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Introduction

Clozapine is an atypical antipsychotic typically reserved for patients with schizophrenia who have failed to respond to two or more other antipsychotics. While most clinicians are well aware of clozapine’s rare but potentially life-threatening side effects of agranulocytosis and myocarditis and the associated monitoring, many seem unaware of its marked clinical effectiveness. This Clozapine Toolkit includes an array of information, including dosing, monitoring, side effect management, sample forms, informative articles for healthcare professionals and patient educational materials. Our hope in gathering this information for the creation of this toolkit is to increase clinician comfort with prescribing clozapine when clinically appropriate.

Clozapine, Taking Another Look: A Too-Often-Forgotten Treatment for Schizophrenia

Ken Duckworth, MD Medical Director, NAMI

Excerpts:

“When I am told about severe symptoms of psychosis for a person living with schizophrenia and that two antipsychotics have been unsuccessful, clozapine is my go-to recommendation.”

“Clozapine is unique for two primary—and significant—reasons:
1) It is the only FDA-approved medicine for people with schizophrenia who have not responded to two antipsychotics.
2) It is the only medication shown by the FDA to reduce the risk of suicide in people with schizophrenia and schizoaffective disorder.

We don’t endorse specific treatments at NAMI, but reminding people that this treatment has two special FDA indications is good to remember.”

“The consensus in the medical community is that this is an underutilized treatment.”

“I have personally seen many individuals thrive on this medication when no other treatments worked.”

“It has been a part of some of my happiest moments as a doctor.”

“In spite of these challenges [of side effects and monitoring], many of my patients have done quite well on clozapine. It has been a building block of recovery for many in my own experience and this is borne out in the research literature. In the past decade, two large multisite studies, the NIMH-funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in the U.S. and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS 2) in the U.K., compared multiple antipsychotics for people with schizophrenia and both found clozapine to be the most effective medication. In the U.K. study, the focus was on quality-of-life measures and those taking clozapine reported the highest scores.”

“Clozapine is also unusual in that blood levels are available, which can help to correlate a response to dosage.”

“In addition, there is research that suggests that clozapine is a good mood stabilizer, may reduce substance cravings and may reduce aggression. These are not FDA-approved uses, but the literature can also inform discussions about when it could be considered.”
Indications

FDA Indications

Clozapine is an atypical antipsychotic indicated for:

- Treatment-resistant schizophrenia
- Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder

Use in Pediatrics

Clozapine is not labeled for use in pediatrics.

A trial of clozapine should be considered for youth with treatment-resistant schizophrenia spectrum disorders, according to Recommendation 7 of Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia from the American Academy of Child and Adolescent Psychiatry (AACAP).

Before using clozapine, it is important to review the child’s clinical status and treatment history to ensure that the presentation accurately reflects treatment refractory schizophrenia. For complicated cases or the apparent diagnosis of schizophrenia in a younger child (e.g., <12 years), a diagnostic second opinion may be warranted.


NOTE: Please consider the ability to coordinate care with labs, pharmacy and the prescriber BEFORE initiating therapy. This is especially critical for children in foster/residential care.

Off-Label Uses

<table>
<thead>
<tr>
<th>Diagnosis/behavior</th>
<th>Supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder</td>
<td>Randomized, open-label trial reports mood stabilization benefits</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>Primarily case reports involving psychotic depression</td>
</tr>
<tr>
<td>Borderline personality disorder</td>
<td>Open-label trial reports improvement on multiple rating scales</td>
</tr>
<tr>
<td>Substance use disorders</td>
<td>Multiple studies report decreased cravings for alcohol and illicit drugs in patients with psychotic disorders</td>
</tr>
<tr>
<td>Suicidality</td>
<td>Multiple studies report benefits in patients with psychotic disorders</td>
</tr>
<tr>
<td>Aggression</td>
<td>Multiple studies report benefits in patients with psychotic disorders, independent of the impact on psychotic symptoms</td>
</tr>
<tr>
<td>Psychosis in Parkinson’s disease</td>
<td>Randomized, placebo-controlled study shows benefits at low dosages</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Retrospective studies show benefit from monotherapy</td>
</tr>
<tr>
<td>Tardive dystonia</td>
<td>Retrospective studies show benefit from monotherapy</td>
</tr>
</tbody>
</table>

Clozapine REMS Program

The Clozapine REMS Program (CRP) is an FDA-mandated program implemented by the manufacturers of clozapine to provide a centralized point of access for pharmacists and prescribers to minimize the risk of clozapine-associated neutropenia. Prescribers, pharmacies and patients must be enrolled with this program for the prescribing, dispensing and use of clozapine. The Clozapine REMS Program can be accessed at www.clozapinerems.com or by calling 1-844-267-8678.

Patients must be informed about the risks of clozapine using the *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers* unless to do so would negatively impact treatment adherence.

**Clozapine REMS Process**

### Prescribers
- Enroll & certify with CRP
- Enroll, certify, & assign designee in CRP (optional)
- Enroll patient with CRP (new starts & patients transferred to your care already taking clozapine)
- Order CBC at appropriate interval based on CRP’s ANC monitoring requirements
- Report (or have designee report) ANC value to CRP
- Identify enrolled pharmacy & provide clozapine prescription to patient or pharmacy

### Pharmacies
- Register pharmacy with CRP
- Educate pharmacy staff on processes to comply with CRP
- Report ANC values to CRP (ONLY if pharmacy is prescriber designee)
- Access CRP to obtain pre-dispense authorization (PDA)* prior to each clozapine dispense
- Dispense clozapine quantity not to exceed current monitoring frequency (e.g., 7 days supply if on weekly monitoring)

* PDA ensures that ANC is current and acceptable for each patient or that the prescriber has authorized continuation of clozapine therapy by providing the treatment rationale for patients with ANC < 1000/μL. A pharmacist may be able to override a rejected PDA, if clinically appropriate, while necessary information is updated in CRP, but may only dispense a 7-day supply (regardless of patient’s current monitoring frequency).

**Program Materials**

REMS materials can be found on the Clozapine REMS website at: [https://www.clozapinerems.com/CpmgClozapineUI/resources.u](https://www.clozapinerems.com/CpmgClozapineUI/resources.u)
Three Steps to Prescriber Certification in Clozapine REMS Program

- **Step 1**: Complete and submit 1-time *Clozapine REMS Prescriber Enrollment Form*
- **Step 2**: Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
- **Step 3**: Pass the *Knowledge Assessment for Healthcare Providers*

**Prescriber Designee Process**

Prescribers have the ability to identify and associate designees (e.g., nurse, pharmacist) to their Clozapine REMS program certification record. Prescriber designees have the ability to provide ANC and enroll and manage patients with the following exceptions:

1. Designees cannot categorize a patient diagnosed with BEN
2. Designees cannot authorize the continuation of clozapine treatment for patients with moderate to severe (general population) or severe neutropenia (BEN patients)
3. Designees cannot categorize a patient as a hospice patient

Sources:
- [https://www.clozapinerems.com/CpmgClozapineUI/hcpDesigneeHome.u](https://www.clozapinerems.com/CpmgClozapineUI/hcpDesigneeHome.u)

**NOTE:** Collaborative Practice Agreements with Pharmacists can serve as a mechanism to facilitate clozapine therapy. Pharmacists can be the provider designee as well.
Clozapine Dosage & Administration

Pre-Commencement Screen

Medical History

Patient has had an adequate trial on 2 or more antipsychotics ☐ No ☐ Yes

Patient has chronic medical condition* ☐ No ☐ Yes

Details______________________________________________

Patient has a personal or family history of cardiovascular disease* ☐ No ☐ Yes

Patient has a history of epileptic seizures* ☐ No ☐ Yes

* Not an absolute contraindication to clozapine but may require additional safety measurements or monitoring

Clozapine Checklist

Baseline data

- General and cardiovascular health status
- ANC ≥ 1500/µL (general population) or ≥ 1000/µL (BEN population)
- Drug levels for anticonvulsant drugs, need to be in therapeutic range (if prescribed for seizures)
- Weight, height, body mass index and waist circumference
- Fasting (ideal) or non-fasting blood sugar or HbA1c
- Fasting (ideal) lipids or non-fasting
- Vital signs, including orthostatic blood pressure
- ECG recommended
- Absence or presence of abnormal motor movements on Abnormal Involuntary Movement Scale (AIMS) test
- Pregnancy test in women of childbearing age


Clozapine Pre-screening Red Flags

- Smoking Status (See Drug Interactions section)
  - Smokers have higher clozapine metabolism requiring up to twice the dose of non-smokers.
  - If former smokers resume smoking (e.g., discharged from smoke-free facility), their clozapine levels should be checked within 1-2 weeks of resuming smoking.

- Constipation (See Side Effects section)
  - More lethal than agranulocytosis; assess baseline bowel habits and recommend prophylactic laxative regimen (Standard: Colace BID and Miralax 17gm daily)

- Interacting Medications (See Drug Interactions section)
  - Ciprofloxacin and fluvoxamine increase clozapine levels
  - Carbamazepine reduces levels of clozapine (caution when discontinuing CBZ) & confers additive risk of neutropenia
### Clozapine Initiation and Monitoring Guidelines

<table>
<thead>
<tr>
<th>Timeline</th>
<th>CBC w/diff&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Myocarditis panel&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ECG</th>
<th>HbA1C</th>
<th>Lipid panel (non-fasting)</th>
<th>Glucose, random</th>
<th>Vitals&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Myocarditis Review of Systems (ROS)&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>x&lt;sup&gt;5&lt;/sup&gt;</td>
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<td></td>
<td>Start Clozapine</td>
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<tr>
<td>Weeks 1-4</td>
<td>x&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
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<td></td>
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<td>x</td>
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<td>Week 5</td>
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<td>Week 6</td>
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<td>x&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Weeks 7-8</td>
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<td>Weeks 9-11</td>
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<tr>
<td>Week 12</td>
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<td>x&lt;sup&gt;3&lt;/sup&gt;</td>
<td>x&lt;sup&gt;3&lt;/sup&gt;</td>
<td>x&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Weeks 13-25</td>
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<td>Week 26</td>
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<td>Weeks 27-50</td>
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<td>Week 52</td>
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<td>x&lt;sup&gt;3&lt;/sup&gt;</td>
<td>x&lt;sup&gt;3&lt;/sup&gt;</td>
<td>x&lt;sup&gt;3&lt;/sup&gt;</td>
<td>x</td>
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<tr>
<td>Beyond 1 year</td>
<td>x&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td>x&lt;sup&gt;3&lt;/sup&gt;</td>
<td>x&lt;sup&gt;3&lt;/sup&gt;</td>
<td>x&lt;sup&gt;3&lt;/sup&gt;</td>
<td>x</td>
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</tr>
</tbody>
</table>

<sup>a</sup> weekly CBC w/diff for first 26 weeks (highest risk of agranulocytosis is within 3 months of clozapine initiation)

<sup>b</sup> q2 week CBC w/diff from weeks 26 to 52

<sup>c</sup> q4 week CBC w/diff from 1 year and beyond

<sup>d</sup> 6 week glucose is optional but recommended to screen for rapid onset hyperglycemia

<sup>e</sup> 6 month metabolic labs only recommended for children and adolescents

<sup>f</sup> Beyond 1 year, obtain annual metabolic labs, more frequently if abnormal. Refer abnormal values to PCP for management

<sup>g</sup> Vitals should be obtained at each clinic appointment, not needed for “laboratory-only” appointments

<sup>h</sup> Glucose at 1 year and beyond is optional, only required if HbA1C is not performed

<sup>i</sup> Weekly myocarditis panel for Weeks 1-4: troponin I, CK, CK-MB, pro-BNP, CRP. Consider adding during Weeks 5-8 only if myocarditis ROS suggest concerns.

<sup>j</sup> Myocarditis review of systems (ROS) at each appointment during the first 8 weeks of clozapine (highest risk period)

Myocarditis ROS: chest pain, dyspnea, orthopnea, palpitations, edema, fatigue, fever

Instruct patient to call with any concerns between appts, consider calling patient between appts if not seen weekly.

**IMPORTANT:** If concerned about possible myocarditis and patient is not in distress, obtain ECG and consult cardiology. With any symptomatic distress, have low threshold for bringing patient to ED or instructing patient to go to ED if not in clinic. Must call ED to provide history and clinical details.

06-02-17

Source: Courtesy of the Department of Psychiatry, UNC–Chapel Hill
ANC Monitoring & Treatment Recommendations

- **Absolute neutrophil count (ANC)** is used exclusively for patient monitoring.
  
  **Note:** White blood cell (WBC) counts are no longer reported.

- Patients with **Benign Ethnic Neutropenia (BEN)** can be treated with clozapine, but a separate ANC monitoring algorithm does exist.
  
  - Most commonly observed in those of African descent (approximate prevalence of 25-50%), some Middle Eastern ethnic groups and in other non-Caucasian ethnic groups with darker skin
  - Have normal hematopoietic stem-cell number and myeloid maturation, are healthy and do not suffer from repeated or severe infections
  - Patients with BEN are not at increased risk for developing clozapine-induced neutropenia

- Usual monitoring frequency:
  
  - Initiation to 6 months: weekly
  - 6 – 12 months: every 2 weeks
  - After 12 months: monthly

- Increase ANC monitoring frequency for:
  
  - **General Population:** ANC < 1500/μL
  - **BEN Patients:** ANC < 1000/μL

- Interrupt treatment if neutropenia is suspected to be clozapine-induced for:
  
  - **General Population:** ANC < 1000/μL
  - **BEN Patients:** ANC < 500/μL

- Prescribers have greater flexibility to make patient-specific decisions about continuing and resuming treatment in patients who experience moderate and severe neutropenia

  **Ex:** With ANC < 1000 μL, prescribers can continue clozapine treatment if the prescriber believes the benefits of clozapine therapy outweigh the risk of severe neutropenia (must enter a “treatment rationale” authorizing continuation of therapy)

- Substantial drops in ANC do not require action unless the patient experiences neutropenia. The National Non-Rechallenge Master File (NNRMF) is discontinued. Patients may be re-challenged if the prescriber determines the risk of psychiatric illness is greater than the risk of severe neutropenia. Patients previously on the NNRMF are identified in the REMS registry with a red flag.

- For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the prescriber may reduce the ANC monitoring frequency to once every six months after a discussion with the patient and caregiver.
### Table 1: Recommended Monitoring Frequency and Clinical Decisions by ANC Level

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Treatment Recommendation</th>
<th>ANC Monitoring</th>
</tr>
</thead>
</table>
| Normal Range for a New Patient GENERAL POPULATION | • Initiate treatment  
• If treatment interrupted:  
  - < 30 days, continue monitoring as before  
  - ≥ 30 days, monitor as if new patient | • Weekly from initiation to six months  
• Every 2 weeks from 6 to 12 months  
• Monthly after 12 months  

BEN POPULATION  
• ANC ≥ 1000/µL  
• Obtain at least two baseline ANC levels before initiating treatment | • Discontinuation for reasons other than neutropenia | • See Section 2.4 of the full Prescribing Information |
| Mild Neutropenia (1000 - 1499/µL)* | GENERAL POPULATION  
• Continue treatment | GENERAL POPULATION  
• Three times weekly until ANC ≥ 1500/µL  
• Once ANC ≥ 1500/µL return to patient’s last “Normal Range” ANC monitoring interval** |
| | BEN POPULATION | BEN POPULATION  
• Mild Neutropenia is normal range for BEN population, continue treatment  
• Obtain at least two baseline ANC levels before initiating treatment  
• If treatment interrupted:  
  - < 30 days, continue monitoring as before  
  - ≥ 30 days, monitor as if new patient | • Weekly from initiation to six months  
• Every 2 weeks from 6 to 12 months  
• Monthly after 12 months | • See Section 2.4 of the full Prescribing Information |
| Moderate Neutropenia (500 - 999/µL)* | GENERAL POPULATION  
• Recommend hematology consultation  
• Interrupt treatment for suspected clozapine induced neutropenia  
• Resume treatment once ANC normalizes to ≥ 1000/µL | GENERAL POPULATION  
• Daily until ANC ≥ 1000/µL, then  
• Three times weekly until ANC ≥ 1500/µL  
• Once ANC ≥ 1500/µL, check ANC weekly for 4 weeks, then return to patient’s last “Normal Range” ANC monitoring interval*** |
| | BEN POPULATION | BEN POPULATION  
• Recommend hematology consultation  
• Continue treatment | | • Three times weekly until ANC ≥ 1000/µL or ≥ patient’s known baseline  
• Once ANC ≥ 1000/µL or patient’s known baseline, check ANC weekly for 4 weeks, then return to patient’s last “Normal BEN Range” ANC monitoring interval.**** |
| Severe Neutropenia (< 500/µL)* | GENERAL POPULATION  
• Recommend hematology consultation  
• Interrupt treatment for suspected clozapine induced neutropenia  
• Do not rechallenge unless prescriber determines benefits outweigh risks | GENERAL POPULATION  
• Daily until ANC ≥ 1000/µL  
• Three times weekly until ANC ≥ 1500/µL  
• If patient rechallenged, resume treatment as a new patient under “Normal Range” monitoring once ANC ≥1500/µL | | BEN POPULATION  
• Recommend hematology consultation  
• Interrupt treatment for suspected clozapine induced neutropenia  
• Do not rechallenge unless prescriber determines benefits outweigh risks | BEN POPULATION  
• Daily until ANC ≥ 500/µL  
• Three times weekly until ANC ≥ patients established baseline  
• If patient rechallenged, resume treatment as a new patient under “Normal Range” monitoring once ANC ≥1000/µL or at patient’s baseline |

* Confirm all initial reports of ANC less than 1500/µL (ANC < 1000/µL for BEN patients) with a repeat ANC measurement within 24 hours  
** If clinically appropriate

**Clozapine Plasma Level Monitoring**

Serum clozapine and norclozapine levels can be helpful in the following situations:

- Patients with inadequate response despite adequate dosing and adherence
- CNS toxicity suspected
- Addition/discontinuation of a medication that can induce or inhibit the metabolism of clozapine
- Change in smoking status
- Suspected non-adherence
- Decompensation on a previously effective dosage

**Clozapine Plasma Level**

- Clozapine levels are usually drawn as a steady-state trough (approximately 5 days at stable dose & 12 hours after the last dose).
- Most laboratories report 3 numbers: clozapine, norclozapine and their sum. The vast majority of information available only addresses the clozapine level.
- Levels can be increased by inflammatory reactions.
- Levels can decrease with a switch from brand to generic clozapine.
- If a single evening dose is given, the target concentration should be up to 25% higher (still drawn 12 hours after last dose).

**Interpreting Clozapine Levels and Adjusting the Dose**

- **Low range (50-150 ng/mL):** Not as effective as medium or high levels
- **Medium range (200-300 ng/mL):** Good initial target
- **High Range (350-450 ng/mL):** Can be targeted if clinical response insufficient with medium range
- **Very High Levels (>1,000 ng/mL combined clozapine and norclozapine levels):** No proven benefit but do have increased seizure risk
- Clozapine has linear pharmacokinetics – if you double the dose, the level will double. Likewise, if you halve the dose, you halve the level.


**Available Formulations**

Clozapine is available by prescription as:

- **Clozaril® (clozapine) tablets**
  - Strengths: 25, 50, 100 and 200 mg
- **Fazaclo® (clozapine, USP) orally disintegrating tablets**
  - Strengths: 12.5, 25, 100, 150 and 200 mg
  - Dissolves without requiring additional liquids
- **Versacloz® (clozapine, USP) oral suspension**
  - Strength: 50mg/mL

Disintegrating tablets or suspension may be beneficial for patient with a history of “cheeking” or otherwise disposing of tablets, or a medical condition that affects swallowing.
### Initiating Treatment

<table>
<thead>
<tr>
<th>Step</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>Initiate clozapine at 12.5mg QHS for 1-2 days, then increase to 25mg QHS as tolerated</td>
</tr>
</tbody>
</table>
| **Step 2** | Increase daily dosage by 25mg - 50mg at once or twice weekly intervals to minimize sedation & orthostasis  
Consider giving higher dosage at bedtime to offset sedation |
| **Step 3** | Taper previous antipsychotic once clozapine dose reaches 200mg (if not already done) |
| **Step 4** | Titrate based on clinical response and side effects  
Continue increasing clozapine by 25mg - 50mg per day (max: 100mg/week) |
| **Step 5** | Target dosage is typically between 300mg - 450mg daily, administered twice a day or entirely at night (to limit daytime sedation) |
| **Step 6** | Monitor plasma clozapine level (trough) if indicated  
Generally therapeutic at clozapine level >350 ng/mL |
| **Step 7** | Consider an antiepileptic at higher clozapine dosages due to seizure risk  
Generally toxic at levels >1000 ng/mL |

- **Maximum Recommended Daily Dose**: 900 mg
- An **adequate trial** of clozapine should last at least 8 weeks on a plasma trough level above 350-400ng/L
**Interruption of Therapy**

<table>
<thead>
<tr>
<th>Period of Interruption</th>
<th>Dosage</th>
<th>Monitoring Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 48 hours</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>&gt; 48 hours and &lt; 30 days</td>
<td>Restart titration: 12.5mg once or twice a day (if well tolerated, may be able to titrate to target dose more quickly than a new patient)</td>
<td>May continue current ANC monitoring schedule</td>
</tr>
<tr>
<td>≥ 30 days</td>
<td>Restart titration: 12.5mg once or twice a day</td>
<td>Re-initiate ANC monitoring schedule as a new patient</td>
</tr>
</tbody>
</table>

It is necessary to reinitiate treatment at a low dose to minimize the risk of hypotension, bradycardia and syncope. For additional safety information, please see the full Prescribing Information, including Boxed Warnings, which can be found at [www.clozapinerems.com](http://www.clozapinerems.com).

**Dosage Adjustments with Concomitant Use of Interacting Drugs**

<table>
<thead>
<tr>
<th>Mechanism of Interaction</th>
<th>Common Medications</th>
<th>Scenarios</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Initiating clozapine while taking co-medication OR adding a co-medication while taking clozapine</strong></td>
</tr>
<tr>
<td>CYP1A2 Strong Inhibitors</td>
<td>Fluvoxamine, Ciprofloxacin</td>
<td>Use one-third of the clozapine dose.</td>
</tr>
<tr>
<td>CYP1A2 Weak or Moderate Inhibitors</td>
<td>Oral contraceptives, Caffeine</td>
<td>Monitor for adverse reactions. Consider reducing clozapine dose if necessary.</td>
</tr>
<tr>
<td>CYP3A4 Strong Inducers</td>
<td>Carbamazepine, Phenytoin, St. John’s Wort, Rifampin</td>
<td><strong>Concomitant use not recommended.</strong> If inducer is necessary, may need to increase clozapine dose. Monitor for decreased effectiveness.</td>
</tr>
<tr>
<td>CYP1A2 or CYP3A4 Weak to Moderate Inducers</td>
<td>Smoking, Omeprazole</td>
<td>Monitor for decreased effectiveness. Consider increasing clozapine dose if necessary.</td>
</tr>
</tbody>
</table>

* Not all antidepressants inhibit CYP2D6 or CYP3A4—see p.27 for list of specific antidepressants

Source: Clozaril® Full Prescribing Information. 2.6 Dosage Adjustments with Concomitant use of CYP1A2, CYP2D6, CYP3A4 Inhibitors or CYP1A2, CYP3A4 Inducers. Table 1. [https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019758s084lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019758s084lbl.pdf)
Discontinuation of Therapy

- Method of treatment discontinuation will vary depending on the patient’s last ANC count:
  - Planned termination with normal ANC: reduce dose gradually over 1 to 2 weeks
  - Moderate to severe neutropenia: abrupt discontinuation usually necessary

- Continued monitoring is required after treatment discontinuation:
  - Monitor ANC in any patient reporting fever (temperature ≥ 38.5°C/101.3°F) during the 2 weeks after discontinuation
  - Monitor all patients carefully for the recurrence of both psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhea

---

**Discontinuation for medical condition unrelated to neutropenia**

- **General population:** continue existing ANC monitoring until ANC ≥ 1500/µL
- **BEN population:** continue existing ANC monitoring until ANC ≥ 1000/µL or above baseline

---

**Discontinuation for neutropenia**

- **General population:**
  - daily until ANC ≥ 1000/µL
  - three times weekly until ANC ≥ 1500/µL
- **BEN population:**
  - daily until ANC ≥ 500/µL
  - three times weekly until ANC ≥ patients established baseline

---

**REMEMBER** to report the decision to discontinue clozapine for a patient to the Clozapine REMS Program. You can do this one of three ways:

- By signing into the Clozapine REMS Program website at [www.clozapinerems.com](http://www.clozapinerems.com)
- By calling the Clozapine REMS Program contact center at 844-267-8678
- By completing the “Patient Update – Change Treatment Status” section of the ANC Lab Reporting Form and faxing it to the Clozapine REMS Program at 844-404-8876

Considerations for Rechallenging Patients on Clozapine

Per the Clozapine REMS Guide for Healthcare Providers, patients who experience or have experienced moderate clozapine-related neutropenia (ANC < 1000/µL) or severe clozapine-related neutropenia (ANC < 500/µL) can be rechallenged with clozapine if the risk of serious psychiatric illness from discontinuing clozapine is greater than the risk of rechallenge. This may be relevant for patients with severe schizophrenic illness who have no treatment option other than clozapine.

In making the decision to rechallenge a patient, consider:

- A hematology consult
- The ANC ranges defined in the full Prescribing Information
- The patient’s medical and psychiatric history
- A discussion with the patient and his/her caregiver about the benefits and risks of clozapine rechallenge
- The severity and characteristics of the neutropenic episode

Re-Initiation of Treatment in the clozapine 2/2017 Prescribing Information Section 2.5
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019758s084lbl.pdf pasted below:

When restarting CLOZARIL in patients who have discontinued CLOZARIL (i.e., 2 days or more since the last dose), reinitiate with 12.5 mg once daily or twice daily. This is necessary to minimize the risk of hypotension, bradycardia, and syncope [see Warnings and Precautions (5.3)]. If that dose is well-tolerated, the dose may be increased to the previously therapeutic dose more quickly than recommended for initial treatment.
### Side Effects & Recommended Management Summary

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Usual Time Course for Onset</th>
<th>Recommended Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia/Agranulocytosis</td>
<td>First 18 weeks</td>
<td>Refer to the ANC Monitoring table on page 10.</td>
</tr>
<tr>
<td>Myocarditis/Cardiomyopathy</td>
<td>Myocarditis: Most common in first 2 weeks to 2 months Cardiomyopathy: Usually occurs after first 2 months, but may occur any time</td>
<td>Stop clozapine. May present with flu-like symptoms. See page 22-23.</td>
</tr>
<tr>
<td>Constipation</td>
<td>Usually persists</td>
<td>Potentially life-threatening so effective treatment or prevention is essential. Recommend high fiber diet, bulk-forming laxative and stimulants. See page 18.</td>
</tr>
<tr>
<td>Sedation</td>
<td>First few months &amp; after dose increase</td>
<td>Give smaller dose in the morning. Reduce dose if needed.</td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>First few months, but may persist</td>
<td>Manage according to symptom severity. See page 19-21.</td>
</tr>
<tr>
<td>Hypotension</td>
<td>First 4 weeks</td>
<td>Reduce dose or slow rate of titration. Educate patient to slowly stand from sitting or lying position.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>First 4 weeks</td>
<td>Titrate dose slowly</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>First 4 weeks, but may persist</td>
<td>Common in early stage; If persistent at rest and presents with fever, hypotension or chest pain, it may indicate myocarditis. Refer to cardiology.</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>Usually in first year of treatment</td>
<td>Educate patient on proper diet and regular physical activity when initiating. Consider starting metformin.</td>
</tr>
<tr>
<td>Fever (&gt;101.3°F)</td>
<td>First 3 weeks</td>
<td>Give antipyretic and interrupt clozapine. Check CBC with differential and cardiac enzymes urgently.</td>
</tr>
<tr>
<td>Nausea</td>
<td>First 6 weeks</td>
<td>May give antiemetic; Avoid prochlorpromazine and metoclopramide if previous issue with EPS</td>
</tr>
<tr>
<td>Nocturnal Enuresis</td>
<td>May occur at any time</td>
<td>Avoid fluids before bed</td>
</tr>
</tbody>
</table>

*This is not a comprehensive list of possible side effects. Please see package insert for full information.*


For a comprehensive and informative review of side effects, monitoring and management, please refer to the following review article:
Common Side Effects and Adverse Reactions


Source: Adapted from reference 1
Constipation

Prevent Constipation

• Encourage adequate hydration, physical activity, and a high fiber diet
• Minimize other constipating medications when possible (opiates, benztropine, antihistamines, other anticholinergic agents)
• Strongly recommend a prophylactic bowel regimen in all patients starting clozapine

Treat Constipation

• Prescribe laxatives to soften stool and shorten transit time through GI tract:
  • Osmotic laxatives: lactulose, polyethylene glycol (e.g., Miralax), milk of magnesia
  • Stimulant laxatives: senna, bisacodyl (Dulcolax)
  • Stool softeners: docusate (Colace)
• Avoid bulking agents such as psyllium (Metamucil) or fiber supplements
• Consider magnesium citrate or an enema for persistent constipation

Ask about Bowel Function

• Ask about specific symptoms at each regular clinical assessment
• Develop a plan for ongoing individualized monitoring of patients with a known history of constipation
• Encourage patient, family, and other providers to monitor bowel function

- Abdominal distention or bloating
- Change in amount of gas passed rectally
- Less frequent bowel movements
- Oozing liquid stool
- Rectal fullness or pressure
- Rectal pain with bowel movement
- Small volume of stool
- Unable to pass stool
- Straining
- Sense of difficulty in passing stools
- Imcomplete evacuation
- Hard, lumpy stools
- Prolonged time to stool
- Need for manual maneuvers to pass stool
Sialorrhea

Sialorrhea, or excessive drooling, is one of clozapine’s most common adverse effects. Complications from clozapine-induced sialorrhea (CIS) can range from uncomfortable (i.e., social awkwardness and speech difficulties) to potentially life-threatening (i.e., parotiditis, choking and aspiration). The following are options in the management of CIS:

Clozapine dose reduction

- Clozapine dose reduction has been associated with improvement in CIS, but is often not clinically feasible.

Non-Pharmacologic Interventions

- Sugar-free gum or candy
- Placing towel over pillow

Pharmacologic Interventions

Local anticholinergic agents

- Administered sublingually
- Ipratropium bromide nasal spray
  - minimal systemic absorption and does not cross blood brain barrier (BBB)
  - cost may limit utility/access (covered by NC Medicaid)
- Atropine ophthalmic drops
  - can be difficult to self-administer correct dose
  - administration of > 4 drops/day can lead to anticholinergic toxicity
  - taste aberration can be significant

Systemic anticholinergic agents

- Combined risk of anticholinergic side effects when used with clozapine, especially at higher doses
- Glycopyrrolate
  - does not appreciably cross the BBB (fewer CNS effects)
  - reasonable first choice if systemic agent used
- Trihexyphenidyl
  - does cross BBB (greater CNS effects)
- Scopolamine patch
  - many systemic anticholinergic side effects
  - cost may limit utility/access

Alpha-adrenergic agents

- Clinical experience limited to case reports
- Combined risk of adverse cardiovascular effects (e.g., orthostasis) when used with clozapine
- Taper required upon cessation of therapy due to risk of rebound hypertension
- Clonidine
- Guanfacine
Treatments for Clozapine-Induced Sialorrhea Currently Available in the US

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>PK/PD &amp; Clinical Effects</th>
<th>Drug Interactions &amp; Adverse Reactions</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOCAL ANTICHOLINERGIC TREATMENTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1% Atropine Ophthalmic Drops</td>
<td>Nonselective, competitive muscarinic antagonist</td>
<td>Does cross BBB</td>
<td>Anticholinergic effects¹</td>
<td>Initial: 1 gtt SL QHS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Half-life: 6 hrs</td>
<td>Sour taste and dry mouth common</td>
<td>May increase to BID-TID dependent on severity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onset: 30 min-2 hrs</td>
<td>Atropinism possible from 4 gtts/day</td>
<td>Max: 6 gtts/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration of effect ≤ 4 hours; Swishing after SL application may increase efficacy</td>
<td></td>
<td>No renal/hepatic dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.03% Ipratropium Bromide Nasal Spray</td>
<td>Nonselective muscarinic antagonist</td>
<td>Does not cross BBB</td>
<td>Dry mouth and taste alteration</td>
<td>Initial: 1-2 sprays SL daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal systemic absorption when administered SL</td>
<td></td>
<td>Maintenance: Can increase to 2 sprays SL TID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration of effect: 2-8 hrs (BID-QID dosing may be necessary to maintain effect)</td>
<td></td>
<td>No renal/hepatic dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swishing after SL application may increase efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SYSTEMIC ANTICHOLINERGIC/ANTIMUSCARINIC TREATMENTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Anticholinergic and antimuscarinic properties</td>
<td>Does cross the BBB</td>
<td>Caution: Potential for additive CV side effects with clozapine</td>
<td>25-100 mg PO at bedtime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Half-life: 13-36 hrs</td>
<td>Caution with advanced age and CVD</td>
<td>Hepatic impairment: Caution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May increase clozapine levels via CYP1A2 inhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benztropine</td>
<td>M1 muscarinic antagonist; Possible blockade of M4 receptor activation by clozapine</td>
<td>Does cross BBB</td>
<td>Anticholinergic effects¹</td>
<td>1-2 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Half-life: 12-14 hrs</td>
<td></td>
<td>(May divide doses if drooling persists)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No renal/hepatic dose adjustment</td>
</tr>
</tbody>
</table>
### Systemic Anticholinergic/Antimuscarinic Treatments, Continued

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>PK/PD &amp; Clinical Effects</th>
<th>Drug Interactions &amp; Adverse Reactions</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopyrrolate</td>
<td>Nonselective muscarinic antagonist; High affinity for M&lt;sub&gt;3&lt;/sub&gt; receptor subtype</td>
<td>Does not cross BBB&lt;br&gt;Half-life: 3 hrs&lt;br&gt;Duration of effect for sialorrhea: 7 hrs</td>
<td>Anticholinergic effects&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Initial: 1 mg PO BID or 2-4 mg PO QHS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Max: 2 mg PO TID</td>
<td>Max: 2 mg PO TID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No renal/hepatic dose adjustment</td>
<td></td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Muscarinic antagonist; May be selective for M&lt;sub&gt;1&lt;/sub&gt; subtype</td>
<td>Does cross BBB&lt;br&gt;Onset: 6-8 hrs&lt;br&gt;Relief noted within hours of patch placement possible</td>
<td>Anticholinergic effects&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.5 mg transdermal patch Q72 hrs</td>
</tr>
<tr>
<td>Transdermal</td>
<td></td>
<td></td>
<td>Caution with advanced age and CVD</td>
<td>Renal/Hepatic impairment: Caution</td>
</tr>
<tr>
<td>Patch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidl</td>
<td>M&lt;sub&gt;1&lt;/sub&gt; muscarinic antagonist</td>
<td>Does cross BBB&lt;br&gt;Half-life: 33 hrs</td>
<td>Anticholinergic effects&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5-15 mg PO QHS or divided TID to QID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CNS side effects (i.e. euphoria, confusion, disorientation)</td>
<td>No renal/hepatic dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Systemic Alpha-Adrenergic Treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>PK/PD &amp; Clinical Effects</th>
<th>Drug Interactions &amp; Adverse Reactions</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>Activation of presynaptic α&lt;sub&gt;2&lt;/sub&gt;-autoreceptor; Reduces NE plasma levels, lowers activation of unopposed β-receptors</td>
<td>Half-life: 12-16 hours (normal renal function)&lt;br&gt;Onset: 0.5-3 hours&lt;br&gt;Caution with advanced age, renal impairment and CVD</td>
<td>Caution: Potential additive effects with clozapine on BP: Increased risk of orthostasis&lt;br&gt;Monitor BP (sitting and standing), HR and mental status</td>
<td>0.05-0.1 mg PO daily&lt;br&gt;0.1-0.2 mg/day transdermal patch has also been used&lt;br&gt;Taper required upon cessation of therapy due to risk of rebound hypertension</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Centrally-acting α&lt;sub&gt;2&lt;/sub&gt; agonist; Reduces NE plasma levels, lowers activation of unopposed β-receptors</td>
<td>Half-life: 10-30 hours&lt;br&gt;Onset: Within 4 days&lt;br&gt;Caution with advanced age, hepatic impairment and CVD</td>
<td>Caution: Potential additive effects with clozapine on BP: Increased risk of orthostasis&lt;br&gt;Monitor BP (sitting and standing), HR and mental status</td>
<td>1 mg PO daily&lt;br&gt;Taper required upon cessation of therapy due to risk of rebound hypertension</td>
</tr>
</tbody>
</table>

<sup>1</sup> Anticholinergic effects include tachycardia, constipation, N/V, urinary retention, confusion, blurry vision and delirium. *All include the potential for additive anticholinergic effects with clozapine.*
**Myocarditis & Cardiomyopathy**

Myocarditis and cardiomyopathy have occurred with the use of clozapine and these reactions can be fatal. Discontinue clozapine and obtain a cardiac evaluation upon suspicion of myocarditis or cardiomyopathy.

- **Typical presentation**: Chest pain, dyspnea, persistent tachycardia at rest, palpitations, fever, flu-like symptoms, hypotension, other signs or symptoms of heart failure, electrocardiogram findings
- **Myocarditis**: Most common in first 2 months of clozapine treatment (can occur at any time)
- **Cardiomyopathy**: Usually occurs later than myocarditis (after 8 weeks; can occur at any time)
- **Typical lab findings**: Elevated troponin I or R, elevated creatinine kinase-MB, peripheral eosinophilia, elevated C-reactive protein (CRP)

The risk of clozapine-induced myocarditis is estimated to be between 1 in 100 and 1 in 500. For at least the initial four weeks of clozapine treatment, all patients should be monitored for early signs of myocarditis. Monitoring should include assessment of clinical status for subjective signs of distress; vital signs at each visit; and weekly laboratory tests to include eosinophil count, sedimentation rate, or C-reactive protein and troponins.

Recommendations vary widely for both baseline and maintenance monitoring due to costs, feasibility and appropriateness. A 2018 systematic review of 144 articles published between 1988 and February 2017 concluded that screening for myocarditis and cardiomyopathy in asymptomatic patients receiving clozapine could include the following:

- Perform baseline ECG.
- Perform echocardiography, as a part of a cardiology consult, to establish baseline cardiac function in patients with known cardiac disease, structural abnormalities or cardiac risk factors.
- Observe a low threshold for initiating CRP and troponin monitoring, especially during the first 4 weeks of clozapine therapy if any signs or symptoms suggestive of myocarditis develop, including asymptomatic tachycardia or heart rate increases of 10 to 20 beats per minute.
  - Positive findings warrant a cardiology consultation.
  - Negative results with symptoms suggestive of possible myocarditis support weekly CRP and troponin monitoring during the symptomatic period. Internal medicine/cardiology consultation should be considered for persistent symptoms.

| Myocarditis and cardiomyopathy monitoring for patients receiving clozapine. |
|-----------------------------|-----------------------------|
| **Feature** | **Myocarditis** | **Cardiomyopathy** |
| **Usual onset** | Acute: greatest risk in first 2 months with peak occurrence during third week of therapy. Can occur anytime. | Insidious: commonly detected after at least 6 months of therapy. |
| **Presenting signs and symptoms** | Heterogeneous and non-specific: malaise, sweating, tachycardia, chest pain, palpitations. | Signs and symptoms of heart failure: shortness of breath, cough, peripheral edema, chest pain, persistent tachycardia. |
| **Routine monitoring parameters** | Frequent assessment of clinical presentation. Vital signs, especially new tachycardia or increases in heart rate >10-20 beats per minute. | Cardiomyopathy consultation warranted for known cardiac disease, structural abnormalities, or other cardiac risk factors. |
| **Laboratory or radiographic abnormalities** | Eosinophil count may be elevated but is non-specific. Troponins plus CRP elevations are highly specific and sensitive in symptomatic patients. | No specific/ routine laboratory measures recommended. Echocardiography with LV dysfunction, dilation, or hypertrophy. |

Table 4

Abbreviations: CRP, C-reactive protein; LV, left ventricular; MRI, magnetic resonance imaging.

# Myocarditis & Cardiomyopathy Monitoring Recommendations

<table>
<thead>
<tr>
<th>Test/Procedure</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Routine Physical Monitoring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitals (HR, BP, RR, T&lt;sub&gt;max&lt;/sub&gt;)</td>
<td>- Daily as directed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Usually BID during titration phase</td>
<td></td>
</tr>
<tr>
<td>Physical Symptoms (i.e., SOB, chest pain, s/s of systemic illness)</td>
<td>- Daily as directed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Based on patient report and physical assessment</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnostic Procedures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>- Baseline and ASAP upon clinical concern for myocarditis</td>
<td>No recommendations for routine ECG monitoring beyond baseline exist</td>
</tr>
<tr>
<td></td>
<td>- Consider weekly x first 4 weeks of therapy</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- If Troponin &gt; 2x ULN or HS-CRP &gt; 100 mg/L</td>
<td>Usually reserved for high clinical suspicion but consider for equivocal lab/diagnostic results or physical symptoms</td>
</tr>
<tr>
<td></td>
<td>- Requires cardiology consult</td>
<td></td>
</tr>
<tr>
<td>Endomyocardial Biopsy</td>
<td>Generally reserved for post-mortem assessment</td>
<td>Gold standard for diagnosis</td>
</tr>
<tr>
<td><strong>Laboratory Tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin I &amp; T</td>
<td>- Baseline and weekly x first 4 weeks of therapy</td>
<td>- Increased sensitivity/specificity when assessed with HS-CRP</td>
</tr>
<tr>
<td></td>
<td>- As clinically indicated</td>
<td>- Elevations can lag up to 5 days after symptom onset and/or HS-CRP rise</td>
</tr>
<tr>
<td>ESR (Erythrocyte Sedimentation Rate)</td>
<td>- Baseline and weekly x first 4 weeks of therapy</td>
<td>Non-specific marker of inflammation; May be elevated in other disease states</td>
</tr>
<tr>
<td></td>
<td>- As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>HS-CRP&lt;sup&gt;1&lt;/sup&gt; (High Sensitivity C-Reactive Protein)</td>
<td>- Baseline and weekly x first 4 weeks of therapy</td>
<td>Increased sensitivity/specificity when assessed with Troponin</td>
</tr>
<tr>
<td></td>
<td>- As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>EOS (Absolute Eosinophil Count)</td>
<td>- Baseline</td>
<td>Elevations in EOS have been associated with subclinical myocarditis even after the highest risk period (1&lt;sup&gt;st&lt;/sup&gt; 4 weeks) but can also reflect other end-organ inflammation. Warrants further workup for &gt;1.5K cells/µL</td>
</tr>
<tr>
<td></td>
<td>- Weekly x first 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Additional monitoring driven by REMS CBC monitoring requirements</td>
<td></td>
</tr>
</tbody>
</table>

Monitoring protocol published in the Australian and New Zealand Journal of Psychiatry:


See pages 46-47 for NC Division of State Operated Health Facilities’ myocarditis algorithm
# Comparison with Other First & Second Generation Antipsychotics

<table>
<thead>
<tr>
<th>Weight gain/diabetes mellitus</th>
<th>Hypercholesterolemia</th>
<th>EPS/TD</th>
<th>Prolactin elevation</th>
<th>Sedation</th>
<th>Anticholinergic side effects</th>
<th>Orthostatic hypotension</th>
<th>QTc prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-/±</td>
<td>ND</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-/±</td>
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</tr>
<tr>
<td>Loxapine</td>
<td>++</td>
<td>ND</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>++</td>
<td>ND</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>ND</td>
</tr>
<tr>
<td>Pimozide</td>
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<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>Thoridazine&lt;br&gt;Thoridazine*&lt;br&gt;Thioridazine**</td>
<td>++</td>
<td>ND</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Thiothixene</td>
<td>++</td>
<td>ND</td>
<td>+++</td>
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<tr>
<td>Trifluoperazine</td>
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<td>+++</td>
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<td>ND</td>
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<td><strong>Second generation agents</strong></td>
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<tr>
<td>Aliptoprazole</td>
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<td>+</td>
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<tr>
<td>Aripiprazole</td>
<td>++</td>
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<td>+</td>
<td>++</td>
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<td>-</td>
<td>+</td>
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<tr>
<td>Brexpiprazole&lt;br&gt;Brexpiprazole†</td>
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<td>+</td>
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<td>+</td>
<td>-/±</td>
<td>-/±</td>
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<tr>
<td>Cariprazine†</td>
<td>+</td>
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<td>++</td>
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<tr>
<td>Clozapine&lt;br&gt;Clozapine⁶</td>
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<td>++++</td>
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<tr>
<td>Flupentixol</td>
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<td>++</td>
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<tr>
<td>Lurasidone</td>
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<tr>
<td>Olanzapine</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Paliperidone</td>
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<td>+</td>
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<td>Pinimparazine</td>
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<td>+</td>
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<tr>
<td>Quetiapine</td>
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<tr>
<td>Risperidone</td>
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<td>+</td>
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<tr>
<td>Ziprasidone</td>
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</tbody>
</table>

Adverse effects may be dose dependent.

EPS: extrapyramidal symptoms; TD: tardive dyskinesia; ND: no data.

* Thoridazine is also associated with dose-dependent retinits pigmentosa. Refer to text.
† Based upon limited experience.
⁶ Clozapine also causes granulocytopenia or agranulocytosis in approximately 1 percent of patients requiring regular blood cell count monitoring. Clozapine has been associated with excess risk of myocarditis and various thromboembolic events including fatal pulmonary embolism. These issues are addressed in the UpToDate topic review of guidelines for prescribing clozapine section on adverse effects.

Drug Interactions

Clozapine is a substrate of many cytochrome P450 isozymes, in particular CYP1A2, CYP3A4, CYP2D6, and CYP2C19.

**Clozapine and Smoking**

Baseline smoking habits and regular updates should be assessed and documented. Smoking can cause a reduction in plasma clozapine levels through induction of CYP1A2. Abrupt smoking cessation may lead to clozapine toxicity due to a rise in clozapine levels. Smoking cessation should be supervised and done in a tapered manner. Patients recently discharged from a smoke-free facility who resume smoking may need an increased clozapine dose.

**Note:** It is the polyaromatic-hydrocarbons within the tar of cigarettes that affects clozapine metabolism and levels, **not** the nicotine. Nicotine replacement therapy (NRT) **does not** affect clozapine levels.

Prescription medications used for smoking cessation have been associated with destabilisation of mental state in some patients. Consider a strategic approach in consultation with the psychiatrist.

**Clozapine and Caffeine**

Caffeine (i.e., tea, coffee, cola, energy drinks) may significantly inhibit the metabolism of clozapine. Changes in caffeine intake can lead to clinically significant changes in serum clozapine levels. Concurrent use of caffeine in moderate to high quantities, which is common among those with schizophrenia, with clozapine may result in an increased risk of clozapine toxicity. Clinicians should regularly assess and monitor caffeine consumption.

Important Drug Interactions with Clozapine

Potential to Increase or Decrease Clozapine Levels

See ‘Dosage Adjustments with Concomitant Use of Interacting Drugs’ section on page 13 for further information on recommended clozapine dosage adjustment and monitoring.

Potential to Depress Bone Marrow
- Carbamazepine, trimethoprim/sulfamethoxazole, nitrofurantoin, cytotoxic medication, immunosuppressant medication
- Clozapine use not recommended concomitantly with other agents having a well-known potential to suppress bone marrow function.

Potential to Depress Respiration (CNS Depressants)
- Benzodiazepines (especially large parenteral doses or at start of therapy), alcohol, narcotics
- Caution is advised if clozapine is used concomitantly. Advise patient of possible additive sedative effects and caution them not to drive or operate machinery.

Potential for Anticholinergic Side Effects (Constipation, urinary retention, delirium)
- TCAs (amitriptyline), antipsychotics (chlorpromazine, quetiapine), benztropine, antihistamines (diphenhydramine, cyproheptadine, promethazine), antispasmodics (atropine, hyoscine)
- Observe patients for anticholinergic side effects, especially when using to help control hypersalivation.

Potential for Hypotension
- Antihypertensives, TCAs, some antipsychotics (chlorpromazine, trifluoperazine, risperidone (initially), quetiapine (initially))
- Caution advised due to potentiation of hypotensive effects, especially during initial titration.

Important Drug Interactions with Clozapine (continued)

Proton Pump Inhibitors (PPIs)

- Pantoprazole does not affect the enzyme systems involved in clozapine metabolism
- Omeprazole has the potential to induce CYP1A2 and decrease clozapine concentrations by nearly half, though data has been discrepant and limited to case reports.
- When initiating omeprazole, discontinuing omeprazole, or changing a patient from omeprazole to pantoprazole, it is likely unnecessary to make pre-emptive dosage changes. Given the generally expected timeline for enzyme induction and de-induction, it may be appropriate to continue to monitor clinical status and obtain a clozapine concentration within one month of the therapy change.
Medication & Community Resources

The following is a list of resources available for uninsured patients:

- **Lab Work**
  - Community Health Centers  https://ncchca.site-ym.com/page/FindCHC
  - Free Clinic: https://www.freeclinics.com/sta/north_carolina
  - http://pals-labs.org/

- **Patient Medication Assistance Programs**
  - As of May 2017, Mylan and Teva Pharmaceuticals both offer Clozapine Patient Assistance Programs (See Community Resources/Care Coordination Section).
  - To find a local patient medication assistance program, in North Carolina visit  https://www.ncdhhs.gov/assistance/low-income-services/medication-assistance-program

- **County Specific Programs**
  - Durham County
    - Pharmacy: Gurley’s Pharmacy has clozapine available thru patient assistance
    - Consider establishing primary care with Lincoln Community Health Center or Samaritan Health Center in Durham for lab work
  - Wake County
    - Wake County Human Services Pharmacy offers patient assistance for clozapine AND free basic lab work if an uninsured consumer gets medication through them

- **Web-Based Patient Assistance Programs**
  - Rxassist.org
  - Needymeds.org
  - Rxhope.com
Community Pharmacy Enhanced Services Network (CPESN)

In 2014, Community Care of North Carolina (CCNC) created the Community Pharmacy Enhanced Services Network (CPESN), an open network of approximately 250 NC pharmacies committed to broadening the availability of medication management resources to our state’s highest-needs population. The goal of the CPESN is to improve quality of care and patient outcomes related to optimal medication use, thereby improving the patient’s overall health trajectory, leading to a reduction in total cost of care.

In partnership with CCNC, CPESN pharmacies provide enhanced pharmacy services that go above and beyond conventional prescription dispensing and basic patient education. Enhanced services include interventions such as synchronization of a patient’s chronic medication fill dates, adherence monitoring and coaching, compliance packaging and home delivery. Additional enhanced and optional services offered include DME billing, home visits, point of care testing, immunizations, multilingual staff, naloxone dispensing, compounding, collection of vital signs or standardized assessments (PHQ, etc.) and many others.

The Pharmacy Locator is a tool developed to communicate to care managers, providers and other partners regarding which pharmacies are participating in the NC CPESN and what types of enhanced services are offered at each location. Based on the information provided in the pharmacy locator, a user can identify which local pharmacies offer the types of services needed by a particular patient.

Please visit the NC CPESN Pharmacy Locator website at https://collaboration.cpesn.com/finder for complete information on participating pharmacies and their services.

In the Compounding and Dispensing section, click to select ‘Clozapine Dispensing and Monitoring’ to view pharmacies that perform this activity.
## Appendix 1: Initiation Monitoring Form

### Clozapine Monitoring Form: First 8 Weeks

<table>
<thead>
<tr>
<th>Blood Type</th>
<th>Height</th>
<th>Smoking Status: ☐ Smoker ☐ Non-Smoker</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Intervals</th>
<th>Date</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clozapine baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Day 14</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Day 21</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Day 28</td>
<td>☐</td>
<td></td>
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<tr>
<td>Day 35</td>
<td>☐</td>
<td></td>
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<tr>
<td>Day 42</td>
<td>☐</td>
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<tr>
<td>Day 49</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Day 56</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>After 8 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Intervals

- **Full physical exam**: ☐ Performed
- **Waist Circumference**
- **Weight**
- **Height**
- **BMI**
- **Blood Pressure**
- **CBC w/diff**: ☐ Performed
- **WBC**
- **ANC**
- **Eosinophils**
- **LFTs**: ☐ Performed
- **Cr/BUN/Lytes**: ☐ Performed
- **Glucose (Random or fasting) OR HgA1c**
- **Total Cholesterol**
- **LDL**
- **HDL**
- **Trig**
- **Troponin I**
- **CRP**
- **Pro-BNP**
- **CK**
- **CK-MB**
- **ECG (QT interval)**
- **Baseline AIMS**
- **Beta-HCG**
- **EEG (optional)**

### Notes

- **Most common symptoms of myocarditis**: Fever, tachycardia and chest pain
- **Other symptoms**: Shortness of breath, dry cough, elevated white cell count, peripheral eosinophilia, diarrhea, vomiting, dysuria and rash

---

*All fields marked with ☐ must be completed.*

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*All fields marked with ☐ must be completed.*
Appendix 2: Monitoring Form

Antipsychotic Monitoring Form for Children & Adolescents (Symptoms and Side Effects)

This form can be downloaded at: https://keltymentalhealth.ca/sites/default/files/resources/antipsychotic_monitoring_form_-_may_2013_0.pdf

<table>
<thead>
<tr>
<th>Name</th>
<th>Start Date</th>
<th>Weight</th>
<th>Height</th>
<th>Medication Name</th>
<th>Rate’s Name</th>
<th>Relationship to Patient</th>
</tr>
</thead>
</table>

**Purpose**

If you have been given this form, it may mean you will be taking an antipsychotic to help you decrease your symptoms of a thought disorder (psychosis), schizophrenia, tic disorder or another condition. This form is designed to help you, your caregivers and your doctor monitor how well your medication is working and also to measure any side effects you may be experiencing. There are several blank spaces in this monitoring form. Please use these spaces by listing any specific symptoms or side effects you want to monitor. Please bring this form with you when you visit your doctor. It can help guide your discussions with your doctor. For example, use it to point out which symptoms and side effects bother you the most.

**Directives:** Before you start the antipsychotic (“baseline”) and at each of the time periods listed below (whether you see your doctor or not), please rate the following possible symptoms and side effects. In other words, please write the number that best describes your experience (on average over the past week) in the appropriate box based on the following scale:

<table>
<thead>
<tr>
<th>0 - not present</th>
<th>1 - a little</th>
<th>2 - a moderate amount</th>
<th>3 - a severe amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>[I haven’t noticed this]</td>
<td>[It doesn’t bother me]</td>
<td>[It bothers me]</td>
<td>[It bothers me a lot]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Baseline</th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
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<tr>
<td>Delusions</td>
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<tr>
<td>Disorganized thoughts</td>
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<td>Aggression</td>
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<td>Hyperactivity</td>
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<td>Low mood</td>
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<td>Anxiety</td>
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<tr>
<td>Tics (uncontrolled motor movements or vocalizations)</td>
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<tr>
<td>Disruptive behaviours</td>
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<tr>
<td>Trouble falling or staying asleep</td>
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<tr>
<td>Feeling overly excited or happy</td>
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Antipsychotic Monitoring Form for Children and Adolescents ©May 2013
Child & Adolescent Mental Health Programs
BC Mental Health & Addiction Services, 4500 Oak Street, Vancouver, B.C., Canada V6H 3N1
<table>
<thead>
<tr>
<th>Possible Side Effects</th>
<th>Baseline</th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite loss</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Disruption with either menstrual cycles or sexual functioning</td>
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<tr>
<td>Dry mouth</td>
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<tr>
<td>Feeling agitated</td>
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<td>Feeling dizzy or Lightheaded</td>
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<tr>
<td>Feeling nauseated or vomiting</td>
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<tr>
<td>Feeling drowsy</td>
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<td>Headaches</td>
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<tr>
<td>Increased appetite</td>
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<tr>
<td>Racing heart beat</td>
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<td>Skin rash</td>
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<tr>
<td>Stiff muscles</td>
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<td>Urinary problems</td>
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<td>Weight gain</td>
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<tr>
<td>Weight loss</td>
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<tr>
<td>Blood work*</td>
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<td></td>
</tr>
<tr>
<td>Approximate # of missed doses of your antipsychotic (in the past week)</td>
<td>N/A</td>
<td></td>
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</tr>
</tbody>
</table>

Please list any other medications you are taking: ________________________________________________

*Note: This form is from Canada so blood work monitoring requirements are less stringent than US Clozapine REMS Program requirements*
Appendix 3: Patient Consent Forms

The following are sample patient consent forms:

- **State of Wisconsin Department of Health Services Informed Consent for Medication Form for Clozapine**
  
  [Link](https://www.dhs.wisconsin.gov/forms/f24277cd-clozaril.pdf)

- **Alameda County Behavioral Health Care Services Clozapine Form**
  
  [Link](http://www.acbhcs.org/meddir/MedConsent/English/clozapine(Clozaril).pdf)

- **American Correctional Association Clozapine Informed Consent**
  
  [Link](http://www.aca.org/ACA_Prod_IMIS/DOCS/OCHC/Informed%20Consent%20Form.pdf)

- **California Correctional Health Care Services Page 14**
  
Appendix 4: Informative Articles

  https://www.mdedge.com/psychiatry/article/110900/schizophrenia-other-psychotic-disorders/rediscovering-clozapine-adverse

  https://www.mdedge.com/psychiatry/article/109956/schizophrenia-other-psychotic-disorders/rediscovering-clozapine-after

- A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia
Appendix 5: Patient and Family Education Materials

The following resources provide patient and family education materials that are able to be printed and provided when needed:

- **SMI Advisor: A Clinical Support System for Serious Mental Illness (SAMHSA)**
  

- **National Alliance on Mental Illness (NAMI) Clozapine Drug Information**
  

- **Clozapine REMS – A Guide for Patients and Caregivers**
  

- **California Correctional Health Care Services**
  

Appendix 6: Pediatric Resources

American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia

Recommendation 7: A trial of clozapine should be considered for youth with treatment resistant schizophrenia spectrum disorders. [CS]

Clozapine is the only antipsychotic agent for which there is established superiority over other agents. For treatment-refractory EOS, clozapine was more beneficial than haloperidol (n = 21) or high-dose olanzapine (n = 39) for positive and negative symptoms (n = 21) \(^1\) \([\text{rct}]\), \(^2\) \([\text{rct}]\) and superior to olanzapine for negative symptoms (n = 25). \(^3\) \([\text{rct}]\) A naturalistic follow-up study of EOS found clozapine more effective than haloperidol, risperidone, or olanzapine (n = 47). \(^4\) \([\text{cs}]\) However, owing to potential side effects, clozapine is reserved for treatment refractory cases, i.e., patients with two or more failed trials of a first-line antipsychotic agent.

Before using clozapine, it is important to review the child’s clinical status and treatment history to ensure that the presentation accurately reflects treatment refractory schizophrenia. For complicated cases or the apparent diagnosis of schizophrenia in a younger child (e.g., <12 years), a diagnostic second opinion may be warranted.

When using clozapine, systematic monitoring of side effects, including following established protocols for blood count monitoring, is required. White blood cell and absolute neutrophil counts are obtained at baseline and weekly for the first 6 months to monitor the risk for agranulocytosis. These protocols require a coordinated effort among the pharmacy, laboratory, and physician to ensure that the blood count parameters are being monitored concurrently with prescriptions.

\([\text{rct}]\) = Randomized controlled trial
\([\text{cs}]\) = Case series/report is applied to a case series or a case report

The following resources provide children and adolescent patient and family education materials that are able to be printed and provided when needed:

- **Kelty Mental Health: Using Clozapine in Children and Adolescents**
  Patient education brochure (4 pages)
Appendix 7: NC Division of State Operated Health Facilities
Clozapine Medication Use Policy June 2018
Note: This policy was developed for inpatient use in May 2018 and may not be the most up to date and is intended for use as guidance only

SOHF 172-AL (2)

DIVISION OF STATE OPERATED HEALTHCARE FACILITIES
ADATCs/Developmental Centers/Neuro-Medical Treatment Centers/Psychiatric Hospitals
POLICIES AND PROCEDURES

Approved By: [Signature] Approval Date: 6/12/18

Clozapine Medication Use

I. Purpose:
To establish suggested policy and procedures for the use of clozapine in DSOHF facilities.

II. Policy:
Clozapine is a Food and Drug Administration (FDA) approved drug for treatment resistant schizophrenia and for the reduction in risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorders. In addition, clinically it may offer hope of improvement for treatment of resistant schizophrenia/schizoaffective disorder and refractory bipolar patients. Even though the patient may meet the criteria for initiating treatment, this does not imply that he/she must receive clozapine.

III. Definitions:
Absolute Neutrophil Count (ANC): WBC X % neutrophils

Benign ethnic neutropenia (BEN): condition in certain ethnic groups whose average ANCs are lower than standard.

Complete blood count (CBC)-clozapine: blood test that provides the absolute neutrophil count and panic values that conform to the clozapine guidelines.

Designee: A health care provider other than the prescriber) who can enroll patients, enter ANC values on the prescriber’s behalf, and review patient lists and patient lab history, designated by the prescriber.

General Population (GP): for purposes of this policy and clozapine monitoring, the general population are all patients without BEN.

Risk Evaluation and Mitigation Strategy (REMS): strategy to manage known or potential risks associated with a drug or group of drugs. REMS is required for clozapine to ensure the potential benefits outweigh the risk of neutropenia.

IV. Scope:
This policy applies to all facilities within the Division of State Operated Healthcare Facilities (DSOHC).

EFFECTIVE: 06/18/18
SUPERSEDES: SOHF 172-AL 6/18/16, SOHF 172-AL (1), 6/30/16
OPR: Director, Division of State Operated Healthcare Facilities
DISTRIBUTION: All State-Operated Healthcare Facilities
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Clozapine Medication Use Policy June 2018 (page 2)

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V. Procedures:
A. Criteria For Consideration In Initiating Treatment
   1. Prior to the initiation of clozapine, consideration of the following should be made by the attending physician:
      a. Diagnoses – DSM 5 diagnosis of schizophrenia, schizoaffective disorder, refractory bipolar disorder, or borderline personality disorder. Clozapine may be indicated for use in other disorders where there are treatment resistant signs/symptoms of mental illness.
      b. Severity of Illness/Side Effects characterized by:
         1) Prominent positive and/or negative symptoms, conceptual disorganization, violent behavior directed at others, or suicidal/self-injurious thoughts or behavior.
         2) Lack of responsiveness to other antipsychotic medication at an adequate dose and for an adequate duration.
         3) Tardive Dyskinesia - Persistent tardive dyskinesia with disabling psychotic symptoms while not taking antipsychotic medication.
         4) Extrapyramidal Side Effects - Severe, drug-induced, extrapyramidal side effects which cannot be managed with either anti-Parkinsonian drugs or by reducing the dose of the antipsychotic medication.
      c. Opportunity for improved quality of life - Considerations should include a reasonable expectation of the patient being discharged and living more independently in the community or an improved quality of life while in the hospital.

B. Clinical Guidelines
1. Registration
   a. Physicians must be registered with the Clozapine REMS Program before prescribing clozapine.
   b. Physicians must approve a pharmacy designee to enroll patients and enter ANC results on the prescriber’s behalf in the Clozapine REMS program.

2. Education / Informed Consent
   a. Prescribers may provide the patient/legally responsible person with What you Need to Know about Clozapine: A Guide for Patients and Caregivers
   b. Prescribers must inform the patient/legally responsible person about the risk of severe neutropenia associated with clozapine
   c. Informed consent should be obtained from the patient/legally responsible person prior to the initiation of clozapine therapy and documented on the Clozapine Informed Consent form.
   d. The patient should be willing and able to cooperate in taking oral medications and allowing required blood testing.

3. Patients admitted to facilities and already actively taking clozapine
   a. Complete steps 2 a and b under “Clinical Guidelines.”
   b. Complete step 1 below under “Prescribing.”
   c. Upon receipt of a CBC with differential done within the last seven days, or as compliant with the REMS schedule, clozapine can be dispensed for the patient if the ANC is at least 1500 for the GP or at least 1000 for patients with BEN. Bloodwork from an outside agency is acceptable if within the last 7 days or as compliant with the REMS schedule.

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Clozapine Medication Use Policy June 2018 (page 3)

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4. Prescribing
   a. Each facility will establish a Clozapine Committee or consultation service with expertise in Clozapine that serves as a consultation service. The committee and/or consultation function may be performed by an existing committee (i.e. P&T Committee).
   b. Required pre-clozapine baseline studies include a CBC with differential, a myocarditis panel (Troponin-I, CRP, BNP) and ECG.
   c. The Committee may impose additional requirements which must be met prior to the initiation of clozapine.
   d. If a physician is unable to meet these requirements after reasonable effort, the case may be presented to the Clozapine Committee for consideration.
   e. Patients must be enrolled in the Clozapine REMS Program before Clozapine can be dispensed and/or administered. A patient can be enrolled one of two ways: by logging into the website and enrolling or completing the 'Patient Enrollment form' and faxing the form into the program.
   f. Attending physicians are responsible for initial and subsequent dosing decisions based on clozapine prescribing information published by the manufacturer.
   g. Prior to initiation of clozapine, the patient must have a current (no older than seven (7) days) ANC that meets the minimum standards recommended by the Clozapine REMS Program.
   h. If a clozapine patient has had an interruption in clozapine treatment of greater than 48 hours, restart with 12.5 mg once or twice daily to minimize the risk of hypotension, bradycardia and syncope. If this re-initiation dose is well tolerated, clozapine may be titrated to a previously therapeutic dose more quickly than recommended at initiation of therapy. There are clinical circumstances whereby starting at a higher dose could be justified. Following the consultant's review, the rationale for starting at the higher dose should be documented in the medical record.

C. Monitoring
   1. The prescribing physician orders a weekly CBC-clozapine (or less frequently as described below). The pharmacist or designee checks the ANC information for each patient with labs scheduled for that day. Each patient's ANC is reported to the Clozapine REMS Program. Missing results are investigated by the pharmacist to determine the reason for omission. If the CBC was not drawn on the designated day, nursing staff on the PCU (and, if necessary, the prescriber) are verbally contacted to request a CBC within 24 hours. If a patient’s ANC is less than 1500 then the Laboratory notifies the attending physician and Pharmacy. Detailed guidance related to ANC can be found in the Clozapine REMS summarized in Table 1.
   

2. Recommended Monitoring Frequency and Clinical Decisions by ANC Level. Additional laboratory monitoring or termination of clozapine may be necessary as recommended by the Clozapine REMS Program guidelines.

3. Patients first started on clozapine have an ANC monitored weekly for the first 6 months. If ANC has remained acceptable for this six-month period, then the frequency of monitoring ANC may be decreased to every 2 weeks for the next 6 months. If ANC remains acceptable during this next 6 month period, the monitoring frequency may be decreased again to every 4 weeks.

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Clozapine Medication Use Policy June 2018 (page 4)

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4. Metabolic monitoring should be done for all patients on anti-psychotic medications in accordance with recommended guidelines.

5. A physician or designee reviews baseline clozapine laboratory results. A Myocarditis Symptom Progress Note for Patients on Clozapine may be used as an additional screening tool or to guide clinical inquiry for patients with signs and symptoms that could be consistent with clozapine myocarditis. The physician or designee will review labs and, if used, the myocarditis symptom progress notes to bring significant abnormalities promptly to the attention of the attending psychiatrist.

6. In order to monitor for the development of clozapine related myocarditis, a myocarditis panel (Troponin, CRP and BNP) will be performed prior to initiation of clozapine, then weekly for at least for 4 weeks, and then as clinically indicated. ECG will be performed prior to initiation of clozapine, then weekly for at least 4 weeks, then weekly as clinically indicated.

7. Actions to be taken when the monitoring of symptoms, signs or tests raises a concern for clozapine related myocarditis (see policy Attachment C for algorithms outlining the information below):
   a. If patient develops any of below (a. i.-v.) symptoms or signs, prescribing provider is to consider whether rise could be due to clozapine or other medical condition and, if clozapine is felt to be the cause, implement enhanced monitoring to include increased frequency myocarditis panel, increased VS monitoring and increased ECG frequency. Additionally, provider will consider dose or titration adjustment.
      i. Symptoms suggestive of infectious illness or myocarditis or,
      ii. Sustained HR greater >= to 120 or,
      iii. CRP > 50 but < 100 (with troponin that is < 2 x upper limit of normal) or,
      iv. Significant increase in BNP from baseline or,
      v. ECG changes

8. Actions to be taken when the monitoring of symptoms, signs or tests strongly suggests or confirms clozapine related myocarditis:
   a. If patient develops symptoms strongly suggestive of myocarditis (chest pain, heart failure, arrhythmia, fevers without other identified cause) and one or both of below (8. a. i.-ii.) provider should consider clozapine myocarditis to be present, discontinue clozapine and implement enhanced monitoring to include daily myocarditis panels, cardiac telemetry monitoring (until clinical improvement is noted), a 2D echocardiogram and, if clinically indicated, a cardiology consultation.
      i. Troponin > 2 x upper limit of normal or
      ii. CRP > 100

   b. If patient develops one or both of above (8. a. i.-ii.) in a clinical situation that suggests a non-myocarditis cause is significantly more likely than myocarditis (e.g., severe bacterial infection, NSTEMI, STEMI, clozapine associated colitis) then MD will initiate the monitoring and care appropriate for the situation and discontinue clozapine if indicated.

   c. If patient develops a CRP >100 in the absence of an elevated troponin and in the absence of symptoms suggestive of myocarditis and there is no other identified or reasonably likely clinical explanation for the elevation, the MD will discontinue clozapine and monitor with daily exams, myocarditis panels and ECG.

EFFECTIVE: 06/18/18
SUPERSEDES: SOHF 172-AL 6/16/16, SOHF 172-AL (1), 6/30/16
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Clozapine Medication Use Policy June 2018 (page 5)

Note: This policy was developed for inpatient use in May 2018 and may not be the most up to date and is intended for use as guidance only

D. Dispensing
   1. Clozapine is supplied by pharmacy and made available for administration by nursing, either through stocking in the automated dispensing cabinet located on the nursing unit, in patient specific medication bins on the nursing unit, or may be obtained directly from the pharmacy.
   2. Nursing can administer Clozapine as long as blood work values are within acceptable limits.
   3. If a CBC-clozapine is not obtained, the clozapine is NOT immediately stopped. The charge nurse on the patient care unit is notified and informed of the need for the lab work. If the lab work is not received within 2 days, the prescribing physician is contacted and informed clozapine will be discontinued unless the CBC-clozapine is obtained.
   4. Treatment Recommendations:
      Follow recommended monitoring frequency and clinical decisions by ANC level as outlined in Section C 1-3.

E. Notification of Others
   1. The Pharmacy notifies the prescribing physician if clozapine must be discontinued due to ANC monitoring guidelines.

F. Discontinuation
   1. The attending physician is responsible for discontinuing clozapine based on the patient/legally responsible person’s request, lack of therapeutic response, side effects or unacceptable ANC results. The attending physician schedules ANC monitoring following Clozapine REMS Program guidelines.
   2. If Clozapine is discontinued for neutropenia, follow guidelines in the Clozapine REMS: Recommendations for Monitoring After Discontinuation of Clozapine.

G. Prescription of Clozapine at Discharge
   1. The patient’s treatment team provides the patient’s outpatient provider the date of the last CBC with differential, and the current monitoring frequency.
   2. A seven-day continuation supply is offered to all patients discharging on clozapine. The patient may receive up to a 28-day (4 weeks) supply if permitted based on the appropriate ANC monitoring frequency per clozapine REMS requirements and if he/she has a qualifying access/financial justification as approved by the facility chief medical officer or designee.

VI. Any exceptions to the above policy must be approved by the Director, State Operated Healthcare Facilities or designee.
Appendix 7: NC Division of State Operated Health Facilities
Clozapine Medication Use Policy June 2018 (page 6)

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Related Documents/Forms:
Attachment A - Clozapine Informed Consent
Attachment B - Myocarditis Symptoms Progress Note for Patients on Clozapine
Attachment C – Monitoring for Signs and Symptoms and Response

Review/Approval History:
CEO Approval: ___________________________ Date: ________________
Appendix 7: NC Division of State Operated Health Facilities
Clozapine Medication Use Policy June 2018 (Attachment A)

Note: This policy was developed for inpatient use in May 2018 and may not be the most up to date and is intended for use as guidance only

Clozapine Informed Consent

SOHF 172 (2)
ATTACHMENT A

CLOZAPINE INFORMED CONSENT

Patient’s Name ____________________________________________

1) I understand that clozapine is presently approved for or has been shown to help psychiatric conditions such as mine and that my Doctor has recommended it for me.

2) I understand that this medicine can have side effects like rapid heartbeat, higher body temperature, increased salivation, drowsiness, dizziness, constipation, weight gain, and high levels of fat or sugar in the blood.

3) Clozapine can have rare but serious side effects like seizures, pulmonary emboli, or an inflammation of the heart that may cause death. Blood will be drawn regularly to check for heart inflammation.

4) A condition called agranulocytosis (decrease of white blood cells) can occur in about one out of 100 patients taking clozapine. With proper monitoring, this can be detected quickly and clozapine will be stopped. For this reason, I agree to get my blood tested every week for at least six (6) months, then every other week for another six months, then once a month for as long as I stay on this medication. If I stop taking clozapine I will get my blood tested weekly for one month. If I refuse blood tests the Pharmacist cannot give me the clozapine.

5) I agree to tell my doctor immediately if I do not feel well, as this could be an early sign of a problem with clozapine.

6) I agree to release information about my blood counts to the Clozapine Alert Program. This is to assure that clozapine can be used safely.

7) I have discussed other treatments for my illness as well as risks and benefits of taking clozapine with my Doctor.

8) I have read and understand this consent form and give my permission voluntarily for clozapine treatment.

Date_________________________  Signature of Patient/Guardian

Date_________________________  Signature of Physician

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Clozapine Medication Use Policy June 2018 (Attachment B)

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Myocarditis Questionnaire

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**Myocarditis Symptom Progress Note for Patients on Clozapine**
To be completed weekly for 4 weeks

<table>
<thead>
<tr>
<th>Does the patient have any of the following symptoms?</th>
<th>CIRCLE WEEK #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fatigue or decreased exercise capacity?</td>
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</tr>
<tr>
<td>□ Yes □ No If Yes, explain:</td>
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<td>2. Dyspnea, orthopnea?</td>
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<td>□ Yes □ No If Yes, explain:</td>
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<tr>
<td>3. Complaints of chest pain/pressure?</td>
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<tr>
<td>□ Yes □ No If Yes, explain:</td>
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<tr>
<td>4. Persistent palpitations?</td>
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<td>□ Yes □ No If Yes, explain:</td>
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<td>5. Fever or flu-like symptoms?</td>
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<td>□ Yes □ No If Yes, explain:</td>
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<tr>
<td>6. Peripheral edema?</td>
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<td>□ Yes □ No If Yes, explain:</td>
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<tr>
<td>7. If the answer to any of the questions above is yes, please order CBC with differential, Myocarditis panel and EKG.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Signature: ___________________________ Date/Time: ___________________________
Appendix 7: NC Division of State Operated Health Facilities
Clozapine Medication Use Policy June 2018 (Attachment C – Pg 1)

Note: This policy was developed for inpatient use in May 2018 and may not be the most up to date and is intended for use as guidance only

Clozapine Related Myocarditis Algorithm

When the monitoring of symptoms, signs or tests raises a concern for clozapine related myocarditis:

- symptoms suggestive of infectious illness or myocarditis or,
- sustained HR greater >= to 120 or,
- CRP > 50 but < 100 (with troponin that is < 2 X upper limit nl) or,
- Significant increase in BNP from baseline or,
- ECG changes

Due to clozapine

Assess for other medical condition(s)

Continue Clozapine with no change in dosage

Implement enhanced monitoring:
- Increase frequency myocarditis panel
- Increase VS monitoring
- Increase ECG frequency
- Adjust dose/titration

Yes

No
Appendix 7: NC Division of State Operated Health Facilities
Clozapine Medication Use Policy June 2018 (Attachment C –Pg 2)

Note: This policy was developed for inpatient use in May 2018 and may not be the most up to date and is intended for use as guidance only

**Clozapine Related Myocarditis Algorithm**

When the monitoring of symptoms, signs or tests strongly suggests/confirms clozapine related myocarditis:

- **Patient symptoms:** chest pain, heart failure, arrhythmia, fevers without other identified cause
- **Clinical situation suggests non-myocarditis cause**
  - **Troponin > 2 x upper limit nl AND/OR CRP > 100**
    - Yes: **Clozapine related Myocarditis**
    - No: **Discontinue clozapine**
  - Yes: **Discontinue clozapine**
- **Troponin > 2 x upper limit nl AND/OR CRP > 100**
  - Yes: **Initiate the monitoring and care appropriate for the situation and discontinue clozapine if indicated**
  - No: **Absence of symptoms suggestive of myocarditis and no other identified or reasonably likely clinical explanation for inflammation**
    - **CRP > 100 AND Troponin > 2 x upper limit nl**
      - Yes: **Discontinue clozapine**
      - No: **Daily exams, daily myocarditis panels, daily ECG**
Appendix 8: Clozapine Prescribers and Pharmacies*
References

6. Clozapine Initiation and Monitoring Guidelines per Department of Psychiatry, UNC – Chapel Hill.

Sialorrhea References

Myocarditis References

Pediatric References
Acknowledgments

This document was conceptualized by the North Carolina Psychiatric Pharmacist Collaborative and created with assistance from the following individuals:

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Your feedback is welcome. Please contact Vera Reinstein at vreinstein@alliancehealthplan.org with any feedback, including corrections, additional resources, etc.

June 2019
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Psych MD Vs BCCP Clozapine Monitorir
Psych PharmD Role in Overcoming Barri
Managing SE Part 1 _ PsychoPharm Ins

Managing SE Part 2 _ PsychoPharm Ins
Myocarditis case presentation_MDEd