Psychosis Clinical and Research Program
Massachusetts General Hospital

Psychosis Clinical and Research Program (PCRP) Clozapine Care Framework

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I. Background

Clozapine is the most effective antipsychotic for treating schizophrenia spectrum disorders and remains the only FDA-approved medication for treatment-resistant schizophrenia (TRS) and for reducing suicidality in schizophrenia spectrum disorders. Clozapine treatment is also associated with reduced all-cause mortality.[1] It effectively mitigates aggression and has minimal extrapyramidal side effects (EPS), making it suitable for catatonia, tardive dyskinesia, and psychosis associated with Parkinson's disease. In addition, modest evidence supports its use in refractory mood disorders, substance use disorders, and psychogenic polydipsia.[2-4]

Despite its well-established benefits, clozapine remains underutilized, primarily due to challenges involving regular blood monitoring, side effect management, and limited clinician familiarity with optimal prescribing practices. The discontinuation of the Clozapine Risk Evaluation and Mitigation Strategy (REMS) requirement in 2025 may help reduce barriers to clozapine's broader use.

This summary incorporates guidance from three international expert consensus statements (the global Delphi panel guideline,[5] the proposed European monitoring guideline,[6] and the Clozapine Associated Myocarditis [CAM] guideline[7]), emphasizing proactive monitoring strategies and interdisciplinary collaboration. This approach aims to minimize adverse effects and improve the safe and effective management of clozapine treatment in adult outpatients. Ultimately, this summary supports clinicians in promptly identifying appropriate candidates for a clozapine trial, safely initiating therapy, and effectively maintaining clozapine treatment.

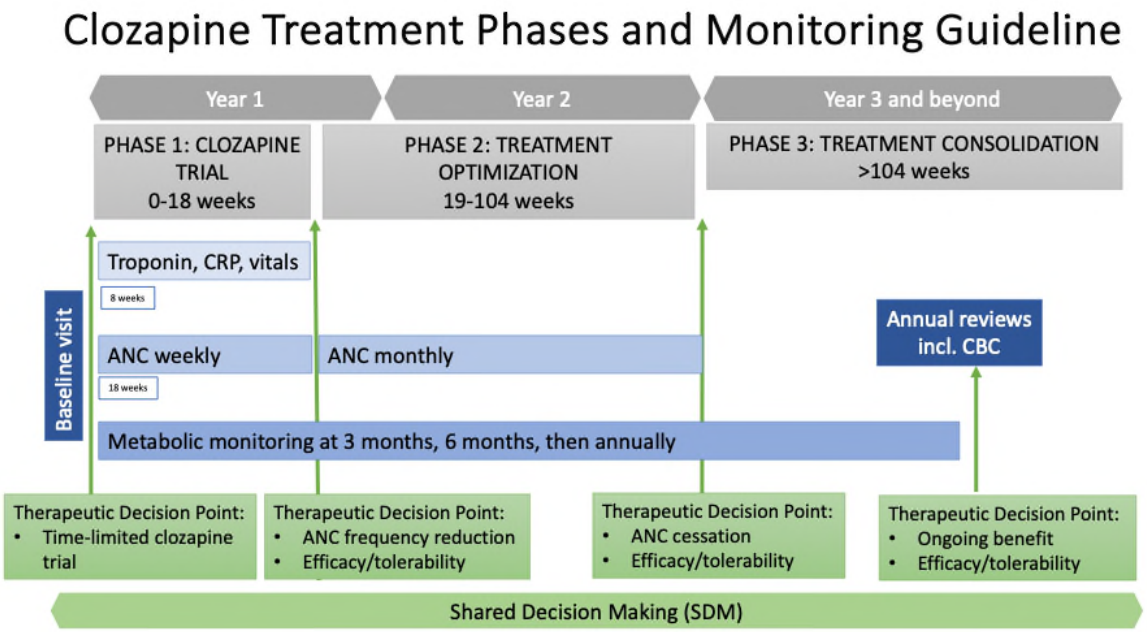
Clozapine is associated with an increased risk of severe neutropenia and agranulocytosis, making absolute neutrophil count (ANC) monitoring a critical component of safe prescribing. The risk for clozapine-associated severe neutropenia is not constant: it is highest in the first few months, with a sharp decline after 4 months.[5] While the risk never reaches zero, it becomes low and comparable to that of many other medications, including other antipsychotics, for which routine ANC monitoring is not performed. Until recently, the FDA required participation in the Clozapine REMS monitoring system, which mandated continuous ANC monitoring throughout treatment. In response to increased clinical evidence of actual risk and stakeholder advocacy for a less burdensome process, effective June 13, 2025, the FDA eliminated the Clozapine REMS, with the aim of increasing access to clozapine. As a result, clinicians are now responsible for managing neutropenia risk, weighing current clinical evidence against the very conservative monitoring schedules still present in the FDA package insert.

To support outpatient clinicians, the MGH PCRP Clozapine Workgroup, in collaboration with the Massachusetts Department of Mental Health (DMH), reviewed recent published guidelines,[5-7] and developed the following clinical summary. This summary is not intended to replace established hospital policies or information presented on Lexi-Drugs or UpToDate. Instead, this summary is created to assist front-line clinicians with using clozapine appropriately. This summary allows patients to reduce and eventually cease ANC monitoring, when clinically appropriate, consistent with the well-established reduced risk of clozapine-associated neutropenia over time.

II. Overview

Clozapine Treatment Phases

Conceptually, clozapine treatment can be organized into three phases: Clozapine initiation trial, clozapine optimization, and clozapine maintenance. Each phase has different goals and safety concerns. At the end of each phase, there is an opportunity to review with the patient, family and/or legal guardian the risks and benefits of clozapine. During the treatment maintenance phase, annual reviews of clozapine efficacy and medical illness burden should be completed with the patient and family or legal guardian.



- **<u>Core principles of clozapine treatment</u>**
  - Shared decision-making (SDM) and structured patient/family education are critical components of safe and effective clozapine treatment.
  - Safe prescribing requires clozapine-capable clinics with robust infrastructure (including laboratory and electrocardiogram [EKG] access) and trained clinicians capable of assessing and managing serious adverse effects (e.g., myocarditis, neutropenia, gastrointestinal hypomotility). Collaboration with primary care is an important aspect of clozapine treatment as few psychiatrists will have the medical expertise to manage all side effects of clozapine optimally (e.g., metabolic syndrome).
  - Consensus guidelines and harmonized protocols enhance safe prescribing and clinical management, helping clinicians navigate areas where regulatory guidance (e.g., package inserts) differs from current evidence-based practice.
  - When regulatory guidance differs from current evidence-based recommendations, clinical decisions should be collaborative and tailored to individual patient needs. The rational for deviating from regulatory guidance (most relevant for severe granulocytopenia monitoring) and the informed consent

discussion with the patient and their family or legal guardian must be well documented in the medical record.

- Safety monitoring for clozapine extends beyond agranulocytosis; clinicians must recognize and proactively manage other potentially life-threatening complications such as constipation, pneumonia, myocarditis, seizures, and cardiometabolic risks.
- Clozapine's clinical value extends beyond treatment-resistant schizophrenia (TRS), with additional indications including suicidality, aggression, and severe psychosis with partial response.

➢ **Other clinical considerations**

- Clozapine can be life-saving, especially for patients with TRS.
- About one-third of patients with schizophrenia are treatment-resistant;[8] notably, 84% of those are treatment-resistant from their first episode.[9]
- On average, about 50% of patients with TRS respond to clozapine;[10] if clozapine is tried during the first episode, the response rate increases to 75%.[11]
- Clozapine should be initiated as soon as treatment resistance is apparent which may be within 4 to 6 months of unsuccessful, sequential treatment with two first-line antipsychotics.
- All parties (clinician, patient, family or legal guardian) should commit to a full clozapine trial lasting at least 18 weeks at a tolerable and therapeutic dose, as indicated by therapeutic drug monitoring. Although 30% improve significantly after 6 weeks of clozapine treatment, up to 60% respond after 1 year.[12]
- Regular ANC monitoring substantially reduces the risk of agranulocytosis (0.9% incidence in the first month)[5] through early detection of neutropenia.
- Slow titration is essential to increase tolerability and avoid excessive sedation, syncope, myocarditis, and seizures.
- Dosing is based on serum levels of clozapine; therapeutic drug monitoring (TDM) is used to guide titration and to avoid toxic clozapine levels which increase seizure risk. A blood level of 350ng/ml is the initial target with a level greater than 450ng/mL for those patients who show no initial response. The risk of seizure increases with higher levels, and 1000ng/mL is generally considered the upper limit.
- Abrupt smoking cessation, excessive caffeine, or intense inflammatory reactions (e.g., COVID-19) can cause clozapine toxicity by increasing the blood level of clozapine.
- Clozapine has five FDA boxed warnings (formerly black box warnings): severe neutropenia/agranulocytosis, orthostatic hypotension/bradycardia/syncope, seizures, myocarditis/pericarditis/cardiomyopathy, and increased mortality in elderly patients with dementia-related psychosis.
- Common side effects include sedation, tachycardia, sialorrhea, constipation, and metabolic effects (e.g. weight gain, diabetes, hyperlipidemia).
- Collaborative monitoring and management with the patient's PCP can minimize clozapine side effects, ensuring benefits significantly outweigh risks.

Core Recommendations for Neutropenia Monitoring Frequency

- Baseline ANC prior to clozapine initiation to ensure ANC is $\geq 1.5 \times 10^9$/L, or $\geq 1 \times 10^9$/L for people with constitutional neutropenia
- Weekly ANC for the initial 18 weeks
- Monthly ANC thereafter for the first 2 years of treatment, unless leukopenia or neutropenia occurs
- Stop ANC monitoring after 2 years if no leukopenia/neutropenia occurred during this period
- Annual CBC with differential, as clozapine increases the risk for blood dyscrasias

- If treatment is interrupted within 18 weeks of initiation, reset schedule with weekly ANC
- If treatment is interrupted after the initial 18 weeks, resume monthly ANC
- If neutropenia develops after 2 years of treatment, consult hematology to evaluate for causes other than clozapine

Medicolegal Considerations

Reducing the frequency of monitoring should be considered only for patients who tolerate clozapine without a clinically significant reduction in neutrophils.

Since these recommendations deviate from the current FDA-approved clozapine package insert, informed consent discussion with the patient, family or legal guardian needs to be documented in the medical record when considering a reduced monitoring frequency (after 18 weeks) or cessation of monitoring (after 2 years). The discussion should include the rationale for the proposed change, its risks and benefits, and the option to continue the current monitoring frequency. Patients should receive education on how to recognize and respond to symptoms of agranulocytosis. See Section C. III for an example of documentation.

Clozapine E-Consults

Clozapine E-Consults allow MGB clinicians to ask patient-related clozapine questions through an Epic e-consult. E-consults are appropriate for straightforward clozapine questions that can be answered without the respondant seeing the patient. Clinicians can expect a response within 3 business days. E-consults are not a mechanism for second opinion consultations or for a transfer of care.

How to place an E-Consult order in EPIC:

a. Click “Add Order” and enter "Ambulatory MGH clozapine (advice) E-consult"
b. Enter patient information and the e-consult question, including relevant patient history, testing, labs (including clozapine level, if available)

A. Is clozapine appropriate for my patient?

I. Eligibility for clozapine

Clinical Indications with Strong Evidence

1) Treatment-resistant schizophrenia (FDA-approved indication)

   Definition:

   - ***Diagnosis:*** Schizophrenia using DSM-5 TR criteria (rule out other causes of psychosis such as substance/medication use and medical conditions)
   - ***Symptom severity:*** At least moderate psychotic symptom severity (on PANSS, BPRS, or clinical judgement equivalent) with at least moderate functional impairment (on Social and Occupational Functioning Assessment Scale, or clinical judgement equivalent) for at least 12 weeks
   - ***Minimal response:*** <20 percent symptom reduction to two trials of non-clozapine antipsychotics of:
     - adequate dose (equivalent to chlorpromazine 600mg)
     - adequate duration (at least 6 weeks)
     - adequate adherence (at least 80%)
       - confirm by checking blood levels of the antipsychotic drug
         ⁎ be mindful of rapid metabolizers and drug-drug interactions
         (e.g., carbamazepine reduces the levels of all antipsychotics except paliperidone, smoking reduces olanzapine levels)
       - consider confirming adherence by conducting your own, prospective trial with a long-acting injectable antipsychotic (LAI)

2) Suicidality in schizophrenia spectrum disorder (FDA-approved indication)
3) Aggression in schizophrenia spectrum disorder (APA Practice Guideline 3rd edition, 2020)

Additional Clinical Indications:

1) Sensitivity to extrapyramidal symptoms
2) Movement abnormalities from pre-existing conditions, including:
   - Tardive dyskinesia
   - Catatonia in schizophrenia
   - Psychosis in neurological conditions such as Parkinson's disease
3) Refractory mood disorders
4) Substance use disorder in schizophrenia spectrum disorder
5) Psychogenic polydipsia

II. Clozapine contraindications

- Absolute contraindications
  - Allergic reactions to clozapine
  - Severe CNS depression or comatose states from any cause

- Relative contraindications (do not use unless prescriber and patient determine benefits outweigh risks)
  - Poor compliance with medication and blood work
    *Adherence may improve as psychosis improves with clozapine treatment
    *Consider strategizing to put more support/structure in place so that a clozapine trial can be successful (i.e., visiting nurse, transportation to appointments)
  - History of clozapine-associated severe neutropenia (ANC<0.5×10^9/L) or agranulocytosis
  - History of clozapine-associated myocarditis
  - Severe heart diseases (obtain cardiology consult for clearance)
  - Myeloproliferative disorders
  - Uncontrolled epilepsy
  - Paralytic ileus
  - Severe renal or liver diseases

B. Prior to clozapine initiation

I. The FDA removed the REMS registry in February 2025, with all operations ceased in June 2025. Suggested current monitoring parameters are:

- Baseline ANC must be within the normal range before clozapine initiation:
  - For the general population: **at least 1.5×10^9/L**
  - For patients diagnosed with constitutional neutropenia: **at least 1.0×10^9/L**
    - Constitutional neutropenia (also known as benign ethnic neutropenia [BEN]) is diagnosed if neutropenia (≤1500/µL) is seen on repeated blood draws over time. It is most commonly seen in individuals of African descent (approximate prevalence of 25-50%), some Middle Eastern ethnic groups, and in other non-Caucasian ethnic groups with darker skin although it can also be seen in Caucasians.
    - Most patients with constitutional neutropenia have a fluctuating neutrophil count above 1000/µL and can be safely treated with clozapine.
  - If questionable, consider hematology consultation before starting clozapine treatment.

II. Establish baseline levels and safety prior to clozapine initiation

- Vital signs (postural blood pressure, heart rate, oxygen saturation, temperature)
- CBC with diff (including ANC), CMP (including liver and renal function tests)
- Cardiac monitoring (hs-troponin, C-reactive protein [CRP], Electrocardiogram [EKG])
- Metabolic monitoring (HgA1c, fasting glucose, fasting lipid panel, weight, waist circumference)
- Abnormal movements (including completing the Abnormal Involuntary Movement Scale [AIMS])
- Pregnancy test for people with childbearing potential

III. Patient and family education (facilliated through shared decision-making)

- Recommend a time-limited trial of 18 weeks at a therapeutic dose to assess the efficacy of clozapine given its accrued benefits over time.
- Discuss the requirement of regular blood work to safely receive clozapine.
- Educate that abrupt clozapine discontinuation may result in psychotic relapse, confusion (mimicking delirium), sweating, headache, nausea, vomiting, and diarrhea due to cholinergic rebound.

- If patients miss taking clozapine for more than 2 days, they should contact their provider - clozapine will need to be reinitiated at 12.5-25 mg and titrated gradually based on the duration of interruption. (If previous standard dosage titration was uneventful, may titrate the dose more rapidly than is recommended for initial treatment.)
- If clozapine is interrupted for 30 days or more, the initial dose titration and monitoring frequency should be followed.
- Cigarette smoking reduces clozapine blood levels; excessive caffeine intake increases clozapine blood levels.
- Intense inflammatory reactions (e.g., COVID-19) can cause clozapine toxicity by increasing clozapine blood levels.
- Caution not to drive or engage in potentially hazardous activities during the early titration phase given the common side effects of sedation and dizziness.
- Discuss rare side effects and reasons to contact the clinician immediately (or proceed to the ED):
  - Myocarditis: shortness of breath, chest pain, flu-like symptoms, malaise
  - Agranulocytosis: fever, sore throat
  - Seizures: early warning signs include myoclonic jerks
- Discuss common side effects and the plan for monitoring and intervention (see Section D- Side Effects):
  - Metabolic side effects (weight gain, diabetes, hyperlipidemia); constipation; sialorrhea; sedation; dizziness; palpitations
- Emphasize the importance of psychosocial treatments (CBT for psychosis, social skills training, CBT for negative symptoms) and behavioral interventions (exercise, healthy diet) in conjunction with clozapine treatment.

C. Clozapine initiation and titration

I. Preparation for an optimal clozapine trial

- While clozapine monotherapy is the goal, it is important to slowly taper off the existing antipsychotic to avoid withdrawal phenomena, including worsening of motor symptoms or psychosis. It is safe to administer both clozapine and another antipsychotic during the period of cross taper.
- Reduce polypharmacy before starting clozapine.
  - Clozapine is metabolized by CYP1A2 and 3A4. 2C19 and 2D6 have minimal contributions.
    - Evaluation of drug-drug interactions (e.g., ciprofloxacin, fluvoxamine)
    - Evaluation of other effects on drug metabolism (e.g., smoking)
  - Other medications that may worsen side effects:
    - Cautious use of antihypertensive medications
    - Minimize or avoid CNS depressants (e.g., benzodiazepines)
    - Minimize or avoid anticholinergic and cardiotoxic medications (e.g., TCAs)
    - Minimize or avoid medications that reduce seizure threshold (e.g., bupropion)
    - Minimize or avoid medications that cause weight gain (e.g., valproate)
    - Minimize or avoid medications that suppress bone marrow (e.g., carbamazepine)

II. Clozapine initiation

- Slow clozapine titration is preferred to increase tolerability, avoid excessive side effects, and may mitigate the risk of clozapine-associated myocarditis.

- Dosing schedule is determined by the treatment setting (inpatient, outpatient with limited support, outpatient with significant support, group home) and patient variables (age, medical comorbidities, etc.). No one schedule will fit all situations.
- A typical outpatient titration schedule is presented below, which can be adjusted depending on the tolerability and symptom response.
  - After a single test dose of 12.5mg at bedtime, start with clozapine 25mg at bedtime for 1 week.
  - In the second week and beyond, orthostatic hypotension and sedation usually determine the speed of titration.
    - If the initial week is well tolerated, increase the dose by 25 mg every week.
    - With ongoing tolerability, may increase by 25mg every 3-4 days (increments of 50mg every week).
    - If poorly tolerated, dosage can be titrated as slow as by 12.5mg every week.
- A slower titration is particularly recommended for patients with a first episode of schizophrenia, older or severely debilitated patients, those who are sensitive to side effects, and those with a pre-existing CNS condition that may increase risk of seizures.

III. Medical Monitoring

General monitoring schedule:

Parameter	Recommended frequency
ANC	At baseline, then weekly to 18 weeks → monthly to 24 months → stop thereafter if there has been no neutropenia or leukopenia
CBC with differential	At baseline, then weekly during weeks 1-8 (CAM consensus guidelines[7] recommend weekly for weeks 1-4, with 30% of experts suggesting extending to biweekly through week 8). Annually thereafter for hematological malignancy screen.
hs-Troponin + CRP	At baseline, then weekly during weeks 1-8 (although CAM consensus guidelines[7] recommend weekly for weeks 1-4, and a significant minority of experts recommended extending biweekly to week 8, we prefer a more conservative approach).
EKG	At baseline, and once when the dose reaches 100 mg or between weeks 2-4, whichever occurs first. If in an inpatient setting or where EKG is readily available, perform an EKG at both week 2 and week 4.
Vital signs (postural BP, HR, T°, SpO_2)	At baseline, then weekly during weeks 1-8 → BP and HR q3months thereafter (CAM consensus guidelines[7] recommend twice weekly HR and T, and weekly SpO2 and postural BP. In inpatient settings or where frequent monitoring is readily available, consider increased frequency.)
Comprehensive adverse drug-reaction (ADR) review (see **Table 3**)	Weekly to 18 weeks → monthly to 24 months → every 3 months lifelong (can occur in primary-care setting under shared-care model)

Metabolic panel (HbA1c, fasting glucose & lipids)	At baseline → at 3 months → at 6 months → Annually

Enhanced myocarditis monitoring schedule (changes in bold):

- **Enhanced monitoring may be considered in any of the following situations:**
  - Valproate co-medication, CYP1A2-inhibitor co-medication, obesity, Asian or Native American ancestry, chronic infectious disease (e.g., HIV), preceding bacterial or viral infection, preceding mRNA vaccination, cardiac conditions.
  - Fever, chest pain, or dyspnea.
  - New mild CRP elevation with or without clinical symptoms.
  - New mild hs-troponin elevation with or without clinical symptoms.
  - Isolated CRP elevation >10x ULN without clinical symptoms.
  - New EKG alteration (new ST-segment and T-wave deviations) without clinical symptoms.
- Utilization of the enhanced monitoring schedule must be balanced with the risk from delaying initiation of treatment to complete testing (eg, TTE).

Parameter	Recommended frequency
ANC	At baseline, then weekly to 18 weeks → monthly to 24 months → stop thereafter if there has been no neutropenia or leukopenia
CBC with differential	At baseline, then weekly during weeks 1-8 (CAM consensus guidelines[7] recommend weekly for weeks 1-4, with 30% of experts suggesting extending to biweekly through week 8. Annually for hematological malignancy screen
NT-proBNP	**At baseline, then weekly during weeks 1-4**
hs-Troponin + CRP	At baseline, then weekly during weeks 1-8 (although CAM consensus guidelines[7] recommend weekly for weeks 1-4, and a significant minority of experts recommended extending biweekly to week 8, we prefer a more conservative approach)
Transthoracic echocardiogram (TTE)	**At baseline**
EKG	At baseline, **then weekly during weeks 1-4, once during weeks 5-8**
Vital signs (postural BP, HR, T°, SpO_2)	At baseline, then weekly during weeks 1-8 → BP and HR q3months thereafter **(CAM consensus guidelines[7] recommend daily HR and T, and twice weekly SpO2 and postural BP)**
Comprehensive adverse drug-reaction (ADR) review (see **Table 3**)	Weekly to 18 weeks → monthly to 24 months → Every 3 months lifelong (can occur in primary-care setting under shared-care model)
Metabolic panel (HbA1c, fasting glucose & lipids)	At baseline → at 3 months → at 6 months → Annually

ANC Monitoring:

- ANC monitoring schedule during treatment, per the Global Delphi Guideline 2025:[5]
    - Initial 18 weeks: Weekly
    - After 18 weeks: Monthly until 2 years (as long as there has been no leukopenia or neutropenia)
    - After 2 years:
        - Discontinue routine ANC monitoring (as long as there has been no neutropenia or leukopenia)
        - Annual CBC with differential monitoring recommended for hematological malignancy screening
    - Of note, as of July 14, 2025, the FDA package insert continues to recommend ANC monitoring weekly for 6 months, followed by every other week for the subsequent 6 months, and then monthly thereafter.
    - See "Management of Side Effects" for a discussion on the management of neutropenia
- A therapeutic discussion using shared decision-making and documentation of this discussion in the medical record are critical. Discuss the existing FDA monitoring guidelines as well as the updated ANC monitoring guidelines, aligned with the 2025 Global Delphi consensus statements, with both the patient and family or legal guardian.
    - If the patient chooses monthly blood monitoring after 18 weeks, clearly document this decision. Prescribers can use the EPIC SmartPhrase **(.clozapineANC**) provided below:
        - "*I discussed with the patient, caregivers, and/or legal guardian the risks, benefits, and alternatives of changing clozapine ANC monitoring from weekly to monthly starting at week 18. Risks included the rare possibility of missing severe neutropenia and potential associated mortality; benefits included fewer blood draws and logistical barriers to facilitate continued clozapine adherence. Alternatives include making no change in the monitoring schedule. Although monthly monitoring after 18 weeks differs from the current FDA label, it aligns with the 2025 Global Delphi guideline, which notes that most neutropenia cases occur within the initial 18 weeks, after which the risk becomes similar to other antipsychotics. The patient, caregivers, and/or legal guardian understood, had their questions answered, and chose to proceed with monthly monitoring. They agreed to immediately contact us for urgent evaluation if signs of neutropenia (fever, sore throat, flu-like symptoms) occur. They understood we would resume more frequent monitoring if clinically indicated or ANC falls below FDA thresholds.*"
    - If the patient opts to discontinue ANC monitoring after 24 months or chooses a less frequent schedule (e.g., every 3, 4, 6 months, etc, clearly document using the EPIC SmartPhrase **(.clozapineANCstop**) provided below:
        - "*I discussed with the patient, caregivers, and/or legal guardian the risks, benefits, and alternatives of stopping clozapine ANC monitoring from monthly to as clinically indicated. Risks included the rare possibility of missing severe neutropenia and potential associated mortality; benefits included fewer blood draws and logistical barriers to facilitate continued clozapine adherence. Alternatives include making no change in the monitoring schedule. Although cessation of monthly monitoring after two years differs from the current FDA label, it aligns with the 2025 Global Delphi guideline, which notes that most neutropenia cases occur within the initial 18 weeks, after which the risk becomes similar to other antipsychotics. The patient's history of clozapine treatment was reviewed - s/he has no history of neutropenia and has been*

successfully treated with clozapine for >2 years. Further regular appointments for psychiatric and ADR assessment will continue with at least annual comprehensive bloodwork, including complete blood count, metabolic monitoring, and therapeutic drug monitoring. The patient, caregivers, and/or legal guardian understood, had their questions answered, and chose to proceed with this change. They agreed to immediately contact us for urgent evaluation if signs of neutropenia (fever, sore throat, flu-like symptoms) occur. They understood we would resume more frequent monitoring if clinically indicated or ANC falls below FDA thresholds."

IV. Dosing Schedules

- Most patients can be managed with nightly dosing to minimize daytime sedation.
  - Clozapine has a short half-life of less than 12 hours.
- Some patients prefer twice daily dosing to avoid morning grogginess or nocturnal enuresis.
- More frequent dosing can be used for patients who benefit from the ataractic effects of clozapine.

V. Clozapine titration: Therapeutic Drug Monitoring (TDM)

- When the clozapine dose reaches 100mg, obtain a clozapine blood level and perform an EKG (if not done between Weeks 2 and 4) to assess QTc prolongation.
  - Levels of clozapine should be drawn at steady state (3 days or more after a dose change).
  - The clozapine level should be a trough, ideally about 12 hours after the last dose.
  - Dosing is based on serum levels of clozapine alone. However, norclozapine (an active metabolite) is also reported – its individual value in clinical practice is unclear, but because the half-life of norclozapine is greater than that of clozapine, a low ratio (<0.5) could suggest poor adherence or rapid metabolism. A higher ratio (>3) could suggest saturated metabolic pathways or inhibition by a concomitant medication.
- During the acute phase, titrate the dose to aim for a blood level of at least 350ng/mL. If ineffective, then aim for a level greater than 450ng/mL.
- A target dose of 300 to 450 mg/day is often required for efficacy, but the optimal highest dose for clozapine has not been established. Use caution when prescribing above 600mg to avoid toxicity. The max total daily dose (TDD) is 900mg. Use clozapine blood levels to guide titration.
- A toxic blood level has not been established. Avoid excessive blood levels (no data for benefit but there is a dose-related increase in seizure risk).
  - Rule-of-thumb for "excessive" is 1,000 ng/mL (combined clozapine and norclozapine levels).
  - For simplicity, avoid a blood clozapine level greater than 600ng/mL.
  - However, some patients do need and tolerate a higher dose/blood level. Periodic shared decision-making conversations reviewing the risks should be had with patients and families/legal guardians.

VI. When starting clozapine, it is recommended to concurrently or within the first month start **metformin** to blunt metabolic side effects, unless there is renal impairment (eGFR <60 ml/min) or an active alcohol use disorder. If the patient declines metformin at initiation, revisit the discussion at the three-month follow-up when metabolic labs are reviewed. Metformin improves glucose utilization and mitigates clozapine-associated insulin resistance. Some clinicians may decide to wait if motivated patients want to manage their weight with diet and exercise. However, metformin is not used for weight management per se but to manage the insulin resistance that all patients develop with varying degrees when taking clozapine.

- The GI side effects of metformin can be limited by gradually increasing the dose, taking the medication with food or switching to a longer-acting preparation.
  - Week 1: metformin 500mg QPM
  - Week 2: metformin 500mg BID or metformin XR 1000mg QPM
  - Week 3: metformin 1000mg BID or metformin XR 2000mg QPM
  - The target dose for adults is 2000 mg daily. Lower doses have significantly less efficacy.

D. Management of Side Effects

I. Common early effects

- **Orthostatic hypotension (FDA black box warning)**
  - Rates: Up to 40%.
  - Change of >20 mmHg systolic or >10 mmHg diastolic is the diagnostic threshold.
  - Try reducing the speed of titration or dividing doses.
  - Older patients with peripheral vascular disease or a compromised cardiovascular system may be at particular risk.
  - Can cause dizziness, syncope, or falls.
  - Recommend increasing dietary salt and fluid intake and getting up slowly.
  - Monitoring: vital signs including postural BP at every visit.

- **Sedation**
  - Very common during initiation.
  - Strategies: bedtime dosing, reinforce sleep hygiene, split dosing or slower titration, tincture of time (sedation often improves over several months)
  - Adding a stimulant (e.g., modafinil) is generally not helpful and should not be used routinely. If a time-limited trial is undertaken, patients need to be stable with well-controlled symptoms.
  - Could consider adjunctive aripiprazole (evidence modest).
  - Morning coffee can be helpful but could contribute to tachycardia and overall caffeine intake should not be excessive.
  - Sedation can contribute to nocturnal enuresis and risk of sleep apnea (although the effect is bidirectional).
    - Obstructive sleep apnea: mediated by clozapine-associated obesity and sedation.
    - Screening tool: The STOP-Bang questionnaire (freely available on MDCalc)
    - Monitoring for sleep apnea should be part of the comprehensive ADR monitoring
  - Extreme sedation can contribute to the risk of pulmonary embolism.

- **Palpitations (tachycardia)**
  - Point prevalence: 68%, often transient during initiation.
  - Tachycardia can be primary, a reflex in response to orthostatic hypotension, and/or a result of anticholinergic effects.
  - Heart rates above 110-120 bpm warrant an EKG and evaluation to rule out organic etiologies (e.g., anemia, smoking, hyperthyroidism, respiratory or cardiovascular disease, caffeine or stimulants).
  - Treatment is not indicated unless the patient is symptomatic or the heart rate is greater than 120 bpm.

- First-line: Beta blockers (e.g. atenolol, propranolol) can be safely prescribed for persistent palpitations, but caution is advised because they can lower blood pressure and worsen orthostatic hypotension. Ivabradine can be used if beta blockers are contraindicated.
- If tachycardia is accompanied by chest pain, shortness of breath or fever, myocarditis should be suspected, and the patient should be immediately evaluated in the ED.

- **Fever (>38°C)**

  - Reported in 4-13% of clozapine-treated patients.
  - Commonly occurs within the first 3 weeks of treatment.
  - Usually benign, transient, and responds to supportive measures.
  - Not usually related to blood dyscrasias.
  - Essential to assess for and rule out potentially life-threatening complications such as myocarditis, severe neutropenia, and Neuroleptic Malignant Syndrome (NMS).

II. Rare but serious early side effects

- **Severe neutropenia or agranulocytosis (FDA boxed warning)**

  - Incidence 0.9% in the first month with monitoring.[5] Risk is highest during the first 18 weeks then declines sharply but never reaches zero; risk increases with age.[5]
  - Symptoms: fever, sore throat.
  - ANC monitoring schedule: see medical monitoring schedule
  - Steps to take when ANC falls below recommended thresholds:
    - Immediate repeat ANC testing to confirm any abnormal ANC results
    - Increased Monitoring (Twice Weekly):
      - ANC 1.0–1.5 × 10^9/L (general population): Continue clozapine; monitor twice weekly
      - ANC 0.5–1.0 × 10^9/L (constitutional neutropenia): Continue clozapine; monitor twice weekly
    - Clozapine cessation threshold: $< 1.0 \times 10^9$/L ($<0.5 \times 10^9$/L for people with constitutional neutropenia).
    - If abnormal ANC occurs after 2 years of clozapine, consider alternative causes before discontinuing clozapine.
    - Alternative causes: co-administration of valproic acid, chemotherapy, infection, or inflammation disorders.
  - Third line: Lithium boosts low WBC/ANC but use caution as lithium increases risk of NMS, neurotoxicity, and ketoacidosis. Granulocyte colony-stimulating factor (G-CSF) can be used to reduce the duration of neutropenia in cases of clozapine-induced agranulocytosis.
  - Rechallenge only if benefits outweigh the risks.

- **Myocarditis (FDA boxed warning)**

  - Incidence ~0.7% overall; risk highest in first 4 weeks.
  - Symptoms: shortness of breath, tachycardia, chest pain, malaise.

- The non-specific symptoms of myocarditis overlap with common initiation side effects (fatigue, tachycardia, light-headedness, eosinophilia, and a brief self-limiting fever). Clinicians must maintain a high level of suspicion.

- Diagnosis requires cardiac troponin elevation (new or significant change from baseline) plus either one major criterion or two minor criteria.
    - Major criterion: Diagnostic cardiac MRI (Lake Louise criteria).
    - Minor criteria: clinical symptoms (fatigue, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower-extremity edema, palpitations, light-headedness/dizziness, syncope, muscle weakness, cardiogenic shock), ventricular arrhythmia, decline in left ventricular systolic function, suggestive cardiac MRI, abnormal global longitudinal strain on echocardiography.
    - Exclude acute coronary syndrome and infectious myocarditis.
- Confirmation requires mandatory use of at least one cardiac imaging technique (echocardiography or cardiac MRI), if possible without causing treatment delays.
- Monitoring protocol: see Medical Monitoring section.
- Prevention/mitigation:
    - Slower titration rates significantly reduce myocarditis risk. (Recommended starting dose is 12.5 mg per day, gradually increasing up to 50 mg/day by day 7, and further titrating to a dose of approximately 100–125 mg/day by day 14, based on patient tolerance and clinical response.)
    - Wait at least 4 weeks after mRNA vaccination and 2-3 weeks after viral or bacterial infection (post-fever resolution) before initiating clozapine.
    - Pre-initiation baseline and weekly monitoring of CBC with differential, cardiac troponin and CRP for the first 8 weeks improve early detection of myocarditis. The value of monitoring beyond 8 weeks is unclear but an additional troponin level should be drawn if symptoms consistent with myocarditis occur.
- Risk factors requiring slower titration and enhanced monitoring include valproate co-medication, CYP1A2 inhibitors, obesity, alcohol/IV drug use, Asian or indigenous American ancestry, recent or concurrent viral or bacterial infection, chronic infectious diseases, pre-existing cardiac conditions.
- Triggers for action during initiation:
    - Stop uptitration of clozapine (enhanced monitoring is triggered by any of the following conditions.)
        - Fever, chest pain, or dyspnea.
        - New mild CRP elevation with or without clinical symptoms.
        - New mild hs-troponin elevation with or without clinical symptoms.
        - Isolated CRP elevation >10x ULN without clinical symptoms.
        - New EKG alteration (new ST-segment and T-wave deviations) without clinical symptoms.
    - Stop clozapine and refer to an ED (to initiate immediate cardiology consultation + TTE or cardiac MRI if available):
        - Hs-troponin >2x ULN with or without clinical symptoms.
        - CRP >10x ULN with clinical symptoms.
        - New EKG alteration with clinical symptoms.
        - Potentially life-threatening conditions (e.g., torsades de pointes, cardiogenic shock) would trigger clozapine discontinuation even before laboratory results are confirmed.
- Rechallenge cautiously if the benefit outweighs risk, after consultation with cardiology.
    - Required pre-rechallenge conditions:[7]
        - Minimum 8-week waiting period after myocarditis resolution, extended to 6 months in severe cases

    - Transthoracic echocardiography with LVEF at least 50%.
    - Consider cardiac MRI depending on case/clinical situation
    - hs-troponin, CRP, EKG, vitals, CBC with differential must be within range.
    - Enhanced pre-rechallenge: +NT-proBNP
    - Discontinue valproate before rechallenge if clinically possible.
- Restart clozapine at a lower dose (6.25mg/day initially, preferred dose at day 7: 25mg/day, at day 14: 50mg/day, at the end of week 4: 100mg), with slower titration and increased monitoring.
- Monitoring Protocol Weeks 1-4[7]
    - Monitoring frequency is intensified for a re-challenge
    - Minimum requirements:
        - Twice weekly: CRP, hs-troponin, oxygen saturation, postural BP
        - Weekly: CBC with differential, EKG
        - Daily: HR, Temperature
    - If mild elevation of CRP without clinical symptoms or new EKG changes without clinical symptoms, stop clozapine uptitration and increase monitoring frequency to <u>enhanced requirements</u>:
        - Twice weekly: CRP, hs-troponin, EKG, oxygen saturation, postural BP
        - Weekly: CBC with differential, NT-proBNP
        - Daily: HR, temperature
    - Stop clozapine and initiate immediate cardiology consultation (with TTE or cardiac MRI if available) if:
        - Fever, chest pain, or dyspnea.
        - Any elevation of hs-troponin with or without clinical symptoms.
        - Severe elevation of CRP >10x ULN.
        - Potentially life-threatening conditions (e.g., torsades de pointes, cardiogenic shock) would trigger clozapine discontinuation even before laboratory results are confirmed.
- Minimum Cardiac Monitoring for Rechallenge, weeks 5-8[3]
    - If stable without complications, step down to weekly hs-troponin, CRP, CBC with differential, EKG, and twice weekly vital signs (HR, oxygen saturation, postural BP, temperature)

III. Dose-dependent side effects

While many side effects may be dose related, individual sensitivities vary, and some people experience significant side effects even at very low doses. Likewise, simply reducing the dose is often not sufficient to manage adverse effects.

- **<u>Constipation and gastrointestinal hypomotility</u>**

    - Very common.
    - Leading cause of clozapine-related mortality.
    - Recommend increased water and increased physical activity.
    - Minimize other anticholinergic medications and opioids.
    - Active management of constipation:

        - 1st line: osmotic laxatives (e.g. polyethylene glycol) ± stool softener (e.g. docusate) and/or stimulant laxatives (e.g. senna)
        - 2nd line: An enema (e.g. Fleet) should be considered if ileus impending
        - Psyllium (e.g., Metamucil) and other bulking agents are <u>contraindicated</u>; they should be avoided, as they tend to accumulate in an already slow gut and can exacerbate constipation.
        - Linaclotide is also an option
    - Schedule standing laxatives particularly for patients at increased risk (e.g., older patients) or those with cognitive impairment who may not report or recognize constipation.
        - Untreated constipation may lead to fecal impaction, intestinal obstruction, bowel perforation, and toxic megacolon.
        - Paralytic ileus can be lethal.

- **<u>Gastro-esophageal reflux</u>**

    - Common
    - Recommend eating small meals, weight loss, head elevation when lying down
    - Active management:
        - Proton pump inhibitors are most effective.
        - Omeprazole should be avoided as it can lower clozapine levels by inducing CYP1A2 activity.

- **<u>Sialorrhea</u>**

    - Very common, up to 92%; worse at night.
    - Placing a towel on the pillow can help absorb saliva but does not represent treatment.
    - Chewing gum during the day helps stimulate the swallowing reflex. Sugarless gum is preferred.
    - First-line: Ipratropium sublingual 0.03% spray. Start with 1–2 sprays under the tongue at bedtime.
    - Second line: sublingual ophthalmic atropine 1% drops, hyoscine lozenges only with close constipation monitoring. Start with 300 µg at night (tablet should be sucked/chewed, not swallowed whole).
    - Third line: glycopyrrolate 1-2mg at bedtime.
    - If untreated, can lead to aspiration pneumonia**,** especially in elderly.

- **<u>Urinary incontinence and nocturnal enuresis</u>**

    - Estimated prevalence: Up to 40%, likely underreported due to stigma and embarrassment.
    - Risk is high at night. Sedation can contribute to nocturnal enuresis.
    - α-adrenergic antagonism leads to decreased internal bladder sphincter tone.
    - Managed by limiting water intake at night, treating constipation, or using divided dosing.
    - Pharmacological intervention:
        - Aripiprazole adjunct has shown promise.
        - dDVAP (desmopressin) for symptomatic treatment but requires monitoring for hyponatremia.
        - Third line: ephedrine 25mg at bedtime or 25mg BID or pseudoephedrine 30-60mg BID.

- **<u>Seizures (black boxed warning)</u>**

    - The overall seizure rate is 2.8%. Typically occur with high doses of clozapine, rapid titration, or shifts in clozapine level (e.g., drug-drug interactions, smoking cessation).

- Less than 300 mg/day – 1.0 %
- 300 to 600 mg/day – 2.7 %
- More than 600 mg/day – 4.4 %

o Most seizures are generalized tonic clonic. Myoclonus is a warning sign (dropping objects, spilling liquid).
o There is no cut-off dose (or blood level) that can be considered safe, but a clozapine level above 600ng/mL likely carries a higher risk.
o Slow titration and therapeutic drug monitoring are essential. Therapeutic blood monitoring is key to avoid unnecessarily high clozapine blood levels, particularly in patients with unusual metabolism.
o Prophylactic treatment is not necessary unless the patient has comorbidities or takes medications that increase the seizure risk. If a high-dose clozapine trial is pursued for treatment-resistance, treatment with an AED can be considered.
o If a seizure occurs with clozapine, reduce the clozapine dose if possible, obtain neurology consultation and consider adding an AED (e.g. valproate, lamotrigine). Avoid carbamazepine (bone marrow toxicity and pan-enzyme induction).

IV. Other common side effects

1) Metabolic side effects

- Most patients experience **weight gain** and have a higher risk of developing **diabetes, elevated LFTs, and hyperlipidemia** (triglycerides go up first).
- Side effects related to metabolic syndrome are common and generally observed in the initial months of treatment but can also occur later in treatment.
  o Weight gain is usually progressive over the first 6-12 months of treatment and may reach a plateau, but some patients continue to experience weight gain indefinitely.
- Prevention through active monitoring and management is important.
  o Encourage healthy eating and exercise (consider nutrition consultation and an exercise program)
  o Early detection and management of diabetes is important to prevent **diabetic ketoacidosis**
  o Ideally measure weight at every visit
  o Regularly monitor (baseline, weekly to 18 weeks, monthly to 24 months, then every 3 months) weight, waist circumference, postural blood pressure, heart rate
  o Regularly monitor (baseline, at 3 months, at 6 months, then annually) HbA1c, fasting blood glucose and lipid panel
  o Metformin titrated to 1000mg BID is recommended when initiating clozapine to blunt antipsychotic-associated metabolic side effects
    - In addition, or if metformin is not well tolerated, the addition of aripiprazole may be effective in counteracting clozapine-related weight gain (driven in part by 5-HT-2c antagonism).
    - In addition, or if metformin is not well tolerated, topiramate with a target dose of 100 mg twice daily may also be used. However, fatigue and impaired cognition are commonly reported.
    - If these interventions are not effective, collaborate with the patient's PCP or refer to a Weight Center specialty service for consideration of alternative medications, including glucagon-like peptide-1 agonists (e.g., semaglutide, tirzepatide).

2) Pneumonia

- Clozapine is linked to the highest incidence of pneumonia of all antipsychotics, and cases can be fatal.
- Risk is amplified by sialorrhea-related nocturnal choking and marked sedation.

- Monitor with routine ADR review (with ANC visits for the first 2 years of treatment, then q3 months). See **Table 3**.
- A preceding or concurrent bacterial/viral infection increases vulnerability to pneumonia; manage such infections before or during treatment.
- During infections, check clozapine serum levels, as systematic inflammation can elevate concentrations and precipitate clozapine toxicity. Can consider clozapine dose reduction particularly if the level is high.
- When an acute infection has occurred, delay initiation or slow titration of clozapine until at least 2–3 weeks after fever resolution and return of CRP to baseline (given increased risk of clozapine-associated myocarditis).
- Prevention: advise head-of-bed elevation for patients with significant drooling and ensure up-to-date influenza, pneumococcal and COVID-19 vaccinations to reduce respiratory-infection risk.

V. Very rare side effects

- Movement abnormalities
  - Movement disorders (EPS, tremors, TD) are less likely compared to many first-line antipsychotics, but it is still recommended to assess AIMS at least annually because motor side effects are not impossible and can occur.
  - **Tardive dyskinesia:** use VMAT-2 inhibitors
  - **NMS** can also occur and can present atypically, with less prominent rigidity
- **Cardiomyopathy** is a rare side effect that can occur later in the treatment course. No evidence for routine monitoring
- **Pancreatitis** (often due to hypertriglyceridemia or immune-mediated reaction)
- **Pulmonary embolism** (often due to immobility, weight gain, and increased platelet aggregation)
- **Hematological malignancies** (i.e., lymphoma, leukemia): annual CBC with differential is recommended for screening
- **Obsessive-compulsive symptoms**
- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome**

E. Augmentation and combination strategies for partial or non-responders

I. If there is no meaningful improvement <u>after at leaset 8 weeks at a clozapine plasma level of 450 ng/mL</u>, reassess the clinical value of clozapine and consider adjunctive strategies. Where tolerated, higher-dose clozapine may be trialed, as no definitive upper limit of efficacy has been established.

II. For the partial- or non- responders, augmentation strategies targeting specific residual symptoms need to be considered. An adequate trial of augmentation may need to be up to 8 -10 weeks.

- Residual psychotic symptoms: While the best clinical evidence suggests treating clozapine-resistant psychosis with electroconvulsive therapy (ECT), other adjunctive treatments can be considered:
  - Aripiprazole (15mg-30mg)
    - May offer symptomatic benefit.
    - May reverse or partially reverse the metabolic abnormalities associated with clozapine use.
    - Reduces the risk for a psychiatric hospitalization by up to 23%.[13]
    - Option of LAI to provide steady blood levels and improve adherence.
  - Other antipsychotic augmentation

        - May consider augmentation with FGAs or SGAs. There is limited research on these augmentation strategies thus 2nd and 3rd line augmentation strategies may be trial and error.
        - Cobenfy (xanomeline and trospium) may offer augmentation benefit given its different mechanism of action.
    - Electroconvulsive therapy
        - ECT has the best clinical evidence in clozapine-resistant psychosis.
        - ECT should be particularly considered for patients who have catatonia or significant suicide risk or who require a rapid response because of the severity of their psychiatric condition.
        - Between 54% and 66% of patients improve with the addition of ECT to clozapine treatment.[14]
        - It is unclear if ECT truly augments clozapine or if ECT alone is able to achieve the same results.
        - For individuals who show a response to ECT, ECT maintenance treatment may be the best option treatment as an adjunct to clozapine.
- Insufficiently controlled aggression or agitation
    - Valproate
        - Long-term use is not recommended given serious side effects.
- Depression, suicidality, or persistent negative symptoms
    - SSRIs
    - Mirtazapine (However, may worsen sedation and weight gain)
    - L-Methylfolate 15mg (bioactive form of the B vitamin folate) may help with negative symptoms
        - More affordable option: 2 mg of folate with 400 mcg of B12.
    - TMS is an area of active research with some encouraging results
    - Lamotrigine
    - Lithium (increases WBC/ANC which can be helpful in clozapine-induced neutropenia, but carries the risk of neurotoxicity when combined with antipsychotics)
        - Despite initial concern for masking neutropenia and for causing neutropenia to appear more abruptly, there is no evidence that lithium increases the overall risk of clozapine-related agranulocytosis.

III. If there continues to be no evidence of benefit, the value of the medication should be assessed periodically in terms of the patient's response, the medication side effects, and the availability of any newer treatment options.

- If clozapine must be discontinued due to lack of efficacy, a gradual taper over several months is recommended to avoid cholinergic rebound and withdrawal psychosis. (See Section G. Clozapine discontinuation)

F. Optimizing maintenance treatment with Clozapine

- If a patient is responding well to clozapine treatment, continuing with clozapine is appropriate.
- While it is recommended to reach clozapine levels of 350-450ng/mL during an acute phase, during the maintenance phase, a clozapine blood level between 200 and 300 ng/mL can minimize adverse effects while still maintaining efficacy.
- Once a target clozapine level is achieved, ongoing plasma level monitoring is not necessary. At a minimum, annual monitoring is recommended. Therapeutic drug monitoring may help assess adherence as well as factors that may influence clozapine levels such as addition or discontinuation of interacting medications, or changes in smoking status, body mass, renal or hepatic status, etc.

- Periodic review of the patient's medication regimen is important to identify and reduce concomitant medications that are not effective or no longer necessary or contributing to side effect burden.
- Comprehensive adverse drug-reaction monitoring (See **Table 3**) should be completed weekly through the first 18 weeks, monthly through 24 months, then at least every 3 months
- Ongoing assessment is needed to assess if the psychiatric benefit outweighs the medical risk of clozapine.

G. Clozapine discontinuation

- If clozapine must be discontinued due to urgent medical reasons, a gradual taper over a period of 1 to 2 weeks is recommended, if possible. Sudden discontinuation can lead to severe psychotic relapse and delirium.
- If clozapine must be discontinued due to lack of efficacy, a gradual taper over several months is recommended.
- If the patient plans to discontinue clozapine after having achieved desired symptom improvement, a gradual taper over 6 to 12 months is recommended.
- Additional ANC monitoring is required for any patient reporting the onset of fever (temperature of 38.5°C or 101.3°F, or greater) during the 2 weeks after discontinuation.[15]
- Monitor for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea. Patients may look delirious.
    - Adding an anticholinergic medication (e.g., benztropine) can help prevent or mitigate cholinergic rebound. Adding alternative antipsychotics and symptomatic adjunctive treatments (e.g., hypnotics) can help with rebound psychosis and insomnia after clozapine is discontinued.

Acknowledgements

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Table 1. Checklist before starting clozapine

Clinical Indications with Strong Evidence

- [ ] **Treatment Resistant Schizophrenia (FDA-approved indication)**
  - Rule out psychosis due to:
    - Substances and medications
    - Medical conditions
  - Failed two adequate trials of non-clozapine antipsychotics
    - Chlorpromazine 600mg daily equivalent for at least 6 weeks
    - Obtain blood levels to confirm sufficient drug levels
    - Confirm adherence using a trial of LAI antipsychotic
- [ ] **Suicidality in schizophrenia spectrum disorders (FDA-approved indication)**
- [ ] **Aggression in schizophrenia spectrum disorders**

Other Clinical Indications

- [ ] Sensitivity to EPS
- [ ] Tardive dyskinesia
- [ ] Catatonic schizophrenia
- [ ] Psychosis in neurological condition (Parkinson's)
- [ ] Refractory mood disorders
- [ ] Substance use in schizophrenia spectrum disorders
- [ ] Psychogenic polydipsia

Safety

- [ ] **Ability to comply with medications, regular follow up, and blood work**
  - **ANC**
    - At least 1500/μL for the general population
    - At least 1000/μL for patients with constitutional neutropenia
- [ ] **Baseline Labs**
  - Vital signs, CBC, CMP
  - Troponin, CRP, EKG
  - HgA1c, Fasting lipid panel
- [ ] **Absolute Contraindications**
  - Allergic reaction to clozapine
  - Severe CNS depression or comatose state
- [ ] **Relative Contraindications**
  - Hx of clozapine related myocarditis
  - Hx of clozapine related agranulocytosis
  - Severe heart disease
    - Cardiology consult for clearance
  - Myeloproliferative disorders
  - Uncontrolled epilepsy
  - Paralytic ileus
  - Severe renal or liver disease
- [ ] **Patient and Family Education**
  - A time-limited trial of at least 18 weeks
  - Risks of abrupt clozapine discontinuation
  - If clozapine is missed for more than 2 days, contact provider for clozapine reinitiation
  - Cigarette smoking reduces the blood level of clozapine
  - Discuss the five FDA black box warnings and other side effects

Table 2. Monitoring Schedule

Parameter	Baseline	W1	W2	W3	W4	W5	W6	W7	W8	3mo	6mo	9mo	12mo	15mo	18mo	21mo	24mo	>24mo
Hematology																		
Absolute Neutrophil Count (ANC)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	Weekly to 18 weeks → Monthly from 19 weeks to 24 months								—
Complete Blood Count (with differential)	☐	☐	☐	☐	☐	☐	☐	☐	☐	—	—	—	☐	—	—	—	☐	annually
Cardiac: Inflammatory																		
Troponin (hs-cTnT or TnT)	☐	☐	☐	☐	☐	☐	☐	☐	☐	—	—	—	—	—	—	—	—	—
C-Reactive Protein (CRP)	☐	☐	☐	☐	☐	☐	☐	☐	☐	—	—	—	—	—	—	—	—	—
NT-proBNP	☐*	☐*	☐*	☐*	☐*	☐*	☐*	☐*	☐*	—	—	—	—	—	—	—	—	—
Electrocardiogram (EKG)	☐	—	once when the dose reaches 100 mg or between weeks 2-4, whichever occurs first			—	—	—	—	—	—	—	☐*	—	—	—	☐*	annually *
Echocardiogram (TTE)	☐*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Therapeutic Drug Monitoring																		
Clozapine level	—	—	once when the dose reaches 100 mg			as needed or at least annually												
Vital Signs																		
Heart Rate (resting)	☐	☐	☐	☐	☐	☐	☐	☐	☐	Weekly to 18 weeks → Monthly from 19 weeks to 24 months								q3months
Postural Blood Pressure	☐	☐	☐	☐	☐	☐	☐	☐	☐	Weekly to 18 weeks → Monthly from 19 weeks to 24 months								q3months
Temperature	☐	☐	☐	☐	☐	☐	☐	☐	☐	—	—	—	—	—	—	—	—	—
Oxygen Saturation (SpO2)	☐	☐	☐	☐	☐	☐	☐	☐	☐	—	—	—	—	—	—	—	—	—
Metabolic parameters																		
Weight / Waist Circumference	☐	☐	☐	☐	☐	☐	☐	☐	☐	Weekly to 18 weeks → Monthly from 19 weeks to 24 months								q3months
Metabolic Labs (HbA1C, Lipids)	☐	—	—	—	—	—	—	—	—	☐	☐	—	—	—	☐	—	—	annually
ADR Checklist																		
Comprehensive ADR Symptom Review	☐	☐	☐	☐	☐	☐	☐	☐	☐	Weekly to 18 weeks → Monthly from 19 weeks to 24 months								q3months

Notes: ☐ = Required monitoring * = Use clinical discretion depending on patient-specific factors and resource availability — = Not routinely required ** = changes in the ANC monitoring schedule require the absence of neutropenia and a shared-decision making discussion with the patient which should be documented in the medical record

ANC Monitoring: Weekly from baseline to 18 weeks → Monthly from 18 weeks to 24 months → Discontinue routine monitoring after 24 months (as long as no neutropenia/leukopenia)

Table 3. Post-2yrs: Long-term clozapine adverse drug reaction quarterly monitoring checklist in collaboration with PCP[5]

Adverse drug reaction	Screen Q3months
Heart rate and blood pressure	☐
Metabolic syndrome	☐
Constipation / GI hypomotility	☐
Gastro-esophageal reflux	☐
Sialorrhea / drooling / choking	☐
Sedation & daytime somnolence	☐
Nocturnal enuresis & urinary incontinence	☐
Dizziness & orthostatic hypotension	☐
Tachycardia	☐
Sleep apnea / snoring	☐
Obsessive–compulsive symptoms	☐
Seizures / myoclonus	☐
Pneumonia & respiratory status	☐
Sexual dysfunction	☐
Heart failure symptoms	☐
Less common adverse events: cardiomyopathy, pulmonary embolism, skin rash, and DRESS syndrome	☐

Table 4. Clozapine side effect monitoring and interventions[5,7]

Adverse effect	Monitoring parameters & frequency	Key thresholds	Recommended interventions
Neutropenia / Agranulocytosis	ANC weekly x 18 wks, then q4 wks to 2 yrs; discontinue routine after 2 yrs (as long as no neutropenia). Annual CBC with differential thereafter.	ANC 1.0–1.5 × 10^9/L (general population): Continue clozapine; monitor twice weekly. ANC 0.5–1.0 × 10^9/L (constitutional neutropenia): Continue clozapine; monitor twice weekly. Clozapine cessation threshold: < 1.0 × 10^9/L (<0.5 × 10^9/L for people with constitutional neutropenia).	If cessation threshold crossed: Hold clozapine, repeat test, investigate other causes; consider G-CSF. Resume when ANC recovers per guidelines.
Clozapine-Associated Myocarditis (CAM)	Baseline hs-troponin, CRP, CBC, vitals, EKG (± TTE). During wks 1-8: hs-troponin & CRP weekly; one EKG during wks 2-4; vitals weekly. Rechallenge: modified schedule.	hs-troponin >2xULN OR CRP >10xULN with symptoms, new ECG changes, fever, chest pain or dyspnea.	Stop titration + increase monitoring → fever/chest pain/dyspnoea; new mild CRP elevation ± sxs; new mild hs-troponin elevation ± sxs; isolated CRP > 10× ULN without sxs; new ECG change without sxs. Stop clozapine + urgent work-up (same-day cardiology + TTE / cardiac MRI) → hs-troponin > 2× ULN ± sxs; CRP > 10× ULN with sxs; new ECG change with sxs. Slower rechallenge after ≥8 wks if indicated.
Metabolic syndrome / Weight gain	Weight & waist circumference at each visit; HbA1c & lipids at baseline, at 3mo, at 6mo, then annually.	BMI ≥25 kg/m² or metabolic parameters outside targets.	Lifestyle (diet, exercise, smoking cessation); metformin, GLP-1 RA; weight center referral.
Constipation / GI hypomotility	Ask every visit about bowel habits, pain; use Bristol Stool Chart. High vigilance life-long.	Reduced frequency, hard stools, pain, ileus symptoms.	Baseline & prophylactic laxative (docusate + senna ± macrogol); encourage fluids, activity; avoid constipating drugs.
Gastro-esophageal reflux	Symptom review each visit.	Heartburn, regurgitation, dyspepsia.	Small meals, elevate head, weight loss; proton pump inhibitor (avoid omeprazole).
Sialorrhea / Drooling	Ask each visit (day & night). Drooling scales if needed.	Choking, aspiration risk, distress.	Sugar-free gum, towel on pillow, elevate head; ipratropium spray, sublingual atropine (caution), glycopyrrolate* (monitor constipation).
Nocturnal enuresis / Urinary incontinence	Ask sensitively each visit.	Bed-wetting ≥1 night/week.	Fluid restriction before bed, timed voiding alarms; add oxybutynin; consider desmopressin (monitor Na+).
Orthostatic Hypotension / Dizziness	Postural blood pressure each visit during titration, then prn.	Drop >20 mmHg systolic or >10 mmHg diastolic with symptoms.	Slow titration, increase fluids, rise slowly, compression stockings, fludrocortisone (monitor K+).
Tachycardia	HR every visit during titration, then periodically.	HR >110 bpm persistent.	Rule out myocarditis; consider β-blocker (atenolol/bisoprolol) or ivabradine after cardiology review.
Sleep apnea	Screen q3mo (STOP-Bang); query snoring, daytime somnolence.	High STOP-Bang or witnessed apneas.	Weight loss, CPAP, sleep hygiene, side-lying; GLP-1 RA if obese.
Sedation / Hypersomnia	Ask each visit; Epworth scale if indicated.	Interferes with function, daytime sleepiness.	Dose at night, split dosing, optimize sleep hygiene; Consider aripiprazole or modafinil; slow dose increase.
Seizures / Myoclonus	Clinical review; clozapine level if symptoms; EEG prn.	Myoclonus, tonic-clonic seizure.	Check clozapine level; dose reduction; add valproate or lamotrigine if needed.
Obsessive-compulsive symptoms	Ask q3months or if behavior change.	Emergence of intrusive thoughts, compulsions.	Behavioral therapy; SSRI (caution CYP1A2); adjust clozapine dose.
Pneumonia risk / Respiratory infection	Clinical vigilance esp. winter; vaccinate.	Cough, dyspnea, fever.	Early antibiotics, monitor clozapine levels (can rise); smoking cessation; vaccination (influenza, pneumococcal, COVID-19).
Sexual dysfunction	Ask q3months or if concern.	Decreased libido, erectile or orgasm issues.	Assess prolactin & hormones; manage contributing factors; consider switching adjuncts.
Heart failure / Cardiomyopathy	Clinical review; EKG annually optional; TTE if symptoms.	Dyspnea, edema, reduced EF on imaging.	Cardiology referral; manage heart failure per guidelines; reconsider clozapine dose.

Abbreviations: ANC: Absolute Neutrophil Count; CBC: Complete Blood Count; CRP: C-Reactive Protein; DARC: Duffy Antigen Receptor for Chemokines; EKG: Electrocardiogram; EF: Ejection Fraction; G-CSF: Granulocyte Colony-Stimulating Factor; GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonist; HR: Heart Rate; SSRI: Selective Serotonin Reuptake Inhibitor; TTE: Transthoracic Echocardiogram; ULN: Upper Limit of Normal

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