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REVIEW

Medical Management of Patients on Clozapine: A Guide for Internists

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Clozapine was approved by the US Food and Drug Administration in 1989 for the management of treatment-resistant schizophrenia, and has since proven to reduce symptom burden and suicide risk, increase quality of life, and reduce substance use in individuals with psychotic disorders. Nevertheless, clozapine's psychiatric benefits have been matched by its adverse effect profile. Because they are likely to encounter medical complications of clozapine during admissions or consultations for other services, hospitalists are compelled to maintain an appreciation for these iatrogenic conditions. The authors outline common (eg, constipation, sialorrhea, weight gain) and serious (eg, agranulocytosis, seizures, myocarditis) medical complications of clozapine treatment, with internist-targeted recommendations for management, including indications for clozapine discontinuation. *Journal of Hospital Medicine* 2015;10:537–543. © 2015 Society of Hospital Medicine

Clozapine is a second-generation antipsychotic (SGA) medication that was developed in 1959, introduced to Europe in 1971, and withdrawn from the market in 1975 due to associated concerns for potentially fatal agranulocytosis. In 1989, the US Food and Drug Administration (FDA) approved use of clozapine for the management of treatment-resistant schizophrenia, under strict parameters for complete blood count (CBC) monitoring. Clozapine has since gained an additional FDA indication for reducing suicidal behavior in patients with schizophrenia and schizoaffective disorder,[1–3] and displayed superiority to both first generation antipsychotics and other SGA agents in reducing symptom burden.[2,4,5]

Clozapine's clinical benefits include lowering mortality in schizophrenia,[6] reducing deaths from ischemic heart disease,[7] curtailing substance use in individuals with psychotic disorders,[8] increasing rates of independent living and meaningful occupational activity, and reducing psychiatric hospitalizations and need for involuntary treatment.[9] Because schizophrenia, itself, is associated with a 15- to 20-year decrease in average lifespan,[10] these benefits of clozapine are particularly salient. Yet the mechanism by which clozapine mitigates otherwise-refractory psychotic symptoms is a conundrum. Structurally a tricyclic dibenzodiazepine, clozapine has relatively little effect on the dopamine D2 receptor, which has classically been thought to mediate the treatment effect of antipsychotics.[11,12]

The unique nature of clozapine extends to its adverse effect profile. A significant percentage of patients who discontinue clozapine (17%–35.4%) cite medical complications, the most common being seizures, constipation, sedation, and neutropenia.[13,14] Yet several studies, including the landmark Clinical Antipsychotic Trials for Interventions Effectiveness (CATIE) study, have found that patients were more likely to adhere to clozapine therapy than to other antipsychotics.[2,15] In the CATIE study, 44% of subjects taking clozapine continued the medication for 18 months, compared to 29% of individuals on olanzapine, 14% on risperidone, and 7% on quetiapine. Median time until discontinuation of clozapine was 10.5 months, significantly longer than for quetiapine (2.8 months) and olanzapine (2.7 months).[2] Because patients who experience clozapine-related medical complications are likely to present first to the primary care or general hospital setting, internists must be aware of potential iatrogenic effects, and of their implications for psychiatric and medical care. Using case examples, we will examine both common and serious complications associated with clozapine, and discuss recommendations for management, including indications for clozapine discontinuation.

NEUROLOGICAL

Case Vignette 1

Mr. A is a 29-year-old man with asthma and schizophrenia who experienced a generalized tonic-clonic seizure during treatment at a psychiatric facility. The patient started clozapine therapy 5 weeks prior, with gradual titration to 425 mg daily. Mr. A's previous medication trials included olanzapine and chlorpromazine, which rendered little improvement to his chronic auditory hallucinations. Clozapine was temporarily withheld during further neurologic workup, in which

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both electroencephalogram (EEG) and brain magnetic resonance imaging were unremarkable. After 60 hours, clozapine titration was reinitiated, and valproic acid was started for mood stabilization and seizure prophylaxis. Mr. A was discharged 6 weeks later on clozapine, 600 mg at bedtime, and extended-release divalproate, 2500 mg at bedtime. The patient suffered no further seizure activity throughout hospitalization and for at least 1 year postdischarge.

Seizures complicate clozapine use in up to 5% of cases, with a dose-dependent risk pattern.[16] Seizures are most commonly associated with serum clozapine levels above 500 μg/L), but have also been reported with lower levels of clozapine and its metabolite norclozapine.[17] Though nonspecific EEG changes (ie, focal or generalized spikes, spike-wave and polyspike discharges) have been associated with clozapine administration, they do not reliably predict seizure tendency.[17] Prophylaxis with antiepileptic drugs (AEDs) is not recommended, though AED treatment may be undertaken for patients who experience a seizure while on clozapine. When seizures occur in the context of elevated serum levels, reducing clozapine to the lowest effective dose is preferred over initiating an AED. Although this reduces the potential for exposure to anticonvulsant-associated adverse effects, it may also introduce the risk of relapsed psychotic symptoms, and therefore requires close monitoring by a psychiatrist. For those who opt to initiate AED therapy, we recommend consideration of each medication's therapeutic and side-effect profiles based on the patient's medical history and active symptoms. For example, in the case of Mr. A, valproate was used to target concomitant mood symptoms; likewise, patients who experience troublesome weight gain, as well as seizures, may benefit from topiramate. The occurrence of seizures does not preclude continuation of clozapine therapy, in conjunction with an AED[18] and after consideration of potential risks and benefits of use. Clozapine is not contraindicated in patients with well-controlled epilepsy.[19]

Sedation, the most common neurologic side effect of clozapine, is also dose dependent and often abates during titration.[20] Though clozapine may induce extrapyramidal symptoms, including rigidity, tremor, and dystonia, the risk is considerably lower with clozapine than other antipsychotics, owing to a lesser affinity for D2 receptors. Associated parkinsonism should prompt consideration of dose reduction, in discussion with a psychiatrist, with concurrent monitoring of serum clozapine levels and close follow-up for emergence of psychotic symptoms. If dose reduction is ineffective, not indicated, or not preferred by the patient, the addition of an anticholinergic medication may be considered (eg, diphenhydramine 25–50 mg, benztropine 1–2 mg). Neuroleptic malignant syndrome, although rare, is life-threatening and warrants immediate discontinuation of clozapine, though successful rechallenge after has been reported in case reports.[21]

CARDIAC

Case Vignette 2

Mr. B is a 34-year-old man with sinus tachycardia, a benign adrenal tumor, and chronic paranoid schizophrenia that had been poorly responsive to numerous antipsychotic trials. During a psychiatric hospitalization for paranoid delusions with aggressive threats toward family, Mr. B was started on clozapine and titrated to 250 mg daily. On day 16 of clozapine therapy, the patient began to experience cough, and several days later, diffuse rhonchi were noted on examination. Complete blood count revealed WBC 20.3 * 10^3/μL, with 37% eosinophils and absolute eosinophil count of 7.51 (increased from 12%/1.90 the week before), and an electrocardiogram showed sinus tachycardia with ST-segment changes. Mr. B was transferred to the general medical hospital for workup of presumed myocarditis.

Approximately one-quarter of patients who take clozapine experience sinus tachycardia, which may be related to clozapine's anticholinergic effects causing rebound noradrenergic elevations[22]; persistent or problematic tachycardia may be treated using a cardio-selective β-blocker. Clozapine has also been linked to significant increases in systolic and diastolic blood pressure in 4% of patients (monitoring data); the risk of hypertension increases with the duration of clozapine treatment, and appears to be independent of the patient's weight.[23] Orthostatic hypotension has been reported in 9% of patients on clozapine therapy, though effects can be mitigated with gradual titration, adequate hydration, compression stockings, and patient education. Sinus tachycardia, hypertension, and orthostatic hypotension are not absolute indications to discontinue clozapine; rather, we advocate for treating these side effects while continuing clozapine treatment.[24]

Myocarditis represents the most serious cardiac side effect of clozapine.[25,26] Although the absolute risk appears to be lower than 0.1%,[24] Kilian et al. calculated a 1000-to-2000–fold increase in relative risk of myocarditis among patients who take clozapine, compared to the general population.[26] Most cases occur within the first month of treatment, with median time to onset of 15 days. This time course is consistent with an acute immunoglobulin E–mediated hypersensitivity (type 1) reaction, and eosinophilic infiltrates have been found on autopsy, consistent with an acute drug reaction.[20]

Because of this early onset, the physician should maintain a particularly high index of suspicion in the first months of treatment, rigorously questioning patients and families about signs and symptoms of cardiac disease. If patients on clozapine present with flu-like symptoms, fever, myalgia, dizziness, chest

pain, dyspnea, tachycardia, palpitations, or other signs or symptoms of heart failure, evaluation for myocarditis should be undertaken.[25] Several centers have utilized cardiac enzymes (e.g., troponin I, troponin T, creatine kinase-myocardial band) as a universal screen for myocarditis, though this is not a universal practice.[24] Both tachycardia and flu-like symptoms may be associated with clozapine, particularly during the titration period, and these are normally benign symptoms requiring no intervention. If the diagnosis of myocarditis is made, however, clozapine should be stopped immediately. Myocarditis is often considered to be a contraindication to restarting clozapine, though cases have been reported of successful clozapine rechallenge in patients who had previously experienced myocarditis.[21]

Recommendations for clozapine-associated electrocardiography (ECG) monitoring have not been standardized. Based on common clinical practice and the time course of serious cardiac complications, we recommend baseline ECG prior to the start of clozapine, with follow-up ECG 2 to 4 weeks after clozapine initiation, and every 6 months thereafter.

GASTROINTESTINAL

Case Vignette 3

Mr. C is a 61-year-old man with chronic paranoid schizophrenia and a history of multiple-state hospital admissions. He had been maintained on clozapine for 15 years, allowing him to live independently and avoid psychiatric hospitalization. Mr. C was admitted to the general medical hospital with nausea, vomiting, and an inability to tolerate oral intake. He was found to have a high-grade small-bowel obstruction, and all oral medications were initially discontinued. After successful management of his acute gastrointestinal presentation and discussion of potential risks and benefits of various treatment options, clozapine was reinitiated along with bulk laxative and stool softening agents.

Affecting 14% to 60% of individuals who are prescribed clozapine, constipation represents the most common associated gastrointestinal complaint.[27] For most patients, this condition is uncomfortable but nonlethal, though it has been implicated in several deaths by aspiration pneumonia and small-bowel perforation.[28,29] Providers must screen regularly for constipation and treat aggressively with stimulant laxatives and stool softeners,[18] while reviewing medication lists and, when possible, streamlining extraneous anticholinergic contributors. Clozapine-prescribed individuals also frequently suffer from gastrointestinal reflux disease (GERD), for which behavioral interventions (eg, smoking cessation or remaining upright for 3 hours after meals) should be considered in addition to pharmacologic treatment with proton pump inhibitors. Clozapine therapy may be continued while constipation and GERD are managed medically.

Potentially fatal gastrointestinal hypomotility and small-bowel obstruction are rare but well-described complications that occur in up to 0.3% of patients who take clozapine.[27] This effect appears to be dose dependent, and higher blood levels are associated with greater severity of constipation and risk for serious hypomotility.[27] Clozapine should be withheld during treatment for such serious adverse events as ileus or small-bowel perforation; however, once these conditions have stabilized, clozapine therapy may be reconsidered based on an analysis of potential benefits and risks. If clozapine is withheld, the internist must monitor for acute worsening of mental status, inattention, and disorientation, as clozapine withdrawal-related delirium has been reported.[30] Ultimately, aggressive treatment of constipation in conjunction with continued clozapine therapy is the recommended course of action.[28]

Given the increased risk of ileus in the postoperative period, it is particularly important for physicians to inquire about preoperative bowel habits and assess for any existing constipation. Careful monitoring of postoperative bowel motility, along with early and aggressive management of constipation, is recommended. Concurrent administration of other constipating agents (eg, opiates, anticholinergics) should be limited to the lowest effective dose.[27] Although transaminitis, hepatitis, and pancreatitis have all been associated with clozapine in case reports, these are rare,[31] and the approach to management should be considered on a case-by-case basis.

HEMATOLOGIC

Case Vignette 4

Ms. D is a 38-year-old woman with a schizoaffective disorder who was started on clozapine after 3 other agents had failed to control her psychotic symptoms and alleviate chronic suicidal thoughts. Baseline CBC revealed serum white blood cell count (WBC) of 7800/mm^3 and absolute neutrophil count (ANC) of 4700/mm^3. In Ms. D's third week of clozapine use, WBC dropped to 4400/mm^3 and ANC to 2200/mm^3. Repeat lab draw confirmed this, prompting the treatment team to initiate twice-weekly CBC monitoring. Ms. D's counts continued to fall, and 10 days after the initial drop, WBC was calculated at 1400/mm^3 and ANC at 790/mm^3. Clozapine was discontinued, and though the patient was asymptomatic, broad-spectrum antibiotics were initiated. She received daily CBC monitoring until WBC >3000/mm^3 and ANC >1500/mm^3. An alternate psychotropic medication was initiated several weeks thereafter.

Neutropenia (white blood cell count <3000/mm^3) is a common complication that affects approximately 3% of patients who take clozapine.[32] This may be mediated by clozapine's selective impact on the precursors of polymorphonuclear leukocytes, though the mechanism remains unknown.[33] Although neutropenia is not an absolute contraindication for clozapine therapy, guidelines recommend cessation of clozapine

when the ANC drops below 1000/mm^3.[34] A meta-analysis of 112 patients who were rechallenged following neutropenia found that 69% tolerated a rechallenge without development of a subsequent dyscrasia.[21]

In the case of chemotherapy-induced neutropenia, several case reports support the continued use of clozapine during cancer treatment[35]; this requires a written request to the pharmaceutical company that manufactures clozapine and documentation of the expected time course and contribution of chemotherapy to neutropenia.[36] Clozapine's association with neutropenia warrants close monitoring in individuals with human immunodeficiency virus (HIV) and other causes of immune compromise. Reports of clozapine continuation in HIV-positive individuals underscore the importance of close collaboration between infectious disease and psychiatry, with specific focus on potential interactions between clozapine and antiretroviral agents and close monitoring of viral load and ANC.[37]

The most feared complication of clozapine remains agranulocytosis, defined as ANC < 500/mm^3,[33] which occurs in up to 1% of monitored patients. In 1975, clozapine was banned worldwide after 8 fatal cases of agranulocytosis were reported in Finland.[38] The drug was reintroduced for treatment-resistant schizophrenia with strict monitoring parameters, which has sharply reduced the death rate. One study found 12 actual deaths between 1990 and 1994, compared to the 149 predicted deaths without monitoring.[39]

The risk of agranulocytosis appears to be higher in older adults and in patients with a lower baseline WBC count. Although there are reports of delayed agranulocytosis occurring in patients after up to 19 years of treatment,[40] the incidence of leukopenia is greatest in the first year. Given this high-risk period, mandatory monitoring is as follows: weekly WBC and neutrophil counts for the first 26 weeks, biweekly counts for the second 26 weeks, and every 4 weeks thereafter. Of note, many of the later cases of agranulocytosis appear to be related to medication coadministration, particularly with valproic acid, though no definitive link has been established.[40]

Treatment of clozapine-induced agranulocytosis consists of immediate clozapine cessation, and consideration of initiation of prophylactic broad-spectrum antibiotics and granulocyte colony-stimulating factor (such as filgrastim) until the granulocyte count normalizes.[41,42] Although few case reports describe successful clozapine rechallenge in patients with a history of agranulocytosis, the data are sparse, and current practice is to permanently discontinue clozapine if ANC falls below 1000/mm^3.[21,41]

ADDITIONAL COMPLICATIONS (METABOLIC, RENAL, URINARY)

Moderate to marked weight gain occurs in over 50% of patients treated with clozapine, with average gains of nearly 10% body weight.[43] In a 10-year follow-up study of patients treated with clozapine, Henderson et al. reported an average weight gain of 13 kg, with 34% percent of studied patients developing diabetes mellitus. Metabolic side effects of second-generation antipsychotics, including clozapine, are a well-documented and troubling phenomenon.[44] Limited evidence supports use of metformin, alongside behavioral therapy, for concerns related to glucose dysregulation.[45] Some patients have also experienced weight loss with adjunctive topiramate use, particularly if they have also suffered seizures.[46]

Urinary incontinence and nocturnal enuresis are both associated with clozapine, but are likely underreported because of patient and provider embarrassment; providers also may not think to ask about these specific symptoms. First-line treatment for nocturnal enuresis is to limit fluids in the evening. Desmopressin has a controversial role in treating nocturnal enuresis owing to its risk of hyponatremia; appropriate monitoring should be implemented if this agent is used.[18]

Clozapine has been associated with acute interstitial nephritis (AIN), although this is thought to be a relatively rare side effect. Drug-induced AIN typically appears soon after initiation and presents with the clinical triad of rash, fever, and eosinophilia. Given that weekly CBC is mandatory in the initiation phase, eosinophilia is easily detectible and may serve as a marker for potential AIN.[47]

Sialorrhea, particularly during sleep, is a bothersome condition affecting up to one-third of patients who take clozapine.[48] Although clozapine is strongly anticholinergic, its agonist activity at the M4 muscarinic receptor and antagonism of the alpha-2 adrenergic receptor are postulated as the mechanisms underlying hypersalivation. Sialorrhea is frequently seen early in treatment and does not appear to be dose dependent.[48] Excessive salivation is typically managed with behavioral interventions (eg, utilizing towels or other absorbent materials on top of bedding). If hypersalivation occurs during the day, chewing sugar-free gum may increase the rate of swallowing and make symptoms less bothersome. If this does not provide adequate relief, practitioners may consider use of atropine 1% solution administered directly to the oral cavity.[49]

DRUG-DRUG INTERACTIONS

For hospitalists, who must frequently alter existing medications or add new ones, awareness of potential drug-drug interactions is crucial. Clozapine is metabolized by the cytochrome p450 system, with predominant metabolism through the isoenzymes 1A2, 3A4, and 2D6.[50] Common medications that induce clozapine metabolism (thereby decreasing clozapine levels) include phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and corticosteroids. Conversely, stopping these medications after long-term therapy will

TABLE 1. Recommended Monitoring Parameters During Clozapine Use

	Clinical Lab/Study	Frequency of Monitoring
Cardiac	Electrocardiogram	Baseline, 2–4 weeks after initiation, every 6 months thereafter
	Cardiac enzymes (eg, troponin I) echocardiogram	No standard guidelines, unless clinically indicated
Hematologic	Complete blood count with differential	Baseline, then weekly × 26 weeks, then every 2 weeks × 26 weeks, then every 4 weeks thereafter
Metabolic	Body mass index; circumference of waist	Baseline, then every 3 to 6 months
	Fasting glucose	Baseline, then every 6 months
	Fasting lipid panel	Baseline, then yearly
Neurologic	Electroencephalogram	No standard guidelines, unless clinically indicated
Vital signs	Heart rate, blood pressure, temperature	Baseline and at each follow-up visit

TABLE 2. Medical Indications for Altering Clozapine Therapy

Requires Acute Clozapine Discontinuation*	Clozapine Interruption During Management†	Does Not Typically Require Clozapine Discontinuation†
Agranulocytosis (ANC<1.0 × 10^9/mm^3)	Diabetic complications (eg, ketoacidosis, hyperosmolar coma)	Constipation
Cardiomyopathy (severe)	Gastrointestinal obstruction, ileus	Diabetes mellitus
Myocarditis	Neuroleptic malignant syndrome	Gastroesophageal Reflux
	Venous thromboembolism	Hyperlipidemia
		Hypertension
		Orthostatic hypotension
		Sedation
		Seizures
		Sialorrhea
		Sinus tachycardia
		Urinary changes (eg, enuresis, incontinence)
		Weight gain

NOTE: **Abbreviations:** ANC, absolute neutrophil count. *Limited case reports suggest possibility of rechallenge under close multidisciplinary supervision. †Requires symptomatic management, consideration of more frequent monitoring or clozapine dose adjustment and weighing risks-benefits of continuation or discontinuation.

raise clozapine levels. Substances that inhibit clozapine metabolism (thereby increasing clozapine levels) include ciprofloxacin, erythromycin, clarithromycin, fluvoxamine, fluoxetine, paroxetine, protease inhibitors, verapamil, and grapefruit juice. We recommend caution when concurrently administering other agents that increase risk for agranulocytosis, including carbamazepine, trimethoprim-sulfamethoxazole, sulfasalazine, and tricyclic antidepressants.

Cigarette smoking decreases clozapine blood levels by induction of CYP1A2. Patients require a 10% to 30% reduction to clozapine dose during periods of smoking cessation, including when smoking is stopped during inpatient hospitalization.[51] Nicotine replacement therapy does not induce CYP1A2 and therefore does not have a compensatory effect on clozapine levels. On discharge or resumption of smoking, patients may require an increase of their dose of clozapine to maintain adequate antipsychotic effect.

TABLE 3. Take-Home Points

Take-Home Points
1. Clozapine is the gold standard for treatment-resistant schizophrenia; however, its use is limited by side effects, many of which can be successfully treated by internists.
2. There are few indications for discontinuing clozapine (myocarditis, small-bowel obstruction, agranulocytosis). The psychiatry service should be consulted in the event that clozapine is discontinued.
3. Seizures are not an indication for discontinuing clozapine; instead, we recommend adding an antiepileptic drug.
4. All second-generation antipsychotics are associated with diabetes mellitus and significant weight gain. Clozapine is more highly associated with metabolic side effects than many other medications in this class.
5. Sedation, sialorrhea, and constipation are common and can be managed pharmacologically and with behavioral interventions.

SUMMARY OF RECOMMENDATIONS

Medical complications are cited as the cause in 20% of clozapine discontinuations; most commonly, these include seizures, severe constipation, somnolence, and neutropenia. Given the high risk of psychiatric morbidity posed by discontinuation, we recommend managing mild-moderate symptoms and side effects while continuing the drug, when possible (Table 1). We encourage hospitalists to confer with the patient's psychiatrist or the inpatient psychiatry consultation service when making changes to clozapine therapy. Specific recommendations are as follows:

1. We advocate withholding clozapine administration pending medical optimization for several conditions, including: small-bowel obstruction, neuroleptic malignant syndrome, venous thromboembolism, diabetic ketoacidosis, or hyperosmolar coma.
2. Clinical scenarios requiring acute discontinuation of clozapine include agranulocytosis and myocarditis. Successful rechallenge with clozapine has been described after both conditions; at the same time, given the high morbidity and mortality of myocarditis and agranulocytosis, re-initiation of clozapine requires an extensive risk-benefit discussion with the patient and family, informed consent, and, in the case of agranulocytosis, approval from the national clozapine registry (Table 2).

3. Although adjunctive therapy with filgrastim was initially thought to permit a clozapine rechallenge in patients with a history of agranulocytosis, case reports on this strategy have been equivocal, and further research is necessary to determine the most effective strategy for management.

CONCLUSION

Clozapine has been a very successful treatment for patients with schizophrenia who have failed other antipsychotic therapies. However, fears of potential side effects and frequent monitoring have limited its use and led to unnecessary discontinuation. To mitigate risk for serious complications, we hope to increase hospitalists' awareness of prevention, monitoring, and treatment of side effects, and to promote comfort with circumstances that warrant continuation or discontinuation of clozapine (Table 3). The hospitalist plays a crucial role in managing these complications as well as conveying information and recommendations to primary care providers; as such, their familiarity with the medication is essential for proper management of individuals who take clozapine.

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