

# Managing clozapine-induced neutropenia and agranulocytosis

Jeremy S. Daniel, PharmD, BCPS, BCPP, and Tonya Gross, PharmD

**M**r. S, age 43, has schizophrenia and been stable on clozapine for 6 years after several other antipsychotic regimens failed. Mr. S also has a history of hypertension, dyslipidemia, and gastroesophageal reflux disorder. His medication regimen includes clozapine, 400 mg/d, lisinopril, 20 mg/d, atorvastatin, 40 mg/d, omeprazole, 40 mg/d, and a multivitamin. During routine blood monitoring, Mr. S shows a significant drop in absolute neutrophil count (ANC) (750/ $\mu$ L) (reference range, 1,500 to 8,000  $\mu$ L). Mr. S, who is African American, has no history of benign ethnic neutropenia (BEN) or ANC <1,000/ $\mu$ L. While reviewing his chart, clinicians note that Mr. S had an ANC of 1,350/ $\mu$ L 3 years earlier in 2013. Because a complete workup reveals no other cause for this lab abnormality, we determine that is clozapine-induced. Mr. S's physician asks about treatment options that would allow him to stay on clozapine.

Because of clozapine's efficacy in treatment-resistant schizophrenia, many psychiatrists aim to manage patients who develop abnormal laboratory values without discontinuing clozapine. This article will examine the evidence behind 2 potential management strategies.

Dr. Daniel is Assistant Professor, South Dakota State University, College of Pharmacy, Brookings, South Dakota, and Clinical Pharmacist, Avera McKennan Hospital and University Health Center, Sioux Falls, South Dakota. Dr. Gross is PGY-2 Psychiatric Pharmacy Resident, Avera McKennan Hospital and University Health Center, Sioux Falls, South Dakota.

#### Disclosures

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

## Clozapine-induced neutropenia

Clozapine was approved in 1989 for managing treatment-resistant schizophrenia after demonstrating better efficacy than chlorpromazine.<sup>1</sup> However, the adverse effects of neutropenia (white blood cell count [WBC] <3,000/ $\mu$ L) and agranulocytosis (ANC <500/ $\mu$ L<sup>3</sup>) leading to death were reported in later studies.<sup>2,3</sup> One study in the United Kingdom and Ireland reported a prevalence of 2.9% for neutropenia and 0.8% for agranulocytosis among patients taking clozapine.<sup>3</sup> Because of this risk, the FDA mandated WBC and ANC monitoring before initiating clozapine and periodically thereafter. In October 2015, the Risk Evaluation and Mitigation Strategies program for clozapine updated recommended ANC levels and eliminated WBC monitoring. ANC monitoring frequencies are summarized in the *Table (page 52)*.<sup>1</sup>

The exact mechanism of clozapine-induced neutropenia is unknown, although it is possible it stems from the drug's effect on white blood cell precursors.<sup>2</sup> Neutropenia




Vicki L. Ellingrod,  
PharmD, FCCP  
Department Editor

#### Practice Points

- There is lack of evidence for long-term use of filgrastim for clozapine-induced neutropenia and agranulocytosis; short-term treatment is recommended.
- There is potential risk of lithium masking the preliminary state of neutropenia leading to severe agranulocytosis.
- Patients who experience neutropenia with clozapine are at an increased risk for a repeat neutropenia on rechallenge.

Savvy Psychopharmacology is produced in partnership with the College of Psychiatric and Neurologic Pharmacists

cpnp.org  
mhc.cpnp.org (journal)



Clinical Point

Most patients rechallenged with clozapine experience a more severe, faster, and longer episode of neutropenia

Table

Absolute neutrophil count monitoring frequencies with clozapine

ANC level	Monitoring
<b>Initiation</b> General population: $\geq 1,500/\mu\text{L}$ BEN population: $\geq 1,000/\mu\text{L}$ (Obtain at least 2 baseline ANC values before initiating treatment)	<ul style="list-style-type: none"> <li>Weekly for 6 months</li> <li>Every 2 weeks from 6 to 12 months</li> <li>Monthly after 12 months</li> </ul>
<b>Mild neutropenia</b> 1,000 to 1,499/ $\mu\text{L}$	BEN population: <ul style="list-style-type: none"> <li>No additional monitoring needed. ANC still in normal range</li> </ul> General population: <ul style="list-style-type: none"> <li>Monitor ANC 3 times weekly until <math>\geq 1,500/\mu\text{L}</math></li> <li>Then can return to patient's last ANC monitoring interval</li> </ul>
<b>Moderate neutropenia<sup>a</sup></b> 500 to 999/ $\mu\text{L}$	BEN population: <ul style="list-style-type: none"> <li>Monitor ANC 3 times weekly until <math>\geq 1,000/\mu\text{L}</math> or the patient's baseline</li> <li>Then monitor ANC weekly for 4 weeks, then return to patient's last ANC monitoring interval</li> </ul> General population: <ul style="list-style-type: none"> <li>Interrupt clozapine</li> <li>Monitor ANC daily until <math>\geq 1,000/\mu\text{L}</math>, then restart clozapine</li> <li>Then monitor ANC 3 times weekly until <math>\geq 1,500/\mu\text{L}</math></li> <li>Then monitor ANC weekly for 4 weeks</li> <li>Then return to patient's last ANC monitoring interval</li> </ul>
<b>Severe neutropenia<sup>a</sup></b> <500/ $\mu\text{L}$	BEN population <sup>b</sup> : <ul style="list-style-type: none"> <li>Discontinue clozapine</li> <li>Daily ANC until <math>\geq 500/\mu\text{L}</math></li> <li>Then 3 times weekly until ANC is more than or equal to the patient's established baseline</li> </ul> General population <sup>b</sup> : <ul style="list-style-type: none"> <li>Discontinue clozapine</li> <li>Daily ANC until <math>\geq 1,000/\mu\text{L}</math></li> <li>Then 3 times weekly until ANC <math>\geq 1,500/\mu\text{L}</math></li> </ul>

<sup>a</sup>Recommend hematology consultation

<sup>b</sup>May rechallenge if prescriber determines benefits outweigh risks

ANC: absolute neutrophil count; BEN: benign ethnic neutropenia

Source: Reference 1

typically appears within 3 months of clozapine initiation; however, delayed cases have been reported. Additionally, the risk is higher in certain patient populations (African heritage, Yemenite, West Indians, and Arab). Patients with a lower ANC at clozapine initiation and advanced age appear to be at higher risk.<sup>2</sup>

Filgrastim

The use of granulocyte-colony stimulating factor, such as filgrastim, often

is viewed as a "rescue" treatment. Filgrastim's mechanism of action is related to neutrophil production and proliferation. Several articles from the 1990s reported efficacy in the short-term management of low WBC or ANC. However, few articles, mainly case reports, have looked at long-term use of these agents. One article examined 3 patients, average age 45, who developed neutropenia during clozapine treatment.<sup>4</sup> Filgrastim at an average dosage of 0.6 to 0.9 mg/week was



Discuss this article at [www.facebook.com/CurrentPsychiatry](http://www.facebook.com/CurrentPsychiatry)

used successfully. The dosage was reduced to 0.3 mg/week in 1 patient, although neutropenia returned.

Because of the lack of literature regarding long-term therapy, it is recommended to consider short-term treatment with filgrastim to normalize ANC after a severe drop in a symptomatic patient. Physicians also must consider the potential barriers to filgrastim treatment including adverse effects, such as allergic reactions, bone pain, and thrombocytopenia, and high cost.

### Adjunctive lithium

Lithium could cause leukocytosis, which could balance neutropenia induced by clozapine. One of the largest studies evaluating lithium therapy with clozapine-induced neutropenia and agranulocytosis studied 25 patients taking clozapine with a previous “red result” (WBC <3,000/ $\mu$ L, ANC <1,500/ $\mu$ L, or platelets <50,000/ $\mu$ L).<sup>3</sup> Lithium treatment was started before or simultaneously with the reinitiation of clozapine in most patients; the remaining patients started treatment at a later date. Only 1 of 25 patients experienced a repeat “red result.” The average lithium level was 0.54 mEq/L.

It is important to remember that initiating adjunctive lithium carries risk. Adverse effects include gastrointestinal upset, tremors, polyuria, polydipsia, and nephrotoxicity.

Additionally, there is risk that lithium simply masks the preliminary states of neutropenia leading to a more severe agranulocytosis without warning.<sup>3</sup> Again, the mechanism of action of clozapine-induced neutropenia is thought to be related to the drug’s effect on WBC precursors. The mechanism of lithium-induced leukocytosis is unknown, therefore it’s

## Related Resources

- Clozapine REMS Program. [www.clozapinerems.com](http://www.clozapinerems.com).
- Newman BM, Newman WJ. Rediscovering clozapine: adverse effects develop—what should you do now? *Current Psychiatry*. 2016;15(8):40-46,48,49.
- Whiskey E, Taylor D. Restarting clozapine after neutropenia: evaluating the possibilities and practicalities. *CNS Drugs*. 2007;21(1):25-35.

### Drug Brand Names

Atorvastatin • Lipitor	Lisinopril • Prinivil
Chlorpromazine • Thorazine	Lithium • Eskalith, Lithobid
Clozapine • Clozaril	Omeprazole • Prilosec
Filgrastim • Neupogen	

possible that lithium will not protect a patient from clozapine-induced neutropenia or agranulocytosis, and can lead to serious adverse events.

When deciding whether to rechallenge a patient on clozapine who had a prior episode of moderate or severe neutropenia or agranulocytosis, a risk vs benefit discussion is necessary. One study found that 20 of 53 patients (38%) experienced a repeat dyscrasia when rechallenged.<sup>5</sup> Of these patients, most experienced a lower ANC that presented faster and took longer to resolve.<sup>5</sup> If a patient has experienced true agranulocytosis, the recommendation is to not rechallenge clozapine.

### References

1. Clozapine [package insert]. North Wales, PA: TEVA Pharmaceuticals USA; 2015.
2. Lundblad W, Azzam PN, Gopalan P, et al. Medical management of patients on clozapine: a guide for internists. *J Hosp Med*. 2015;8(8):537-543.
3. Kanaan RA, Kerwin RW. Lithium and clozapine rechallenge: a retrospective case analysis. *J Clin Psychiatry*. 2006;67(5):756-760.
4. Hägg S, Rosenius S, Spigset O. Long-term combination treatment with clozapine and filgrastim in patients with clozapine-induced agranulocytosis. *Int Clin Psychopharmacol*. 2003;18(3):173-174.
5. Dunk LR, Annan LJ, Andrews CD. Rechallenge with clozapine following leucopenia or neutropenia during previous therapy. *Br J Psychiatry*. 2006;188:255-263.

## Clinical Point

There is more evidence supporting the efficacy of lithium for clozapine-induced neutropenia than filgrastim