



Clozaril (clozapine)

Generic name: Clozapine

Available strengths: 12.5 mg, 25 mg, 100 mg tablets

Available in generic: Yes

Drug class: Second-generation antipsychotic

General Information

Clozaril (clozapine) is a **serotonin and dopamine antagonist** belonging to the class of second-generation antipsychotics that are often called *atypical* antipsychotics. (Refer to the handout on “Second-Generation Antipsychotics” for an explanation of how these antipsychotics work.) These agents are atypical in that they are significantly different, both in structure and pharmacology, from the older, *typical* antipsychotics medications such as Thorazine (chlorpromazine), Mellaril (thioridazine), and Haldol (haloperidol). The second-generation antipsychotics block both serotonin and dopamine receptors, whereas the typical antipsychotics are mainly dopamine-receptor antagonists. Clozaril possesses unique pharmacological properties that confer other therapeutic benefits as well as side effects.

Clozaril has been in use in Europe for more than 30 years. In the mid-1970s, the medication was reported to cause **agranulocytosis**, a life-threatening condition in which white blood cells are fatally diminished. When deaths were reported from Clozaril-induced agranulocytosis, the medication was withdrawn from general use. Clozaril was not made available in the United States until the late 1980s, but the U.S. Food and Drug Administration (FDA) restricted its use, requiring close monitoring conditions and reserving the medication for treatment-resistant schizophrenia unresponsive to conventional antipsychotics. The FDA approved Clozaril for the treatment of schizophrenia. The use of a drug for its approved indications is called its *labeled* use. In clinical practice, however, physicians often prescribe drugs for *unlabeled* (“off-label”) uses when published clinical studies, case reports, or their own clinical experiences support the efficacy and safety of the medications for these uses. Unlabeled uses of Clozaril include treatment of other psychiatric disorders, such as bipolar disorder, schizoaffective disorder, and psychotic depression, when these disorders are refractory to other treatments.

Dosing Information

Use of Clozaril requires strict monitoring of the patient’s white blood cell count (WBC) to ensure that therapy is quickly interrupted when agranulocytosis is suspected. Three companies currently produce Clozaril. Each

manufacturer has a registry system in place, operating as the clearinghouse for their Clozaril patients. The patient's pharmacy is responsible for registering the patient and patient's physician with the manufacturer's registry. The pharmacy is also responsible for weekly reporting of the patient's WBC. A national databank maintains the history of patients whose Clozaril treatment was discontinued because of a low WBC or agranulocytosis. These patients are then precluded from taking Clozaril again, regardless of the company or system.

The recommended starting dosage for Clozaril is 25 mg at bedtime. The dosage is slowly increased over the first 2–3 weeks in increments of 25–50 mg every 4–5 days until a dosage of 200 mg/day is reached. If necessary, the dosage may be further increased to achieve a target dosage of 300–600 mg/day. At higher dosages, taking Clozaril on a twice-daily schedule may minimize some of the side effects. The median Clozaril dosage is approximately 600 mg/day, but some patients may require higher dosages. However, a maximum dosage of 900 mg/day should not be exceeded.

Common Side Effects

The more common and bothersome side effects of Clozaril are sedation; gastrointestinal distress such as nausea, cramping, heartburn, and diarrhea; flu-like symptoms; and excessive drooling, especially at night. Because Clozaril can inhibit **cholinergic neurons** in the nervous system, it frequently produces a cluster of side effects called **anticholinergic** side effects, which include blurred vision, dry mouth, constipation, and difficulty urinating. Seniors are particularly sensitive to anticholinergic side effects. Generally, as the patient develops greater tolerance the medication, these side effects subside.

The advantage of Clozaril is that it rarely causes **extrapyramidal symptoms** (EPS), which are common with conventional antipsychotics. EPS are neurological disturbances produced by antipsychotics (or other causes) in the area of the brain that controls motor coordination.

Most people taking Clozaril will gain weight. For some, it may be significant and problematic. It appears that stimulation of appetite and overeating are the major causes of Clozaril-related weight gain. Weight should be monitored closely during therapy, and if weight gain occurs, an intervention program of diet and exercise should be started.

Clozaril may alter glucose (sugar) metabolism and cause elevation of glucose levels (**hyperglycemia**). People with diabetes and individuals with a family history of diabetes should be aware of this side effect and monitor glucose levels periodically while taking Clozaril.

Clozaril may block a compensatory response—the narrowing of blood vessels—that counterbalances postural change, resulting in a momentary drop in blood pressure when the person rises too rapidly, which may cause dizziness and lightheadedness. This reaction is known as **orthostatic hypotension**. Patients, especially seniors and those taking antihypertensive medications, need to be cautious and rise slowly to allow their body to adjust to the change in position, avoiding a sudden drop in their blood pressure.

Adverse Reactions and Precautions

Clozaril may cause drowsiness and sedation and impair physical coordination and mental alertness. Patients should avoid potentially dangerous activities, such as driving a car or operating machinery, until they are sure that these side effects will not affect their ability to perform these tasks.

The major concern with Clozaril is the danger of developing agranulocytosis. This adverse reaction affects about 1.2% of all treated patients in the United States. It starts with a drop in the level of white blood cells, which then may fall precipitously such that the WBC is almost undetectable. When all white blood cells are diminished, a particular type of white blood cells called **granulocytes** is also decreased. Granulocytes play an important role in the body's defense against infections. When granulocytes are drastically

decreased (**agranulocytosis**), the body's immunity is compromised, and the person becomes susceptible to life-threatening infections.

There is no test to determine whether a person is susceptible to agranulocytosis from Clozaril. Therefore, Clozaril therapy requires weekly monitoring of the white blood cells. Therapy is quickly interrupted at the earliest sign of an adverse reaction. The monitoring system requires the patient to have weekly blood draws for a WBC, and the pharmacy may dispense only 1 week's supply at a time. If the individual is treated for 6 months without interruption in therapy, the person may start biweekly monitoring and receive a 2-week supply of medication each time.

The risk of Clozaril-induced seizures appears to be dosage-related, and at dosages greater 600 mg/day, seizures occur in about 15% of patients. The FDA has required the manufacturers of Clozaril to issue a "black-box" warning of seizures in their package insert. Patients with a history of seizure disorder may not be good candidates for Clozaril unless the seizures can be adequately controlled with anticonvulsant medications. Some physicians may add an anticonvulsant medication with Clozaril at dosages of more than 600 mg/day to prevent seizures.

Tardive dyskinesia (TD) is a potential adverse reaction from antipsychotic medications. It is a late-onset abnormal involuntary movement disorder. It is a potentially irreversible condition with symptoms that commonly include "pill-rolling" movements of the fingers, darting and writhing movements of the tongue, lip puckering, facial grimacing, and other irregular movements. Clozaril, however, is unlikely to cause TD. Moreover, patients with tardive TD may benefit from Clozaril, which may reverse the dyskinetic symptoms caused by conventional antipsychotics.

Neuroleptic malignant syndrome (NMS) is a rare, toxic reaction to antipsychotics, including Clozaril. The symptoms of NMS associated with Clozaril are generally milder than those associated with conventional antipsychotics. The symptoms may include increased heart rate and blood pressure, irregular pulse, and sweating. NMS may lead to delirium and coma. It can be fatal if medical intervention is not immediately provided. There are no tests to predict whether an individual may be susceptible to developing NMS when exposed to an antipsychotic. Thus NMS must be recognized early because it is a medical emergency that requires immediate discontinuation of the antipsychotic, hospitalization, and intensive medical treatment.

Use in Pregnancy and Breastfeeding: Pregnancy Category B

Clozaril has not been tested in women to determine its safety in pregnancy. The effects of the medication on the developing fetus in pregnant women are unknown. In animal studies, there was no evidence of harm to the fetus when exposed to Clozaril. Animal studies, however, are not always predictive of effects in humans. Women who are pregnant or may become pregnant should discuss this with their physician. Some women may experience a recurrence of their psychosis when they stop Clozaril. In these circumstances, the physician may discuss the need to restart the medication or seek an alternative medication or treatment.

Nursing mothers should not take Clozaril, because small amounts will pass into breast milk and be ingested by the baby. If stopping the antipsychotic is not an alternative, breastfeeding should not be started or should be discontinued.

Possible Drug Interactions

Some medications when taken with Clozaril may result in drug interactions that alter their levels, producing undesired reactions. The possible drug interactions with Clozaril are summarized in the table on the next page.

Patients taking Clozaril should not consume alcohol because the combination may increase sedation and impair thinking, judgment, and coordination.

Tegretol (carbamazepine)	Tegretol, as well as other medications that may reduce white blood cells, should not be combined with Clozaril, because the combination may increase the risk of agranulocytosis. Moreover, Tegretol may significantly decrease the levels of Clozaril, decreasing its therapeutic effectiveness.
Antihypertensive medications (e.g., Catapres)	Medications for lowering blood pressure may increase orthostatic hypotension and exaggerate its effects when combined with Clozaril.
Antihistamines, sedatives, and narcotic pain medication	When central nervous system depressants are combined with Clozaril, the sedative effects are additive and the sedation may be made worse, impairing the patient's ability to function.
Caffeine	Caffeine in coffee and cola beverages and in over-the-counter products may increase the blood levels of Clozaril, possibly increasing its adverse effects. Avoid caffeine if the interaction is suspected.
Selective serotonin reuptake inhibitors (SSRIs)	SSRIs such as Prozac, Celexa, Luvox, Zoloft, and Paxil may increase the blood levels of Clozaril, which may increase effects as well as toxicity. When an SSRI is started or discontinued, the Clozaril dosage may need to be adjusted accordingly.

Overdose

Toxic symptoms from Clozaril overdose include confusion, excessive drooling, low blood pressure, irregular heartbeat (arrhythmias), and seizures. The outcome also depends on the amount ingested and whether Clozaril was combined with any other medications. Clozaril has significant anticholinergic properties. Anticholinergic toxicity may include diarrhea, elevated temperature, dilated pupils, rapid heart rate, delirium, hallucinations, and respiratory failure.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency department for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought as well, because the information on the prescription label can be helpful to the treating physician in determining the number of pills ingested.

Special Considerations

- Do not discontinue your medication without consulting your physician. Stopping Clozaril abruptly may result in rapid return of symptoms.
- If you miss a dose, take it as soon as possible before your next scheduled dose. If it is close to the next scheduled dose, skip the missed dose and continue on your regular dosing schedule, but do not take double doses.
- Clozaril may be taken with or without food.
- Clozaril may cause sedation and drowsiness, especially during initiation of therapy, and impair your alertness. Use caution when driving or performing tasks that require alertness.

