Clozapine Monitoring

In February 2025, the U.S. Food and Drug Administration (FDA) eliminated the Risk Evaluation and Mitigation Strategies (REMS) program for clozapine[1], which had placed an excessive focus on neutropenia resulting in mandatory monitoring by providers and pharmacies as well as frequent and overly burdensome lab tests for patients.

Clozapine is the only approved antipsychotic for treatment-resistant schizophrenia and has demonstrated superior efficacy in reducing suicide, psychotic symptoms, relapse, rehospitalization, medication adherence, aggression and substance use; yet only one-third of people with treatment-resistant schizophrenia are prescribed clozapine.[2]

The European Clozapine Task Force[2], which advises European Medicines Agency (EMA) regulation, cite several recent studies[3-5] that highlight the low incidence (around 1%) of clozapine-induced agranulocytosis, which was mostly limited to the first 18 weeks of therapy and became negligible after 24 months. The incidence of any severity of neutropenia was also very low after clozapine was reintroduced in patients with no history of neutropenia over 2 years of cumulative monitoring.[4]

With new flexibility around frequency of blood tests, there is an opportunity to expand clozapine access to patients who were previously deterred from using clozapine due to the cumbersome monitoring parameters associated with it.

How to prescribe clozapine

Clozapine can be prescribed and dispensed like other antipsychotic medications.

- Clozapine is not subject to mandatory reporting and monitoring.
- Prescribers can exercise clinical judgement in determining when to initiate clozapine and frequency of monitoring.
- FDA Boxed Warning for severe neutropenia with clozapine still exists and monitoring for severe neutropenia is still recommended.[1,2]

Monitoring Recommendations for Clozapine

European Clozapine Task Force Proposed Recommendations[2]	
Baseline (units: cells/μL)	Initiate if ANC >1500 If BEN, initiate if ANC >1000
Monitoring Frequency^	Weekly for 18 weeks, then monthly for rest of year 1, then every 3 months for year 2*, then yearly*.
Managing Neutropenia (units: cells/μL)	• ANC 1000-1500: monitor twice a week • ANC < 1000: stop clozapine • If BEN and ANC 500-1000: monitor twice weekly • If BEN and ANC < 500: stop clozapine
Treatment Interruptions (irrespective of duration)	No need to resume weekly monitoring if no history of neutropenia during 2 cumulative years of monitoring

Abbreviations: ANC = absolute neutrophil count; BEN = Benign Ethnic Neutropenia (hematology consult can confirm diagnosis).

^Obtain ANC immediately in the event of possible symptoms of infection (e.g., fever, sore throat, mouth/throat ulcers). Consider additional ANC after addition of valproic acid to clozapine, especially during initiation period.

*If no history of leukopenia or neutropenia

Monitoring and managing side effects of clozapine

(Adapted from Cascadia Health)

Side Effect	Incidence	Management
Weight gain	60%	• Early weight gain is a predictor • Consider metformin early in treatment
Sedation	40%	• Usually develop tolerance • Consolidate most of dose in the evening

Constipation	30%	• **Risk factors**: higher doses, concomitant anticholinergic medication or opioids
		• Can lead to necrosis and bowel obstruction
		• Assess at every visit
		• **Preferred treatments**:
		  ○ Polyethylene glycol (Miralax)
		  ○ Lactulose
		  ○ Senna plus docusate (Senokot-S)
		• **Avoid**: psyllium (Metamucil)

Salivation	30%	• Atropine eye drops sublingually • Scopolamine patch • Glycopyrrolate tablets • Benztropine or other anticholinergics (note: increases anticholinergic burden)
Tachycardia (isolated)	25%	• Transient tachycardia is common during titration • If persistent, evaluate for cardiac toxicity (see below) and determine if lower dose of clozapine is appropriate
Dyspepsia/heartburn	4-14%	• Famotidine

		• May try short course of proton pump inhibitor
Hypotension, bradycardia	9%	• Higher risk during initial titration and after missed doses • If missed >2 days, consider starting at lower doses to avoid hypotension
Cardiac toxicity (myocarditis/cardiomyopathy)	Rare (0.02-1%)	• Obtain baseline (or close to baseline): troponin I and c-reactive protein; monitor for the first 4-8 weeks • Most likely to occur within first 8 weeks • Could be related to rapid titration of clozapine dose • Peak incidence at 3-4 weeks of therapy • Early signs/symptoms: tachycardia, fever, chest pain, malaise, flu-like symptoms • Re-trial not recommended if cardiac toxicity occurs

References

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