clozapine (kloe-za-peen)

**Classification**

Therapeutic: antipsychotics

**Pregnancy Category:** B

**Indications**

Schizophrenia unresponsive to or intolerant of standard therapy with other antipsychotics (treatment refractory). To reduce recurrent suicidal behavior in schizophrenic patients.

**Action**

Binds to dopamine receptors in the CNS. Also has anticholinergic and alpha-adrenergic blocking activity. Produces fewer extrapyramidal reactions and less tardive dyskinesia than standard antipsychotics but carries high risk of hematologic abnormalities. Therapeutic Effects: Diminished schizophrenic behavior. Diminished suicidal behavior.

**Pharmacokinetics**

Absorption: Well absorbed after oral administration.

Distribution: Rapid and extensive distribution; crosses blood-brain barrier and placenta.

Protein Binding: 95%.

Metabolism and Excretion: Mostly metabolized on first pass through the liver (by CYP1A2, CYP2D6, and CYP3A4 isoenzymes). (The CYP2D6 enzyme system exhibits genetic polymorphism; 7% of population may be poor metabolizers and may have significantly lower clozapine concentrations and an increased risk of adverse effects).

Half-life: 8–12 hr.

**TIME/ACTION PROFILE (antipsychotic effect)**

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>ONSET</th>
<th>PEAK</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO</td>
<td>unknown</td>
<td>6 hr</td>
<td>4–12 hr</td>
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</table>

- **CNS:** Sedation, dizziness, sedation.
- **EENT:** Visual disturbances.
- **CV:** Cardiac arrhythmias, tachycardia, hypertension, syncope, QT interval prolongation, hypotension, tachycardia, bradycardia, ECG changes, hypotension, edema.
- **GI:** Constipation, abdominal discomfort, dry mouth, nausea, vomiting, weight gain.
- **GU:** Nocturnal enuresis.
- **Derm:** Rash, sweating.
- **Endo:** Hyperglycemia, hyperlipidemia, weight gain.
- **Hemat:** Agranulocytosis, leukopenia.
- **Neuro:** Extrapyramidal reactions.
- **Resp:** Pulmonary embolism.
- **Misc:** Fever.

**Contraindications/Precautions**

Contraindicated in: Hypersensitivity; Bone marrow depression; Severe CNS depression/coma; Uncontrolled epilepsy; Glaucoma; Uncontrolled hypertension or severe glucosuria; Glaucoma; Lifethreatening, underlines indicate most frequent. Strikethrough indicates discontinued.

**Use Cautiously in:** Long QT syndrome; Risk factors for QT interval prolongation or ventricular arrhythmias (i.e., recent myocardial infarction, heart failure, arrhythmia); Concurrent use of CYP1A2, CYP2D6, or CYP3A4 inhibitors or other interval prolonging drugs; Hypokalemia or hypomagnesemia; Prostate enlargement; Angina; diabetes mellitus; hyperglycemia; hepatic, renal dysfunction; or patients on antihypertensives (see dosage and administration section for renal dose adjustment). Risk factors for stroke (increased risk of stroke in patients with dementia); Diabetes; Seizure disorder; OB: Advise discontinuation in the first trimester; Pedi: Children >16 yr (safety not established); Geri: Increased risk of mortality in elderly patients treated for dementia-related psychosis.

**Adverse Reactions/Side Effects**

CNS: Neutropenia, leukopenia, agranulocytosis, sedation.

CV: Hypertension, hypotension, ventricular tachycardia, heart failure, arrhythmias, cardiac arrest, deep vein thrombosis, mycocarditis, torsades de pointes, ventricular arrhythmias, myocardiitis, syncope, ECG changes, hypotension, edema.

GI: Abdominal pain, dry mouth, nausea, vomiting, weight gain.

GU: Nocturnal enuresis.

Derm: Rash, sweating.

Endo: Hyperglycemia, hyperlipidemia, weight gain.

Hemat: Agranulocytosis, leukopenia.

Neuro: Extrapyramidal reactions, sedation.

Resp: Pulmonary embolism.

Misc: Fever.

**Drug Interactions**

**Drug-Drug:**

- **Anticholinergic effects with other agents having anticholinergic properties:** Including antihistamines, quinidine, disopyramide, and antidepressants. Concurrent use with strong CYP1A2 inhibitors, including fluvoxamine or ciprofloxacin may cause clozapine levels to increase significantly. Concurrent use with moderate or weak CYP1A2 inhibitors, including paroxetine or citalopram, may result in decreased clozapine levels. Concurrent use with CYP2D6 inhibitors or CYP3A4 inhibitors, including clomipramine, citalopram, paroxetine, imipramine, fluoxetine, quinidine, disopyramide, tolterodine, or sertraline may increase clozapine levels.

**Contraindications/Precautions:**

Contraindicates: Hypersensitivity; Bone marrow depression; Severe CNS depression/coma; Uncontrolled epilepsy; Glaucoma; Uncontrolled hypertension or severe glucosuria; Glaucoma; Lifethreatening, underlines indicate most frequent. Strikethrough indicates discontinued.
Monitor patient for onset of akathisia (restlessness or desire to keep moving) and:

- Observe patient carefully when administering medication to ensure that medication is actually taken and not hoarded or cheeked.

Assessment

- Monitor patient’s mental status (orientation, mood, behavior) before and periodically during therapy. Entire sleep and monitor closely; may cause orthostatic hypotension, bradycardia, syncope, and cardiac arrest.

- Observe patient carefully when administering medication to ensure that medication is actually taken and not hoarded or cheeked.

- Monitor for signs of myocarditis (unexplained fatigue, dyspnea, tachycardia, fever, chest pain, palpitations, other signs and symptoms of heart failure, ECG changes, such as U-T wave abnormalities, atrial fibrillation, or tachycardia during first month of therapy). If these occur, clonazepam should be discontinued and not restarted.

- Monitor for onset of akathisia (restlessness or desire to keep moving) and extrapyramidal side effects (parkinsonism — difficulty speaking or swallowing, loss of balance control, pill-rolling motion of hands, slow, clumsy, shuffling gait, rigidity, tremors and dystonic muscle spasms, twisting motions, trismus, inability to move eyes, weakness of arms or legs) every 2 mo during therapy and for 6–12 mo after therapy has been discontinued. North health care professional if these symptoms occur; reduction in dose or discontinuation of medication may be necessary.

- Tolerophylactic or benzodiazepine may be used to control these symptoms.

- Monitor for possible tardive dyskinesia (uncontrolled rhythmic movement of mouth, face, and extremities, lip-smacking or puckering, pulling of cheek, uncontrolled chewing, rapid or worm-like movements of tongue). Report these symptoms immediately; may be irreversible.

- Monitor frequency and consistency of bowel movements. Increasing bulk and fluids in the diet may help to minimize constipation.

- Clonazepam lowers the seizure threshold. Institute seizure precautions for patients with history of seizure disorders.

- Treat seizure with 0.5 mg p.o. (adults) or twice weekly (not to exceed 900 mg/day). Treatment should be continued for at least 2 yr in patients with suicidal behavior.

- PO (Adults): Initial dose: 0.5 mg 1–2 times daily initially; titrate by 25–50 mg/day over a period of 1 wk to target dose of 300–450 mg/day; may then be up to 100 mg/day once or twice weekly (not to exceed 900 mg/day). Treatment should be continued for at least 2 yr in patients with suicidal behavior.

NURSING IMPLICATIONS

- Assess weight and BMI initially and throughout therapy. Refer as appropriate for nutritional/weight management and medical management.

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**cloZAPine**

- pancytopenia (WBC 2000/mm³ to 3000/mm³ and/or ANC 1000/mm³ to 1500/mm³), interrupt therapy. Monitor daily until WBC > 3500/mm³ and ANC > 2000/mm³, may rechallenge at this level. If rechallenged, monitor weekly for 1 year before returning to usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks. Because of the risk of agranulocytosis, clozapine is available only through the Clozaril National Registry, Fazaclo Patient Registry or Versacloz Patient Registry, which combines WBC testing, patient monitoring, and controlled distribution through participating pharmacies.

- Assess fasting blood glucose and cholesterol levels initially and throughout therapy.

- **Toxicity and Overdose:** Overdose is treated with activated charcoal and supportive therapy. Monitor patient for several days because of risk of delayed effects.

- Avoid use of epinephrine and its derivatives when treating hypotension, and avoid quinidine and procainamide when treating arrhythmias.

**Potential Nursing Diagnoses**

- Risk for other-directed violence (Indications)
- Disturbed thought process (Indications)
- Risk for injury (Side Effects)

**Implementation**

- Do not confuse clozapine with clonazepam or clonidine. Do not confuse Clozaril with Colazal.

- **PO:** Administer capsules with food or milk to decrease gastric irritation.

- Leave oral disintegrating tablet in blister until time of use. Do not push tablet through foil. Just before use, peel foil and gently remove disintegrating tablet. Immediately place tablet in mouth and allow to disintegrate and swallow with saliva. If 1/2 tablet dose used, dispose of other half of tablet.

- Oral solution may be taken without regard to food. Shake bottle for suspension for 10 seconds prior to withdrawals. Use oral syringes and oral adaptor provided for accurate dosing. Do not store dose in syringe; wash between doses.

**Patient/Family Teaching**

- Instruct patient to take medication as directed. Patients on long-term therapy may need to discontinue gradually over 1–2 wk.

- Explain purpose and procedures for Clozaril National Registry, Fazaclo Patient Registry, Versacloz Patient Registry to patient.

- Inform patient of possibility of extrapyramidal symptoms. Instruct patient to report these symptoms immediately.

- Inform patient that cigarette smoking can decrease clozapine levels. Risk for tolerance increases if patient begins or increases smoking.

- Instruct patient to change position slowly to minimize orthostatic hypotension.

- Instruct patient to avoid driving or other activities requiring alertness while taking clozapine.

- Instruct patient to notify health care professional of all Rx or OTC medications, vitamins, or herbal products being taken and to consult health care professional before taking any other Rx, OTC, or herbal products. Caution patient to avoid concurrent use of alcohol and other CNS depressants.

- Instruct patient to use frequent mouth rinses, good oral hygiene, and sugarless gum or candy to minimize dry mouth.

- Advise patient to notify health care professional of medication regimen before treatment or surgery.

- Instruct patient to notify health care professional promptly if unexplained fatigue, dyspnea, tachypnea, chest pain, palpitations, sore throat, fever, lethargy, weakness, malaise, or flu-like symptoms occur.

- Advise female patients to notify health care professional of pregnancy if planned or suspected, or breast feeding or planning to breast feed.

- Advise patient of need for continued medical follow-up for psychotherapy, eye exams, and laboratory tests.

**Evaluation/Desired Outcomes**

- Decreased positive symptoms (delusions, hallucinations) of schizophrenia.

- Decrease in negative symptoms (social withdrawal, flat, blunt affect) of schizophrenia.

Why was this drug prescribed for your patient?