SECOND-GENERATION ANTIPSYCHOTIC

Clozapine

Clozaril, Versacloz, FazaClo

The only agent proven in treatment-resistant schizophrenia and for reducing suicidality, and the most dangerous drug in psychiatry to dose casually.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
300-450 mg/day PO divided	12 h (range 4-66 h)	CYP1A2 > CYP3A4, CYP2D6	Weeks; 6-12 mo full trial

⚠ FDA BOXED WARNING

Severe neutropenia with risk of serious and fatal infection, requiring baseline and ongoing ANC monitoring; orthostatic hypotension, bradycardia, syncope, and cardiac arrest; seizures; myocarditis, pericarditis, and cardiomyopathy; and increased mortality in elderly patients with dementia-related psychosis.

INDICATIONS

- Treatment-resistant schizophrenia, defined as failure of two adequate trials of other antipsychotics, where clozapine is uniquely and substantially superior.
- Reduction of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder judged to be at chronic risk.
- Guidelines place it after two failed adequate antipsychotic trials, yet it is typically delayed by years, which costs response rates.
- Off-label uses include psychosis in Parkinson disease at low doses, tardive dyskinesia, and refractory aggression in schizophrenia.
- Also used off-label in treatment-resistant bipolar disorder, where evidence is weaker but clinically meaningful in refractory cases.

DOSING & TITRATION

- Start **12.5 mg once or twice daily**, then increase by 25-50 mg/day as tolerated to reach 300-450 mg/day in divided doses by the end of week 2.
- Subsequent increases should be no more than **100 mg** once or twice weekly, with a labeled maximum of **900 mg/day**.
- Most responders sit between **300 and 600 mg/day**, and a trough level of at least **350 ng/mL** should be documented before calling it a failure.
- If treatment is interrupted for 2 days or more, restart at **12.5 mg once or twice daily** and retitrate, because hypotension risk resets.
- Reduce the dose by roughly half in significant renal or hepatic impairment, and titrate more slowly in older adults.
- Taper over at least 1-2 weeks when stopping electively, since abrupt withdrawal causes cholinergic rebound and rapid psychotic relapse.

MECHANISM OF ACTION

- Low-affinity, rapidly dissociating **D2** antagonist with high **D4** and very high **5-HT2A** affinity, a profile no other agent reproduces.
- Weak striatal D2 occupancy explains why clozapine causes almost no extrapyramidal symptoms and can treat tardive dyskinesia.
- Potent muscarinic effects are mixed, with M1 antagonism causing dry mouth and constipation while M4 agonism drives paradoxical sialorrhea.
- Strong histamine H1 and alpha-1 blockade produce the sedation, weight gain, and orthostatic hypotension that dominate early treatment.
- The reason for its unique efficacy in resistant illness remains unexplained by receptor occupancy alone and is still an active question.

PHARMACOKINETICS

- Absorption is essentially complete and food independent, with bioavailability near 27 percent after substantial first-pass metabolism.
- Metabolized mainly by **CYP1A2**, with CYP3A4 and CYP2D6 secondary, to norclozapine, an active metabolite used in level interpretation.
- Mean half-life is about **12 hours** with wide interindividual variation, supporting divided or predominantly evening dosing.
- Cigarette smoke induces **CYP1A2** and lowers levels by 30-50 percent, so stopping smoking abruptly can push levels into toxicity.
- Women, nonsmokers, older adults, and patients with infection or inflammation all show higher levels at the same milligram dose.

ADVERSE EFFECTS

- Severe neutropenia occurs in about **1 percent** and is the reason for absolute neutrophil count monitoring throughout treatment.
- Constipation is near universal and can progress to ileus, bowel obstruction, and death; it is a more common cause of mortality than agranulocytosis.
- Sedation, sialorrhea, tachycardia, orthostatic hypotension, and weight gain of **4-10 kg** are expected rather than exceptional.
- Seizure risk is dose related, reaching about 5 percent above **600 mg/day**, and often prompts adding valproate for prophylaxis.
- Myocarditis typically presents in weeks 2 to 4 with fever, tachycardia, chest pain, or dyspnea, and cardiomyopathy can appear later.
- Metabolic burden is the highest in the class alongside olanzapine, with high rates of new diabetes and severe hypertriglyceridemia.

MONITORING

- Obtain a baseline ANC and do not start if it is below **1500/uL**, or below 1000/uL in benign ethnic neutropenia, also called Duffy-null neutrophil count.
- Monitor ANC **weekly for 6 months**, then every 2 weeks through month 12, then monthly, with more frequent testing after any interruption or fever.
- Interrupt for ANC 500-999/uL and discontinue permanently for ANC below **500/uL**, obtaining hematology consultation in both cases.
- Watch for myocarditis in the first 8 weeks with troponin, C-reactive protein, and clinical review; discontinue if troponin exceeds twice the upper limit.
- Ask about bowel movements at every visit and start a bowel regimen prophylactically, plus routine metabolic labs and periodic clozapine levels.

INTERACTIONS & CAUTIONS

- Starting or stopping cigarettes changes **CYP1A2** induction and can shift levels by 50 percent or more, a frequent cause of toxicity after admission.
- **Fluvoxamine** and ciprofloxacin are potent CYP1A2 inhibitors that can multiply clozapine levels severalfold and precipitate seizures or delirium.
- Avoid **carbamazepine** because of additive bone marrow suppression, and be cautious with other myelosuppressive agents.
- Benzodiazepines, especially given parenterally during titration, have been associated with respiratory arrest and profound hypotension.
- Anticholinergics and opioids compound constipation and are the usual co-factors in clozapine-associated ileus.

SPECIAL POPULATIONS

- The Clozapine REMS was eliminated by the FDA in 2025, but the labeled ANC monitoring schedule remains and should still be followed.
- In pregnancy clozapine is not withheld from a stabilized patient; monitor the neonate for neutropenia, sedation, and floppy infant syndrome.
- Clozapine concentrates in breast milk and infant agranulocytosis has been reported, so breastfeeding is generally discouraged.
- Not approved in pediatric patients, though it is used in refractory childhood-onset schizophrenia with more sedation and seizures.
- Older adults need lower doses and slower titration given orthostasis, anticholinergic load, and ileus risk.

☆ PRESCRIBING PEARLS

- Constipation kills more clozapine patients than agranulocytosis; prescribe a laxative on day one.
- Fever in weeks 2-4 means check troponin and CRP for myocarditis, not just an ANC.
- A level under 350 ng/mL means the trial was never adequate, whatever the milligram dose.

References

HLS Therapeutics (USA), Inc. (2025). *CLOZARIL (clozapine) tablets [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Backers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., & Leucht, S. (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. *The Lancet, 394*(10202), 939-951. https://doi.org/10.1016/S0140-6736(19)31135-3

National Institute for Health and Care Excellence. (2014). *Psychosis and schizophrenia in adults: Prevention and management* (Clinical guideline CG178). https://www.nice.org.uk/guidance/cg178

National Institute of Diabetes and Digestive and Kidney Diseases. (2023). Clozapine. In *LiverTox: Clinical and research information on drug-induced liver injury*. National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK548412/

Siskind, D., McCartney, L., Goldschlager, R., & Kisely, S. (2016). Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: Systematic review and meta-analysis. *The British Journal of Psychiatry, 209*(5), 385-392. https://doi.org/10.1192/bjp.bp.115.177261

Stahl, S. M. (2021). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (5th ed.). Cambridge University Press.

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.