QUETIAPINE

THERAPEUTICS

Brands • Seroquel • Seroquel XR

see index for additional brand names

Generic? Yes

Class
• Neuroscience-based Nomenclature: dopamine, serotonin multimodal (DS-MM)
• Atypical antipsychotic (serotonin-dopamine antagonist; second-generation antipsychotic; also a mood stabilizer)

Commonly Prescribed for
(bold for FDA approved)
• Acute schizophrenia in adults (quetiapine, quetiapine XR) and ages 13–17 (quetiapine)
• Schizophrenia maintenance (quetiapine XR)
• Acute mania in adults (quetiapine and quetiapine XR, monotherapy and adjunct to lithium or valproate) and ages 10–17 (quetiapine, monotherapy and adjunct to lithium or valproate)
• Bipolar maintenance (quetiapine, quetiapine XR)
• Bipolar depression (quetiapine, quetiapine XR)
• Depression (quetiapine XR, adjunct)
• Other psychotic disorders
• Mixed mania
• Behavioral disturbances in dementias
• Behavioral disturbances in Parkinson’s disease and Lewy body dementia
• Psychosis associated with levodopa treatment in Parkinson’s disease
• Behavioral disturbances in children and adolescents
• Disorders associated with problems with impulse control
• Severe treatment-resistant anxiety

Interactions at a myriad of other neurotransmitter receptors may contribute to quetiapine’s efficacy in treatment-resistant depression or bipolar depression, especially 5HT1A partial agonist action, norepinephrine reuptake blockade and 5HT2C antagonist and 5HT7 antagonist properties

Specifically, actions at 5HT1A receptors may contribute to efficacy for cognitive and affective symptoms in some patients, especially at moderate to high doses

How Long Until It Works
• Psychotic and manic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition and affective stabilization
• Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients require up to 16–20 weeks to show a good response, especially on cognitive symptoms

How the Drug Works
• Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
• Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms

How the Drug Works
• Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
• Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms

If It Works
• Most often reduces positive symptoms in schizophrenia but does not eliminate them
• Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
• Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
• Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
• Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
• Many bipolar patients may experience a reduction of symptoms by half or more
• Continue treatment until reaching a plateau of improvement
• After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
• For second and subsequent episodes of psychosis, treatment may need to be indefinite
• Even for first episodes of psychosis, it may be preferable to continue treatment indefinitely to avoid subsequent episodes
• Treatment may not only reduce mania but also prevent recurrences of mania in bipolar disorder

If It Doesn’t Work
• Try one of the other atypical antipsychotics (risperidone, olanzapine, ziprasidone, aripiprazole, paliperidone, amisulpride, asenapine, iloperidone, lurasidone)
• If 2 or more antipsychotic monotherapies do not work, consider clozapine
• Some patients may require treatment with a conventional antipsychotic
• If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
• Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
• Consider initiating rehabilitation and psychotherapy such as cognitive remediation
• Consider presence of concomitant drug abuse

Best Augmenting Combos for Partial Response or Treatment Resistance
• Valproic acid (valproate, divalproex, divalproex ER)
• Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
• Lithium
• Benzodiazepines

Tests
Before starting an atypical antipsychotic
• Weigh all patients and track BMI during treatment
• Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
• Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
• Determine if the patient is
  • overweight (BMI 25.0–29.9)
  • obese (BMI ≥30)
  • has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
• has diabetes (fasting plasma glucose >126 mg/dL)
• has hypertension (BP >140/90 mm Hg)
• has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
• Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic
• BMI monthly for 3 months, then quarterly
• Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
• Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% of initial weight
• Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic
• Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma
• Although US manufacturer recommends 6-month eye checks for cataracts, clinical experience suggests this may be unnecessary
• Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and quetiapine should be discontinued at the first sign of decline of WBC in the absence of other causative factors
SIDES EFFECTS

How Drug Causes Side Effects
• By blocking histamine 1 receptors in the brain, it can cause sedation and possibly weight gain
• By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
• By blocking muscarinic 1 receptors, it can cause dry mouth, constipation, and sedation
• By blocking dopamine 2 receptors in the striatum, it can cause motor side effects (rare)
• Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

Notable Side Effects
• Dose-dependent weight gain
  ✺ May increase risk for diabetes and dyslipidemia
  ✺ Dizziness, sedation
• Dry mouth, constipation
• Dyspepsia, abdominal pain
• Tachycardia
• Orthostatic hypotension, usually during initial dose titration
• Theoretical risk of tardive dyskinesia

Life-Threatening or Dangerous Side Effects
• Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
• Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
• Rare seizures
• Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

Weight Gain
• Many patients experience and/or can be significant in amount at effective antipsychotic doses
• Can become a health problem in some
• May be less than for some antipsychotics, more than for others

Sedation
• Frequent and can be significant in amount
• Some patients may not tolerate it
• More than for some other antipsychotics, but never say always as not a problem in everyone
• Can wear off over time
• Can reemerge as dose increases and then wear off again over time
• Not necessarily increased as dose is raised

What to Do About Side Effects
• Wait
• Wait
• Wait
• Usually dosed twice daily, so take more of the total daily dose at bedtime to help reduce daytime sedation
• Start dosing low and increase slowly as side effects wear off at each dosing increment
• Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
• Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects
• Many side effects cannot be improved with an augmenting agent

DOSEING AND USE

Usual Dosage Range
• 400–800 mg/day in 1 (quetiapine XR) or 2 (quetiapine) doses for schizophrenia
• 400–800 mg/day in 1 (quetiapine XR) or 2 (quetiapine) doses for bipolar mania
• 300 mg once daily for bipolar depression

Dosage Forms
• Tablets 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg
• Extended-release tablets 50 mg, 150 mg 200 mg, 300 mg, 400 mg

How to Dose
• (According to manufacturer for quetiapine in schizophrenia): initial 25 mg/day twice a day; increase by 25–50 mg twice a day
QUETIAPINE (continued)

<table>
<thead>
<tr>
<th>Dosing Tips</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>More may be much more:</strong> clinical practice suggests quetiapine often underdosed, then switched prior to adequate trials</td>
</tr>
<tr>
<td>Clinical practice suggests that at low doses it may be a sedative hypnotic, possibly due to potent H1 antihistamine actions, but this can risk numerous antipsychotic-related side effects and there are many other options</td>
</tr>
<tr>
<td><strong>Initial target dose of 400–800 mg/day should be reached in most cases to optimize the chances of success in treating acute psychosis and acute mania, but many patients are not adequately dosed in clinical practice</strong></td>
</tr>
<tr>
<td><strong>Many patients do well with immediate-release as a single daily oral dose, usually at bedtime</strong></td>
</tr>
<tr>
<td><strong>Recommended titration to 400 mg/day by the fourth day can often be achieved when necessary to control acute symptoms</strong></td>
</tr>
<tr>
<td><strong>Rapid dose escalation in manic or psychotic patients may lessen sedative side effects</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Higher doses generally achieve greater response for manic or psychotic symptoms</strong></td>
</tr>
<tr>
<td><strong>In contrast, some patients with bipolar depression may respond well to doses less than 300 mg/day and as little as 25 mg/day</strong></td>
</tr>
<tr>
<td><strong>Dosing in major depression may be even lower than in bipolar depression, and dosing may be even lower still in GAD</strong></td>
</tr>
<tr>
<td><strong>Occasional patients may require more than 800–1,200 mg/day for psychosis or mania</strong></td>
</tr>
<tr>
<td><strong>Rather than raise the dose above these levels in acutely agitated patients requiring acute antipsychotic actions, consider augmentation with a benzodiazepine or conventional antipsychotic, either orally or intramuscularly</strong></td>
</tr>
<tr>
<td><strong>Rather than raise the dose above these levels in partial responders, consider augmentation with a mood-stabilizing anticonvulsant such as valproate or lamotrigine</strong></td>
</tr>
<tr>
<td><strong>Children and elderly should generally be dosed at the lower end of the dosage spectrum</strong></td>
</tr>
<tr>
<td><strong>Quetiapine XR is controlled-release and therefore should not be chewed or crushed but rather should be swallowed whole</strong></td>
</tr>
<tr>
<td><strong>Quetiapine XL may theoretically generate increased concentrations of active metabolite norquetiapine, with theoretically improved profile for affective and anxiety disorders</strong></td>
</tr>
<tr>
<td><strong>Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³</strong></td>
</tr>
</tbody>
</table>

**Overdose**
- Rarely lethal in monotherapy overdose; sedation, slurred speech, hypotension

**Long-Term Use**
- Approved for long-term maintenance in schizophrenia and bipolar disorder, and often used for long-term maintenance in various behavioral disorders

**Habit Forming**
- No

**How to Stop**
- See also the Switching section of individual agents for how to stop quetiapine
- Rapid discontinuation may lead to rebound psychosis and worsening of symptoms

**Pharmacokinetics**
- Parent drug has 6–7 hour half-life
- Substrate for CYP450 3A4
- Food may slightly increase absorption
Cardiac Impairment
• Drug should be used with caution because of risk of orthostatic hypotension

Elderly
• Lower dose is generally used (e.g., 25–100 mg twice a day), although higher doses may be used if tolerated
• Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
• Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

Children and Adolescents
• Approved for use in schizophrenia (ages 13 and older) and manic/mixed episodes (ages 10 and older)
• Clinical experience and early data suggest quetiapine may be safe and effective for behavioral disturbances in children and adolescents
• Children and adolescents using quetiapine may need to be monitored more often than adults
• Use with caution, observing for activation of suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
• May tolerate lower doses better

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• There is a risk of abnormal muscle movements and withdrawal symptoms

Do Not Use
• If there is a proven allergy to quetiapine

Other Warnings/Precautions
• In the USA, manufacturer recommends examination for cataracts before and every 6 months after initiating quetiapine, but this does not seem to be necessary in clinical practice
• Quetiapine should be used cautiously in patients at risk for aspiration pneumonia, as dysphagia has been reported
• Priapism has been reported
• Use with caution in patients with known cardiovascular disease, cerebrovascular disease
• Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
• Monitor patients for activation of suicidal ideation, especially children and adolescents
• Avoid use with drugs that increase the QT interval and in patients with risk factors for prolonged QT interval

Drug Interactions
• CYP450 3A inhibitors and CYP450 2D6 inhibitors may reduce clearance of quetiapine and thus raise quetiapine plasma levels, but dosage reduction of quetiapine usually not necessary
• May increase effect of anti-hypertensive agents
• There are case reports of increased international normalized ratio (INR) (used to monitor the degree of anticoagulation) when quetiapine is coadministered with warfarin, which is also a substrate of CYP450 3A4

SPECIAL POPULATIONS

Renal Impairment
• No dose adjustment required

Hepatic Impairment
• Downward dose adjustment may be necessary

QUETIAPINE

Drug should be used with caution because of risk of orthostatic hypotension

Lower dose is generally used (e.g., 25–100 mg twice a day), although higher doses may be used if tolerated

Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

Children and adolescents using quetiapine may need to be monitored more often than adults

Use with caution, observing for activation of suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients

May tolerate lower doses better

Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

Controlled studies have not been conducted in pregnant women

There is a risk of abnormal muscle movements and withdrawal symptoms

If there is a proven allergy to quetiapine
in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
• Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
• Quetiapine may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
• National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/

Breast Feeding
• Unknown if quetiapine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
• Recommended either to discontinue drug or bottle feed
• Infants of women who choose to breast feed while on quetiapine should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• Bipolar depression
• Some cases of psychosis and bipolar disorder refractory to treatment with other antipsychotics

Pearls

✽ May be the preferred antipsychotic for psychosis in Parkinson’s disease and Lewy body dementia
• Anecdotal reports of efficacy in treatment-refractory cases and positive symptoms of psychoses other than schizophrenia
✽ Efficacy may be underestimated for psychosis and mania since quetiapine is often under-dosed in clinical practice
✽ Approved in bipolar depression
• The active metabolite of quetiapine, norquetiapine, has the additional properties of norepinephrine reuptake inhibition and antagonism of 5HT2C receptors, which may contribute to therapeutic effects for mood and cognition
• Dosing differs depending on the indication, with high-dose mechanisms including robust blockade of D2 receptors above 60% occupancy and equal or greater 5HT2A blockade; medium-dose mechanisms including moderate amounts of NET inhibition combined with 5HT2C antagonism and 5HT1A partial agonism; and low-dose mechanisms including H1 antagonism and 5HT1A partial agonism and, to a lesser extent, NET inhibition and 5HT2C antagonism
• More sedation than some other antipsychotics, which may be of benefit in acutely manic or psychotic patients but not for stabilized patients in long-term maintenance
✽ Essentially no motor side effects or prolactin elevation
• May have less weight gain than some antipsychotics, more than others
✽ Controversial as to whether quetiapine has more or less risk of diabetes and dyslipidemia than some other antipsychotics
• Commonly used at low doses to augment other atypical antipsychotics, but such antipsychotic polypharmacy has not been systematically studied and can be quite expensive
• Anecdotal reports of efficacy in PTSD, including symptoms of sleep disturbance and anxiety
• Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and,
if low, a dosage increase even beyond the usual prescribing limits

- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring

In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic.

**THE ART OF SWITCHING**

**Switching from Oral Antipsychotics to Quetiapine**

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin quetiapine at middle dose
- With risperidone, ziprasidone, iloperidone, and lurasidone, it is generally advisable to begin quetiapine gradually, titrating over at least 2 weeks to allow patients to become tolerant to the sedating effect
- For more convenient dosing, patients who are currently being treated with divided doses of immediate-release tablets may be switched to extended-release quetiapine at the equivalent total daily dose taken once daily

*May need to taper clozapine slowly over 4 weeks or longer

### Target dose

**dose**

| amisulpride | amisulpride | amisulpride |
| aripiprazole | aripiprazole | aripiprazole |
| brexpiprazole | brexpiprazole | brexpiprazole |
| paliperidone ER | paliperidone ER | paliperidone ER |
| 1 week | 1 week | 1 week |

**dose**

| iloperidone | iloperidone | iloperidone |
| lurasidone | lurasidone | lurasidone |
| risperidone | risperidone | risperidone |
| ziprasidone | ziprasidone | ziprasidone |
| 1 week | 1 week | 1 week |

**dose**

| clozapine* | clozapine* | clozapine* |
| olanzapine | olanzapine | olanzapine |
| asenapine | asenapine | asenapine |
| 1 week | 1 week | 1 week |
Citrome L. Adjunctive aripiprazole, olanzapine, or quetiapine for major depressive disorder: an analysis of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Postgrad Med 2010;122(4):39–48.


