SECOND-GENERATION ANTIPSYCHOTIC

Quetiapine

Seroquel, Seroquel XR

Sedating, broad-spectrum agent with the strongest bipolar depression data in the class, paid for in weight and somnolence.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
150-800 mg/day PO	6 h (12 h norquetiapine)	CYP3A4 (CYP2D6 minor)	1-2 wks; 4-6 wks full

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis; quetiapine is not approved for that use. Antidepressants increased the risk of suicidal thoughts and behaviors in children, adolescents, and young adults; monitor closely for worsening and emergent suicidality.

INDICATIONS

- Schizophrenia in adults and adolescents ages 13-17, with both immediate-release and extended-release formulations approved for acute and maintenance use.
- Acute manic or mixed episodes of bipolar I disorder in adults and in children ages 10-17, as monotherapy or as adjunct to lithium or valproate.
- Depressive episodes of bipolar I or II disorder in adults, where quetiapine has the strongest monotherapy evidence base of any antipsychotic.
- Maintenance treatment of bipolar I disorder in adults as adjunct to lithium or divalproex, and extended-release adjunctive treatment of major depressive disorder.
- Off-label uses include generalized anxiety disorder, which has controlled trial support, and low-dose use for insomnia, which is not recommended.

DOSING & TITRATION

- Schizophrenia with immediate-release: start **25 mg twice daily**, titrate to 300-400 mg/day by day 4, usual range 150-750 mg/day, maximum **800 mg/day**.
- Extended-release for schizophrenia: start **300 mg once daily** in the evening, then adjust within 400-800 mg/day at intervals of at least one day.
- Bipolar depression: **50 mg** at bedtime day 1, 100 mg day 2, 200 mg day 3, and 300 mg day 4, which is the target and effective dose.
- Adjunctive extended-release for major depressive disorder: start **50 mg** at bedtime, then 150 mg on day 3, with a maximum of 300 mg/day.
- Hepatic impairment: start **25 mg/day** and increase by 25-50 mg/day increments; no adjustment is needed for renal impairment or dialysis.
- Taper over one to two weeks when possible, since abrupt discontinuation commonly causes insomnia, nausea, and rebound anxiety.

MECHANISM OF ACTION

- Low-affinity, fast-dissociating **D2** antagonist, which explains the very low rate of extrapyramidal symptoms and negligible prolactin elevation.
- Potent **5-HT2A** and moderate 5-HT1A partial agonist activity contributes to mood effects and to tolerability in Parkinson disease psychosis.
- The active metabolite **norquetiapine** inhibits the norepinephrine transporter and blocks 5-HT2C, which underlies antidepressant efficacy.
- High histamine H1 affinity drives profound sedation and appetite stimulation, prominent even at doses of 25-50 mg.
- Alpha-1 blockade causes orthostatic hypotension and dizziness, especially during initial titration and in older adults.

PHARMACOKINETICS

- Immediate-release absorption is rapid and largely food independent, but extended-release should be taken without food or with a light meal under 300 kcal.
- Extensively metabolized by **CYP3A4** to norquetiapine, an active metabolite with a distinct noradrenergic and antidepressant pharmacology.
- Parent half-life is about **6 hours** and norquetiapine about 12 hours, so immediate-release usually needs twice-daily dosing.
- Only about 1 percent is excreted unchanged, so renal impairment needs no adjustment while hepatic impairment lowers clearance by about 30 percent.
- The short half-life makes quetiapine unforgiving of missed doses and prone to rebound insomnia and nausea if stopped abruptly.

ADVERSE EFFECTS

- Somnolence occurs in **50 percent** or more at higher doses and is the most common reason for discontinuation early in treatment.
- Weight gain and metabolic effects are high, second only to olanzapine and clozapine, with meaningful rises in triglycerides and glucose.
- Orthostatic hypotension, dizziness, dry mouth, and constipation are frequent, largely from alpha-1, histaminergic, and muscarinic effects.
- Extrapyramidal symptoms and prolactin elevation are minimal, which is the main reason quetiapine is used in Parkinson disease and in tardive risk.
- Serious risks include neuroleptic malignant syndrome, modest QT prolongation, cataracts on long-term use, and rare thyroid hormone reduction.

MONITORING

- Weight, BMI, waist circumference, and blood pressure at baseline and each visit early, with fasting glucose or A1c and lipids at 12 weeks then annually.
- The label recommends slit-lamp lens examination at initiation and every 6 months during chronic treatment, based on preclinical cataract findings.
- Check thyroid function periodically, since quetiapine can lower total and free thyroxine in a dose-related fashion.
- Obtain an ECG when combining with other QT-prolonging drugs, in known cardiac disease, or in patients with electrolyte disturbance.
- Screen for sedation-driven falls in older adults and reassess whether nighttime dosing alone can carry the therapeutic load.

INTERACTIONS & CAUTIONS

- Strong **CYP3A4** inhibitors such as ketoconazole, clarithromycin, and ritonavir require reducing quetiapine to about one sixth of the usual dose.
- Strong inducers including **phenytoin**, carbamazepine, and rifampin can cut exposure up to fivefold; increase the dose and reverse on withdrawal.
- Marked additive sedation and respiratory depression risk with opioids, benzodiazepines, and alcohol, a common cause of harm in practice.
- Additive orthostasis with antihypertensives and additive QT effect with methadone, ondansetron, and Class IA or III antiarrhythmics.
- Avoid in patients with known hypersensitivity; caution with anticholinergics given constipation and urinary retention risk.

SPECIAL POPULATIONS

- Third-trimester exposure risks neonatal extrapyramidal signs and withdrawal; quetiapine is among the better-studied antipsychotics in pregnancy.
- Milk levels are low with a relative infant dose typically under 1 percent, so lactation is usually compatible with infant monitoring.
- Approved from age 10 for bipolar mania and 13 for schizophrenia, but adolescents gain substantially more weight than adults at equal doses.
- In older adults clearance falls about 40 percent; start at **25 mg/day** and titrate slowly, weighing fall risk against sedation benefit.
- No renal adjustment even on dialysis; in hepatic impairment start low and titrate at half the usual increments.

PRESCRIBING PEARLS

- Low-dose quetiapine for insomnia gives full metabolic risk for a hypnotic effect; use a real hypnotic.
- 300 mg at bedtime is the evidence-based bipolar depression dose, not a dose on the way to higher.
- Its weak, fast-off D2 binding is why it is a first choice in Parkinson disease psychosis.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.