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Wolters Kluwer

Schizophrenia in adults: Guidelines for prescribing clozapine

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INTRODUCTION

[Clozapine](#) has been found to be an effective treatment in persons with schizophrenia resistant to treatment with other antipsychotic drugs. In addition, clozapine is an effective treatment for schizophrenia accompanied by persistent suicidal or self-injurious behavior. (See "[Schizophrenia in adults: Maintenance therapy and side effect management](#)".)

[Clozapine's](#) unique side effect profile, which includes a low rate of life-threatening agranulocytosis, gives rise to numerous considerations in prescribing, monitoring, and side effect management in the use of the drug.

This topic describes [clozapine's](#) indications/contraindications, pharmacology, adverse effects, and administration in schizophrenia or schizoaffective disorder. The efficacy of clozapine in schizophrenia is discussed separately. Clozapine is compared with other antipsychotic drugs separately. (See "[Evaluation and management of treatment-resistant schizophrenia](#)", section on '[Clozapine](#)' and "[Second-generation antipsychotic medications: Pharmacology, administration, and side effects](#)".)

INDICATIONS

Primary indications for [clozapine](#) in patients with schizophrenia or schizoaffective disorder are schizophrenia symptoms partially or fully resistant to treatment with other antipsychotic drugs, or accompanied by persistent suicidal or self-injurious behavior. Other clinical indications in schizophrenia patients include sensitivity to extrapyramidal symptoms and patients with tardive dyskinesia. (See "[Evaluation and management of treatment-resistant schizophrenia](#)", section on '[Clozapine](#)'.)

CONTRAINDICATIONS AND PRECAUTIONS

Neutropenia — Potentially life-threatening agranulocytosis led to restrictions on [clozapine](#)'s use in many countries, but neutrophil monitoring has allowed for safer use of the medication. The US Food and Drug Administration requires patients in the United States to have a minimum absolute neutrophil count (ANC) greater than or equal to 1500/microL to initiate clozapine [1]. An exception is made for patients with Duffy-null associated neutrophil count (DANC) who are subject to a lower ANC level. (See '[Duffy-null associated neutrophil count \(DANC\)](#)' below.)

A history of clozapine-induced severe neutropenia or agranulocytosis (ANC below 500/microL) is a relative contraindication for restarting [clozapine](#). Because the adverse effects and benefits of the drug vary widely among patients, the risks, benefits, and alternatives need to be weighed for each patient, and clozapine can be restarted if the harm from not using clozapine greatly outweighs the potential risks. Clozapine should be used with extreme caution when restarted. Many patients will quickly develop agranulocytosis again, but they cannot be identified in advance through testing. In a study of 53 patients who had experienced leukopenia or neutropenia from clozapine, 20 patients developed another blood dyscrasia that was more severe and occurred more rapidly upon rechallenge [2].

Continuing [clozapine](#), as opposed to initiating, is subject to further restrictions in the United States based on ANC monitoring, described below. (See '[Monitoring](#)' below.)

Duffy-null associated neutrophil count (DANC) — Lower neutrophil thresholds were established for starting and treating [clozapine](#) in patients with confirmed DANC, a cause of neutropenia not associated with recurrent or severe infection that is most often seen in individuals of African descent and Sephardic Jews [3]. Treatment can be instituted and continued in patients with an ANC of at least 1000/microL. Collaboration with hematology is recommended to manage moderate or severe neutropenia in this patient group. (See "[Approach to the adult with unexplained neutropenia](#)", section on '[Normal variants <1500/microL](#)'.)

Cardiac disease — In patients with risk factors for cardiovascular disease, a more complete baseline cardiovascular evaluation (including baseline echocardiogram) may be useful. The prevalence of asymptomatic left ventricular dysfunction is approximately 3 to 5 percent in adults 50 to 70 years old, and is higher among men, older patients, and patients with coronary disease.

Patients with a history of clozapine-induced myocarditis should only be rechallenged if the harm from not using [clozapine](#) greatly outweighs the potential risks. Individuals with preexisting heart disease are at greater risk of morbidity from clozapine-induced myocarditis or the effects of orthostatic hypotension; they have less cardiac reserve should any, even temporary, cardiac damage and malfunction occur during the initiation of clozapine. When a rechallenge is considered after an episode of myocarditis due to clozapine or clozapine is used in individuals with preexisting heart disease, clozapine should be initiated in the inpatient setting with close monitoring of cardiac function. (See '[Cardiovascular](#)' below and '[Myocarditis/cardiomyopathy](#)' below.)

Seizures — [Clozapine](#) is relatively contraindicated in patients with a history of seizure, to be used only if the harm from not using clozapine greatly outweighs the potential risks. Individuals with a seizure disorder should have their seizures optimally controlled before clozapine is started. Patients with an elevated seizure risk, including those with an alcohol use disorder or a history of febrile seizures or epilepsy, should be considered for prophylactic treatment with an anticonvulsant medication when clozapine is initiated. They should be observed carefully as clozapine is initiated, using a conservative titration schedule and therapeutic drug monitoring to avoid excessive clozapine blood levels. A follow-up electroencephalogram may be indicated after clozapine treatment is established, and adjustment of anticonvulsant treatment may be necessary. (See "[Overview of the management of epilepsy in adults](#)".)

Other conditions — The metabolic effects of [clozapine](#) should be taken into account when weighing the risks and benefits from clozapine. Individuals with obesity, diabetes mellitus, dyslipidemias, or atherosclerotic cardiovascular disease may have worsening of these conditions when treated with clozapine, and more aggressive treatment of these disorders will be required.

PHARMACOLOGY

The pharmacologic mechanisms underlying [clozapine](#)'s superiority for treatment-resistant schizophrenia are not known.

Pharmacodynamics — [Clozapine](#) binds loosely and transiently to dopamine D2 receptors. Clozapine does not induce catalepsy or inhibit apomorphine-induced stereotypy in animal models as is seen with conventional antipsychotic medications; this may explain its reduced potential for producing movement abnormalities relative to tightly binding dopamine D2 antagonists such as [haloperidol](#). Clozapine also binds to D1, D3, and D5 receptors, and has a high affinity for the D4 receptor, but the implications of these binding activities are unclear.

[Clozapine](#) also interacts at histamine H1, acetylcholine muscarinic M1 and serotonin 5-HT2A, 5-HT2C, 5-HT6, and 5-HT7 receptors, and at alpha-1-adrenoceptors. Postural dizziness, sedation, and increased appetite may reflect actions of clozapine at alpha-1, H1, and 5-HT2c receptors, respectively. Actions at the 5-HT2A and M1 receptors may reduce movement side effects [4].

Pharmacokinetics — [Clozapine](#) is well absorbed. First-pass metabolism reduces its bioavailability to 60 to 70 percent of the administered dose; food has little effect on the bioavailability of clozapine. The elimination half-life of clozapine averages approximately 14 hours under steady state conditions, but there is substantial variability across individuals [5].

[Clozapine](#) is extensively metabolized by the cytochrome P450 system in the liver, and excreted in both the urine and feces. Cytochrome P450 1A2 is primarily responsible for clozapine metabolism; cytochromes 2C19, 2C9, 2D6, and 3A4 play less important roles. Agents that induce cytochrome CYP1A2, such as tobacco cigarette smoke, will increase the metabolism of clozapine. Tobacco smokers may require twice the dose of nonsmokers to achieve similar blood levels. Strong inducers of CYP3A4 (eg, [phenobarbital](#), [carbamazepine](#)) will also reduce serum concentrations of clozapine; additive bone marrow toxicity with carbamazepine has been described [6-10]. Agents that inhibit CYP1A2 (eg, [ciprofloxacin](#), [fluvoxamine](#)) will decrease the metabolism of clozapine and may produce clinical toxicity at usual doses [11]. Cytochrome-related problems can be avoided by monitoring clozapine plasma levels while gradually increasing clozapine from a low starting dose. (See '[Dose titration and plasma levels](#)' below.)

In addition, patients prescribed [clozapine](#) should have their medication regimen analyzed for drug interactions when initiating and adjusting therapy; this may be done by use of the [Lexicomp drug interactions](#) program.

The major metabolite of [clozapine](#), norclozapine (desmethylclozapine), has failed to demonstrate any therapeutic activity in clinical trials. Clozapine and norclozapine plasma levels are both reported by clinical labs, but only the clozapine level is useful for dose optimization [12].

ADMINISTRATION

Pretreatment assessment — Assessment prior to treatment with [clozapine](#) should include evaluation of the patient's general and cardiovascular health status. Other components of an evaluation include documentation and testing of:

- Complete blood count that includes an absolute neutrophil count (ANC). The minimum ANC required to initiate [clozapine](#) is described above [3]. (See '[Neutropenia](#)' above.)
- Weight and height (body mass index), waist circumference, fasting blood sugar (or HbA1c), and fasting lipids. (See '[Weight gain](#)' below and '[Insulin resistance and diabetes mellitus](#)' below.)
- Drug levels for patients on anticonvulsant medications (need to be in the therapeutic range). (See '[Seizures](#)' below.)
- Vital signs.
- Electrocardiogram.
- An Abnormal Involuntary Movement Scale documenting absence or presence of abnormal motor movements ([form 1](#)).
- Pregnancy test in women of childbearing age.

In addition, consider obtaining measures of inflammation (eg, C-reactive protein) and cardiac muscle damage (eg, troponin levels). (See '[Cardiovascular](#)' below.)

Dose titration and plasma levels

- **Starting dose and titration** – For patients initially starting [clozapine](#) in nonurgent situations, we prefer a slow titration. As an example, we suggest 12.5 to 25 mg once daily at bedtime for three to four days, then 25 to 50 mg once daily at bedtime for three to four days. We then increase further by 25 mg twice weekly. An initial test dose of 12.5 mg is recommended to confirm tolerability in patients who have never received clozapine.

In urgent situations (active aggression/violence or self-injury/suicide) we double the titration rate above. For example, we suggest 50 mg once daily for three or four days, then 100 mg once daily for three to four days followed by increases of 50 mg twice weekly. Sleepiness is the primary clinical ceiling side effect, so as [clozapine](#) dose is increasing, we

simultaneously taper off other sedating agents. We monitor for seizure risk by asking patients or their families to report myoclonic jerking movements.

We adjust dosing for individuals of Asian descent as they require less [clozapine](#) to reach therapeutic blood levels.

- **Initial target dose** – The initial target dose for healthy, young adults is 300 mg/day. Older adult patients and patients with cardiac disease may need a lower target dose and a slower titration, particularly if they experience sedation or orthostatic hypotension to avoid falls or worsening cardiac function.
- **Target plasma levels** – Plasma levels can be checked after the initial target dose is reached or earlier (eg, after reaching 100 mg). A [clozapine](#) plasma level in the range of 250 to 350 ng/mL is a reasonable target for a patient with schizophrenia. However, patients show great variation in both their symptomatic response and side effects and the target plasma level should be individualized based on these outcomes [13]. Once the therapeutic plasma level is reached, the patient's clinical response should be monitored for two weeks before considering any further dose increase. For those who have refractory symptoms, it is reasonable to target levels higher than 350 ng/mL, despite there being limited evidence to suggest greater efficacy. In our experience, some patients can benefit from higher levels, and this approach is consistent with recommendations from the Treatment Resistance in Psychosis Working Group [14]. Side effects such as sleepiness and electroencephalogram slowing increase as clozapine blood levels increase [15].

Plasma levels should be checked in the morning, ideally 8 to 10 hours following the previous evening dose. Given the pharmacokinetics of [clozapine](#), differences of a few hours in the time of evening dosing or morning plasma sampling will lead to large differences in reported plasma levels.

Maintenance dosing — A maintenance dose of 300 to 600 mg/day is usually required for efficacy. The average final daily dose in patients with treatment-resistant psychosis is approximately 400 mg daily. Doses higher than 900 mg/day are not recommended.

Due to great interindividual variability in [clozapine](#) metabolism, in rare instances, levels can reach toxic range with lower doses (eg, 100 mg/day) or fail to achieve therapeutic levels at higher doses (eg, 600 to 900 mg/day). Checking plasma levels is thus important during the titration phase; however, once a target dose is achieved, ongoing plasma level monitoring is not routinely necessary. Regular therapeutic drug monitoring can help detect unsuspected adherence problems early enough to take counter measures. (See '[Dose titration and plasma levels](#)' above.)

Once the patient is stabilized on an effective maintenance dose, all or most of the daily dose may be given at bedtime. This will aid patients in getting to sleep and avoiding daytime sedation. Adherence can be improved by taking the medication at the time of routine, consistent behaviors, such as breakfast or bedtime preparations, and by prescribing once or twice daily rather than more frequently. However, some patients require split doses to avoid bed wetting or morning grogginess.

Re-initiation after interruption — If [clozapine](#) treatment is interrupted for two or more days, we start clozapine at 12.5 mg once or twice daily in order to assess tolerability and decrease the risk of severe cardiovascular effects including orthostatic hypotension, syncope, and cardiac arrest [16]. If well tolerated, however, the previous dose can be achieved more quickly compared with patients who are initially started on clozapine.

MONITORING

Neutrophil count — For all patients taking [clozapine](#) in the United States, the US Food and Drug Administration (FDA) requires regular monitoring and registry reporting of neutrophil counts [1]. This process has been successful in allowing safe use of clozapine while avoiding deaths due to clozapine-induced agranulocytosis [17]. Revisions to United States regulations in 2015 lowered certain absolute neutrophil count (ANC) thresholds, expanding the number of patients eligible to receive the medication, and permitted clinicians to override ANC-based treatment recommendations to continue or restart clozapine in patients for whom the benefits of clozapine clearly exceed the risk of agranulocytosis [1]. Six separate registries administered by clozapine manufacturers were replaced with a single registry (the Clozapine Risk Evaluation and Mitigation Strategy [REMS] Program, available at their [website](#)).

As part of REMS, clinicians need to be registered and demonstrate that they are competent to prescribe [clozapine](#) (ie, review clozapine-related materials from the Clozapine REMS Program website and pass a knowledge test). Pharmacies also need to be certified if they dispense clozapine. In order to receive clozapine, a patient must be entered into this registry and undergo regular monitoring of ANC that continues as long as a patient receives clozapine (“No blood, no drug”). Routine neutrophil monitoring is performed at the following intervals:

- Weekly during the first six months of [clozapine](#) administration
- Every other week for the second six months
- Every four weeks after one year, for the duration of treatment

If neutropenia develops during treatment, [clozapine](#) would either need to be monitored more frequently, stopped temporarily, or discontinued, based on the severity of neutropenia [1]:

- Mild neutropenia (ANC: 1000 to 1499/microL) – Continue treatment but increase monitoring frequency to three times per week.
- Moderate neutropenia (ANC: 500 to 999/microL) – Interrupt [clozapine](#) treatment, increase monitoring to daily until ANC is 1000/microL at which point clozapine can be reinstituted.
- Severe neutropenia/agranulocytosis (ANC: <500/microL) – Discontinue [clozapine](#).
Rechallenge should only occur if the benefits outweigh the risks, in consultation with hematology.

ANC-based guidelines for continuing [clozapine](#) differ in patients with Duffy-null associated neutrophil count (DANC) in the United States. (See '[Duffy-null associated neutrophil count \(DANC\)](#)' above.)

Hospice patients receiving [clozapine](#) only require ANC monitoring at six-month intervals.

All initial reports of an ANC under 1500/microL should be confirmed with a repeat ANC within 24 hours.

Clinicians can override the registry rules for treatment interruption due to neutropenia and continue [clozapine](#) treatment despite moderate or severe neutropenia if continuing clozapine is clinically justified (ie, the psychiatric benefit outweighs the medical risk). Clinicians can similarly decide to rechallenge a patient who developed severe neutropenia. (See '[Contraindications and precautions](#)' above.)

If agranulocytosis occurs, [filgrastim](#) hastens the return to ANC counts [18,19], although it is not clear this alters infection rates or mortality.

Required bloodwork and COVID-19 — Monitoring ANC is required for prescribing and dispensing [clozapine](#). However, the coronavirus 2019 (COVID-19) public health emergency has necessitated social isolation and staying at home, which poses problems for patients treated with this medication. Patients and clinicians need to decide whether the risks of infection outweigh the benefits of obtaining blood work according to the monitoring schedule mandated by the FDA.

On March 22, 2020, the FDA offered guidance regarding the COVID-19 public health emergency and access to medications that are subject to REMS-required testing [20]. The guidelines allow patients to receive [clozapine](#) in the absence of laboratory testing of ANC if there are compelling

reasons not to complete the testing. Based upon the existing evidence with respect to clozapine and neutropenia, the FDA guidance, and an expert consensus statement [21], we suggest the following approach to using clozapine and monitoring ANC:

- For patients treated with [clozapine](#), one may reasonably decide that obtaining mandated clozapine blood work (ANC monitoring) during the COVID-19 pandemic is impossible or entails unacceptably high risks for patients or others. As an example, patients may be in isolation or in quarantine, or at high risk for mortality if they get infected with COVID-19 while traveling to a clinic or laboratory for blood work.
- One factor that determines whether it is acceptable to waive ANC testing is duration of [clozapine](#) treatment. As an example, it is reasonable to temporarily forego testing in patients who have received the drug for at least one year and have never had an ANC <2000/microL (or <1500/microL if there is a history of DANC). The rationale is that the risk of severe neutropenia after 12 months of clozapine treatment is very low. In a meta-analysis of seven studies that included more than 31,000 patients who were treated with clozapine and followed for up to two years, the cumulative incidence of severe neutropenia after 12 months of treatment declined to an almost negligible level of 0.3 to 0.4 cases per 100 person-years of exposure [22]. The peak incidence of severe neutropenia occurred at one month of exposure.
- Clinicians should decide whether to continue [clozapine](#) treatment in the absence of scheduled ANC monitoring in collaboration with patients and family members (or legal guardian), explaining the risks and benefits of proceeding without ANC monitoring and the rationale for this approach.
- For patients without a current ANC, [clozapine](#) prescriptions should specify the appropriate number of pills. For many patients on long-term clozapine treatment, this may simply be an additional 30-day supply of clozapine, if an ANC can be obtained the next month. However, a 60- or 90-day supply may be prudent if patients remain at high risk due to the pandemic. For patients newly started on clozapine, we suggest dispensing only a one- or two-week supply during the first six months of treatment, in conjunction with weekly ANC monitoring.
- Patients who develop flu-like symptoms such as fever, cough, and sore throat during a period without ANC monitoring should obtain an ANC and an urgent assessment for clozapine-associated neutropenia, either in-person or by telehealth, depending upon local protocols. Symptoms should not simply be attributed to possible COVID-19.

- Patients with flu-like symptoms may develop [clozapine](#) toxicity (eg, sedation, myoclonus, or seizures) that requires reducing the dose by up to one-half. The reason is that some acute systemic infections are associated with increased serum clozapine concentrations. In addition, patients with respiratory illnesses may cease smoking, which is also associated with increased serum concentrations.

The reduced dose should continue until the fever has abated for three days, after which the dose is then increased stepwise back to the dose used prior to onset of flu-like symptoms. Serum [clozapine](#) concentrations can help with the dose adjustments.

Cardiovascular

Myocarditis — In rare cases, clozapine-induced myocarditis can progress rapidly into cardiomyopathy and congestive heart failure. (See '[Myocarditis/cardiomyopathy](#)' below.)

All patients should be monitored closely for at least the initial four weeks of treatment. This should include assessment of symptoms concerning for myocarditis (eg, malaise, chest pain, shortness of breath), vital signs each visit, electrocardiogram (ECG) at baseline, and then weekly laboratory tests including:

- Sedimentation rate or C-reactive protein
- Troponins

A significant increase in C-reactive protein (over 100 mg/L) and troponin elevation (greater than twice the upper limit of normal) have been reported to be 100 percent sensitive in detecting clozapine-induced myocarditis in symptomatic patients [23]. The eosinophil count often rises as well but less reliably and delayed.

In patients with suspected myocarditis or cardiomyopathy, echocardiography is a key imaging test to assess ventricular function and valve function. (See "[Clinical manifestations and diagnosis of myocarditis in adults](#)" and "[Determining the etiology and severity of heart failure or cardiomyopathy](#)".)

QTc prolongation — Due to its propensity to cause a dose-dependent QTc prolongation, we try to obtain an ECG prior to starting [clozapine](#) for all patients, regardless of cardiovascular risk. A repeat ECG may be desirable once steady state is obtained.

The formula that most ECG machines use to calculate the corrected QT interval (Bazett formula) may overestimate it in patients with tachycardia. We typically seek consultation with a cardiologist in patients who develop tachycardia and a QTc >500 msec while on [clozapine](#). Some of these patients may have a lower QTc and be able to safely continue the medication.

Metabolic — In order to detect treatment-emergent hyperglycemia and prevent diabetic ketoacidosis, fasting plasma glucose monitoring should be considered monthly at the beginning of treatment. Obtaining fasting glucose, however, can be difficult in outpatient settings; rising triglycerides may be a better indicator of developing insulin resistance. (See ['Insulin resistance and diabetes mellitus'](#) below.)

Gastrointestinal — Gastrointestinal hypomotility, which can result in an adynamic ileus, requires close clinical attention [24]. In patients who cannot reliably identify bowel problems, a preventive laxative (stool softener) is often prescribed when starting [clozapine](#). (See ['Gastrointestinal hypomotility'](#) below.)

ADVERSE EFFECTS

Neutropenia/agranulocytosis — Clozapine-induced agranulocytosis was estimated to occur at a rate of approximately 0.8 percent in a study of 12,760 patients receiving the medication; leukopenia occurred in almost 3 percent of cases [25]. The peak risks for both occurred early in treatment, between 6 to 18 weeks from initiation. Advancing age was a risk factor for agranulocytosis in this cohort. Regular blood monitoring over a five-year period has been estimated to reduce the risk of agranulocytosis from approximately 1 to 2 percent to 0.38 percent [26]. Neutrophil-monitoring during [clozapine](#) treatment is discussed above. (See ['Monitoring'](#) above.)

Myocarditis/cardiomyopathy — Studies have estimated the risk of clozapine-induced myocarditis to be 1 in 500 to 1 in 10,000 [27]. The true risk is likely closer to the 1 in 500 rate, as often only a minority of adverse medication-related events are diagnosed and reported. Early myocarditis is more common than later development of cardiomyopathy; cardiomyopathy may be accompanied by mitral regurgitation [28].

Most cases of myocarditis occur early in the course of [clozapine](#) treatment. The condition was detected within 16 days (median) of initiating clozapine in a study of 116 cases [27]. Approximately 80 percent of cases of clozapine-induced myocarditis occur within four weeks of drug initiation, and 90 percent occur within eight weeks.

Postmortem examination has most commonly revealed damaged myocytes and eosinophilic infiltration suggesting a type I Ig E-mediated acute hypersensitivity reaction. The time of onset of clozapine-induced myocarditis and the pathological findings support this hypothesis. Other contributing mechanisms may include cytokine release and high levels of catecholamines.

A typical pattern of nonspecific clinical symptoms (fever, tachycardia) and laboratory findings (elevated eosinophil count, sedimentation rate or c-reactive protein, troponins, creatine phospho-kinase, and brain natriuretic peptide), combined with a high index of suspicion for myocarditis (nonspecific symptoms, including malaise, as well as more alarming symptoms like chest pain or shortness of breath) in a patient started on [clozapine](#) within the past four to eight weeks is needed to diagnose myocarditis in a clozapine patient. Some patients will have a mild and temporary increases in inflammatory markers and eosinophils at the beginning of treatment without progression to myocarditis.

In patients with suspected myocarditis or cardiomyopathy, echocardiography is a key imaging test to assess ventricular function and valve function. (See "[Clinical manifestations and diagnosis of myocarditis in adults](#)" and "[Determining the etiology and severity of heart failure or cardiomyopathy](#)".)

A diagnosis of myocarditis should be followed by prompt discontinuation of [clozapine](#) and medical follow-up with the patient's primary care clinician for supportive treatment. This course will usually lead to spontaneous resolution. Subsequent use of clozapine in cases with clear clozapine-induced myocarditis leads to recurrence of myocarditis in most cases when the drug is restarted.

Use of [clozapine](#) in patients with preexisting heart disease and monitoring of patients at the initiation of clozapine treatment are discussed above. (See '[Cardiac disease](#)' above and '[Cardiovascular](#)' above.)

QTc interval prolongation — [Clozapine](#) causes dose-dependent prolongation of the QT interval on electrocardiogram (ECG) similar in magnitude to [olanzapine](#) and [quetiapine](#) [29-32]. QT prolongation increases the risk of torsade de pointes and potentially lethal arrhythmias. Clozapine should be avoided in patients with congenital long QT syndrome; labeling cautions against use in persistent corrected QT interval (QTc) >500 ms on ECG [33]. Higher risk clinical scenarios such as patients with known heart disease, treatment-emergent increase of QTc interval >60 ms from baseline, or co-administration of high-risk medications, may warrant cardiology consultation ([table 1](#)). (See '[QTc prolongation](#)' above and "[Acquired long QT syndrome: Definitions, pathophysiology, and causes](#)", section on '[Risk factors for drug-induced long QT syndrome](#)'.)

Pulmonary embolism — [Clozapine](#) has been associated with an increased risk of venous thromboembolic events including pulmonary embolism leading to death [34-40]. Of the published cases with a known outcome, the mortality rate of a clotting complication while on clozapine was 44 percent [41].

Risk factors for thromboembolic disease in the general population include:

- Genetic factors (mainly the factor V Leiden mutation or a high concentration of factor VIII)
- Recent immobilization
- Recent surgery
- Pregnancy or the postpartum state
- Obesity

Clinicians starting patients on [clozapine](#) should advise recipients to remain physically active.

Although prophylactic use to prevent clozapine-associated venous thrombosis of [aspirin](#) and statins has not been studied in patients receiving [clozapine](#), aspirin has been shown to reduce the risk of venous thromboembolism in patients undergoing orthopedic surgery [42], and statins have been shown to reduce venous thromboembolism among individuals receiving chemotherapy for cancer [43]. The routine use of these agents among individuals without contraindications may reduce risk of venous thromboembolism. (See "[Statins: Actions, side effects, and administration](#)" and "[Aspirin in the primary prevention of cardiovascular disease and cancer](#)".)

Weight gain — [Clozapine](#) can cause significant weight gain [44-48]. The average weight gain in a 10-year cohort study of clozapine was 30 pounds [44]. While most weight gain occurs during the first 6 to 12 months, some patients continue to gain weight without reaching a plateau [46]. Weight should be routinely monitored and behavioral interventions recommended if patients gain weight on clozapine. [Metformin](#) has been used to blunt antipsychotic-induced weight gain and improve insulin sensitivity [49]. The benefits of added metformin, however, are lost when it is discontinued [50]. (See "[Schizophrenia in adults: Maintenance therapy and side effect management](#)", section on 'Metabolic dysregulation' and "[Schizophrenia in adults: Maintenance therapy and side effect management](#)", section on 'Endocrinologic and metabolic side effects'.)

Insulin resistance and diabetes mellitus — Of 96 patients with chronic schizophrenia treated with [clozapine](#) and followed for up to 10 years, 34 percent developed diabetes mellitus [44]. The progressive increases in obesity, diabetes, elevated triglycerides, and hypertension in their population resulted in substantially increased cardiovascular risk. The insulin resistance from clozapine treatment is at least in part independent from clozapine-induced weight gain [51]. Screening for diabetes at six-month intervals or more frequently (ie, fasting blood sugar or HbA1c) should be done. (See "[Screening for type 2 diabetes mellitus](#)".)

Seizures — [Clozapine](#) is associated with a dose-dependent seizure risk at a rate higher than that seen with most other antipsychotic drugs [52,53]. In a review of 1418 patients treated with

clozapine, the cumulative seizure risk was estimated to be 10 percent after 3.8 years of treatment [54]. Higher doses of clozapine were associated with a greater rate of seizures:

- 600 mg/day or more – 4.4 percent
- 300 to 600 mg/day – 2.7 percent
- 300 mg/day or less – 1.0 percent

In a review of 101 patients experiencing a seizure while receiving [clozapine](#), the most frequently described type of seizure was tonic-clonic; myoclonic/atonic seizures comprise approximately one-quarter of reported seizures [55]. The mean clozapine dose in the cohort was less than 600 mg per day. (See '[Seizures](#)' above.)

Excessive salivation — Clozapine-induced hypersalivation is a common side effect that can be treatment-limiting as patients are unable to tolerate incessant drooling that is stigmatizing during the day and hinders sleeping at night. It often occurs at low doses [56] and can worsen during sleep. Its mechanism is thought to be due to a disturbance of deglutition and not merely an increase in salivary flow rate [57]. Hypersalivation may be a risk factor for aspiration pneumonia, which has been observed in clozapine-treated patients [58].

A reduction in [clozapine](#) dose can be tried to limit salivation, but this step alone is often inadequate. Among treatment options, [glycopyrrolate](#) at a dose of 2 to 4 mg given at night is a good initial choice. A randomized trial compared glycopyrrolate with biperiden [59]. While both were associated with a reduced rate of drooling, a larger decrease was seen in the group taking glycopyrrolate. Glycopyrrolate does not penetrate the blood-brain barrier, thus avoiding central anticholinergic effects such as impairment of memory. However, it adds to clozapine's already significant intrinsic peripheral anticholinergic burden. (See '[Gastrointestinal hypomotility](#)' below.)

Other treatment approaches, based on case reports or case series, include the use of sugarless chewing gum to increase the rate of swallowing, anticholinergic agents (eg, 5 to 15 mg/day of [trihexyphenidyl](#)), topical agents (eg, sublingual [atropine](#) or [ipratropium](#) spray) or alpha-2 agonists (eg, [clonidine](#)). In refractory cases, botulinum toxin injections into the salivary glands can be effective if this treatment can be arranged.

Urinary incontinence — Treatment with [clozapine](#) appears to be associated with an increased incidence of urinary incontinence. The potent anti-alpha-adrenergic effects of clozapine, which relax the bladder-neck sphincter, are hypothesized to contribute to the incontinence. An open trial of 16 patients suggested that [ephedrine](#), an alpha-adrenergic agonist, may be highly effective in treating clozapine induced urinary incontinence, supporting the hypothesis [60]. A dose of 25 mg ephedrine at night or 25 mg twice daily is often sufficient to treat urinary

incontinence. Ephedrine may be difficult to obtain due to concerns about diversion to the synthesis of methamphetamines; [pseudoephedrine](#) may be a reasonable substitute at doses of 30 to 60 mg twice daily.

Gastrointestinal hypomotility — Gastrointestinal hypomotility likely due to the anticholinergic properties of the medication [61] may lead to constipation. Constipation has been reported in approximately 14 percent of patients treated with [clozapine](#) [62]. Delayed diagnosis and treatment may result in fecal impaction, megacolon, intestinal obstruction, perforation, ulceration, or necrosis [63].

Severe constipation, culminating in adynamic ileus, can be fatal. In a report of 102 cases of life-threatening gastrointestinal hypomotility suspected to be caused by [clozapine](#), considerable morbidity was seen (largely due to bowel resection) along with a mortality rate of 27.5 percent [64]. Probable risk factors included:

- Recent initiation of [clozapine](#)
- High [clozapine](#) doses or serum levels
- Use of other drugs with anticholinergic activity
- Comorbid medical illness

In a retrospective analysis of diagnostic and pharmacy data on 26,720 inpatients with schizophrenia over an 11-year period, 123 cases of ileus were observed [65]. Female sex and [clozapine](#) treatment were associated with an increased risk of ileus. Nine of the ileus cases (7.3 percent) had a fatal course, with clozapine treatment and anticholinergic use associated with lethality. The onset of ileus occurred on average more than three years after the first prescription of the offending drug. In a comparative effectiveness study of 3123 patients who initiated clozapine, intestinal obstruction emerged as a clinically significant adverse effect, seen in a greater proportion of clozapine patients compared with patients on a standard antipsychotic (0.9 versus 0.3 percent; hazard ratio 2.50, 95% CI 0.97-6.44) [66].

Patients receiving psychotropics associated with significant anticholinergic properties should undergo proper clinical monitoring and interventions in order to minimize the burden of constipation and the risk of ileus. Patients can be encouraged to eat a diet high in fiber, drink plenty of fluids, and exercise. (See "[Management of chronic constipation in adults](#)".)

Sedation — [Clozapine](#) can cause significant sedation, particularly during the initiation of treatment. Tolerability of the sedating effect can be enhanced by gradually titrating to a therapeutic dose. Some clinicians add stimulants or stimulant-like drugs if patients continue to experience sedation. However, two small randomized trials in patients with clozapine-induced

sedation found no benefit from [modafinil](#) (200 to 300 mg/day) on measures of fatigue or wakefulness [67,68].

Teratogenic and neonatal risks — Although no definitive association has been found between use of antipsychotic medications during pregnancy and an increased risk of congenital anomaly or other adverse outcomes, there is a paucity of information, with a lack of large, well-designed, prospective studies. Second-generation antipsychotics cross the placenta [69]. Case reports have demonstrated concentrations of [clozapine](#) in breast milk [70]. The American College of Obstetricians and Gynecologists does not recommend the routine use of second-generation antipsychotics during pregnancy; however, assessment of risk-benefit may indicate that such use is appropriate [71]. The American Academy of Pediatrics has classified clozapine as a drug whose effect on the nursing infant is unknown but may be of concern [72]. (See "[Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy](#)", section on 'Second-generation'.)

Mortality risk — The US Food and Drug Administration has reported that the use of first- and second-generation antipsychotic medications for the treatment of behavioral symptoms in older adult patients with dementia is associated with increased mortality [73,74]. (See "[Management of neuropsychiatric symptoms of dementia](#)", section on 'Mortality risk'.)

Movement disorders — Compared with other antipsychotics, [clozapine](#) has a reduced risk of causing tardive dyskinesia or extrapyramidal movement disorders including akathisia. However, patients can still develop these movement disorders and need to be monitored for their development (eg, standardized motor exam with the Abnormal Involuntary Movement Scale every six months) ([form 1](#)). Despite clozapine's weak affinity for the dopamine receptor, the neuroleptic malignant syndrome can develop [75]. (See "[Tardive dyskinesia: Prevention, treatment, and prognosis](#)" and "[Neuroleptic malignant syndrome](#)".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "[Society guideline links: Psychotic disorders](#)".)

SUMMARY AND RECOMMENDATIONS

- **Indications** – Primary indications for [clozapine](#) include schizophrenia or schizoaffective disorder partially or fully resistant to treatment with other antipsychotic drugs, or

schizophrenia/schizoaffective accompanied by persistent suicidal or self-injurious behavior. (See '[Indications](#)' above.)

- **Pretreatment assessment** – Prior to beginning [clozapine](#), we do the following baseline evaluation (see '[Pretreatment assessment](#)' above):
 - General and cardiovascular health status, vital signs, weight, height, body mass index
 - Complete blood count (absolute neutrophil count [ANC] must be $\geq 1500/\text{microL}$ to initiate [clozapine](#))
 - Check for therapeutic drug levels of anticonvulsant medications
 - Fasting blood sugar or HbA1c, fasting lipids (non-high-density lipoprotein cholesterol if nonfasting)
 - Electrocardiogram (ECG)
 - Baseline Abnormal Involuntary Movement Scale test
 - Pregnancy test in women of childbearing age
- **Administration** – For patients initially starting [clozapine](#) in nonurgent situations, we prefer a slow titration. As an example, we suggest 12.5 to 25 mg once daily at bedtime for three to four days, then 25 to 50 mg once daily at bedtime for three to four days. We increase by 25 mg twice weekly. In urgent situations (active aggression/violence or self-injury/suicide) we double the titration rate above.

The initial target dose for healthy, young adults is 300 mg/day. A maintenance dose of 300 to 600 mg/day is usually required for efficacy. Doses higher than 900 mg/day are not recommended. We are cautious with older adults (>65 years) and in individuals with comorbid medical or cardiac disease. Typical maintenance dose may be as low as 100 to 150 mg/day. We titrate slowly in these individuals to avoid adverse effects. We check plasma levels once target dose is reached or earlier (after 100 mg are reached). (See '[Administration](#)' above.)

- **Monitoring** – For all patients taking [clozapine](#) in the United States, the US Food and Drug Administration requires regular monitoring and registry reporting of neutrophil counts. Patients taking clozapine should receive routine weekly-to-monthly monitoring and maintain an ANC $\geq 1500/\text{microL}$ ($\geq 1000/\text{microL}$ for individuals with Duffy-null associated neutrophil count. Lower ANC levels require more frequent monitoring, and possible interruption of clozapine and/or reevaluation of its use. Monitoring frequency is as follows (see '[Monitoring](#)' above):
 - Weekly during the first six months of [clozapine](#) administration
 - Every other week for the second six months

- Every four weeks after one year, for the duration of treatment

If neutropenia develops during treatment, [clozapine](#) we either monitored more frequently, stopped the medication temporarily, or discontinued the medication, based on the severity of neutropenia.

- **Adverse effects** (see '[Adverse effects](#)' above)
 - **Neutropenia/agranulocytosis** – Clozapine-induced agranulocytosis occurs at a rate of approximately 0.8 percent. Leukopenia occurs in approximately 3 percent of cases. The peak risks for both occurred early in treatment, between 6 to 18 weeks from initiation. (See '[Neutropenia/agranulocytosis](#)' above.)
 - **Cardiovascular effects** – Clozaril is associated with early myocarditis that can lead to the development of cardiomyopathy. Additionally, it can cause a dose dependent QTc prolongation. We obtain an ECG prior to starting [clozapine](#); we repeat the ECG once steady state is obtained. (See '[Myocarditis/cardiomyopathy](#)' above.)
 - **Insulin resistance, weight gain, metabolic dysregulation** – [Clozapine](#) can cause insulin resistance, metabolic dysregulation and weight gain. While most weight gain occurs during the first 6 to 12 months, some patients continue to gain weight without reaching a plateau. We monitor metabolic parameters at regular intervals. (See '[Insulin resistance and diabetes mellitus](#)' above.)
 - **Seizures** – [Clozapine](#) is associated with a dose-dependent seizure risk at a rate higher than that seen with most other antipsychotic drugs (See '[Seizures](#)' above.)
 - **Other effects** – Treatment with [clozapine](#) can cause constipation, sedation, sialorrhea, incontinence, pulmonary embolism. Treatment with antipsychotics including clozapine is associated with increased mortality in individuals with dementia. (See '[Adverse effects](#)' above.)

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