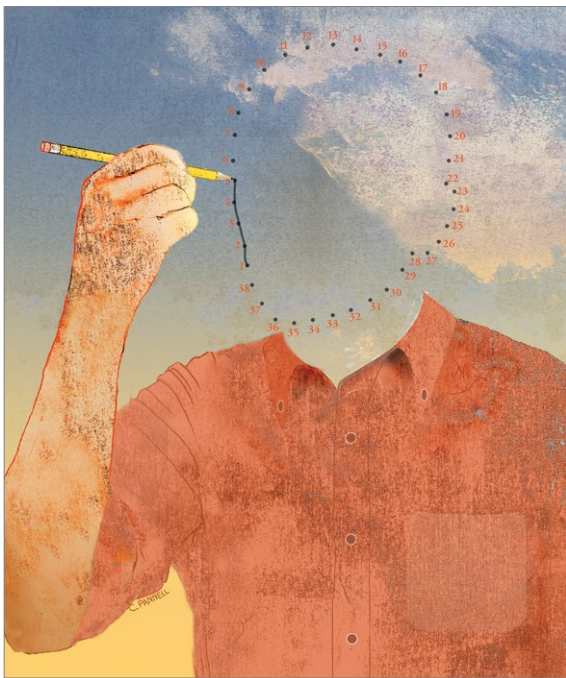


SECOND OF 3 PARTS

Rediscovering clozapine: Adverse effects develop—what should you do now?



CAP PANNELL

Benefit comes at the expense of monitoring for, and treating, an array of potential problems

Clozapine is a highly effective antipsychotic with superior efficacy in treatment-resistant schizophrenia, but its side effect profile is daunting (*Figure 1*).¹ Adverse reactions lead to approximately 17% of patients who take clozapine eventually discontinuing the medication.¹ As we noted in Part 1 of this 3-part series,² clozapine remains the most efficacious, but most tedious, antipsychotic available to psychiatrists because of its monitoring requirements and potential side effects.

A powerful rationale for prescribing clozapine, despite its drawbacks, is its association with a reduced risk of all-cause mortality.^{3,4} People with serious mental illness, including schizophrenia, have a median 10-year shorter life expectancy than the general population.⁵

A recent cohort study⁶ examined electronic health records to test whether intensive monitoring or lower suicide risk might account for the reduced mortality with clozapine. The authors found that the reduced mortality rate was *not* directly related to clozapine's clinical monitoring or other confounding factors. They did find an association between clozapine use and reduced risk of death from both natural and unnatural causes.

This second article in our series examines clozapine's adverse effects from a systems perspective. Severe neutropenia, myocarditis, sedation, weight gain, orthostatic hypotension, and sialorrhea appear to be the most studied adverse effects, but myriad others can occur.⁷ We offer guidance to help the astute clinician continue this effective antipsychotic

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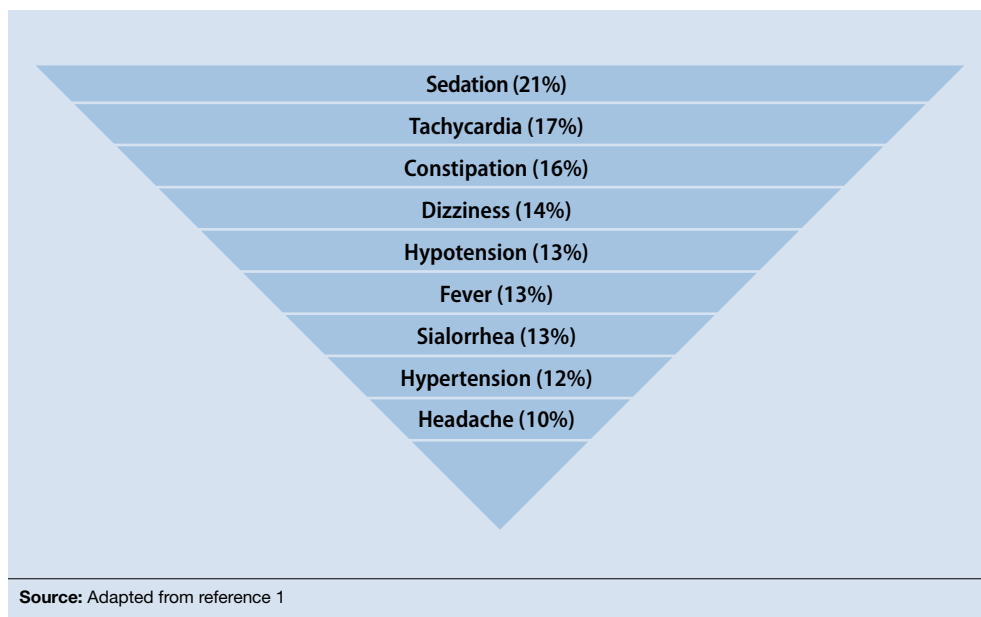
Dr. W. J. Newman is a member of the Editorial Board of CURRENT PSYCHIATRY.

Disclosures

The authors report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Figure 1

Common side effects of clozapine



by monitoring carefully, treating side effects early, and managing potential drug interactions (Table 1, page 42).⁸

Hematologic events

Severe neutropenia, defined as absolute neutrophil count (ANC) $<500/\mu\text{L}$, is a well-known adverse effect of clozapine that requires specific clinical monitoring, a requirement that was updated by the FDA in 2015.² The incidence of severe neutropenia peaks in the first 2 months of clozapine therapy and tapers after 6 months, but some risk always remains.

Older efficacy studies in the United States gauged the 1-year cumulative incidence of severe clozapine-induced neutropenia to be 2%.⁹ A 1998 study of the effects of using a clozapine registry reported a lower incidence—0.38%—than the 2% noted above.¹⁰ Early recognition and recommended interventions can improve clinical outcomes.²

Drug interactions and neutropenia. A retrospective study of mental health inpatients taking clozapine concurrently with oseltamivir during an influenza outbreak found a statistically significant—but not clinically

significant—change in ANC values.¹¹ The authors noted that viral infection might lead to blood dyscrasia early in illness, and that oseltamivir has been associated with a small incidence of blood dyscrasia.^{11–13} This information might be useful when treating influenza in patients taking clozapine, although no specific change in management is recommended.

Similarly, concomitant treatment with clozapine and lithium can affect both white blood cell and ANC values.^{14,15} Lithium-treated patients often demonstrate increased circulating neutrophils via enhancement of granulocyte-colony stimulating factor.¹⁶ Case studies describe how initiating lithium treatment enabled some patients to continue clozapine after developing neutropenia.^{14,17} Leukocytosis can affect blood monitoring, possibly masking other blood dyscrasias, when lithium is used concurrently with clozapine.

Eosinophilia (blood eosinophil count $>700/\mu\text{L}$) occurs in approximately 1% of clozapine users, usually in the first 4 weeks of treatment.¹⁸ It can be benign and transient or a harbinger of a more rare adverse reaction such as myocarditis, pancreatitis, hepatitis, colitis, or nephritis.¹⁹ If a patient taking clo-

Clinical Point

Concomitant treatment with clozapine and lithium can affect white blood cell and absolute neutrophil count values



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Clozapine

Clinical Point

Reducing the dosage of clozapine or slowing titration could reverse common cardiac side effects

Table 1

Clinically relevant drug interactions with clozapine

Mechanism of interaction	Medications and other substances involved	Effect on clozapine
CYP1A2 strong inhibitors	Fluvoxamine, ciprofloxacin	↑ Clozapine levels
CYP1A2 weak or moderate inhibitors	Oral contraceptives, caffeine	May ↑ clozapine levels
CYP2D6 and CYP3A4 inhibitors	Antidepressants (escitalopram, paroxetine, bupropion, fluoxetine, duloxetine, sertraline) Antibiotic (erythromycin) Miscellaneous (cimetidine, quinidine, terbinafine)	May ↑ clozapine levels
CYP1A2 moderate inducer	Smoking	↓ Clozapine levels
CYP3A4 strong inducers ^a	Carbamazepine, phenytoin, St. John's wort, rifampin	↓ Clozapine levels
CYP2D6 substrates	Certain antidepressants (fluoxetine), phenothiazines, carbamazepine, Type 1C antiarrhythmics (propafenone, flecainide)	Clozapine may ↑ levels of these medications

^aClozapine dosing instructions recommend against concurrent use of clozapine with strong CYP3A4 inducers
CYP: cytochrome P450 enzymes
Source: Adapted from reference 8

zapine develops eosinophilia, clozapine's package insert recommends that you:

- evaluate promptly for other systemic involvement (rash, other evidence of allergic reaction, myocarditis, other organ-specific disease)
- stop clozapine immediately if any of these are found.

If other causes of eosinophilia are identified (asthma, allergies, collagen vascular disease, parasitic infection, neoplasm), treat these and continue clozapine.

The manufacturer also mentions the occurrence of clozapine-related eosinophilia without organ involvement that can resolve without intervention, with careful monitoring over several weeks.⁸ In this scenario, there is flexibility to judge whether clozapine should be stopped or re-challenged, or if close monitoring is adequate. Consulting with an internal medicine or hematology specialist might be helpful.

Cardiovascular side effects

Most common events. Three of the 10 most common clozapine side effects are cardiac: tachycardia, hypotension, and hyperten-

sion (*Figure 1, page 41*).¹ Orthostatic hypotension, bradycardia, and syncope also can occur, especially with rapid clozapine titration. Baseline electrocardiogram (ECG) can help differentiate whether abnormalities are clozapine-induced or related to a preexisting condition.

Reducing the dosage of clozapine or slowing titration could reverse cardiac side effects.⁸ If dosage reduction is not an option or is ineffective, first consider treating the side effect rather than discontinuing clozapine.²⁰

Sinus tachycardia is one of the most common side effects of clozapine. First, rule out serious conditions—myocarditis, cardiomyopathy, neuroleptic malignant syndrome (NMS)—then consider waiting and monitoring for the first few months of clozapine treatment. If tachycardia continues, consider dosage reduction. Slower titration, or treatment with a cardio-selective beta blocker such as atenolol.^{21,22} Note that a recent Cochrane Review concluded that there is not enough randomized evidence to support any particular treatment for clozapine-induced tachycardia; the prescriber must therefore make a case-by-case clinical judgment.²²

Similarly, orthostatic hypotension can be managed with a reduced dosage of clozapine or slower titration. Increased fluid intake, compression stockings, and, if necessary, fludrocortisone also can be initiated.²⁰

Rare, potentially fatal events. Myocarditis, pericarditis, and cardiomyopathy are among the rare but potentially fatal adverse effects of clozapine. A recent study reported the incidence of myocarditis with clozapine at a range of 0.015% to 1.3%; cardiomyopathy was even more rare.²³ Pulmonary embolism and deep venous thrombosis also are very rare possibilities; keep them in mind, however, when patients taking clozapine report new cardiovascular symptoms.

Patients with clozapine-induced cardiovascular effects most commonly report shortness of breath (60%), palpitations (36%), cough (16%), fatigue (16%), and chest pain (8%).^{7,24}

Clozapine's "black-box" warning specifically recommends discontinuing clozapine and consulting cardiology when myocarditis or cardiomyopathy is suspected. In 50% of cases, myocarditis symptoms present in the first few weeks of clozapine treatment.²³ The manufacturer states that myocarditis usually presents in the first 2 months, and cardiomyopathy after 8 weeks of treatment; however, either can present at any time.⁸ *Figure 2 (page 44)* provides a clinical reference for monitoring a clozapine patient for cardiomyopathy.²⁴

Laboratory findings that support a diagnosis of clozapine-related myocarditis include:

- elevated C-reactive protein
- elevated troponin I or T
- elevated creatine kinase-MB
- peripheral eosinophilia.^{8,25}

ECG, echocardiography, and cardiac MRI can be helpful in diagnosis, in consultation with a cardiologist.

Neurologic side effects

Seizures are listed in the "black-box" warning for clozapine. Seizure incidence with clozapine is 5% per year, with higher incidence at dosages ≥ 600 mg/d.⁸ Because clozapine-induced seizures are dosage-dependent, slow titration can mitigate this

risk. Tonic-clonic seizures are the most common type associated with clozapine.

The manufacturer recommends caution when using clozapine in patients with a known seizure disorder, alcohol use disorder, or other CNS pathology.⁸ Patients with a seizure disorder may be at increased risk of experiencing clozapine-induced seizures, but this is not an absolute contraindication.²⁶ Smoking cessation increases clozapine blood levels by an average of 57.4%, further increasing seizure risk.^{26,27}

Discontinuing clozapine is unnecessary when a patient experiences a seizure. Instead, you can:

- halve the dosage prescribed at the time of the seizure (or at least reduce to the last seizure-free dosage)
- consider any medications or medical problems that might have contributed to a lower seizure threshold
- consider prophylaxis with an anti-epileptic medication (eg, valproic acid has efficacy for both myoclonic and tonic-clonic seizures).^{20,26}

Sedation is the most common side effect of clozapine.¹ Patients experiencing severe sedation should not drive or operate heavy machinery. To reduce sedation, consider instructing the patient to take all or most of the clozapine dosage at bedtime. A critical review of modafinil for sedation caused by antipsychotics in schizophrenia found only 1 open-label study that showed any positive effects; the authors concluded that further study is needed.²⁸

Cognitive and motor slowing are possible neurologic side effects of clozapine. Caution patients about the risk of participating in activities that require cognitive or motor performance until the individual effects of clozapine are known.⁸

Tardive dyskinesia. Clozapine carries some risk of tardive dyskinesia, although that risk is lower than with other antipsychotics. Similarly, all antipsychotics including clozapine are associated with a risk of NMS. In the rare case of clozapine-induced NMS, stop clozapine immediately and initiate supportive therapy. Clozapine-induced NMS is *not* an absolute contrain-

Clinical Point

To reduce sedation, consider instructing the patient to take all or most of the clozapine dosage at bedtime

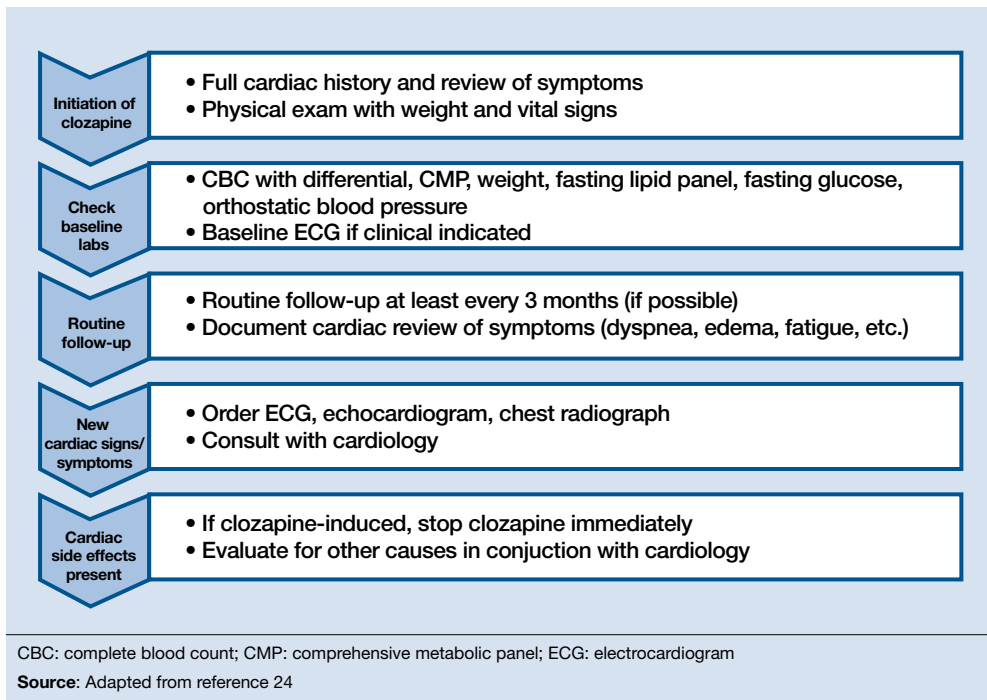


Clozapine

Clinical Point

In the rare case of clozapine-induced neuroleptic malignant syndrome, stop clozapine immediately, initiate supportive therapy

Figure 2
Monitoring strategy for clozapine-associated cardiomyopathy



dication to re-challenging a patient with clozapine, however, if doing so is clinically appropriate.²⁰

Cerebrovascular events. In older people with dementia, the use of antipsychotics—including clozapine—has been shown to increase the risk of cerebrovascular events. Because most antipsychotics are not FDA-approved for treating psychosis associated with dementia (only pimavanserin is FDA-approved for symptoms of psychosis in Parkinson’s disease), a risk-benefit analysis should be documented when prescribing any antipsychotic in this population. In practice, clozapine’s benefits may outweigh the mortality risks in specific situations.^{29,30}

CASE Sialorrhea puts progress at risk

Ms. B, age 40, has a history of treatment-resistant schizophrenia and is starting clozapine because of residual psychosis during trials of other antipsychotics. She develops severe persistent drooling, mostly at night, during clozapine titration. Sugar-free candy, multiple bed pillows, and changing the dosing schedule do not significantly improve the sialorrhea.

As a result, Ms. B is embarrassed to continue her usual activities. She asks to stop clozapine, even though her psychotic symptoms have improved and she is functioning at her highest level in years.

Ms. B already is taking trihexyphenidyl, 5 mg, 3 times daily, to manage extrapyramidal symptoms related to haloperidol decanoate treatment. After discussing other medication options for sialorrhea, she agrees to a trial of glycopyrrolate, 1 mg, twice daily. She experiences significant improvement and continues taking clozapine.

Sialorrhea develops in 13% of patients taking clozapine.¹ As in Ms. B’s case, this side effect can be embarrassing, can limit social or occupational functioning, and might lead patients to discontinue clozapine treatment despite efficacy. Nonpharmacotherapeutic options include covering the pillow with a towel, lowering the clozapine dosage or titrating slowly (or both), and using sugarless gum or candy to increase swallowing.

If the benefits of additional medications targeting side effects outweigh the risks,

Table 2

Medications for managing clozapine-induced sialorrhea

Medication	Class	Dosage
Locally administered		
Atropine sulfate ophthalmic solution, 1%	Antimuscarinic	1 drop sublingually at bedtime
Ipratropium bromide spray, 0.06%	Antimuscarinic	1 spray sublingually at bedtime
Oral systemic		
Glycopyrrolate	Antimuscarinic	1 mg, twice daily
Benztropine	Antimuscarinic	1 mg, twice daily
Trihexyphenidyl	Antimuscarinic	5 to 15 mg at bedtime
Amitriptyline	Tricyclic antidepressant	75 to 100 mg at bedtime
Clonidine	α_2 -adrenergic agonist	0.05 to 0.1 mg, once daily
Terazosin	α_1 -adrenergic antagonist	2 mg at bedtime
Benzotropine-terazosin combination	Antimuscarinic plus α_1 -adrenergic antagonist	Benzotropine, 1 mg, twice daily, plus terazosin, 2 mg at bedtime

Source: Adapted from reference 31

pharmacotherapeutic intervention may be appropriate. Options include the tricyclic antidepressant amitriptyline³¹; alpha-adrenergic agonists or antagonists (clonidine, terazosin); and anti-muscarinic medications (benztropine, atropine, trihexyphenidyl, glycopyrrolate) (Table 2³¹). Scopolamine transdermal patch is another possible treatment strategy; however, the scopolamine patch was used for clozapine-induced sialorrhea in only a few case reports, and it is not considered a first-line treatment choice.³⁰

When prescribing, consider the possibility of combined side effects with clozapine and adjunct medications having antimuscarinic or alpha-adrenergic activity, or both. Even atropine ophthalmic drops, administered sublingually, are readily absorbed and cross the blood-brain barrier.³¹ Another antimuscarinic agent, glycopyrrolate, is less likely to cross the blood-brain barrier and therefore is less likely to cause cognitive side effects. Glycopyrrolate is 5 times more potent at blocking the muscarinic receptor than atropine.^{31,32} Ipratropium bromide, another non-selective muscarinic receptor antagonist, has less systemic absorption than atropine drops, with less anticholinergic side effects when administered sublingually.

Limited evidence supports the efficacy of alpha-adrenergic medications for manag-

ing clozapine-induced sialorrhea. Monitor blood pressure when prescribing terazosin or clonidine, which could potentiate clozapine's hypotensive effects.

Endocrine side effects

Among antipsychotics, clozapine is associated with the greatest weight gain—averaging nearly 10% of body weight.^{33,34} Similarly, the risk of new-onset diabetes mellitus is highest with clozapine in relation to other antipsychotics: 43% reported in a 10-year naturalistic study.³⁵ The risk of hyperlipidemia also increases with clozapine treatment.³⁶ These metabolic changes increase the risk of cardiovascular-related death, with a 10-year mortality rate from cardiovascular disease reported at 9% in clozapine-treated patients.³⁵

Despite clozapine's metabolic side effects, patients with schizophrenia who are treated with clozapine show a significant reduction in overall mortality compared with patients not treated with clozapine.⁶ Effective identification and management of metabolic side effects can prevent the need to discontinue clozapine.

Behavioral weight management and exercise are recommended as initial therapy.²⁰ If, based on clinical judgment, these

Clinical Point

Behavioral weight management and exercise are recommended as initial therapy to control metabolic side effects



Clozapine

Clinical Point

When treating a pregnant patient, weigh the benefits of clozapine against risk of adverse events, and clearly document your analysis

alone are insufficient, data support the use of pharmacotherapeutic interventions. Metformin demonstrates a positive effect on body weight, insulin resistance, and lipids, making it the first choice for adjunctive treatment of clozapine-induced metabolic side effects.³⁷⁻³⁹

Gastrointestinal side effects

Clozapine's anticholinergic activity can lead to serious gastrointestinal (GI) side effects, including constipation, intestinal obstruction, fecal impaction, and paralytic ileus.⁸ Ileus has produced more fatal adverse reactions with clozapine than has severe neutropenia.^{20,40} Co-administered anticholinergic medications could increase the risk of ileus. Obtaining a GI review of systems and monitoring bowel movements (in inpatient or residential facilities) can aid in early identification and limit morbidity and mortality from GI adverse events. A high-fiber diet, adequate hydration, bulk laxatives in patients who can reliably maintain hydration, and GI consultation (if needed) may help manage GI side effects.²⁰

Constitutional side effects

Fever can occur with clozapine, most often in the first month of treatment, but the incidence is quite variable (0.5% to 55%).^{20,41} Although benign fever is common, agranulocytosis with infection, NMS, and other systemic illness must be ruled out. The recommended workup when a patient develops fever while taking clozapine includes physical examination and relevant testing (urinalysis, measurement of ANC and serum creatine kinase, chest radiograph, ECG, and, possibly, blood cultures).⁴¹

If evidence supports a serious adverse reaction, stop clozapine immediately.²⁰ If benign clozapine-related fever is suspected, acetaminophen or another antipyretic might provide symptomatic relief; discontinuing clozapine is then unnecessary.⁴¹

Pregnancy. When a patient with schizophrenia requires clozapine treatment during pregnancy, reliable clinical guidance is limited. The American College of

Obstetricians and Gynecologists Practice Bulletin on the use of psychiatric medications during pregnancy and lactation can be a useful resource.⁴²

Be aware that the FDA very recently made major changes to the format and content of pregnancy and lactation labeling, removing the letter categories that have been used for medications approved on or after June 30, 2001. The manufacturers of medications (such as clozapine) that were approved before June 30, 2001, have 3 years to comply with new requirements.⁴³

The FDA had rated clozapine a pregnancy risk category B medication, meaning no evidence of risk in humans. In 2011, the FDA issued a general warning that antipsychotic use in pregnancy can cause extrapyramidal symptoms and discontinuation symptoms in newborns.^{44,45}

A 2015 review of psychotropic medications and pregnancy noted that approximately 60% of women with schizophrenia became pregnant, with an increased incidence of unplanned pregnancy. A high risk of psychotic relapse (65%) during pregnancy and in the postpartum period may lead to insufficient prenatal care, drug use, and obstetric complications.⁴⁵ Some data suggest low fetal birth weight and an increased rate of therapeutic abortions in women with schizophrenia.^{42,46}

When treating a pregnant patient, weigh the benefits of clozapine against the risks of adverse events, and clearly document the analysis. Clozapine treatment is not recommended during breast-feeding because of the risk of side effects for newborns.⁸

We highly recommend keeping updated on the literature regarding pregnancy and lactation information with antipsychotics, including clozapine, because prescribing information will likely be updated in the near future to comply with recent FDA labeling changes.

Final installment: Using clozapine off-label

Clozapine is FDA-approved for refractory schizophrenia and for reducing the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder. In Part 3 of



Clozapine

Clinical Point

Sialorrhea develops in 13% of patients taking clozapine. This side effect can be embarrassing and limit social or occupational functioning

Related Resources

- ACOG Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol.* 2008;111(4):1001-1020.
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- Smith TL, Mican LM. What to do when your patient who takes clozapine enters a smoke-free facility. *Current Psychiatry.* 2014;13(5):47-48,57.
- U.S. Food and Drug Administration. Pregnancy and Lactation Labeling (Drugs) Final Rule. <https://s3.amazonaws.com/public-inspection.federalregister.gov/2014-28241.pdf>.

Drug Brand Names

Amitriptyline • Elavil	Ipratropium bromide spray, 0.06% • Atrovent
Atropine sulfate ophthalmic solution, 1% • Atropine-Care	Lithium • Eskalith, Lithobid
Benzotropine • Cogentin	Metformin • Glucophage
Bupropion • Wellbutrin	Modafinil • Provigil
Carbamazepine • Tegretol	Osetamivir • Tamiflu
Cimetidine • Tagamet	Paroxetine • Paxil
Ciprofloxacin • Cipro	Phenytoin • Dilantin
Clonidine • Catapres	Pimavanserin • Nuplazid
Clozapine • Clozaril	Propafenone • Rythmol
Duloxetine • Cymbalta	Quinidine • Quinidex
Erythromycin • E-Mycin	Rifampin • Rifadin
Escitalopram • Lexapro	Scopolamine • Transderm-Scop
Flecainide • Tambocor	Sertraline • Zoloft
Fludrocortisone • Florinef	Terazosin • Hytrin
Fluoxetine • Prozac	Terbinafine • Lamisil
Fluvoxamine • Luvox	Trihexyphenidyl • Artane
Glycopyrrolate • Robinul	Valproic acid • Depakote
Haloperidol decanoate • Haldol Decanoate	

this series, we review off-label uses—such as managing bipolar disorder, borderline personality disorder, and aggressive behavior—that have varying degrees of scientific support.

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Bottom Line

Clozapine is highly efficacious but requires greater clinician monitoring than most other psychotropics. Early identification and management of side effects can help patients continue clozapine, which is associated with reduced risk of mortality from natural and unnatural causes.

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Clinical Point

Clozapine's anticholinergic activity can lead to serious GI side effects, including constipation, fecal impaction, and paralytic ileus