AAPP Pharmacist Toolkit: Clozapine in Practice

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This toolkit is intended to highlight both the evidence base available as well as strategies of clinical decision making used by expert clinicians. The content reflects the views and practice of the authors as substantiated with evidence-based facts as well as opinion and experience. Authors and AAPP review and update toolkits annually and strive to use up-to-date, non-stigmatizing language. Terminology does evolve rapidly and often regionally such that there may be differences between reader experiences and expectations and those of the author(s).

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History/overview

Clozapine is an antipsychotic with a unique history. Despite synthesis in 1958, clozapine was first commercially available in Europe during the early 1970s, around the same time phase II studies were starting in the United States.[1] In 1975, a publication reported that 18 patients exposed to clozapine developed a severe blood dyscrasia with 9 of these cases being fatal.[2] This significantly impacted and delayed the approval process of clozapine in the United States. With the implementation of a compassionate need program for patients who had already been receiving clozapine, the use of the medication continued but in a limited fashion through the 1980s. This use grew as well as the knowledge that severe neutropenia could be mitigated with close monitoring and early detection. This resulted in the Food and Drug Administration (FDA) allowing the submission of a New Drug Application for review. For approval, the FDA required that clozapine be tested in a treatment-resistant (in part defined as having failed two antipsychotic trials) population and demonstrate superiority over a comparator antipsychotic.[1] In 1988, a positive landmark study was completed setting the stage for clozapine's FDA approval and the initial monitoring program to mitigate hematologic concerns.[3]

Based on this landmark study and other important studies, clozapine continues to be recommended by treatment guidelines as the drug of choice for treatment-resistant psychotic disorders.[4,5] Following a randomized, controlled trial comparing clozapine to olanzapine, the FDA also approved clozapine for the use of reducing suicidality in patients with schizophrenia or schizoaffective disorder.[6] In addition to these FDA approved indications, clozapine is also used clinically for several off-label indications supported by varying degrees of literature, including but not limited to treatment-resistant mood disorders and as a preferred option for patients with tardive dyskinesia requiring antipsychotic medication.[7,8] Clozapine use remains low in the United States, despite clinical benefits, due to multiple barriers as discussed in depth in multiple publications.[9–12]

In 2011, the Mental Health Clinician (MHC) published an edition related to clozapine use with an accompanying toolkit. This toolkit was first updated in 2019, with additions made in 2022 and 2025. Updates to several clozapine-related adverse effects and monitoring parameters since the 2011 toolkit have occurred, including content on neutropenia (with the elimination of a Risk Evaluation and Mitigation Strategy (REMS) program), myocarditis, severe gastrointestinal hypomotility, and pneumonia. Throughout this toolkit, readers will find basic information on clozapine-related boxed warnings, common side effects, and drug interactions. Increasing awareness and knowledge of these important issues can help prepare the clinician for adequate and appropriate monitoring and management of issues when they arise. This toolkit should serve as a starting point for clinicians to increase and reinforce baseline clozapine knowledge.

Barriers to clozapine use, pre-treatment considerations, baseline screening, and drug interactions

Select barriers to clozapine use

Provider knowledge, familiarity, fears

Available guidelines, primary literature, as well as this toolkit should help arm pharmacists and clinicians to overcome persistent barriers. Education and increasing knowledge of clozapine use and monitoring are fundamental for successful use. Literature suggests that prescribers' fears and perceived burdens of clozapine are significant. This is evident in several titles of published works colloquially discussing the term "clozaphobia".[13–15]

Patient acceptance of medication, care models, and monitoring parameters

Providers often overestimate patients' aversion to starting and continuing clozapine.[16] With proper planning, clozapine is more routinely perceived as a positive experience by patients. Given barriers perceived by prescribers, clozapine management should stem from a multidisciplinary approach. While no one model of clozapine management has been shown to be superior over another, the use of pharmacists can have a positive impact on outcomes associated with clozapine use.[17–19] Clozapine specialty clinics or integrated primary care settings have been explored and serve as two types of possible care structures to enhance the successful use and continuation of clozapine. If multidisciplinary approaches cannot be structured due to limitations of resources, tools could be suggested to help standardize the approach to monitoring the many complexities of clozapine. In addition to the monitoring outlined by the FDA, the Glasgow Antipsychotic Side Effects Scale for Clozapine (GASS-C) is one example described within this toolkit.

Medication access, laboratory access, and care coordination

With the Clozapine REMS program retirement, clozapine should now be more accessible in hospitals and the community. However, clozapine remains widely underutilized, and advocacy and promotion of use should continue. The notion that, "clozapine cannot be managed because of monitoring complexities" enhances the stigma and fear surrounding clozapine. Accessibility to laboratory services and ensuring adherence to laboratory monitoring may pose a barrier. Again, this highlights the need for multidisciplinary approaches to clozapine management, clozapine clinics, or integrated behavioral health primary care settings with laboratory services. Endeavors to simplify access to absolute neutrophil count (ANC) monitoring could be explored based on available resources. Point-of-care devices for finger stick hematology monitoring, clinic integrated laboratory services, or mobile laboratory services are examples.[20,21]

Considerations prior to initiation

- Assess patient acceptability of clozapine as a treatment and laboratory monitoring requirements
- Accessibility to laboratory and pharmacy services
- Educate on risks/benefits and obtain medication informed consent from patient
- Educate on consequences of intermittent adherence
- Contraindications to clozapine use
  - Hypersensitivity to clozapine
- Multiple Boxed Warnings
  - Severe Neutropenia
  - Orthostatic Hypotension, Bradycardia, Syncope
  - Seizures
  - Myocarditis, Cardiomyopathy, and Mitral Valve Incompetence
  - Increased Mortality in Elderly Patients with Dementia-Related Psychosis (applies to all antipsychotics)
- Special populations:
  - Pediatrics: not FDA approved but may be considered for psychotic disorders following the failure of 2 or more antipsychotic trials. Guidelines from the American Academy of Child and Adolescent Psychiatry recommend this based on a few small randomized, controlled trials.[22] Lower initial doses and slower titration may be considered. Lower target doses and increased monitoring may be required.
  - Geriatric: considerations as per adult use, considering comorbidities and potential for decreased tolerability. Lower initial doses and slower titration may be considered. Lower target doses and increased monitoring may be required.[23,24]
  - Pregnancy: Limited data suggest there is no increased risk of congenital malformations compared to the general population, but gestational diabetes risk is increased. Fetal clozapine accumulation during pregnancy and accumulation in breast milk does occur. The risk of clozapine-related adverse events to the mother during a new start, adverse events during pregnancy delivery, and concerns of infant exposure/monitoring during pregnancy or breastfeeding must be considered.[25] Fetal heart rate variabilities, infant neutropenia, sedation, seizure, and floppy infant syndrome have been reported.[25–27]

Baseline screening prior to clozapine initiation, suggested titrations for initiation, and use of therapeutic drug monitoring

- Relevant past medical history in which the disease state or treatment of the disease state could result in a compounded risk of clozapine-related adverse events
- Complete Blood Count (CBC) with differential
- C-reactive protein, and troponin
- Vital signs: heart rate, blood pressure, temperature
- Metabolic parameters: lipid panel, fasting glucose or hemoglobin A1c (HbA1c), weight
- Electrolytes, renal function tests, liver function tests
- Pregnancy test for women of childbearing potential
- Clinical assessment of baseline extrapyramidal side effects
- Potential drug interactions (Table 1)

Table 1. Select clinically relevant drug interactions with clozapine*

Medication	Examples	Comments
Anticholinergic agents	Benztropine, diphenhydramine, glycopyrrolate, trihexyphenidyl	• Use cautiously due to additive anticholinergic activity; monitor for worsening GIH, urinary retention, confusion, etc.
Anti-hypertensive agents	Alpha-blockers, beta-blockers, ACE-I	• Clozapine may potentiate the hypotensive effects of anti-hypertensive agents, monitor blood pressure
Bone marrow suppressing agents	Antineoplastic agents, carbamazepine	• Medications that suppress bone marrow function should be avoided when feasible; consider more frequent monitoring based on clinical scenario • In the case of chemotherapy, clozapine has successfully been continued through treatment of malignancy, but close monitoring is needed in determining appropriate cell count recovery; care coordination between specialties is needed

Table 1. Select clinically relevant drug interactions with clozapine*

Medication	Examples	Comments
CYP450 enzyme inducers*	Smoking, cruciferous vegetables (broccoli, cauliflower, Brussels sprout, cabbage, etc), omeprazole, carbamazepine, phenytoin, rifampin, phenobarbital	• Inducers may decrease clozapine levels resulting in decreased efficacy and/or increase norclozapine levels leading to decreased tolerability • In general, dosage adjustments are likely necessary when an inducer is discontinued • Some enzyme-inducing antiepileptic agents may induce clozapine by up to 50% to 85% (e.g., carbamazepine, phenytoin)[28] • Valproate may unpredictably increase or decrease clozapine concentrations.[29] It has been associated with increased risk of myocarditis.[30] • Smoking increases the clearance of clozapine by 30-50%; de-induction after smoking cessation occurs over 7 to 14 days and increases risk of side effects and toxicity (smoking cessation should be coordinated with the appropriate monitoring). Interaction with smoking is related to inhaled polycyclic aromatic hydrocarbons; use of nicotine replacement, chewing tobacco, vaping will not directly impact 1A2 activity • Phytochemicals in cruciferous vegetables can induce CYP1A2; a dietary change in consumption has the potential to alter clozapine concentration. One study found that 7 days of broccoli (2 cups), cauliflower (1 cup), cabbage (1 cup), or radish sprouts (1/2 cup) increased CYP1A2 activity by 18%–37%.[31] • Co-administration of omeprazole could reduce clozapine concentrations. One case reported about a 40% decrease; change from omeprazole to a different proton pump inhibitor could lead to increased clozapine concentrations[32]

Table 1. Select clinically relevant drug interactions with clozapine*

Medication	Examples	Comments
CYP450 1A2 enzyme inhibitors*	Fluvoxamine, ciprofloxacin, viloxazine, caffeine, acute inflammatory/ infectious processes	• Inhibition of clozapine by strong 1A2 inhibitors (i.e., ciprofloxacin, fluvoxamine) is unpredictable and should be avoided when possible[33] • Viloxazine is contraindicated with concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range • Use of fluvoxamine to increase clozapine serum levels relative to norclozapine levels has been described, but this practice cannot be recommended in usual care without significant oversight and monitoring[34] • Caffeine is a mild 1A2 inhibitor in larger doses, and cases have reported clinically meaningful adverse events secondary to this interaction[35] • Acute inflammatory/infectious processes have been estimated to reduce 1A2 activity by up to 90%, and several reports of clozapine toxicity during medical illness have been reported[36]
Other CYP450 enzyme inhibitors*	Fluoxetine, paroxetine, amiodarone, estrogen containing oral contraception (OC)	• Use of an antidepressant or other medication that inhibits the metabolic pathways of clozapine are not contraindicated, but increased monitoring for emerging side effects is warranted; consider therapeutic drug monitoring where accessible • The combination of amiodarone and clozapine should be accounted for due to an amiodarone metabolite causing CYP1A2 inhibition; one case published reported a decrease in clozapine dose by 50%.[37] • A 50% reduction of clozapine dose may be required in the setting of an OC[38]
Medications that lower seizure threshold	Bupropion, TCAs, tramadol	• Use caution when co-administering medications that lower the seizure threshold, especially at high doses and during initial titration
CNS depressants and respiratory depressants	Alcohol, opioids, benzodiazepines	• Medications with additive CNS depressant effects should be used with caution; avoid alcohol

*Clozapine is a substrate for multiple CYP450 isoenzymes, predominantly 1A2, and also 2C19, 3A4, and 2D6; Abbreviations: ACE-I = Angiotensin-converting enzyme-inhibitor, CNS = Central nervous system, GIH = Gastrointestinal hypomotility, QTc = corrected QT interval, TCA= Tricyclic antidepressant

Suggested titration schedule for clozapine naïve patients

- Schedules serve only as an example; titration should be based on patient tolerability and clinical effect. Maximum FDA-approved dose of 900 mg/day
- Titration rate may influence the risk of seizures, hypotension, myocarditis, and excessive sedation. However, "too rapid" of titration is difficult to define given the patient factors that influence clozapine clearance.[39] (See section: *Personalizing titrations based on patient specific factors for more details*).
- Once daily at bedtime or larger evening doses may be considered for adherence and/or daytime sedation
- Slower titration may minimize inflammatory adverse reactions associated with clozapine

Figure 1. Example of an initial clozapine titration schedule for healthy adults **in hospital settings**

Day	AM Clozapine Dose (mg)	HS Clozapine Dose (mg)	Total Daily Dose (mg)
Day 1	0	12.5	12.5
Day 2	0	25	25
Day 3	0	50	50
Day 4	25	50	75
Day 5	50	50	100
Day 6	50	75	125
Day 7	50	100	150
Day 8	75	100	175
Day 9	100	100	200
Day 10	100	125	225
Day 11	100	150	250
Day 12	100	175	275
Day 13	100	200	300

- Further dose titration should be done at 25-50 mg/day intervals as tolerated to achieve optimal effectiveness

Figure 2. Example of initial clozapine titration schedule for inpatients who are older adults, taking CYP1A2 inhibitors, are CYP1A2 poor metabolizers, do not tolerate standard titration, or otherwise at increased risk for adverse effects with clozapine

Day	AM Clozapine Dose (mg)	HS Clozapine Dose (mg)	Total Daily Dose (mg)
Day 1	0	12.5	12.5
Day 2	0	25	25
Day 3	0	25	25
Day 4	25	25	50
Day 5	25	25	50
Day 6	25	50	75
Day 7	25	50	75
Day 8	50	50	100
Day 9	50	50	100
Day 10	50	75	125
Day 11	50	75	125
Day 12	50	100	150

- Further dose titration should be done at 12.5-25 mg/day intervals as tolerated to achieve optimal effectiveness

Figure 3. Example of initial clozapine titration schedule for healthy adults in **ambulatory settings**

Week	AM Clozapine Dose (mg)	HS Clozapine Dose (mg)	Total Daily Dose (mg)
Week 1	0	25	25
Week 2	25	25	50
Week 3	25	50	75
Week 4	50	50	100
Week 5	50	75	125
Week 6	75	75	150
Week 7	75	100	175
Week 8	100	100	200
Week 9	100	125	225
Week 10	100	150	250
Week 11	100	175	275
Week 12	100	200	300

- Titrations may be conducted more conservatively, especially in the setting of a potential cross taper where monitoring is not as rigorous as inpatient settings
- A patient's tolerability, ability to manage medication or access to assistance, frequency of provider follow-up, and urgency of maximizing clozapine should be considered to individualize the outpatient rate of titration.
- Typically, consider 25 mg increases every 3-7 days with target doses as noted above. Further dose titration should be done at 12.5-25mg/day intervals as tolerated to achieve optimal effectiveness.

Figure 4. For target dose considerations, one study reported the following *mean* dosage corresponded to a serum level of 350 ng/mL for the following populations[40]

Demographic, smoking status: dose
Male, smoker: 525 mg/day
Male, non-smoker: 325 mg/day
Female, smoker: 435 mg/day
Female, non-smoker: 265 mg/day

Use of therapeutic drug monitoring

Figure 4 may be considered when planning for target dosing (rounded to the nearest dose available) for patients while considering other clinical factors. Practically, it is reasonable to check a serum clozapine level once a patient has reached 200-300 mg/day to assess safety in further maximizing doses. Earlier levels may allow for assessment of how the patient is metabolizing clozapine.

The half-life of clozapine is approximately 12 hours (though slightly longer with chronic exposure or older patients). In general, it can be presumed that a steady state concentration is reached in approximately 3 days of stable dosing. Clozapine serum levels may be obtained as a 12-hour post-dose morning level. For most institutions, this is a send-out laboratory test; thus, decisions to await results or continue titration should be based on a patient's clinical status.

Laboratory results are reported generally as "clozapine" and "norclozapine". Just the clozapine level (not norclozapine or total clozapine plus norclozapine) correlate to efficacy based on numerous studies. Beneficial serum levels have been cited as 200-370 ng/mL.[41,42] A target of approximately 350 ng/mL as a serum goal for clozapine response has been replicated.[43–45] However, it is important to treat the patient, not the number. Dose/serum level should be individualized, based on response and tolerability.

The clozapine concentration to dose (C/D) ratio can be used as a measure of clozapine clearance. A low C/D ratio indicates a rapid metabolizer, while a high C/D ratio indicates a poor metabolizer. The average C/D ratio for patients with European ancestry would typically range between 0.6–1.2. C/D ratios have been found to be different among different ancestral groups. For example, patients of East Asian ancestry have average C/D ratios of 1.2–2.4, indicating a lower clozapine clearance relative to those of European ancestry.[46]

The clozapine to norclozapine ratio is also used to assess clinical factors related to clozapine. Ratios greater than 2:1 (e.g., 5:1) may indicate the presence of a metabolic inhibitor, CYP450 polymorphism (i.e., poor metabolizer), a level drawn too early or not as a trough. A clozapine ratio less than 2:1 (i.e., 1:2) is an inverted ratio and suggestive of a metabolic inducer, CYP450 polymorphism (i.e., rapid to ultrarapid metabolizer), or non-adherence within the previous 24 hours.[47]

While the assessment of clozapine serum levels is not mandatory to safely and effectively use clozapine, they may be helpful to establish a baseline level when efficacy is maximized, assess adherence, guide dosing in certain situations, and attempt to answer questions related to unexpected tolerability or response.

There is no upper threshold of clozapine that is widely accepted. Higher doses and associated serum levels increase the risk for seizure and can increase the risk of severe clozapine-induced gastrointestinal hypomotility (CIGH)[48,49], although seizures may also occur during the initial titration phase.[50] A clozapine level greater than ~600-800 ng/mL may be considered a general threshold where the risk of increasing clozapine further may outweigh the clinical benefits.[51]

Personalizing titrations based on patient specific factors

The clozapine prescribing information lays out guidance for titration. However, there is a lack of consideration for other pertinent/important factors. This includes a patient's ancestry and the impact of inflammation on the CYP450 system.

2022 guidelines suggest that using a "typical" clozapine titration schedule may be too rapid for those of Asian ancestry or the Indigenous peoples of the Americas.[39] Literature also suggests C-reactive protein (CRP), nonsmoking status, female sex, and obesity to be patient-specific factors that predict an increase in clozapine levels.[52] These factors should be considered to improve the safety of inpatient clozapine initiation and titration. Assessing weekly CRP (and troponin where feasible) for at least four weeks (but up to eight weeks) is recommended for early detection of an acute inflammatory process evolving secondary to clozapine, which would warrant a decrease or holding the clozapine dose (at least temporarily).[52,53]

The guidelines also account for drug interactions, smoking, and obesity. Figure 5 outlines recommendations from these guidelines, and citations can be accessed for additional reading.[39]

Figure 5. Proposed Ancestry-Based Personalized Clozapine Dosing Titrations that Need Updates as New Data is Available[d]

Population	Expectation of Metabolism Status	Starting Dose	Week One Maximum Dose	Week Two Maximum Dose	Week Three Target Dose**	Week Four+ Target Dose**
Asian/ Indigenous peoples of the Americas	Lower*	6.25 mg	25 mg	50 mg	75 mg	75 mg to 150 mg
Asian/ Indigenous peoples of the Americas	Average	12.5 mg	50 mg	100 mg	150 mg	175 mg to 300 mg
European/ Western Asian^	Lower*	12.5 mg	50 mg	75 mg	100 mg to 125 mg	100 mg to 200 mg
European/ Western Asian^	Average	25 mg	100 mg	200 mg	250 mg to 300 mg	250 mg to 400 mg
American (non-Asian, non-Indigenous peoples of the Americas)	Lower*	12.5 mg	50 mg	100 mg	150 mg	150 mg to 300 mg
American (non-Asian, Indigenous peoples of the Americas); Possibly appropriate for African/Black populations[e]	Average	25 mg	100 mg	200 mg	300 mg	300 mg to 600 mg

* due to drug interaction, obesity, inflammation/infection, or genetic polymorphism; **females and non-smokers require lower doses; ^ ancestry from Asian countries west of Pakistan. This definition will need clarification as future genetic studies are completed. [d] Adapted from de Leon J, Schoretsanitis G, Smith RL, et al. Pharmacopsychiatry. 2022;55(2):73-86. [e] data extrapolated from olanzapine pharmacokinetics, African/Black populations may require higher dosing compared to those of European Ancestry.[54]

Hematologic monitoring

In 2025, the FDA eliminated the clozapine REMS program. This removed requirements for registration of patients, prescribers, and pharmacies. It also eliminated the need for laboratory reporting. However, as of July 2025, the FDA still recommends following the current prescribing information (Table 2).

Additionally, there have been reports published that indicate the most serious neutropenia occurs "within 18 weeks of treatment and becomes negligible after two years."[55] The authors of this toolkit suggest less stringent monitoring could be considered as early as 18 weeks after treatment initiation.[55] A 2025 consensus[53] has recommended the following ANC monitoring:

- Weekly ANC testing for 18 weeks, then -
- Monthly ANC testing until 2 years after clozapine commencement, then -
- Annually ANC screening for hematologic malignancy

Deviation from FDA guidance will likely evolve, prior to updates to the prescribing information. This should be based on the risks and benefits of clozapine continuation in the setting of missing or deferred ANC monitoring, as well as accounting for the greater period of risk for severe neutropenia (i.e., the first 18 weeks). Local or institutional considerations may need to be addressed to reconcile discrepancies from FDA guidance, as monitoring outside the prescribing information would still be considered "off-label".

Table 2. FDA recommended ANC monitoring frequency based on current prescribing information as of July 2025

ANC Level	Treatment Recommendation	ANC Monitoring
Initial requirements	**General Population** • Initiate treatment if ANC ≥ 1500/µL **BEN* Population** • Initiate treatment if ANC ≥ 1000/µL • Obtain at least 2 baseline ANCs prior to initiation	**General/BEN Population** • Weekly from initiation to 6 months • Every 2 weeks from 6-12 months • Monthly after 12 months
Mild Neutropenia (1000 to 1499/µL)	**General Population** • Continue treatment **BEN Population** • As above	**General Population** • Three times/week until ANC ≥ 1500/µL; then return to previous monitoring interval **BEN Population** • As above
Moderate Neutropenia (500 to 999/µL)	**General Population** • Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Resume once ANC ≥1000/µL **BEN Population** • Recommend hematology consultation • Continue treatment	**General Population** • Daily until ANC ≥1000/µL, then 3 times/week until ≥ 1500/µL • Once ≥ 1500/µL weekly ANC for 4 weeks; then return to previous monitoring interval **BEN Population** • 3 times/week until ANC ≥ 1000/µL or ≥ known baseline • Once ANC ≥ 1000/µL, or at known baseline, check ANC weekly for 4 weeks, then resume last "Normal BEN Range" ANC monitoring interval if clinically appropriate
Severe Neutropenia (less than 500/µL)	**General/BEN Population** • Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless the prescriber determines benefits outweigh risks**	**General Population** • Daily until ANC≥1000/µL, then 3 times/week until ≥ 1500/µL • Once ≥ 1500/µL weekly ANC for 4 weeks; then return to previous monitoring interval • If rechallenged, resume as new patient once ANC ≥ 1500/µL** **BEN Population** • Daily until ANC ≥ 500/µL, then 3 times/week until ≥ known baseline • If rechallenged, resume as a new patient once ANC ≥ 1000/µL**

Note: For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), ANC monitoring can be reduced to once every six months, after a discussion with the patient and their caregiver.
*BEN = Benign ethnic neutropenia (BEN is the verbiage used within the prescribing information, however more appropriately referred to as individuals with Duffy antigen receptor for chemokines-null or Duffy-null associated neutrophil count)
**Rechallenge, in general, is not recommended. However, it may be considered based on risk versus benefit. Hematology involvement would be important, along with informed consent from patient/caregiver.

Table 3. Management of clozapine breaks/discontinuations in treatment

If a patient is known to have missed doses of clozapine, some guidance is provided within the prescribing information. Access to rapid therapeutic drug monitoring may help guide clinical decisions as well.

Duration of Missed Dosing	Resumption Strategies	Comments
One day	Resume treatment at 40% to 50% of the established dose and retitrate	• Per prescribing information, retitration plan should be individualized based on risks of lower dosing and patient history • Retitration may be completed faster than the initial titration
Two days	Resume approximately 25% of the established dose	• Per prescribing information, plan should be individualized based on risks of lower dosing and patient history • Retitration may be completed faster than the initial titration
3 or more days	Resume clozapine at 12.5 mg or 25 mg and retitrate to the original dose	• Per prescribing information, plan should be individualized based on risks of lower dosing and patient history • Retitration may be completed faster than the initial titration
Abrupt discontinuation unrelated to neutropenia	N/A	• Continuation of the existing ANC monitoring for general population patients until ANC greater than or equal to 1500/µL and for BEN patients until ANC is greater than or equal to 1000/µL or above their baseline • ANC monitoring is required for any patient reporting onset of temperature that is equal to or greater than 38.5°C or 101.3°F for at least 2 weeks after discontinuation • Monitor for cholinergic rebound (e.g., sweating, headache, nausea, vomiting, diarrhea), emergent dyskinesias, and worsening psychosis
Planned discontinuation	N/A	• Taper clozapine over 1 to 2 weeks, as tolerated • Longer tapers may be necessary

Clozapine and COVID-19 or Other Infectious Processes

While the influence of acute inflammatory or inflammatory process on clozapine metabolism has been known for decades, the COVID-19 pandemic further highlighted this issue. In patients with treatment-resistant schizophrenia managed on clozapine therapy, a concern especially lies in two areas:

1. Managing clozapine therapy in patients with acute infectious processes
2. Monitoring drug interactions for treatment of acute infectious processes

Inflammatory responses associated with respiratory tract infections (like COVID-19) may cause an increase in clozapine serum levels, leading to symptoms of clozapine intoxication (e.g., sedation, lethargy, sialorrhea, ataxia, etc.).[58,59] This is the result of inflammatory cytokines inhibitor effect on the CYP450 system, including CYP1A2. It is possible that greater than a 50% dose reduction may be required in some cases.[60] However, in the absence of fever, significant increase of CRP, or other systemic symptoms of inflammation, reductions may not be needed.[61] A small case series suggested that the severity of infection may be key to the significance of clozapine level elevations, however, more research is needed. Given the nature of clozapine use and risk of psychiatric relapse with discontinuation, literature supports the safe, continued use of clozapine during acute infectious or inflammatory process with careful monitoring and readiness to adjust doses as necessary.

Awareness of interactions between anti-infective agents and clozapine is important as this may further exacerbate any potential for clozapine toxicity.

It is possible that a future pandemic may give rise to similar issues seen with clozapine management during COVID-19.[53–56] Reflecting on published literature may be useful in the future. For patients on monthly monitoring for at least one year or more, a consensus statement was released to maintain access to routine ANC monitoring without causing exposure to COVID-19 infection.[57]

- The frequency of ANC monitoring may be reduced to every 3 months with a dispensed 90-day supply prescription for patients fulfilling the following criteria:
    - Who has been on clozapine for over one year
    - ANC has never been under 2,000/µL (1500/µL if patient has history of BEN)
    - No safe or practical access to ANC testing

This is similar to European Clozapine Task Force 2025 recommendations that proposed weekly ANC monitoring for 18 weeks, then monthly to year one after initiation, then every 12 weeks until year two after initiation, and then annually (assumes no neutropenia throughout).[58]

Other considerations that should be addressed related to the reduced ANC monitoring variance include informed consent regarding the risks, discussions about signs and symptoms of infection, and access to a thermometer. In addition, other practical considerations should be assessed in the presence of infectious processes, including but not limited to changes to smoking, caffeine habits, activity, and diet, which may alter clozapine metabolism or affect gastrointestinal hypomotility.

Potential adverse events associated with clozapine

Gastrointestinal hypomotility

CIGH is a common and potentially life-threatening adverse effect of clozapine, decreasing gastrointestinal (GI) transit up to four times what is considered "normal." It is thought that both significant anticholinergic effects and 5-HT3 antagonism play a role in the cause of CIGH.[49,59] The most serious events that have occurred are necrosis, bowel obstruction, and ischemia which can lead to GI perforation, sepsis, and death.[60] This potential adverse event was concerning enough to prompt the FDA to strengthen warning about clozapine induced constipation in an FDA Drug Safety Communication in 2020.[61]

The monitoring and prevention of CIGH is an important component of clozapine treatment, particularly with the understanding that patient reported constipation does not correlate well to actual hypomotility.[62] Establishing baseline bowel patterns and performing regular monitoring of bowel function can increase awareness and detection of preventable complications. In addition, patients who may not reliably report symptoms should receive thorough monitoring, including a physical exam as needed and documentation of active bowel sounds.

Risk factors for the development of severe complications of CIGH include but are not limited to: higher doses, concomitant anticholinergic agents, concomitant opioids or other medications that slow intestinal motility, and inhibition of CYP450 1A2 (including febrile illness).[36,49,63]

Red flags requiring closer attention and treatment include increased duration between bowel movements, moderate to severe abdominal pain, abdominal distension, diarrhea (i.e., overflow constipation), vomiting, absent/high-pitched bowel sounds, metabolic acidosis, hemodynamic instability, and leukocytosis.

There is no "gold standard" for the prevention and treatment of CIGH, and while some protocols have been published, guidelines have not adopted any one specific treatment algorithm.[64] Recognizing different health care settings that manage clozapine may have site specific protocols or treatment steps to manage CIGH, Table 4 offers information on potential treatment options, rather than a specific algorithm. It should be noted that bulking agents such as psyllium or methylcellulose should be avoided with clozapine. Given that clozapine causes a state of slow-transit constipation, there is an increased risk of bowel perforation in patients with existing CIGH who use bulking agents.

For the treatment of chronic constipation due to clozapine use, there is limited evidence to support the use of any one specific agent. Most evidence is extrapolated from guidelines for chronic constipation.[65–67] A systematic review on the management of chronic constipation supports the use of osmotic agents (e.g., polyethylene glycol) as first line options, generally recommended to be used on a scheduled basis.[66] Other guidelines also support the use of over-the-counter agents initially.[67] Initial drug choice should be maximized and then augmented with a second agent versus discontinuing the first agent. Patients may often require more than one agent for the management of mild to moderate CIGH. For immediate results, magnesium citrate 300 mg by mouth once, glycerin suppository, and/or a sodium phosphate enema may be given (no specific clozapine-related evidence exists). Secretagogues should be considered when first line options are ineffective.[67] These include, linaclotide, plecanatide, or lubiprostone.

There is also no systematic assessment of the benefits of using medication as prophylaxis against CIGH. However, up to 80% of patients will develop some degree of CIGH, thus clinicians must assess the risks and benefits of CIGH prophylaxis, such as a patient's ability to reliably report symptoms, barriers to increasing medication burden, etc. Prophylaxis has been recommended given the frequency of constipation with clozapine.[64]

Table 4. Pharmacotherapy for the prevention of CIGH*

Medication	Class	Usual Dosing Strategies	Comment
Polyethylene glycol 3350	Osmotic	17 grams once to three times daily	• Treatment of choice based on guidelines for chronic constipation • Available only as a powder for oral solution, patient specific considerations for adherence
Lactulose	Osmotic	10-40 grams daily	• Available in liquid and powder for dissolution
Bisacodyl	Stimulant	5-15 mg daily	• A stimulant laxative with supportive evidence for the management of chronic constipation • Considered a second line option[66]
Senna (or Senna plus docusate)	Stimulant (stimulant plus softener)	17.2 mg twice daily; increased by 1-2 tablets every few days until constipation resolved	• No systematic evaluation has been done specifically for CIGH with senna (stimulant), docusate (softener), nor the combination. Recommendations for the combination have been extrapolated from concepts used to manage opioids, which included constipation and as a second line in chronic constipation

Table 4. Pharmacotherapy for the prevention of CIGH*

Orlistat	Lipase inhibitor	120 mg three times daily	• Lacks central nervous system side effects; however, gastrointestinal side effects may limit patient acceptability • One randomized placebo-controlled trial was conducted[68]
Magnesium hydroxide	Laxative; osmotic salt	400-1200 mg four times daily	• Limited evidence to support use in chronic constipation
Lubiprostone	Chloride channel activator	24 mcg daily, increased to twice daily	• Secretory agent • May be cost prohibitive
Linaclotide, Plecanatide	Guanylate cyclase-C agonist	Linaclotide: 72-290 mcg daily Plecanatide: 3 mg daily	• Secretory agent • May be cost prohibitive
Bethanechol	Cholinergic agonist	10 mg three times daily	• Evidence limited to a case report describing benefit in severe CIGH when clozapine is the only antipsychotic effective for a patient[69]
Erythromycin	Motolin agonist	150 to 2000 mg daily in divided doses	• Thought to promote gastric emptying through motolin receptors • Evidence limited to a case report describing benefit and ability to restart clozapine after severe CIGH[70]

*No systematic studies or reports specifically for management of CIGH for agents unless cited otherwise. Data extrapolated from recommendations for the management of chronic constipation.[66,67]
Bulking agents such as psyllium should be avoided.

Sialorrhea and pneumonia

Clozapine-induced hypersalivation is a common side effect (up to 92%) that not only leads to embarrassment, but may also lead to more dangerous sequelae such as aspiration pneumonia.[71,72] Suspected mechanisms of sialorrhea, also known as ptyalism, include potent agonism at muscarinic M3&4 receptors and blockade of α-2 adrenergic receptors that play a role in enhanced salivary flow.[72–74] Pneumonia in general is a leading cause of death among patients treated with clozapine. The underlying mechanism for clozapine-associated pneumonia is likely multifactorial and may involve clozapine-induced sedative effects, decreased swallowing ability, and sialorrhea.[75]

The decision to treat sialorrhea pharmacologically may be based on severity, patient choice, and development of pneumonia or recurrent pneumonia in the setting of sialorrhea. See below for select treatment strategies, noting that the evidence supporting each option is limited, there is a lack of objective measures used in studies to assess change in saliva production, and all options are used off-label.[72,74,76–80] Some medications used to treat sialorrhea may cause or worsen side effects attributed to clozapine such as decreasing gastric motility.

Table 5. Medications used for clozapine-induced sialorrhea

Treatment Option	Mechanism for Reduction of Saliva	Usual Dose Range	Notes
Benztropine tablet	Muscarinic receptor antagonist*	0.5-6 mg daily in one to three divided doses	• There is a warning with clozapine and concomitant anticholinergic agents due to the added systemic anticholinergic effects, especially on the gastrointestinal tract.
Atropine 1%, ophthalmic drops		1-6 drops sublingually in one to three divided doses, swished around like a mouthwash	• Needs multiple daily dosing (fast relief but may not be sustained) • Minimal systemic absorption/well tolerated • Demonstrated to have improved efficacy over amitriptyline and ipratropium in a small randomized trial[81] • A separate chart review evaluation demonstrated efficacy with both atropine and tropicamide drops over the use of amitriptyline[82]

Table 5. Medications used for clozapine-induced sialorrhea

Treatment Option	Mechanism for Reduction of Saliva	Usual Dose Range	Notes
Ipratropium bromide 0.03-0.06%, nasal spray	Muscarinic receptor antagonist*	1-2 sprays sublingually one to three times daily	• Needs multiple daily dosing (fast relief but may not be sustained) • Minimal systemic absorption • Well tolerated • Small reports suggest benefit, negative randomized controlled trial[76,83]
Oxybutynin		5-10 mg in divided doses	• Limited to one case report[84] • Added systemic anticholinergic effects
Trihexyphenidyl		2-15 mg at bedtime or in divided doses	• Limited evidence[85,86] • Added systemic anticholinergic effects
Tropicamide 0.5-1%, ophthalmic drops		1–2 drops placed at each side of the mouth daily, swished around like a mouthwash	• M4 specific antagonist • Experience limited to case reports[87] • A separate chart review evaluation demonstrated efficacy with both atropine and tropicamide drops over the use of amitriptyline
Scopolamine patch		1 mg patch every 72 hours	• Patch was studied with greater improvement than that reported with oral treatment (tablets not available in the US) • Randomized controlled trial demonstrated benefit over placebo[88]
Amitriptyline tablet		25-100 mg daily	• Added systemic anticholinergic effects, can lower seizure threshold, sedation, and hypotensive side effects

Table 5. Medications used for clozapine-induced sialorrhea

Treatment Option	Mechanism for Reduction of Saliva	Usual Dose Range	Notes
Diphenhydramine	Muscarinic receptor antagonist*	50 mg at bedtime	• Limited evidence[89] • Added systemic anticholinergic and sedative effects • Was endorsed by 2025 Veterans Affairs and US Department of Defense Clinical Practice Guidelines[90]
Glycopyrrolate tablet/solution		1-8 mg daily in one to three divided doses	• Does not cross the blood brain barrier and therefore results in more peripheral rather than central anticholinergic effects • Randomized, crossover study demonstrated benefits and a lack of impact on cognition compared to another oral anticholinergic[91]
Sofpironium bromide		5% gel used once a day externally over the parotid and submandibular glands (Study completed in Japan. Available in the US only as 12.45% gel indicated for axillary hyperhidrosis)	• Small study used "Drooling Severity and Frequency Scale" to demonstrate improvement by 40% after six weeks of treatment[92]
Clonidine tablet/patch	Alpha$_2$-adrenergic agonists	0.05-0.1 mg daily 0.1-0.2 mg patch weekly	• Risk of hypotension in combination with clozapine • Side effects: Hypotension and sedation (clonidine>guanfacine, lofexidine), dizziness, urinary retention, constipation • Limited evidence across the class[77,93,94]
Guanfacine tablet		1 mg daily	
Lofexidine tablet		0.2 mg two times daily (available in the U.S. as 0.18 mg tablets	

Table 5. Medications used for clozapine-induced sialorrhea

Treatment Option	Mechanism for Reduction of Saliva	Usual Dose Range	Notes
Botulinum Toxin	Inhibits acetylcholine release in salivary glands	Variable based on specific agent; 150-2500 IU in divided administrations in the parotid and/or submandibular glands	• Side effects: pain, tenderness, bleeding, jaw dislocation (rare) • Cost/administration barriers • Limited evidence • Duration of action up to 8 to 16 weeks[95,96]
Metoclopramide	Dopamine antagonist, enhances acetylcholine response in GI tract	Initiated at 10 mg once daily, can be increased to 10mg three times daily (total daily dose of 30 mg/day)	• One randomized controlled trial[80] • Associated with tardive dyskinesia (rare)
Sulpiride (not available in the US)	Mesolimbic dopamine antagonist	150-300 mg/day	• Single open study with significant reduction in symptoms • Used "Nocturnal Hypersalivation Rating Scale" (NHRS) as an objective measure
Amisulpiride (only available as parenteral agent in US, approved for postoperative nausea and vomiting)	Dopamine antagonist	50-1000 mg/day	• Case reports, case series and a small, randomized study increased significant improvements • Some utilized NHRS
Moclobemide (not available in the US)	Reversible monoamine oxidase inhibitor	150-300 mg/day	• One small open study with two thirds experiencing benefit in symptoms

*Contraindications: narrow-angle glaucoma, bladder obstruction, prostatic hypertrophy, and gastrointestinal motility disorders. Systemic muscarinic receptor antagonists may increase the risk of blurred vision, constipation, dry mouth, impairment in cognitive functioning, sedation, tachycardia, and urinary retention.

Myocarditis screening

Myocarditis is a boxed warning and can be fatal if unrecognized when early symptoms present. Screening for signs and symptoms of myocarditis is crucial to safely discontinue the medication prior to potentially fatal outcomes. Unfortunately, early signs and symptoms are non-specific such as tachycardia, fever, chest pain, malaise, and flu-like symptoms. These signs and symptoms can mimic the expected side effects of normal clozapine titration, even without myocarditis. Even vague gastrointestinal complaints, nausea, and diarrhea have been reported at the onset of myocarditis.[97–99] Important key facts are that clozapine-induced myocarditis is most likely to occur within the first 8 weeks of therapy with peak incidence at week 3 of exposure.[100]

Medical literature has increased awareness regarding clozapine-induced myocarditis and the potential to detect early cases. Ronaldson et al. described that when troponin was more than twice the upper limit of normal and CRP was over 100 mg/L, there was an estimated sensitivity for symptomatic clozapine-induced myocarditis of 100%.[101] However, there is no accepted approach to screening asymptomatic patients. Some institutions may have monitoring protocols that guide testing for the first four to eight weeks and may include CRP, troponins, brain natriuretic peptide (BNP), creatine kinase (CK), and/or electrocardiogram (ECG).[39,102,103] A 2025 consensus statement highlighted an algorithm for myocarditis monitoring during the first 4 weeks to include high sensitivity troponin, CRP, and CBC. In addition, most experts participating agreed that therapeutic drug monitoring in week 2 would be useful to understand how a specific patient is metabolizing clozapine.[103]

Regardless, there should still be an emphasis on monitoring non-specific signs and symptoms with a low threshold for obtaining troponin and CRP, especially within the first 8 weeks of clozapine initiation. Routine echocardiography prior to starting or during clozapine therapy is controversial outside the setting of new signs/symptoms, may not be cost-effective, and adds a potential barrier to clozapine initiation.[104] Factors such as a patient's physical exam, risk factors, family history, cost, and availability should be taken into account.

For cases where a clozapine rechallenge is warranted after myocarditis, studies report an average success rate of approximately 60%.[105] If a clozapine rechallenge is undertaken, a very slow titration regimen accompanied by standard or intensified screening measures is recommended. When possible, avoiding valproate, olanzapine, and mRNA vaccinations in the weeks before or after initiation may help decrease the risk of myocarditis.[105,106]

Table 6. Select adverse events

System/ Select Adverse Event	Occurrence	Comment/Additional Reading
Cardiovascular		
Cardiomyopathy	Rare (0.02-1.0%)	• Dilated cardiomyopathy is the most common presentation • Secondary to myocarditis or isolated • If in the absence of myocarditis, it usually develops after 6 months of therapy, possibly from persistent tachycardia • Cautious continuation is possible based on severity and ability to continue ongoing monitoring • Suggested reading[107,108]
Hypotension, bradycardia, and syncope	Common (9%)	• High risk in the initial titration period and with rapid titration • Consistent with neurally mediated reflex bradycardia and resulting hypotension • When > 2 days of clozapine are missed, retitration is required to reduce these risks • Rare serious events, including death, have been reported • In the setting of overdose and shock requiring vasopressors, clozapine may blunt the effects of catecholamine vasopressors (e.g., norepinephrine, phenylephrine). Vasopressin or angiotensin II may be preferred.[109]
Myocarditis	Rare (0.02-1.0%)	• Routine troponin and CRP monitoring for 4 to 8 weeks has been recommended • Slower titration may minimize risk
Tachycardia (isolated)	Common (25%)	• Can occur during titration and may be transient; significant changes should warrant investigation of other signs/symptoms consistent with myocarditis • Persistent tachycardia may be a risk factor for cardiomyopathy and cardiovascular mortality • Persistent and/or symptomatic tachycardia should be assessed to determine if a lower dose is possible or to rule out underlying medical causes and for the need of treatment (beta-blocker or non-dihydropyridine calcium channel blocker) despite a lack of clozapine-specific data[110,111]

Table 6. Select adverse events

System/ Select Adverse Event	Occurrence	Comment/Additional Reading
Dermatologic		
SJS/TEN/other hypersensitivity reactions, including DRESS	Rare (<1%)	• Information limited to case reports and post-marketing surveillance • Monitor for prodromal symptoms and, as applicable, rash, lymphadenopathy, organ dysfunction, and fever in combination with eosinophilia
Endocrine/Metabolic		
Hyperlipidemia	Common (5-38%)	• Monitoring and treatment by standard guidelines
Glucose dysregulation (pre- and diabetes mellitus, diabetic ketoacidosis)	Variable based on severity	• Monitoring and treatment by standard guidelines • Monitor for signs of polyphagia, polydipsia, and polyuria • Mild to moderate glucose dysregulation: common • Diabetes mellitus: uncommon • Diabetic ketoacidosis: rare
Food craving/binge eating	Common (> 10%)	• Reported to be as high as 23%[112] • Baseline dietary patterns and weight should be monitored
Weight gain	Common (60-75%)	• ADA guidelines recommend obtaining weight at baseline, after 4 weeks, 8 weeks, 12 weeks, and then quarterly if within normal parameters • Weight gain of 5-13 kg in the first year of therapy would not be unexpected • Metformin has recently been recommended by guidelines to be used prophylactically or use of a GLP-1 receptor agonist when indicated[113]
Gastrointestinal		
Dyspepsia/ heartburn	Uncommon-common (~4-14%)	• Occurs at higher rates compared to other antipsychotics • To avoid interactions, consider pantoprazole over omeprazole, if a PPI is needed[114,115]
Gastrointestinal hypomotility	Common (30%)	• See table 4
Pancreatitis	Rare (<1%)	• Several case reports published • Monitoring triglycerides per guidelines, as well as amylase and lipase if symptomatic
Parotid or submandibular inflammation	Rare (<1%)	• Limited to case reports • Rule out infectious or other pathologies

Table 6. Select adverse events

System/ Select Adverse Event	Occurrence	Comment/Additional Reading
Transaminitis/ hepatic failure	Transaminitis: Common (33-78%) Hepatic failure: Rare (<1%)	• Usually mild and transient elevations with no clinical sequelae[116,117] • As an inflammatory reaction an increase in CRP and eosinophilia may be seen • LFTs may not be commonly monitored but some have suggested baseline and during titration or just clinically as indicated[118] • Fulminant liver failure rare
Sialorrhea	Common (30-80%)	• See table 5
Genitourinary		
Nocturnal enuresis	Common (21%)	• More common than with other antipsychotics[119] • Sedative, anticholinergic, and alpha-adrenergic mechanisms • Dose reduction or division may be beneficial • Limited evidence suggests benefits with aripiprazole, desmopressin, ephedrine, oxybutynin
Hematologic		
Eosinophilia (isolated)	Uncommon (~1%)	• The threshold for discontinuation no longer exists in prescribing information but warrants careful assessment of other pathologies associated with eosinophilia • Very high eosinophil count may lead to eosinophilic infiltration of organs
Neutropenia	Rare (1.3%)	• Monitoring per the package insert is recommended by the FDA (current as of July 2025) • A 2025 consensus statement has suggested looser requirements based on risk period of neutropenia (see hematologic monitoring section)[56,58] • Other causes of neutropenia must be examined • Rechallenges after severe neutropenia have been described. Hematology consult is recommended. Clozapine could be continued if neutropenia is from another cause and cell count recovery occurs as expected (e.g., during chemotherapy treatment).
Thrombocyto-penia	Rare (< 1%)	• Limited to post-marketing and case reports

Table 6. Select adverse events

System/ Select Adverse Event	Occurrence	Comment/Additional Reading
Venous thromboem-bolism (VTE)	Rare (< 1%)	• Clinicians should minimize modifiable risk factors and advise recipients to remain physically active • VTE prophylaxis in outpatient populations is not recommended • Suggested reading[120–122]
Neurologic		
Extrapyramidal symptoms	Rare-uncommon	• Very low D2 occupancy and affinity with fast dissociation at therapeutic doses
Neuroleptic malignant syndrome (NMS)	Rare/ unknown	• NMS presentation may be atypical (i.e., slight variation from FGA-induced NMS) with less frequently seen hyperthermia, rigidity, lower and slower creatine kinase rise
Myoclonus	Rare	• Can occur at any dose but may indicate elevated levels or increased seizure risk • Valproate and derivatives have been shown to successfully mitigate clozapine-induced myoclonus
Sedation	Common (~40%)	• Tolerance may develop • Consolidating the total or majority of the dose to evening dosing may improve daytime somnolence
Seizures	Uncommon	• Higher clozapine doses are associated with increased seizure rates; incidence variable by publication, estimates include[123] ○ > 600 mg/day — 4.4% ○ 300 to 600 mg/day — 2.7% ○ < 300 mg/day — 1% • Most common: generalized tonic-clonic seizures • Prophylaxis in the absence of a prior seizure is controversial • Suggested readings[124,125]
Psychiatric		
Obsessive-compulsive symptoms / disorder	Uncommon-Common (estimates as high as 20%)	• Emergence or worsening of obsessive-compulsive symptoms may occur • Management strategies reported in the literature include starting an antidepressant (e.g., serotonin reuptake inhibitor), lowering the dose (if possible), and/or adding aripiprazole 15 mg/day

Table 6. Select adverse events

System/ Select Adverse Event	Occurrence	Comment/Additional Reading
Renal		
Renal failure/AKI/AIN	Rare (< 1%)	• Limited information, per post-marketing and case reports
Pulmonary		
Pneumonia	Uncommon-common	• Clozapine is associated with a greater risk of pneumonia compared to other antipsychotics • Several mechanisms exist to explain this phenomenon: ○ Aspiration secondary to untreated sialorrhea ○ Drug-induced dysphagia ○ Anticholinergic properties ○ Hypogammaglobulinemia
Pulmonary embolism	Rare (< 1%)	• See VTE under **Hematologic**
Serositis	Rare (< 1%)	• Limited information, per post-marketing and case reports
Other		
Withdrawal	Common with abrupt discontinuation	• Cholinergic rebound can occur after the abrupt discontinuation of clozapine; minimal guidance in the literature to support one treatment over another, including restarting clozapine as able, pharmacotherapy to manage symptoms (e.g., nausea, diarrhea), and use of oral anticholinergic agents can be initiated • Other withdrawal reactions have been reported including rebound psychosis, catatonia, emergent hyperkinetic movements, and serotonin syndrome[126]

Abbreviations: ADA= American Diabetes Association, AIN= Acute interstitial nephritis, AKI=Acute kidney injury, DRESS= Drug Rash with Eosinophilia and Systemic Symptoms, FGA = first-generation antipsychotic, PPI= Proton pump inhibitor, SJS=Stevens-Johnson syndrome, TEN= Toxic epidermal necrolysis

Patient rating scale

Glasgow antipsychotic side effects scale for clozapine

The Glasgow antipsychotic side effects scale is a reliable and valid tool that was modified to be specific to clozapine and address the side effects that are common and/or serious.[127] Patients rate side effects if they have occurred in the past week, as Never (0 points), Once (1 point), A few times (2 points), or Every day (3 points). There is an additional column for patients to indicate if the side effects are severe or distressing, regardless of the frequency. Questions are related to sedation, hypotension, tachycardia, myoclonus, sialorrhea, anticholinergic side effects, gastrointestinal side effects, nocturnal enuresis, diabetes mellitus, weight gain, and sexual dysfunction.

Table 7. Side effect severity based on Glasgow antipsychotic side effect scale score

Score	Severity
0-16	Mild or absent
17-32	Moderate
33-48	Severe

The use of a systematic process to screen for clozapine-related adverse events should be considered to help prevent and detect complications of clozapine that may interfere with treatment success and/or adherence. Use of the scale must also consider the baseline score, the change of score over time, and the clinical interpretation of side effects categorized as “severe or distressing.”

The complete article validating the tool and tool itself can be found in the following publication: Hynes C, et al. Glasgow Antipsychotic Side-effects Scale for Clozapine - Development and validation of a clozapine-specific side-effects scale. Schizophr Res. 2015 Oct;168(1-2):505-13. doi: 10.1016/j.schres.2015.07.052. Epub 2015 Aug 12.

Partial clozapine response

It is estimated that up to 60% of patients prescribed clozapine will not have an adequate response to the medication, accounting for both partial responders and non-responders.[128] It is important to assess several factors before concluding that clozapine treatment has failed or initiating augmentation therapy. When applicable, adherence must be diligently assessed through patient interviews and collateral information from family and/or caregivers. Obtaining a serum level can be useful as a baseline comparison to evaluate adherence, determine optimal dosing, and assess the impact of potential interactions.

Augmentation strategies have not been well studied, and there is no consensus on the optimal clozapine augmentation agent(s). Current options include mood stabilizers, antipsychotics (both first- and second-generation, including long-acting injectables), antidepressants, glutamatergic agents, as well as electroconvulsive therapy (ECT), which has shown efficacy in primary psychotic disorders and has been explored as an adjunct for clozapine-resistant cases.

Several meta-analyses have reviewed clozapine augmentation strategies, identifying agents with varying levels of evidence for efficacy. A 2018 meta-analysis identified aripiprazole, valproate, and memantine as promising options. A 2019 meta-analysis found no augmentation strategies that reached a Grade A recommendation based on SIGN criteria; however, it provided Grade B support for first- or second-generation antipsychotics and certain antidepressants—fluoxetine, duloxetine, and citalopram—for addressing persistent negative symptoms. The meta-analysis noted ECT's potential for persistent positive symptoms. A 2023 meta-analysis found mirtazapine to have the largest effect size, followed by ECT. The 2024 Bayesian network meta-analysis ranked mirtazapine and memantine highest for efficacy and safety. Overall, the choice of augmentation strategies should consider both the target symptoms and the level of supporting evidence.

A complete review of clozapine augmentation strategies is beyond the scope of this toolkit; however, here is a list of selected references, including reviews, meta-analyses, studies of varying degrees of strength **(*including negative reports*)**, and reports that may help guide augmentation selection:

General

- Reviews/meta-analyses[128–146]

Antipsychotics

- Aripiprazole[147–159]
- Cariprazine[160–165]
- Long-acting injectable antipsychotics[166–170]
- Paliperidone[171,172]
- Pimozide[173–175]
- Risperidone[176–186]
- Ziprasidone[181,185,187–189]
- Lurasidone[190]

Antidepressants

- Duloxetine[191]
- Fluoxetine[192]
- Fluvoxamine[193,194]
- Mirtazapine[195,196]

Mood stabilizers/antiepileptics

- Lamotrigine[197–201]
- Lithium[202–205]
- Topiramate[206,207]
- Valproate[202,208,209]

Other

- Clonidine[210]
- D-cycloserine[211,212]
- Donepezil[213]
- ECT[214–224]
- L-carnitine[225]
- Levothyroxine[226]
- Memantine[227–229]
- Minocycline[230–233]
- Modafinil[234,235]
- N-acetylcysteine[236,237]
- Ondansetron[238]

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