 142 mg/day) plus [fluoxetine](#) (maximum dose, 40 mg/day), or placebo (n=18) plus [fluoxetine](#) (maximum dose, 80 mg/day). Mean final YBOCS scores and the mean change from baseline at week 12 (primary endpoint; intent-to-treat), were significantly improved for both [clomipramine](#) (final score, 18; change from baseline, -6.5; 95% CI, -9 to -3.9) and placebo (final score 18; change from baseline, -6.7; 95% CI, -9.6 to -3.8) compared with [quetiapine](#) (final score, 25; change from baseline, -0.1; 95% CI, -2.9 to +2.7) (p less than 0.001 for both). Withdrawal due to adverse effects occurred in 3 patients treated with [clomipramine](#) (QT prolongation from patient-specific baseline on ECG) and in 1 patient treated with [quetiapine](#) (syncope associated with orthostatic hypotension) [24].

3) A 12-week randomized, double-blind, placebo-controlled trial adding [quetiapine](#) to serotonin reuptake inhibitors (SRIs) for refractory [obsessive-compulsive disorder](#) (OCD) found no significant differences in treatment outcomes. All patients had failed to achieve adequate symptom control with at least 12 weeks of maximally tolerated SRI, and had Yale-Brown Obsessive Compulsive Scales (YBOCS) scores of at least 18. Patients continued their SRI therapy and were randomized to placebo (n=20) or [quetiapine](#) (n=20) titrated to a target dose of 300 mg daily. After 12 weeks, intention-to-treat analysis found no significant differences between groups in YBOCS scores, although no power calculations were described detailing the sample size required to show

a clinically significant difference. The [quetiapine](#) group showed a mean decrease in YBOCS score of 5.2 from 24.1 at baseline compared with a mean YBOCS decrease of 3.9 from 25.5 at baseline in the placebo arm ($p=0.4163$). A secondary endpoint of response to therapy (defined as at least 35% decrease in YBOCS) was achieved by 6 [quetiapine](#)-treated and 3 placebo-treated patients; a difference which was not statistically different ($p=0.26$). At least 1 adverse event was reported by all patients, with most reporting at least 5 side effects. Fatigue, vertigo, dry mouth and constipation were reported more commonly in the [quetiapine](#) arm. Dropouts due to side effects occurred in 4 [quetiapine](#) patients and 1 placebo patient. Severe adverse events were increased cardiac enzymes in one [quetiapine](#) patient, and 3 patients in the placebo group who experienced "orthostatic collapse," lower abdominal cramps and headache [25].

4)) No significant differences in [obsessive-compulsive disorder](#) (OCD) symptoms were found when [quetiapine](#) was added to serotonin reuptake inhibitor (SRI) therapy in a 6-week, randomized, double-blind, placebo-controlled trial of patients with refractory OCD. All participants, aged 18 to 65 years old, had incomplete OCD symptom resolution after at least 6 weeks therapy with one SRI. In addition to continuing their SRI, patients were randomized to placebo ($n=21$) or [quetiapine](#) ($n=20$), initiated at 25 mg daily for one week then titrated weekly to a target dose of 200 mg per day. Baseline Yale-Brown Obsessive Compulsive Scale (YBOCS) scores did not differ significantly between groups ($p=0.33$), nor did mean number of SRI's previously tried (1.55 for [quetiapine](#), 1.62 for placebo; $p=0.83$). At 6 weeks, YBOCS scores decreased by 7.1 (26.9%) from baseline of 26.4 in the [quetiapine](#) arm and 7.19 (26%) from baseline of 27.7 in the placebo arm; each demonstrating significant improvement versus baseline (p less than 0.0001 and $p=0.001$, respectively) but not between groups ($p=0.636$). Sedation was noted by 15 [quetiapine](#) and 7 placebo patients; 2 [quetiapine](#) patients dropped out for that reason. Dry mouth and impaired concentration were other adverse events noted in the [quetiapine](#) arm. No serious adverse events were noted in either group [26].

5)) In an 8-week, randomized, double-blind, placebo-controlled trial, adding [quetiapine](#) to serotonin reuptake inhibitor (SRI) therapy significantly reduced symptoms of [obsessive-compulsive disorder](#) (OCD) in refractory patients. All patients had baseline Yale-Brown Obsessive Compulsive Scale (YBOCS) scores of at least 18 and inadequate symptom control despite at least 8 weeks therapy with 2 or more SRIs. Patients continued SRI therapy and were randomized to placebo ($n=20$) or [quetiapine](#) ($n=20$) starting at 50 mg day 1, then titrated up to 300 mg daily. At 8 weeks the mean YBOCS reduction was 9 points from baseline of 28.2 in the [quetiapine](#) arm compared with 1.8 from baseline of 26.4 in placebo (p less than 0.001). Treatment response (defined as at least 35% decrease in YBOCS and final Clinical Global Impressions-Improvement scale rating of much or very much improved) was observed in 8 [quetiapine](#) and 2 placebo patients (40% vs 10%; $p=0.028$). Adverse effects were common, with all patients noted at least 2 or 3. Sedation was most prevalent, reported by 19 [quetiapine](#) patients and 7 placebo patients. Other effects more common with [quetiapine](#) were dry mouth, dizziness, weight gain, increased appetite and difficulty concentrating. The mean [quetiapine](#) dose achieved was not specified. One patient in the [quetiapine](#) arm dropped out due to worsening OCD symptoms; there were no dropouts in the placebo arm [27].

4.5.A.10] [Schizophrenia](#)

FDA Labeled Indication

a)) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(13 to 17 years of age\)](#)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b)) Summary:

Regular- and extended-release [quetiapine](#) is indicated for the treatment of [schizophrenia](#) in adults and pediatric patients age 13 to 17 years [6] [2].

In 3 short-term (6-week), controlled trials of patients with [schizophrenia](#), higher [quetiapine](#) doses were generally more effective than lower doses [6].

In an international, 6-week, double-blind, randomized trial (ANCHOR 112; n=222), [quetiapine](#) regular-release given at a fixed dose of 400 or 800 mg/day significantly reduced the total Positive and Negative Syndrome Scale score compared with placebo in adolescent patients (13 to 17 years of age) with [schizophrenia](#) [12].

In an open-label, 12-week, prospective study (n=56), oral [quetiapine](#), at doses ranging from 200 to 800 mg/day, was well tolerated and yielded clinical benefit in symptoms of early-onset schizopreniform-spectrum disorders in adolescents [13].

c)) Adult:

1)) In 3 short-term (6-week), controlled trials of patients with [schizophrenia](#) who met DSM III-R criteria for [schizophrenia](#), higher [quetiapine](#) doses were generally more effective than lower doses. One of the trials used a single fixed-dose [haloperidol](#) arm as a comparative treatment; however, this single group was inadequate to provide a reliable and valid comparison of [quetiapine](#) and [haloperidol](#) [6].

a)) A placebo-controlled trial (n=361) that involved 5 fixed doses of [quetiapine](#) 75, 150, 300, 600, and 750 mg/day in 3 divided doses reported that the 4 highest doses were superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score, the BPRS [psychosis](#) cluster and the Clinical Global Impression (CGI) severity score. The maximal effect was observed at 300 mg/day, and this dose was superior to placebo on the Scale for Assessing Negative Symptoms (SANS). The observed effects of 150 to 750 mg/day were generally identical [6].

b)) Another placebo-controlled trial (n=286) that involved the titration of [quetiapine](#) in high (up to 750 mg/day in 3 divided doses) and low (up to 250 mg/day in 3 divided doses) doses reported that only the high-dose [quetiapine](#) group was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score, the BPRS [psychosis](#) cluster, the Clinical Global Impression (CGI) severity score, and the Scale for Assessing Negative Symptoms (SANS) [6].

c)) A [dose regimen](#) comparison trial (n=618) that compared 2 fixed doses of [quetiapine](#) (450 mg/day in 2 or 3 divided doses and 50 mg/day in 2 divided doses) reported that only the 450-mg/day (225 mg twice daily) dose group was superior to the 50-mg/day (25 mg twice daily) [quetiapine](#) dose group on the Brief Psychiatric Rating Scale (BPRS) total score, the BPRS [psychosis](#) cluster, the Clinical Global Impression (CGI) severity score, and on the Scale for Assessing Negative Symptoms (SANS) [6].

2j) A 6-week, fixed-dose, placebo-controlled trial of patients who met DSM-IV criteria for [schizophrenia](#) (n=573) demonstrated that 400 mg, 600 mg, and 800 mg once-daily doses of extended-release [quetiapine](#) were superior to placebo. Therapy was initiated with extended-release tablets at 300 mg/day (once daily) on day 1. The dose was increased to either 400 mg or 600 mg on day 2 or to 800 mg by day 3. Change between baseline and endpoint (day 42) for the Positive and Negative Syndrome Scale (PANSS) was used as the primary efficacy measure. Analysis of PANSS total scores indicated the [quetiapine](#) extended-release doses of 400 mg, 600 mg, and 800 mg were all superior to placebo [2].

3j) Several open [14] [15] and placebo-controlled studies [16] [17] [18] [15] of short duration (6 weeks or less) have suggested the efficacy of oral [quetiapine](#) for treating both positive and negative symptoms of [schizophrenia](#) (mostly patients with acute exacerbation of subchronic or chronic illness). In these trials, effects of treatment were mainly evaluated by the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression (CGI) Severity of Illness score, and the modified Scale for Assessment of Negative Symptoms (SANS). Clinical responses were observed within 2 weeks of starting [quetiapine](#) therapy and were best with doses exceeding 300 mg daily; in one study, doses of up to 750 mg daily (mean, 360 mg daily) were significantly superior to lower doses (up to 250 mg daily; mean, 209 mg daily) and placebo at week 6 of treatment on the BPRS total and SANS [18]. The severity of extrapyramidal symptoms (EPS) was similar in patients treated with placebo and [quetiapine](#).

4j) An uncontrolled trial in elderly patients with [psychotic disorders](#) found [quetiapine](#) to be associated with symptom improvement and to be well tolerated. An interim statistical analysis was performed on 151 patients at week 12. The median total daily dose of [quetiapine](#) was 100 mg/day. The most common adverse events were related to the central nervous system (somnolence, dizziness, agitation) and cardiovascular system (postural hypotension). Extrapyramidal symptoms occurred in 6% of patients. Mean Simpson-Angus Scale total score showed significant improvement (p less than 0.0001) at endpoint. In addition, Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI) scores showed significant (p less than 0.0001 and p less than 0.01, respectively) improvement [19].

dj) Pediatric:

1j) Results of an international, 6-week, double-blind, randomized trial (ANCHOR 112; n=222) demonstrated [quetiapine](#) regular-release given at a fixed dose of 400 or 800 mg/day significantly reduced the total Positive and Negative Syndrome Scale (PANSS) score compared with placebo in adolescent patients (13 to 17 years of age) with [schizophrenia](#). Patients with a PANSS total score of at least 60 and a score of at least 4 on at least 1 of the PANSS items (ie, delusions, conceptual disorganization, or hallucinations) were randomized to [quetiapine](#) 400 mg/day (n=73; mean baseline PANSS score, 96.2) or 800 mg/day (n=74; mean baseline PANSS score, 97) or placebo (n=75; mean baseline PANSS score, 96.7). In an intent-to-treat analysis, both doses of [quetiapine](#) were superior to placebo in improving the mean PANSS total score from baseline to study endpoint at day 42; [quetiapine](#) 400 mg vs placebo (treatment difference, -8.16; standard error [SE], 4.008; 95% CI, -16.06 to -0.26; p=0.043) and [quetiapine](#) 800 mg vs placebo (treatment difference, -9.29; SE, 3.518; 95% CI, -16.22 to -2.36; p=0.009). The [quetiapine](#) 800-mg arm also demonstrated a significant improvement compared with placebo on the Clinical Global Impressions-improvement scale (p=0.018) and both the [quetiapine](#) 400-mg and 800-mg groups significantly improved the Children's Global Assessment Scale (p=0.013 and p less than 0.001) compared with placebo as well as the PANSS depression cluster, and sum of PANSS items G1, G2, G3, and G6 (p=0.018 and p=0.005), respectively. Commonly reported adverse events

associated with [quetiapine](#) included somnolence, headache, and dizziness. The mean change in body weight from baseline was 2.2 +/- 2.6 kg, 1.8 +/- 2.8 kg, and -0.4 +/- 3.5 kg in the [quetiapine](#) 400-mg, 800-mg, and placebo groups. and the incidence of adverse events potentially associated with extrapyramidal signs ([akathisia](#), tremor, [extrapyramidal disorder](#), hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, and [dyskinesia](#)) was 12.3%, 13.5%, and 5.3%, respectively [12].

2) In an open-label, 12-week, prospective study (n=56), treatment with oral [quetiapine](#), at doses ranging from 200 to 800 mg/day, was well tolerated and led to significant improvement in symptoms of early-onset schizophreniform-spectrum disorders in adolescents. Following a 1- to 9-day washout period of prior psychoactive medications, patients (mean age, 15.9 years; range, 12 to 17.9 years; 67.9% male) meeting the DSM-IV criteria for [schizophrenia](#), [schizoaffective](#), or [schizophreniform disorder](#) and had a Positive and Negative Syndrome Scale (PANSS) total score of 60 or greater were treated with [quetiapine](#) for 12 weeks. Following a fixed titration protocol during week 1 (50 mg at day 1 increased to 400 mg by day 5-7), the [quetiapine](#) dose was adjusted based on clinical response and tolerability to a range of 200 to 800 mg (mean study dose, 605.6 mg/day (week 6) and 584.2 mg/day (week 12)). The use of [benztropine](#) (1 to 6 mg/day) to treat extrapyramidal symptoms (EPS) and benzodiazepines ([diazepam](#) or [lorazepam](#); up to 40 mg/day of [diazepam](#) equivalents) for anxiety, agitation, or sleep disturbances were allowed during the study. Assessments occurred at weekly visits until week 6, followed by visits every other week during weeks 6 to 12. The majority of study patients (76.8%) were antipsychotic-naïve at baseline. By week 12, 51.8% of study participants had dropped out, with 30.4% discontinuing due to lack of effectiveness. A modified intent-to-treat (ie, patients with at least 1 post-baseline efficacy measurement) revealed a significant reduction in mean +/- standard deviation PANSS total score (primary endpoint) from baseline score of 91.5 to 66.7 at week 12 (difference, 24.9 points; 95% CI, 17.3 to 32.4; p less than 0.0001). The difference was evident as early as week 1 and was maintained throughout the study. A 50% reduction in PANSS total scores occurred in 34.6% at a median of 85 days while 51.9% had a 40% reduction in PANSS total scores at a median of 57 days. Among the PANSS sub-scales, the magnitude of improvement at week 12 was greater for the positive sub-scale (21.4 at baseline to 14.9; 95% CI, 4.8 to 9.1) than the negative sub-scale (22.8 at baseline to 18.2; 95% CI, 2 to 7.1). Additionally, significant improvements occurred among the disorganization, impulsivity/hostility, and anxiety/depression sub-scales of the PANSS, along with the Clinical Global Impressions-Severity of Illness scale (5.2 at baseline to 3.7 at week 12) and the Subjective Well-being under Neuroleptic Treatment Scale (75.5 at baseline to 7.5 at week 12). Adverse events occurred in 78.6% of patients, with somnolence (21.4%), fatigue (17.9%), and headache (17.9%) being the most common. Five (8.9%) and 2 (3.6%) patients developed at least 1 moderate EPS (at doses of 400 to 600 mg/day) and mild-to-moderate [akathisia](#) (at doses of 500 to 600 mg/day), respectively; however, none required treatment or resulted in study discontinuation. Compared with baseline, there was significant increase in weight and BMI at week 12 (mean increase, 6.2 kg (weight), 2.1 kg/m(2) (BMI)), with 60.7% of patients gaining more than 7% of their baseline weight [13].

4.5.A.11] [Schizophrenia](#), Maintenance

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release only); [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](#)

b) Summary:

Extended-release [quetiapine](#) fumarate is indicated for the maintenance treatment of [schizophrenia](#) in adults [2]; regular-release [quetiapine](#) has not been systematically studied for the maintenance treatment of [schizophrenia](#) [6] [2].

In a randomized, double-blind, extension study (n=171), continued treatment with extended-release [quetiapine](#) fumarate 400 to 800 mg/day led to a longer time to [relapse](#) compared with placebo in adult patients who were previously stabilized during 16 weeks of an open-label trial [2].

c) Adult:

1) Maintenance treatment with extended-release [quetiapine](#) fumarate ([quetiapine](#) XR), at doses of 400 to 800 mg per day, led to a statistically significant delay in [relapse](#) compared with placebo in the double-blind, randomized, extension phase of an open-label trial. Clinically stable adult outpatients (n=171) who met the DSM-IV criteria for [schizophrenia](#) and who remained stable following 16 weeks of open-label treatment with [quetiapine](#) XR 400 to 800 mg/day were included. Patients who had a Clinical Global Impression (CGI)-Severity score of 4 or less and a Positive and Negative Syndrome Scale (PANSS) total score of 60 or less beginning to end of the open-label phase (not exceeding a 10- or greater point increase in PANSS total score) were considered to be stabilized. In the double-blind extension phase, patients were randomized to continue receiving [quetiapine](#) XR at their current dose or placebo. Patients were observed for possible [relapse](#), which was defined as a 30% or greater increase in the PANSS total score, a CGI-Improvement score of 6 or greater, hospitalization due to worsening of [schizophrenia](#), or need for any other antipsychotic medication. Treatment with [quetiapine](#) XR led to a significantly longer time to [relapse](#) than placebo [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 [quetiapine](#) was 150 milligrams/ day (equivalent to [chlorproMAZINE](#) 200 milligrams/day) (Woods SW, 2003).

b) [Quetiapine](#) 75 to 750 milligrams daily (mean, 407 mg daily) offered no significant advantage over [chlorproMAZINE](#) 75 to 750 milligrams daily (mean, 384 mg daily) in a double-blind, parallel-group trial involving patients with acute exacerbation of chronic or [subchronic schizophrenia](#), or [schizophreniform disorder](#) (n=201). Both drugs were associated with similar reductions in the Brief Psychiatric Rating Scale (BPRS) scores, Clinical Global Impression (CGI) scores, and negative scale scores of the Positive and Negative Syndrome Scale (PANSS) (negative symptom assessment). The severity of extrapyramidal symptoms was also comparable (assessed by Simpson scale) [187].

4.6.B] [Clomipramine Hydrochloride](#)

4.6.B.1] [Obsessive-compulsive disorder](#)

a) In a 12-week, randomized, placebo-controlled trial, the addition of **clomiPRAMINE** or placebo to **fluoxetine** was more effective than the addition of **quetiapine** to **fluoxetine** in reducing symptoms of **obsessive-compulsive disorder** (OCD; DSM-IV TR criteria) in adult patients refractory to **fluoxetine** monotherapy (n=54). For study inclusion, all patients had a Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores of at least 16, which was also a decrease of less than 35% from baseline, despite at least 8 weeks of **fluoxetine** (maximum dose, 80 mg/day). Enrolled patients were randomized to receive **clomiPRAMINE** (n=18; initial dose, 25 mg/day; weekly titration up to 75 mg/day; mean dose, 55 mg/day) plus **fluoxetine** (maximum dose, 40 mg/day), **quetiapine** (n=18, initial dose, 50 mg/day; weekly titration up to 200 mg/day; mean dose, 142 mg/day) plus **fluoxetine** (maximum dose, 40 mg/day), or placebo (n=18) plus **fluoxetine** (maximum dose, 80 mg/day). Mean final YBOCS scores and the mean change from baseline at week 12 (primary endpoint; intent-to-treat), were significantly improved for both **clomiPRAMINE** (final score, 18; change from baseline, -6.5; 95% CI, -9 to -3.9) and placebo (final score 18; change from baseline, -6.7; 95% CI, -9.6 to -3.8) compared with **quetiapine** (final score, 25; change from baseline, -0.1; 95% CI, -2.9 to +2.7) (p less than 0.001 for both). Withdrawal due to adverse effects occurred in 3 patients treated with **clomiPRAMINE** (QT prolongation from patient-specific baseline on ECG) and in 1 patient treated with **quetiapine** (syncope associated with orthostatic hypotension) [24].

4.6.C] **Haloperidol**

4.6.C.1] **Schizophrenia**

a) In a study involving 361 patients, **quetiapine** (across 5 fixed doses) was found to be superior to placebo in improving depressive symptoms in schizophrenic patients, while **haloperidol** (12 milligrams/day) was not. Additionally, depressive symptoms were improved in a greater proportion of patients treated with **quetiapine** versus **haloperidol** or placebo. None of the **quetiapine** patients withdrew from the study due to extrapyramidal symptoms, while 4 **haloperidol** and 1 placebo patient withdrew [190] [191].

b) A 6-week, multicenter, double-blind trial (n=448) comparing **quetiapine** and **haloperidol** (mean total daily doses of 455 milligrams and 8 milligrams, respectively) in the treatment of acute exacerbation of **schizophrenia** concluded that **quetiapine** in as effective and better tolerated than **haloperidol**. Both agents produced clear reductions in the Positive and Negative Syndrome Scale scores and Clinical Global Impression Severity of Illness and Global Improvement scores. **Quetiapine** was better tolerated in terms of extrapyramidal symptoms. In addition, mean serum prolactin concentration decreased in **quetiapine** patients and increased in **haloperidol** patients [192].

4.6.D] **Lurasidone Hydrochloride**

4.6.D.1] **Schizophrenia**

a) Lurasidone (n=139; 40 to 160 mg/day) was non-inferior to **quetiapine** extended release (n=79; 200 to 800 mg/day) in reducing **relapse** over 12 months (23.7% vs 33.6%) in adult outpatients with **chronic schizophrenia** who demonstrated an initial response to a 6-week acute treatment period in a randomized placebo-controlled trial with either lurasidone or **quetiapine** XR. The probability of hospitalization was significantly reduced in the lurasidone group (9.8% vs 23.1%). Increased body weight occurred with similar incidence in both treatment groups. Lurasidone was associated with a greater incidence of extrapyramidal adverse events during 12 months (11.9%) and in patients who switched from placebo to lurasidone after the initial 6-week acute treatment trial (21.4%) compared with **quetiapine** (3.5%) [195].

4.6.E] **Olanzapine**

4.6.E.1] **Chronic schizophrenia**

a) In a secondary analysis of the randomized superiority CATIE study, [perphenazine](#) was noninferior to each of 3 second-generation antipsychotics with regards to Positive and Negative Syndrome Scale (PANSS) total score at 18 months (noninferiority margin, 6.3 PANSS points). The analysis included adults 18 to 65 years randomized to [perphenazine](#) (n=256), [olanzapine](#) (n=263), [quetiapine](#) (n=261), or [risperidone](#) (n=269); [ziprasidone](#) was not included in the analysis due to a small sample size [188].

b) When newer antipsychotic medications ([olanzapine](#), [quetiapine](#), [risperidone](#), and [ziprasidone](#)) were compared with the first-generation antipsychotic, [perphenazine](#), the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with [chronic schizophrenia](#) were randomized to receive [olanzapine](#) 7.5 to 30 mg/day, [perphenazine](#) 8 to 32 mg/day, [quetiapine](#) 200 to 800 mg/day, [risperidone](#) 1.5 to 6.0 mg/day, or [ziprasidone](#) 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64% to 82%. Time to discontinuation ranged from 3.5 months for [ziprasidone](#) to 9.2 months for [olanzapine](#). The time to discontinuation in the [olanzapine](#) group was significantly 37% longer compared with the [quetiapine](#) group and 25% longer compared with the [risperidone](#) group. Time to discontinuation due to adverse events was similar between all groups. More patients discontinued [olanzapine](#) due to greater weight gain (average of 0.9 kg/month) and greater increases in A1C, total cholesterol, and [triglycerides](#) [189].

4.6.F] [Paliperidone](#)

4.6.F.1] [Schizophrenia](#), Recent exacerbation, in hospitalized patients

a) In a randomized, double-blind, placebo- and active-controlled clinical trial (n=394), treatment with [paliperidone](#) extended-release (ER) produced significantly improved Positive and Negative Syndrome Scale (PANSS) total scores compared with [quetiapine](#) in hospitalized patients with a recent exacerbation of [schizophrenia](#). Hospitalized patients 18 to 65 years of age with an acute episode (defined as lasting less than 4 weeks but more than 4 days) of [schizophrenia](#) (paranoid, disorganized, or undifferentiated types diagnosed using Diagnostic and Statistical Manual of Mental Disorders Fourth edition (DSM-IV)), a Clinical Global Impression of Severity (CGI-S) scale score of 5 or greater, and symptom scores of 4 or greater on 2 or more of the following PANSS items: hostility, excitement, tension, uncooperativeness, and poor impulse control (with a combined score of these items of 17 or greater) were eligible for enrollment. Following the discontinuation of all psychotropic agents, patients were randomized 2:2:1 to 6 weeks of [paliperidone](#) ER (n=157; baseline mean PANSS total score, 102.8 +/- 13.1 points), [quetiapine](#) (n=157; baseline mean PANSS total score, 101.3 +/- 13.3 points), or placebo (n=80; baseline mean PANSS total score, 103.8 +/- 15.7 points). In a 14-day monotherapy phase, [paliperidone](#) ER was initiated at 6 milligrams (mg)/day on days 1 to 3 and then increased to 9 mg/day starting on day 4 with an optional dose increase to 12 mg/day starting on day 8 if necessary (mean dose, 10.4 +/- 1.7 mg/day) and [quetiapine](#) was started at 50 mg/day on day 1, 100 mg/day on day 2, 200 mg/day on day 3, 400 mg/day on day 4, 600 mg/day on day 5 with an optional dose increase to 800 mg/day on day 8 (mean dose, 690.9 +/- 134.3 mg/day). Psychotropic medications (excluding [risperidone](#) or additional [paliperidone](#) ER or [quetiapine](#)) could be added following the 14-day monotherapy phase (one or more psychotropic agents: [paliperidone](#) ER, 52.9%; [quetiapine](#), 55.4%; placebo, 66.7%). The least-squares mean PANSS total score change from baseline to day 14 was significantly decreased in the [paliperidone](#) ER arm (-23.4 +/- 1.8 (standard error (SE)) points) compared with the [quetiapine](#) arm (-17.1 +/- 1.8 (SE) points; p less than 0.001) (primary endpoint) and the placebo arm (p of 0.001 or less). In between group analyses (using a least-squares mean differences in change scores with the last observation carried forward), patients in the [paliperidone](#) ER arm had significantly improved PANSS total score, PANSS scale negative symptoms scores, PANSS scale disorganized thoughts scores, PANSS scale uncontrolled hostility/excitement scores, and CGI-S scores compared with patients in the [quetiapine](#) and placebo arms at day 14 and at the end of 6 weeks of treatment (day 42) (Table 1). Additionally, the PANSS scale positive symptoms score (PANSS-P) and Clinical Global Impression

of Change (CGI-C) score were significantly improved in the [paliperidone](#) ER arm compared with the [quetiapine](#) and placebo arms at day 14 and [paliperidone](#) ER significantly improved PANSS-P and CGI-C compared with placebo at day 42 (Table 1). Serious adverse events were reported in 8.2%, 4.4%, and 2.5% of patients in the [paliperidone](#) ER, [quetiapine](#), and placebo arms, respectively. Extrapyramidal symptoms (EPS) were significantly (p less than 0.001) higher in the [paliperidone](#) ER arm following the 14-day monotherapy phase compared with [quetiapine](#) using the Simpson-Angus Rating Scale (total score). The incidence of movement disorders at day 14 and 42 were not significantly different between the 3 arms using the Barnes [Akathisia](#) Rating Scale and the [Abnormal Involuntary Movement](#) Scale [196].

Table 1: Between Group Analyses

Outcome measures	Day 14	Day 42			
Paliperidone ER versus Quetiapine	Paliperidone ER versus Placebo	Quetiapine versus Placebo	Paliperidone ER versus Quetiapine	Paliperidone ER versus Placebo	Quetiapine versus Placebo
PANSS score Mean (SE)					
Total	-6.3* (1.8)	-8.4* (2.2)	-2.1 (2.2)	-4.7* (2)	-7.8* (2.5)
Positive symptoms	-1.6* (0.6)	-2.1* (0.7)	-0.5 (0.7)	-1.1 (0.6)	-1.9* (0.8)
Negative symptoms	-1.3* (0.5)	-2.2* (0.6)	-0.9 (0.6)	-1.2* (0.5)	-2.1* (0.6)
Anxiety/depression	-0.5 (0.3)	-0.6 (0.4)	-0.1 (0.4)	-0.4 (0.3)	-0.5 (0.4)
Disorganized thoughts	-1.3* (0.4)	-2.1* (0.5)	-0.8 (0.5)	-1* (0.5)	-2* (0.6)
Uncontrolled hostility/excitement	-1.5* (0.4)	-1.6* (0.5)	-0.1 (0.5)	-1* (0.4)	-1.3* (0.5)
CGI-S (Mean SE)	-0.3* (0.1)	-0.4* (0.1)	-0.1 (0.1)	-0.3* (0.1)	-0.5* (0.1)
CGI-C (Mean SE)	-0.4* (0.1)	-0.5* (0.1)	-0.2 (0.1)	-0.1 (0.1)	-0.4* (0.2)
* p less than 0.05					
PANSS, Positive and Negative Syndrome Scale; SE, standard error; CGI-S, Clinical Global Impression of Severity; CGI-C, Clinical Global Impression of Change					

4.6.G] [Perphenazine](#)

4.6.G.1] [Chronic schizophrenia](#)

a) In a secondary analysis of the randomized superiority CATIE study, [perphenazine](#) was noninferior to each of 3 second-generation antipsychotics with regards to Positive and Negative Syndrome Scale (PANSS) total score at 18 months (noninferiority margin, 6.3 PANSS points). The analysis included adults 18 to 65 years randomized to [perphenazine](#) (n=256), [olanzapine](#) (n=263), [quetiapine](#) (n=261), or [risperidone](#) (n=269); [ziprasidone](#) was not included in the analysis due to a small sample size [188].

b) When newer antipsychotic medications ([olanzapine](#), [quetiapine](#), [risperidone](#), and [ziprasidone](#)) were compared with the first-generation antipsychotic, [perphenazine](#), the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with [chronic schizophrenia](#) were randomized to receive [olanzapine](#) 7.5 to 30 mg/day, [perphenazine](#) 8 to 32 mg/day, [quetiapine](#) 200 to 800 mg/day, [risperidone](#) 1.5 to 6.0 mg/day, or [ziprasidone](#) 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64% to 82%. Time to discontinuation ranged from 3.5 months for [ziprasidone](#) to 9.2 months for [olanzapine](#). The time to discontinuation in the [olanzapine](#) group was significantly 37% longer compared with the [quetiapine](#) group and 25% longer compared with the [risperidone](#) group.

Time to discontinuation due to adverse events was similar between all groups. More patients discontinued [olanzapine](#) due to greater weight gain (average of 0.9 kg/month) and greater increases in A1C, total cholesterol, and [triglycerides](#) [189].

4.6.H] [Risperidone](#)

4.6.H.1] [Bipolar I disorder, Acute manic and mixed episodes](#)

a) In a randomized, double-blind, multiphase, parallel-group, active- and placebo-controlled study (n=493), [paliperidone](#) extended-release (ER) therapy was more effective than placebo and not different from [quetiapine](#) in improving Young Mania Rating Scale (YMRS) scores among patients with bipolar I disorder experiencing an acute manic or mixed episode. Enrolled patients (age, 39 +/- 10 yr; 65% manic; 35% mixed) had a minimum YMRS score of 20, had no known or suspected rapid cycling, [schizoaffective disorder](#), [antisocial personality disorder](#) or a history of substance abuse. Following a 1-week washout period where all antimanic medications were discontinued, patients were randomized 2:2:1 to a 3-week, double-blind acute treatment phase of [paliperidone](#) ER (n=195; 3 to 12 mg/day; initial dose, 6 mg/day; dose titration by 3 mg every 2 days), [quetiapine](#) (n=193; 400 to 800 mg/day; initial dose, 100 mg/day; forced titration to 400 mg/day on day 4; dose adjustment by 200 mg every 2 days), or placebo (n=105); during which patients were hospitalized for 10.4 +/- 5.66 days. Patients then proceeded to a 9-week, double-blind, maintenance phase on the same therapy except patients who received placebo in the acute phase were switched to [paliperidone](#) ER. At the end of the 3-week acute treatment phase, the mean change in YMRS total score from baseline (primary endpoint) was -13.2 +/- 8.68 in the [paliperidone](#) ER group compared with -7.4 +/- 10.74 in the placebo group (difference, -5.5; 95% confidence interval (CI), -7.57 to -3.35; p less than 0.001). [Quetiapine](#) also resulted in greater YMRS total score improvement compared with placebo (-11.7 +/- 9.28 vs -7.4 +/- 10.74; between-group difference, -4.2; 95% CI, -6.45 to -1.95; p less than 0.001), but was not statistically different from [paliperidone](#) ER (p=0.099). In the secondary analysis at the 12-week endpoint, [paliperidone](#) ER was noninferior to [quetiapine](#) based on the prespecified noninferiority margin of greater than -4 as the lower limit of the 95% CI. The mean change in YMRS total score at week 12 from baseline was -15.2 +/- 10.26 in the [paliperidone](#) group compared with -13.5 +/- 11.02 in the [quetiapine](#) group (difference, 1.7; 95% CI, -0.47 to 3.96). There was no significant difference between [paliperidone](#) ER and [quetiapine](#) with regards to three efficacy scales (Global Assessment of Functioning (GAF), Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impression-Bipolar Disorder-Severity Scale (CG-BP-S)). The number needed to treat (NNT) to achieve a clinical response (50% or greater reduction from baseline) for the [paliperidone](#) ER group was 5 (95% CI, 4 to 11) and 7 (95% CI, 4 to 40) for the [quetiapine](#) group. Common adverse events for [quetiapine](#) relative to [paliperidone](#) ER during the 3-week treatment phase included somnolence (18% vs 10%), sedation (16% vs 8%), dizziness (12% vs 6%), and dry mouth (15% vs 5%). On the other hand, [paliperidone](#) was associated with higher incidence of [akathisia](#) (10% vs 3%), drooling (6% vs 0%) and hypertonia (5% vs 1%) compared with [quetiapine](#) at 12-week follow-up. Nineteen percent of patients in the [paliperidone](#) ER group received anticholinergic medications during the acute or maintenance phases of treatment compared with 10% in the [quetiapine](#) group and 8% in the placebo/[paliperidone](#) ER group for treatment-emergent extrapyramidal symptoms. At week 12, more patients in the [quetiapine](#) group (17%) compared with the [paliperidone](#) group (up to 8%) experienced weight increase of 7% or greater. [Paliperidone](#) (13.9% to 18%) was associated with more patients who "switched to depression" at 12 weeks compared with the [quetiapine](#) (5.8%; p=0.044) [194].

4.6.H.2] [Chronic schizophrenia](#)

a) In a secondary analysis of the randomized superiority CATIE study, [perphenazine](#) was noninferior to each of 3 second-generation antipsychotics with regards to Positive and Negative Syndrome Scale (PANSS) total score at 18 months (noninferiority margin, 6.3 PANSS points). The analysis included

adults 18 to 65 years randomized to [perphenazine](#) (n=256), [olanzapine](#) (n=263), [quetiapine](#) (n=261), or [risperidone](#) (n=269); [ziprasidone](#) was not included in the analysis due to a small sample size [188].

b) When newer antipsychotic medications ([olanzapine](#), [quetiapine](#), [risperidone](#), and [ziprasidone](#)) were compared with the first-generation antipsychotic, [perphenazine](#), the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with [chronic schizophrenia](#) were randomized to receive [olanzapine](#) 7.5 to 30 mg/day, [perphenazine](#) 8 to 32 mg/day, [quetiapine](#) 200 to 800 mg/day, [risperidone](#) 1.5 to 6.0 mg/day, or [ziprasidone](#) 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64% to 82%. Time to discontinuation ranged from 3.5 months for [ziprasidone](#) to 9.2 months for [olanzapine](#). The time to discontinuation in the [olanzapine](#) group was significantly 37% longer compared with the [quetiapine](#) group and 25% longer compared with the [risperidone](#) group. Time to discontinuation due to adverse events was similar between all groups. More patients discontinued [olanzapine](#) due to greater weight gain (average of 0.9 kg/month) and greater increases in A1C, total cholesterol, and [triglycerides](#) [189].

4.6.H.3] Psychotic disorder

a) [Quetiapine](#) and [risperidone](#) were similarly efficacious in treating psychotic symptoms and had similar overall tolerability, but [quetiapine](#) treatment resulted in fewer extrapyramidal symptoms (EPS) and was more effective in reducing depression. In a 4- month, open-label study, patients with [schizophrenia](#), [schizoaffective disorder](#), or other [psychotic disorders](#) (including [bipolar disorder](#), [major depressive disorder](#) and various forms of [dementia](#)) were randomized in a ratio of 3:1 to receive [quetiapine](#) (n=553) or [risperidone](#) (n=175). A total of 64% of the study population had [schizophrenia](#) or [schizoaffective disorder](#) while 24% had bipolar I disorder or [major depressive disorder](#). The starting dosage of [quetiapine](#) was 50 milligrams/day (mg/day), which was increased in 50- or 100- mg increments every 1 to 2 days, to a maximum of 800 mg/day, given in divided doses. [Risperidone](#) was started at 1 mg twice daily, with upward titration to a target dose of 3 mg twice daily by day 3. Dosages were individually titrated to maximize efficacy while minimizing adverse reactions (mean prescribed dose: [quetiapine](#) 253.9 mg, [risperidone](#) 4.4 mg). At the beginning of the study, approximately half of each group had EPS. There was a steady decline in the number of patients reporting EPS in both groups as the study progressed. The incidence of EPS in the [quetiapine](#) group was lower than in the [risperidone](#) group at one month (41.1 vs 47.3) but not at the end of the study (38.6 vs 39.2). The percentage of patients requiring a change of treatment due to EPS or requiring anti-EPS medication was lower in the [quetiapine](#) group than in the [risperidone](#) group (7% vs 20.5%). Approximately one third of patients in each group withdrew before completion of the study. A higher percentage withdrew from [risperidone](#) treatment for lack of efficacy (10.3% vs 5.8%) and a higher percentage withdrew from [quetiapine](#) treatment because of adverse effects (8.7% vs 5.1%). Somnolence was the most common adverse event in both groups, followed by dry mouth and dizziness, which all occurred significantly more often with [quetiapine](#) treatment (p less than 0.05). Occurrence of weight gain was low in both groups [193].

4.6.I] Ziprasidone

4.6.I.1] Chronic schizophrenia

a) In a secondary analysis of the randomized superiority CATIE study, [perphenazine](#) was noninferior to each of 3 second-generation antipsychotics with regards to Positive and Negative Syndrome Scale (PANSS) total score at 18 months (noninferiority margin, 6.3 PANSS points). The analysis included adults 18 to 65 years randomized to [perphenazine](#) (n=256), [olanzapine](#) (n=263), [quetiapine](#) (n=261), or [risperidone](#) (n=269); [ziprasidone](#) was not included in the analysis due to a small sample size [188].

b) When newer antipsychotic medications ([olanzapine](#), [quetiapine](#), [risperidone](#), and [ziprasidone](#)) were compared with the first-generation antipsychotic, [perphenazine](#), the majority of patients in each group

discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with [chronic schizophrenia](#) were randomized to receive [olanzapine](#) 7.5 to 30 mg/day, [perphenazine](#) 8 to 32 mg/day, [quetiapine](#) 200 to 800 mg/day, [risperiDONE](#) 1.5 to 6.0 mg/day, or [ziprasidone](#) 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64% to 82%. Time to discontinuation ranged from 3.5 months for [ziprasidone](#) to 9.2 months for [olanzapine](#). The time to discontinuation in the [olanzapine](#) group was significantly 37% longer compared with the [quetiapine](#) group and 25% longer compared with the [risperiDONE](#) group. Time to discontinuation due to adverse events was similar between all groups. More patients discontinued [olanzapine](#) due to greater weight gain (average of 0.9 kg/month) and greater increases in A1C, total cholesterol, and [triglycerides](#) [189].

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