What is clozapine and what does it treat?

Clozapine is a medication that works in the brain to treat schizophrenia. It is also known as a second generation antipsychotic (SGA) or atypical antipsychotic. Clozapine rebalances dopamine and serotonin to improve thinking, mood, and behavior.

Symptoms of schizophrenia include:

- Hallucinations – imagined voices or images that seem real
- Delusions - beliefs that are not true (e.g., other people are reading your thoughts)
- Disorganized thinking or trouble organizing your thoughts and making sense
- Little desire to be around other people
- Trouble speaking clearly
- Lack of motivation

Clozapine may help some or all of these symptoms.

Clozapine is also FDA approved to lower the risk of recurrent suicidal behavior in people with schizophrenia or schizoaffective disorder.

Clozapine may also be helpful when prescribed “off-label” for patients with Parkinson’s disease who have psychosis symptoms. Psychosis symptoms may include hallucinations and delusions. “Off-label” means that it hasn’t been approved by the Food and Drug Administration for this condition. Your mental health provider should justify his or her thinking in recommending an “off-label” treatment. They should be clear about the limits of the research around that medication and if there are any other options.

Clozaril®
- Tablets: 25 mg, 50 mg, 100 mg, 200 mg

FazaClo®
- Orally disintegrating tablets: 12.5 mg, 25 mg, 100 mg, 150 mg, 200 mg

If you or someone you know is in crisis, please call 911 and/or the toll-free National Suicide Prevention Lifeline at 800-273-TALK (8255) to speak with a trained crisis counselor 24/7. A help line and other resources are also available through the National Alliance on Mental Illness at nami.org.
What is the most important information I should know about clozapine?

Schizophrenia requires long-term treatment. Do not stop taking clozapine, even when you feel better.

Only your healthcare provider can determine the length of clozapine treatment that is right for you.

Missing doses of clozapine may increase your risk for a relapse in your symptoms.

Do not stop taking clozapine or change your dose without talking to with your healthcare provider first.

For clozapine to work properly, it should be taken every day as ordered by your healthcare provider.

Are there specific concerns about clozapine and pregnancy?

If you are planning on becoming pregnant, notify your healthcare provider to best manage your medications. People living with schizophrenia who wish to become pregnant face important decisions. This is a complex decision since untreated schizophrenia has risks to the fetus, as well as the mother. It is important to discuss the risks and benefits of treatment with your doctor and caregivers.

Caution is advised with breastfeeding since clozapine does pass into breast milk.

What should I discuss with my healthcare provider before taking clozapine?

- Symptoms of your condition that bother you the most
- If you have thoughts of suicide or harming yourself
- Medications you have taken in the past for your condition, whether they were effective or caused any adverse effects
- If you ever had muscle stiffness, shaking, tardive dyskinesia, neuroleptic malignant syndrome, or weight gain caused by a medication
- If you experience side effects from your medications, discuss them with your provider. Some side effects may pass with time, but others may require changes in the medication.
- Any psychiatric or medical problems you have, such as heart rhythm problems, long QT syndrome, heart attacks, diabetes, high cholesterol, or seizures
- If you have a family history of diabetes or heart disease
- All other medications you are currently taking (including over the counter products, herbal and nutritional supplements) and any medication allergies you have
- Other non-medication treatment you are receiving, such as talk therapy or substance abuse treatment. Your provider can explain how these different treatments work with the medication.
- If you are pregnant, plan to become pregnant, or are breast-feeding
- If you smoke, drink alcohol, or use illegal drugs

How should I take clozapine?

Clozapine is usually taken 1 or 2 times per day with or without food.

Typically patients begin at a low dose of medicine and the dose is increased slowly over several weeks.

The dose usually ranges from 25 mg to 700 mg. Only your healthcare provider can determine the correct dose for you.

Clozapine orally disintegrating tablets must remain in their original packaging. Open the package with clean dry hands before each dose. Do not try to put tablets in a pillbox if you take the orally disintegrating tablets.

Clozapine orally disintegrating tablets will dissolve in your mouth within seconds and can be swallowed with or without liquid.

Use a calendar, pillbox, alarm clock, or cell phone alert to help you remember to take your medication. You may also ask a family member a friend to remind you or check in with you to be sure you are taking your medication.

What happens if I miss a dose of clozapine?

If you miss a dose of clozapine, take it as soon as you remember, unless it is closer to the time of your next dose. Discuss this with your healthcare provider. Do not double your next dose or take more than what is prescribed. If you miss more than 2 days of medication, contact your prescriber because he/she may need to adjust your dose.
What should I avoid while taking clozapine?
Avoid drinking alcohol or using illegal drugs while you are taking clozapine. They may decrease the benefits (e.g. worsen your confusion) and increase adverse effects (e.g. sedation) of the medication.

What happens if I overdose with clozapine?
If an overdose occurs call your doctor or 911. You may need urgent medical care. You may also contact the poison control center at 1-800-222-1222.

A specific treatment to reverse the effects of clozapine does not exist.

What are the possible side effects of clozapine?

**Common side effects**
Increased heart rate, low blood pressure, constipation, increased salivation
Feeling drowsy or dizzy

**Rare/serious side effects**
Decreased white blood cells, inflammation of heart muscle, seizures, severely low blood pressure, urinary incontinence

Some people may develop muscle related side effects while taking clozapine. The technical terms for these are “extrapyramidal effects” (EPS) and “tardive dyskinesia” (TD). Symptoms of EPS include restlessness, tremor, and stiffness. TD symptoms include slow or jerky movements that one cannot control, often starting in the mouth with tongue rolling or chewing movements.

Second generation antipsychotics (SGAs) increase the risk of weight gain, high blood sugar, and high cholesterol. This is also known as metabolic syndrome. Your healthcare provider may ask you for a blood sample to check your cholesterol, blood sugar, and hemoglobin A1c (a measure of blood sugar over time) while you take this medication.

- Information on healthy eating and adding exercise to decrease your chances of developing metabolic syndrome may be found at the following sites:
  - http://www.helpguide.org/articles/healthy-eating/healthy-eating.htm

SGAs have been linked with higher risk of death, strokes, and transient ischemic attacks (TIAs) in elderly people with behavior problems due to dementia.

All antipsychotics have been associated with the risk of sudden cardiac death due to an arrhythmia (irregular heart beat). To minimize this risk, antipsychotic medications should be used in the smallest effective dose when the benefits outweigh the risks. Your doctor may order an EKG to monitor for irregular heartbeat.

Neuroleptic malignant syndrome is a rare, life threatening adverse effect of antipsychotics which occurs in <1% of patients. Symptoms include confusion, fever, extreme muscle stiffness, and sweating. If any of these symptoms occur, contact your healthcare provider immediately.

All antipsychotics can cause sedation, dizziness, or orthostatic hypotension (a drop in blood pressure when standing up from sitting or lying down). These side effects may lead to falls which could cause bone fractures or other injuries. This risk is higher for people with conditions or other medications that could worsen these effects. If falls or any of these symptoms occur, contact your healthcare provider.

Severe and life-threatening hepatotoxicity (liver damage) has been reported in patients taking clozapine. Symptoms of hepatotoxicity could include fatigue, weakness, loss of appetite, nausea, jaundice (yellowing of the skin), and confusion. If these symptoms occur, contact your healthcare provider immediately.
Are there any risks for taking clozapine for long periods of time?

Tardive dyskinesia (TD) is a side effect that develops with prolonged use of antipsychotics. Medications such as clozapine have been shown to have a lower risk of TD compared to older antipsychotics, such as Haldol® (haloperidol). If you develop symptoms of TD, such as grimacing, sucking, and smacking of lips, or other movements that you cannot control, contact your healthcare provider immediately. All patients taking either first or second generation antipsychotics should have an Abnormal Involuntary Movement Scale (AIMS) completed regularly by their healthcare provider to monitor for TD.

Second generation antipsychotics (SGAs) increase the risk of diabetes, weight gain, high cholesterol, and high triglycerides. (See “Serious Side Effects” section for monitoring recommendations.)

What other medications may interact with clozapine?

Clozapine may lower your blood pressure. Medications used to lower blood pressure may increase this effect and increase your risk of falling. Propranolol (Inderal®) is an example of this type of medication.

The following medications may increase the risk of heart problems when used with clozapine:

- Antipsychotics, such as chlorpromazine (Thorazine®), thioridizine (Mellaril®), iloperidone (Fanapt®), asenapine (Saphris®) paliperidone (Invega®), quetiapine (Seroquel®), ziprasidone (Geodon®)
- Antiarrhythmics (heart rhythm medications), such as procainamide, quinidine, amiodarone (Cordarone®), dronedarone (Multaq®), sotalol (Betapace®)

The following medications may increase the levels and effects of clozapine: ciprofloxacin (Cipro®), fluvoxamine (Luvox®) and lamotrigine (Lamictal®)

The following medications may decrease the levels and effects of clozapine: carbamazepine (Tegretol®), phenytoin (Dilantin®), phenobarbital, and rifampin (Rifadin®)

Cigarette smoke can decrease levels of clozapine by as much as 50%. Let your healthcare provider know if you start or stop smoking cigarettes. Nicotine patches do not impact clozapine levels.

How long does it take for clozapine to work?

It is very important to tell your doctor how you feel things are going during the first few weeks after you start taking clozapine. It will probably take several weeks to see big enough changes in your symptoms to decide if clozapine is the right medication for you.

Antipsychotic treatment is generally needed lifelong for persons with schizophrenia. Your doctor can best discuss the duration of treatment you need based on your symptoms and illness.

- Hallucinations, disorganized thinking, and delusions may improve in the first 1-2 weeks
- Sometimes these symptoms do not completely go away
- Motivation and desire to be around other people can take at least 1-2 weeks to improve
- Symptoms continue to get better the longer you take clozapine
- It may take 2-3 months before you get the full benefit of clozapine
Summary of Black Box Warnings

Agranulocytosis

Less than 1% of patients taking clozapine may develop a condition called agranulocytosis. Agranulocytosis causes the body to make fewer white blood cells. A decrease in white blood cells increases the risk of infection. If this occurs, it is reversible by stopping clozapine.

The clozapine Risk Evaluation and Mitigation Strategy (REMS) program has been recently updated. Your doctor will inform you whether these changes will affect your scheduled blood work. Blood counts are checked every week for the first 6 months and every two weeks for the next 6 months. After the first year of treatment, blood counts are checked monthly. The pharmacy must have a copy of your blood counts to be able to dispense the medication. Further information may be found here.

Myocarditis, Cardiomyopathy, and Mitral Valve Incompetence

Myocarditis (inflammation of heart muscle) and cardiomyopathy (enlarged heart) have rarely been reported. This condition could be fatal. Symptoms of these heart problems include shortness of breath, racing heart, flu-like symptoms, or chest pain. Contact your healthcare provider right away if these symptoms occur.

Seizures

Dose-dependent seizures have been associated with clozapine (i.e. more likely with high doses or rapid dose increases). Clozapine should be used with caution in patients with a history of seizures, head injury or alcohol dependence.

Orthostatic hypotension

Clozapine may cause a significant drop in blood pressure when changing position from sitting to standing. Notify your prescriber if you feel lightheaded when standing up.

Increased Mortality in Elderly Patients with Dementia Related Psychosis

- Both first generation (typical) and second generation (atypical) antipsychotics are associated with an increased risk of mortality in elderly patients when used for dementia related psychosis.
- Although there were multiple causes of death in studies, most deaths appeared to be due to cardiovascular causes (e.g. sudden cardiac death) or infection (e.g. pneumonia).
- Antipsychotics are not indicated for the treatment of dementia-related psychosis.

Important Disclosure: This information is being provided as a community outreach effort of the College of Psychiatric and Neurologic Pharmacists. This information is for educational and informational purposes only and is not medical advice. This information contains a summary of important points and is not an exhaustive review of information about the medication. Always seek the advice of a physician or other qualified medical professional with any questions you may have regarding medications or medical conditions. Never delay seeking professional medical advice or disregard medical professional advice as a result of any information provided herein. The College of Psychiatric and Neurologic Pharmacists disclaims any and all liability alleged as a result of the information provided herein.