CLOZAPINE

THERAPEUTICS

Brands
- Clozaril
- Leponex
- Versacloz (oral suspension)
- Fazaclo ODT (oral disintegrating tablet)

see index for additional brand names

Generic? Yes

Class
- Neuroscience-based Nomenclature: dopamine, serotonin, norepinephrine receptor antagonist (DSN-RAn)
- Atypical antipsychotic (serotonin-dopamine antagonist; second-generation antipsychotic; also a mood stabilizer)

Commonly Prescribed for (bold for FDA approved)
- Treatment-resistant schizophrenia
- Reduction in risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder
- Treatment-resistant bipolar disorder
- Violent aggressive patients with psychosis and other brain disorders not responsive to other treatments

How the Drug Works
- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms
- Interactions at a myriad of other neurotransmitter receptors may contribute to clozapine’s efficacy
- Specifically, interactions at 5HT2C and 5HT1A receptors may contribute to efficacy for cognitive and affective symptoms in some patients
- Mechanism of efficacy for psychotic patients who do not respond to conventional antipsychotics is unknown

How Long Until It Works
- Likelihood of response depends on achieving trough plasma levels of at least 350 ng/mL

- Median time to response after achieving therapeutic plasma levels (350 ng/mL) is approximately 3 weeks
- If there is no response after 3 weeks of therapeutic plasma levels, recheck plasma levels and continue titration

If It Works
- In strictly defined refractory schizophrenia, 50–60% of patients will respond to clozapine
- The response rate to other atypical antipsychotic in the refractory patient population ranges from 0–9%
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Many patients with bipolar disorder and other disorders with psychotic, aggressive, violent, impulsive, and other types of behavioral disturbances may respond to clozapine when other agents have failed
- Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships; super-responders are anecdotally reported more often with clozapine than with some other antipsychotics
- Treatment may not only reduce mania but also prevent recurrences of mania in bipolar disorder

If It Doesn’t Work
- Obtain clozapine plasma levels and continue titration
- Levels greater than 700 ng/mL are often not well tolerated
- No evidence to support dosing that results in plasma levels greater than 1,000 ng/mL
- Some patients may respond better if switched to a conventional antipsychotic
- Some patients may require augmentation with a conventional antipsychotic or with an atypical antipsychotic (especially risperidone or amisulpride), but these are
the most refractory of all psychotic patients and such treatment can be expensive

✿ Consider augmentation with valproate or lamotrigine

• Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection

• Consider initiating rehabilitation and psychotherapy such as cognitive remediation

• Consider presence of concomitant drug abuse

Best Augmenting Combos for Partial Response or Treatment Resistance

• Valproic acid (valproate, divalproex, divalproex ER)

• Lamotrigine

• Conventional antipsychotics

• Benzodiazepines

• Lithium

Tests

• Lower ANC threshold for starting clozapine:
  - General population: ≥1,500/μL
  - Benign ethnic neutropenia (BEN): ≥1,000/μL

• Testing for myocarditis:
  - Myocarditis is rare and only occurs in the first 6 weeks of treatment
  - Baseline: check troponin I/T, C-reactive protein (CRP)
  - Weekly troponin I/T and CRP for the first month
  - Fever is usually benign and self-limited; suspicion of myocarditis should only be raised based on elevated troponin and other features of myocarditis
  - Clozapine should be stopped if troponin ≥ 2x upper limits of normal or CRP >100 mg/L
  - Cardiomyopathy is a late complication; consider annual ECG

Before starting an atypical antipsychotic

✿ Weigh all patients and track BMI during treatment

• Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease

✿ Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile

• Determine if the patient is
  - overweight (BMI 25.0–29.9)
  - obese (BMI ≥30)
  - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
  - has diabetes (fasting plasma glucose >126 mg/dL)
  - has hypertension (BP >140/90 mm Hg)
  - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)

• Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic

✿ BMI monthly for 3 months, then quarterly

✿ Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics

✿ Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% of initial weight

• Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic

✿ Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness and clouding of sensorium, even coma

• Liver function testing, ECG, general physical exam, and assessment of baseline cardiac status before starting treatment

• Liver tests may be necessary during treatment in patients who develop nausea, vomiting, or anorexia
### SIDE EFFECTS

#### How Drug Causes Side Effects
- **By blocking alpha 1 adrenergic receptors,** it can cause orthostatic hypotension, tachycardia, dizziness, and sedation
- **By blocking muscarinic 1 receptors,** it can cause sialorrhea, constipation, sometimes with paralytic ileus, and sedation
- **By blocking histamine 1 receptors in the brain,** it can cause sedation and possibly weight gain
- **Mechanism of weight gain and increased risk of diabetes and dyslipidemia with atypical antipsychotics** is unknown but insulin regulation may be impaired by blocking pancreatic M3 muscarinic receptors
- **By blocking dopamine 2 receptors in the striatum,** it can cause motor side effects (very rare)

#### Notable Side Effects
- Orthostasis
- Sialorrhea
- Constipation
- Sedation
- Tachycardia
- Weight gain
- Dyslipidemia and hyperglycemia
- Benign fever (~20%)
- Rare tardive dyskinesia (no reports have directly implicated clozapine in the development of tardive dyskinesia)

#### Life-Threatening or Dangerous Side Effects
- Severe neutropenia
- Myocarditis (only in first 6 weeks of treatment)
- Paralytic ileus
- Seizures (risk increases with dose)
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Pulmonary embolism (may include deep vein thrombosis or respiratory symptoms)
- Dilated cardiomyopathy
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Neuroleptic malignant syndrome (more likely when clozapine is used with another agent)

#### Weight Gain
- **Frequent and can be significant in amount**
- **May increase risk for aspiration events**
- **Should be managed aggressively**
- **More than for some other antipsychotics,** but never say always as not a problem in everyone

#### Sedation
- **Frequent and can be significant in amount**
- **Some patients may not tolerate it**
- **More than for some other antipsychotics,** but never say always as not a problem in everyone
- **Can wear off over time**
- **Can reemerge as dose increases and then wear off again over time**

#### What To Do About Side Effects
- **Slow titration to minimize orthostasis and sedation**
  - Minimize use of other alpha 1 antagonists
  - If orthostasis remains a problem, Florines 0.1–0.3 mg qd for volume expansion (contraindicated in congestive heart failure)
  - Take at bedtime to help reduce daytime sedation
- **Sialorrhea management**
  - Atropine 1% drops, 1–3 drops sublingually at bedtime; can use up to 3 times per day if needed
  - Ipratropium bromide 0.06% spray, 1–3 sprays intra-orally at bedtime; can use up to 3 times per day if needed
  - Avoid use of systemic anticholinergic agents, which increase risk of ileus (benztropine, glycopyrrolate, etc.)
- **Constipation management**
  - Avoid psyllium as it may worsen symptoms
  - All patients should receive docusate 250 mg when starting clozapine
  - If needed, add Miralax 17 g
  - If docusate + Miralax are ineffective, add either bisacodyl or sennosides
  - If constipation still remains a problem, prescribe lubiprostone 8–24 mcg twice per day
Weight gain and metabolic effects
Consider prophylactic metformin; start at 500 mg for 1 week, then increase dose
All patients should be referred for lifestyle management and exercise
Tachycardia
Atenolol 12.5 mg qd, increase to keep resting HR <100 bpm
Chest pain during the first 6 weeks
Obtain workup for myocarditis
Fever
In the absence of elevated troponin and myocarditis symptoms, fever is usually self-limited and there is no need to stop clozapine
Seizures
Valproate for myoclonic or generalized seizures
Avoid phenytoin and carbamazepine because of kinetic interactions

Best Augmenting Agents for Side Effects
Many side effects cannot be improved with an augmenting agent

Orally disintegrating tablet 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg
Oral suspension 50 mg/mL

How to Dose
Initial 25 mg at night; increase by 25–50 mg/day every 48–72 hours as tolerated
Obtain trough plasma level on 200 mg at bedtime
Threshold for response is 350 ng/mL
Levels greater than 700 ng/mL are often not well tolerated
No evidence to support dosing that results in plasma levels greater than 1,000 ng/mL
Doses greater than 500 mg per day may require a split dose
See also The Art of Switching, after Pearls

Dosing Tips
Because of the monitoring schedule, prescriptions are generally given 1 week at a time for the first 6 months, then every 2 weeks for months 6–12, and then monthly after 12 months
Plasma half-life suggests twice daily administration, but in practice it may be given once a day at night
Prior to initiating treatment with clozapine, a baseline ANC must be at least 1500/μL for the general population and at least 1000/μL for patients with documented benign ethnic neutropenia (BEN)
### Recommended ANC Monitoring for the General Population

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Recommendation</th>
<th>ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range (at least 1,500 μL)</td>
<td>Initiate treatment If treatment is interrupted for &lt;30 days, continue monitoring as before If treatment is interrupted for 30 days or more, monitor as if new patient</td>
<td>First 6 months: weekly Second 6 months: every 2 weeks After 1 year: every month</td>
</tr>
<tr>
<td>Mild neutropenia (1,000–1,499 μL)</td>
<td>Continue treatment</td>
<td>Confirm all initial reports of ANC &lt;1,500/μL with a repeat ANC measurement within 24 hours Monitor 3 times/week until ANC ≥1,500/μL Once ANC ≥1,500/μL, return to patient’s last “normal range” ANC monitoring interval</td>
</tr>
<tr>
<td>Moderate neutropenia (500–999 μL)</td>
<td>Interrupt treatment for suspected clozapine-induced neutropenia Recommend hematology consultation</td>
<td>Confirm all initial reports of ANC &lt;1,500/μL with a repeat ANC measurement within 24 hours Monitor ANC daily until ≥1,000/μL THEN Monitor 3 times/week until ANC ≥1,500/μL Once ANC ≥1,500/μL, check ANC weekly for 4 weeks, then return to patient’s last “normal range” ANC monitoring interval</td>
</tr>
<tr>
<td>Severe neutropenia (&lt;500 μL)</td>
<td>Interrupt treatment for suspected clozapine-induced neutropenia Recommend hematology consultation Do not rechallenge unless prescriber determines benefits outweigh risks</td>
<td>Confirm all initial reports of ANC &lt;1,500/μL with a repeat ANC measurement within 24 hours Monitor ANC daily until ≥1,000/μL THEN Monitor 3 times/week until ANC ≥1,500/μL If patient is rechallenged, resume treatment as a new patient under “normal range” monitoring once ANC ≥1,500/μL</td>
</tr>
</tbody>
</table>

### Recommended ANC Monitoring for BEN Patients

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Recommendation</th>
<th>ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BEN range (established ANC Baseline ≥1,000 μL)</td>
<td>Obtain at least 2 baseline ANC levels before initiating treatment If treatment is interrupted for &lt;30 days, continue monitoring as before If treatment is interrupted for 30 days or more, monitor as if new patient</td>
<td>First 6 months: weekly Second 6 months: every 2 weeks After 1 year: every month</td>
</tr>
<tr>
<td>BEN neutropenia (500–999 μL)</td>
<td>Continue treatment Recommend hematology consultation</td>
<td>Confirm all initial reports of ANC &lt;1,500/μL with a repeat ANC measurement within 24 hours Monitor 3 times/week until ANC ≥1,000/μL or ≥patient’s known baseline Once ANC ≥1,000/μL or above patient’s known baseline, check ANC weekly for 4 weeks, then return to patient’s last “normal BEN range” ANC monitoring interval</td>
</tr>
<tr>
<td>BEN severe neutropenia (&lt;500 μL)</td>
<td>Interrupt treatment for suspected clozapine-induced neutropenia Recommend hematology consultation Do not rechallenge unless prescriber determines benefits outweigh risks</td>
<td>Confirm all initial reports of ANC &lt;1,500/μL with a repeat ANC measurement within 24 hours Monitor ANC daily until ≥500/μL THEN Monitor 3 times/week until ANC ≥patient’s baseline If patient is rechallenged, resume treatment as a new patient under “normal BEN range” monitoring once ANC ≥1,000/μL or at patient’s known baseline</td>
</tr>
</tbody>
</table>
• If treatment is discontinued for more than 2 days, reinitiate with 12.5 mg once or twice daily; if that dose is tolerated, the dose may be increased to the previously therapeutic dose more quickly than recommended for initial treatment
• If abrupt discontinuation of clozapine is necessary, the patient must be covered for cholinergic rebound; those with higher clozapine plasma levels may need extremely high doses of anticholinergic medications to prevent delirium and other rebound symptoms
• Slow off-titration is preferred if possible to avoid cholinergic rebound and rebound psychosis

**Overdose**
• Sometimes lethal; changes in heart rhythm, excess salivation, respiratory depression, altered state of consciousness

**Long-Term Use**
• Treatment to reduce risk of suicidal behavior should be continued for at least 2 years
• Medication of choice for treatment-refractory schizophrenia

**Habit Forming**
• No

**How to Stop**
• See The Art of Switching section of individual agents for how to stop clozapine, generally over at least 4 weeks
• See Tables for guidance on stopping due to neutropenia
• Rapid discontinuation may lead to rebound psychosis and worsening of symptoms

**Pharmacokinetics**
• Half-life 5–16 hours
• Metabolized primarily by CYP450 1A2 and to a lesser extent by CYP450 2D6 and 3A4

**Drug Interactions**
• Use clozapine plasma levels to guide treatment due to propensity for drug interactions
• In presence of a strong CYP450 1A2 inhibitor (e.g., fluvoxamine, ciprofloxacin): use 1/3 the dose of clozapine

• In the presence of a strong CYP450 1A2 inducer (e.g., cigarette smoke), clozapine plasma levels are decreased
• May need to decrease clozapine dose by up to 50% during periods of extended smoking cessation (>1 week)
• Strong CYP450 2D6 inhibitors (e.g., buproprion, duloxetine, paroxetine, fluoxetine) can raise clozapine levels; dose adjustment may be necessary
• Strong CYP450 3A4 inhibitors (e.g., ketoconazole) can raise clozapine levels; dose adjustment may be necessary
• Clozapine may enhance effects of antihypertensive drugs

**Other Warnings/Precautions**
• Use with caution in patients on other anticholinergic agents (benztropine, trihexyphenidyl, olanzapine, quetiapine, chlorpromazine, oxybutynin, and other antimuscarinics)
• Should not be used in conjunction with agents that are known to cause neutropenia
• Myocarditis is rare and only occurs in the first 6 weeks of treatment
• Cardiomyopathy is a late complication (consider annual ECG)
• Use with caution in patients with glaucoma
• Use with caution in patients with enlarged prostate

**Do Not Use**
• In patients with myeloproliferative disorder
• In patients with uncontrolled epilepsy
• In patients with paralytic ileus
• In patients with CNS depression
• If there is a proven allergy to clozapine

**SPECIAL POPULATIONS**

**Renal Impairment**
• Should be used with caution

**Hepatic Impairment**
• Should be used with caution

**Cardiac Impairment**
• Should be used with caution, particularly if patient is taking concomitant antihypertensive or alpha 1 antagonist
**Elderly**
- Some patients may tolerate lower doses better
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

**Children and Adolescents**
- Safety and efficacy have not been established
- Preliminary research has suggested efficacy in early-onset treatment-resistant schizophrenia
- Children and adolescents taking clozapine should be monitored more often than adults

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Animal studies have not shown adverse effects
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary

**Breast Feeding**
- Unknown if clozapine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
  - Recommended either to discontinue drug or bottle feed
  - Infants of women who choose to breast feed while on clozapine should be monitored for possible adverse effects

**Potential Advantages**
- Treatment-resistant schizophrenia
- Violent, aggressive patients
- Patients with tardive dyskinesia
- Patients with suicidal behavior

**Potential Disadvantages**
- Patients with diabetes, obesity, and/or dyslipidemia
- Sialorrhea, sedation, and orthostatis may be intolerable for some

**Primary Target Symptoms**
- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive symptoms
- Affective symptoms
- Suicidal behavior
- Violence and aggression

**Pearls**
- Clozapine is the gold standard treatment for refractory schizophrenia
- Clozapine is not used first line due to side effects and monitoring burden
- However, some studies have shown that clozapine was associated with the lowest risk of mortality among the antipsychotics, causing the study authors to question if its use should continue to be restricted to resistant cases
<table>
<thead>
<tr>
<th>CLOZAPINE (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May reduce violence and aggression in difficult cases, including forensic cases ✴ Reduces suicide in schizophrenia</td>
</tr>
<tr>
<td>• May reduce substance abuse</td>
</tr>
<tr>
<td>• May improve tardive dyskinesia</td>
</tr>
<tr>
<td>• Little or no prolactin elevation, motor side effects, or tardive dyskinesia</td>
</tr>
<tr>
<td>• Clinical improvements often continue slowly over several years</td>
</tr>
<tr>
<td>• Cigarette smoke can decrease clozapine levels and patients may be at risk for relapse if they begin or increase smoking</td>
</tr>
<tr>
<td>• More weight gain than many other antipsychotics – does not mean every patient gains weight</td>
</tr>
<tr>
<td>• Patients can have much better responses to clozapine than to any other agent, but not always</td>
</tr>
<tr>
<td>• For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring</td>
</tr>
<tr>
<td>• In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic</td>
</tr>
<tr>
<td>• To treat constipation and reduce risk of paralytic ileus and bowel obstruction, taper off other anticholinergic agents and start all patients routinely on docusate</td>
</tr>
<tr>
<td>• The US FDA has changed the requirements for monitoring, prescribing, dispensing, and receiving clozapine in order to address concerns related to neutropenia; in addition to updating the prescribing information for clozapine, the FDA has approved a new, shared risk evaluation and mitigation strategy (REMS)</td>
</tr>
<tr>
<td>• The Clozapine REMS program replaces the six existing clozapine registries, which are maintained by individual clozapine manufacturers. Prescribers, pharmacies, and patients will now be required to enroll in a single centralized program; patients already treated with clozapine will be automatically transferred. In order to prescribe and dispense clozapine, prescribers and pharmacies will be required to be certified in the Clozapine REMS Program. Visit the Clozapine REMS Program homepage for more information.</td>
</tr>
</tbody>
</table>
Switching from Oral Antipsychotics to Clozapine

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin clozapine at middle dose
- With risperidone, ziprasidone, iloperidone, and lurasidone, begin clozapine gradually, titrating over at least 2 weeks to allow patients to become tolerant to the sedating effect

* Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis. However, use with caution in combination with clozapine as this can increase the risk of circulatory collapse.

**Suggested Reading**


