Medications for schizophrenia

First-line and second-line antipsychotics, where clozapine and LAIs fit, and how metabolic monitoring shapes the pick. Reviewed against current guidelines as of June 8, 2026.

In head-to-head trials most antipsychotics are roughly comparable for positive symptoms. Clozapine is the outlier with unique efficacy in treatment resistance and unique protection against suicide. The rest of the choice sits on side effects, delivery format, and what the patient will take. Companion to the full guide at psychiatryrx.org/guides/medications-for-schizophrenia/.

First-line options

Drug	Class	Notes
Risperidone	Second-gen (SGA)	2 to 6 mg. Cheap, effective. Raises prolactin. LAI options.
Paliperidone	SGA	Active metabolite of risperidone. Monthly, 3-monthly, and 6-monthly LAIs. Renal ceiling.
Aripiprazole	SGA (partial agonist)	10 to 30 mg. Less prolactin, less metabolic burden. Sometimes more akathisia. LAI options.
Olanzapine	SGA	10 to 20 mg. Effective. Worst offender for weight and metabolic effects.
Quetiapine	SGA	400 to 800 mg XR. Sedating, less EPS, more metabolic burden.
Ziprasidone	SGA	40 to 80 mg BID with 500 kcal or absorption drops. Metabolically kinder.
Lurasidone	SGA	40 to 160 mg with 350 kcal food. Favorable metabolic profile.
Cariprazine	SGA (partial agonist)	1.5 to 6 mg. Long half-life. Some benefit for negative symptoms.
Brexpiprazole	SGA (partial agonist)	2 to 4 mg. Similar to aripiprazole with less akathisia in trials.
Lumateperone, xanomeline-trospium	SGA (newer)	Favorable metabolic profile in trials. Xanomeline-trospium (Cobenfy, 2024) acts at muscarinic M1/M4 without D2 blockade.

Second-line and augmentation

Drug	Class	When to consider
Clozapine	SGA	Two failed antipsychotic trials at adequate dose and duration. Unique efficacy in treatment resistance and unique suicide reduction. Requires ANC monitoring.
Haloperidol, fluphenazine, perphenazine	First-gen (FGA)	Effective, cheap, LAI depots available. EPS and TD risk. Perphenazine was CATIE-comparable to some SGAs.
Long-acting injectables	SGA or FGA	Aripiprazole (Maintena, Aristada, Asimtufii), paliperidone (Sustenna, Trinza, Hafyera), risperidone (Consta, Uzedy), olanzapine (Zyprexa Relprevv). Adherence-driven choice.
Lithium or valproate adjunct	Mood stabilizer	Aggression or mood symptoms alongside psychosis.
VMAT2 inhibitors (valbenazine, deutetrabenazine)	For tardive dyskinesia	Established TD. May allow continuation of the antipsychotic.

ECT	Neuromodulation	Refractory psychosis, especially with catatonia or affective features.

Special considerations

- Metabolic monitoring: weight and BP at each visit for 6 months then quarterly, waist circumference annually, fasting glucose or HbA1c at baseline, 3 months, then annually, fasting lipids at baseline, 3 months, then every 5 years or as needed. Olanzapine and clozapine need closer surveillance. Co-commencing metformin has a case in high-risk patients.
- EPS: parkinsonism and dystonia respond to benztropine, trihexyphenidyl, or amantadine. Akathisia responds to propranolol. Tardive dyskinesia is treated with valbenazine or deutetrabenazine.
- QTc: ziprasidone, iloperidone, and thioridazine prolong QT. Baseline ECG with cardiac history or other QT-prolonging drugs.
- Pregnancy: haloperidol, olanzapine, quetiapine, and risperidone have the most reproductive data. Untreated schizophrenia in pregnancy is a major risk, so continuation is often the right call.
- Older adults: mortality boxed warning in dementia. Doses in older adults with schizophrenia are usually lower.
- Cardiovascular disease: excess CV mortality is real in schizophrenia. Aggressive statin, BP, and smoking cessation (bupropion or varenicline) matter.

What tips the choice

First episode with no strong risk factors: aripiprazole, risperidone, or paliperidone are common starts, and the metabolically kinder options (lurasidone, aripiprazole, cariprazine, brexpiprazole, ziprasidone, lumateperone) are increasingly favored. Weight or metabolic risk already high: avoid olanzapine and quetiapine when possible. History of nonadherence: LAI. Comorbid mood symptoms: quetiapine, lurasidone, or cariprazine cover both. History of EPS: quetiapine or clozapine have the lowest. Prolactin concern: aripiprazole, brexpiprazole, cariprazine, quetiapine. Two failed trials at adequate dose and duration: clozapine. Comorbid substance use: clozapine has the best evidence for reducing substance use in schizophrenia.

Watchouts

- Clozapine: agranulocytosis, myocarditis (highest risk weeks 4 to 8), seizures, sialorrhea, and constipation with fatal ileus risk. Start a bowel regimen prophylactically.
- Tardive dyskinesia can appear after months to years of D2 blockade. Screen at each visit with AIMS.
- Dementia-related psychosis carries a class boxed warning for mortality with all antipsychotics.
- Anticholinergics for EPS can worsen cognition and precipitate delirium in older adults.
- Missing LAI appointments: call the clinic as soon as an appointment is missed. The window matters.
- Abrupt discontinuation is one of the most common causes of relapse and each relapse erodes long-term function.

Reviewed against current guidelines as of June 8, 2026. Educational reference, not medical advice.