

# Clozapine Care Guide

July 2024



*Information contained in the Care Guide is not a substitute for a health care professional's clinical judgment. Evaluation and treatment should be tailored to the individual patient and the clinical circumstances. Furthermore, using this information will not guarantee a specific outcome for each patient. Refer to "Disclaimer Regarding Care Guides" for further clarification.*

<https://cchcs.ca.gov/clinical-resources/>

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**GOALS**

- ✓ Identify patients for whom clozapine is indicated
- ✓ Individualized titration and adequate therapeutic trial
- ✓ Close monitoring during all phases of treatment (using California Correctional Health Care Services/Division of Health Care Services [CCHCS/DHCS] clozapine patient registry)
- ✓ Minimize interruptions in treatment
- ✓ Recognize and manage common and uncommon adverse effects

**ALERTS**

- ◆ Absolute neutrophil count (ANC) < 500/mcL
- ◆ Constipation, particularly with abdominal pain and/or nausea/vomiting
- ◆ Fever in the first 6-8 weeks of treatment
- ◆ Chest pain/dyspnea/fatigue
- ◆ Dizziness or syncope
- ◆ New or increased seizures
- ◆ Acute rise in clozapine plasma level, particularly to  $\geq$  1000 ng/ml

**DIAGNOSTIC CRITERIA**

- Treatment-resistant Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) schizophrenia or schizoaffective disorder
- Treatment-resistance is defined as the failure to respond adequately to at least two antipsychotic trials, one of which consisted of a second-generation or third-generation agent
- A trial consists of treatment with a standard therapeutic dose of an antipsychotic for a duration of at least four to six weeks. Ideally, evidence of medication adherence is documented. e.g., therapeutic plasma drug levels
- Patients with schizophrenia or schizoaffective disorder characterized by persisting suicidality or chronic aggression
- Patients with treatment-resistant or mixed bipolar disorder.
- Patients with a tardive syndrome or drug-induced parkinsonism who require on-going treatment with an antipsychotic
- Psychosis in patients with Parkinson's disease
- Primary polydipsia in patients with severe mental illness, particularly if associated with symptomatic hyponatremia (water intoxication)
- Mental disorders, including personality disorders, which include impulsive aggression or violence against others or self
- Patients admitted to California Department of Corrections and Rehabilitation (CDCR) already taking clozapine and who are stable on clozapine are to be continued on clozapine if clinically indicated

**Baseline Requirements**

- Pretreatment
- Patient Housing and Clozapine Initiation: Clozapine can be utilized in the following settings:
  - Psychiatric Inpatient Programs (PIP)
  - At approved institutions
  - At levels of care and institutions that obtain approval from the Statewide Chief of Psychiatry or designee
- Prescriber Responsibilities:
  - Ensure no contraindications to clozapine (See pages [3-5](#))
  - Obtain medication informed consent unless there is a court order for involuntary medication
  - Register with Clozapine Risk Evaluation and Mitigation Strategy Program (REMS) (See below)
  - Obtain baseline monitoring data (See page [5-6](#))
  - Assess bowel function carefully (See pages [23-25](#))
  - Ensure there is a Medical Hold in place for patients on clozapine
- Registration with Clozapine REMS
- The Clozapine REMS program is an FDA mandated program that provides a centralized point of access for pharmacists and prescribers in order to minimize the risk of clozapine-associated severe neutropenia (ANC < 500/mcL)

## Baseline Requirements, cont'd

- Prescribers, pharmacies, and patients must be enrolled per the most updated REMS guidelines before prescribing or dispensing clozapine. Go to: <https://www.newclozapinerems.com/home>
- The system tracks patients, identifying those who have developed severe neutropenia
- Patients with Benign Ethnic Neutropenia (BEN) are identified on enrollment allowing application of appropriate ANC monitoring algorithm
- For terminally ill patients in hospice care, a waiver application can be obtained from and submitted to the REMS program. If approved, ANC and other lab monitoring requirements may be suspended.
- Prior to dispensing clozapine, pharmacies must verify the ANC is current, with appropriate monitoring for the range, or that the prescriber has provided rationale for continuing treatment for general population patients with an ANC < 1000/mcL or rechallenging patients with severe neutropenia.

## Clozapine Efficacy

- In patients with treatment-resistant schizophrenia, the response rate with clozapine ranges from 40-60% while with other antipsychotics it is < 5%, and for olanzapine it is 7%<sup>10</sup>
  - Delays in starting clozapine reduce the likelihood of response
- Multiple studies have demonstrated that clozapine treatment is associated with decreased mortality both from natural and unnatural causes compared to other antipsychotics<sup>14</sup>
- The decrease is not associated with increased monitoring
- Only clozapine has demonstrated the ability to normalize plasma osmolality in patients with primary polydipsia (psychogenic polydipsia)<sup>1</sup>
- Clozapine's effect on reducing suicidality and aggression is independent of its antipsychotic effect<sup>9</sup>
- Low dose clozapine treatment of prisoners with personality disorders (median dose 125 mg/day) significantly reduced frequency of self-injury and interpersonal aggression<sup>17</sup>
- Parkinson's disease psychosis is due to loss of serotonergic neurons and upregulation of postsynaptic serotonin 5HT2A receptors. Low dose clozapine treats psychosis via antagonism of 5HT2A receptors without exacerbation of motor function.
- Clozapine is superior to quetiapine which has been associated with an increased risk of mortality<sup>12</sup>

## Contraindications and Precautions

- Clozapine is contraindicated in patients with:
  - Current severe central nervous system depression or coma
  - Pretreatment ANC < 1500 cells/mcL in general population patients or < 1000 cells/mcL in patients with benign ethnic neutropenia
  - Uncontrolled seizure disorder
  - Unstable medical problems that may be complicated by clozapine treatment (e.g., acute narrow angle glaucoma, bowel obstruction, paralytic ileus, unstable hypotension, unstable tachyarrhythmias, etc.)
  - Allergy to clozapine or any components of the preparation
- Clozapine warrants precautions, documentation of risk/benefit, or particular attention when prescribed in the following clinical contexts or with certain medications:
  - Pregnancy or breastfeeding
  - Partially controlled seizure disorder without neurological consultation
  - Personal or family history of morbid obesity, severe diabetes mellitus, or severe dyslipidemia
  - Significant hepatic, renal, or cardiopulmonary disease
  - Prostatic enlargement
  - Narrow angle glaucoma
  - History of paralytic ileus, frequent constipation, or bowel obstruction
  - Medications (See Table below, continued on page 5)

## Contraindications and Precautions, cont'd

<b>MEDICATION INTERACTIONS THAT COMPLICATE CLOZAPINE USE</b> (Note: This Is Not an Exhaustive List. Address all Drug– Drug Interactions While Using Clozapine)	
Drug	Comments and Recommendations
Anticholinergics (e.g., benztropine, diphenhydramine, chlorpromazine, dicyclomine, oxybutynin, amitriptyline)	<ul style="list-style-type: none"> <li>• Clozapine has potent anticholinergic activity, acting as an antagonist at the M<sub>1</sub> and M<sub>4</sub> muscarinic receptors</li> <li>• The combination of clozapine with other anticholinergic medications greatly increases risk of serious bowel problems. (See pages <a href="#">23-25</a>)</li> <li>• Ideally, anticholinergic medications are tapered and discontinued prior to starting clozapine</li> <li>• Benztropine or diphenhydramine can be tapered as clozapine is titrated using the following equivalency:               <ul style="list-style-type: none"> <li>• 50 mg (for patients who do not smoke) to 100 mg (for patients who smoke) of clozapine= 1 mg benztropine = 25 mg diphenhydramine</li> </ul> </li> </ul>
Medications that Suppress Bone Marrow Function (e.g., carbamazepine, phenytoin, antineoplastics, antiretrovirals, propylthiouracil)	<ul style="list-style-type: none"> <li>• The mechanism of clozapine-associated severe neutropenia is still unclear and while an immune hypothesis seems to predominate, it is possible that toxicity of the bone marrow could be playing a role</li> <li>• Observe for possible additive effects on the bone marrow</li> </ul> <p><i>Patients with Benign Ethnic Neutropenia (BEN)</i></p> <ul style="list-style-type: none"> <li>• Adjust ANC monitoring (See Table page <a href="#">12</a>)</li> <li>• Monitor vital signs once or twice daily until ANC has recovered</li> <li>• Aggressive work-up of any signs or symptoms of infection, including chest x-ray and cultures (throat, blood, urine). Treat infection as indicated</li> </ul>
QT Interval Prolonging Drugs: <ul style="list-style-type: none"> <li>• Certain antipsychotics</li> <li>• Antibiotics such as erythromycin</li> <li>• Class IA antiarrhythmics such as quinidine and procainamide</li> <li>• Class III antiarrhythmics such as amiodarone, sotalol</li> <li>• Other drugs such as methadone</li> </ul>	<ul style="list-style-type: none"> <li>• Clozapine by itself tends not to prolong the QT interval; however, cases have been reported</li> <li>• Combination of clozapine with other medications known to prolong the QT interval may result in additive risk</li> <li>• When reviewing a patient’s electrocardiogram (ECG), use the appropriate formula to correct the QT (See page <a href="#">7</a>)</li> <li>• If the pre-treatment QTc exceeds 500 ms after using the appropriate QT correction formula: review ECGs, review medications, check potassium and magnesium, and consider a cardiology consultation</li> </ul>
Highly Protein-bound Drugs (e.g., digoxin, warfarin)	<ul style="list-style-type: none"> <li>• Clozapine is highly protein bound and may increase the free concentrations of other protein-bound drugs by displacing them from plasma proteins</li> </ul>
Central Nervous System Depressants (e.g., benzodiazepines, barbiturates, opioids, anesthetic agents)	<ul style="list-style-type: none"> <li>• Clozapine (and norclozapine to a lesser extent) has high affinity for the H<sub>1</sub> histamine receptor resulting in sedation</li> <li>• Sedation is common, affecting up to 45% of patients taking clozapine</li> <li>• To reduce additive sedative effects, discontinue central nervous system depressants prior to starting clozapine</li> <li>• For patients on opioid replacement treatment, ensure opioid dose is stable and that there is no evidence of sedation prior to starting clozapine</li> </ul>
Constipating Medications (e.g., iron, opioids such as methadone or buprenorphine)	<ul style="list-style-type: none"> <li>• Clozapine significantly increases stool transit time and clozapine-induced constipation is common (incidence is 32 to 60%)</li> <li>• Colonic transit time for patients on clozapine can increase to 110 hours if patients are not prescribed laxative medications</li> <li>• Other medications known to cause constipation can worsen constipation by overlapping mechanisms. Progression to ileus, which can be fatal, can develop over time.</li> <li>• If possible, iron ought to be temporarily discontinued during the first 4-6 weeks of clozapine treatment</li> <li>• If the patient is treated with an opioid agonist or partial agonist, it is recommended that bowel function be optimized prior to starting clozapine</li> </ul>

## Contraindications and Precautions, cont'd

MEDICATION INTERACTIONS THAT COMPLICATE CLOZAPINE USE, Cont'd	
(Note: This Is Not an Exhaustive List. Address all Drug– Drug Interactions While Using Clozapine)	
Drug	Comments and Recommendations
Antihypertensives (e.g., $\alpha$ -blockers, $\beta$ -blockers)	<ul style="list-style-type: none"> <li>• Clozapine and norclozapine are potent <math>\alpha_1</math> antagonists</li> <li>• Combination with certain antihypertensives can increase risk of orthostasis</li> </ul>
<b>Clozapine is a substrate for many cytochrome P450 enzymes, in particular CYP 1A2, 3A4, and 2D6</b>	
CYP 1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin,)	<ul style="list-style-type: none"> <li>• Clozapine is primarily metabolized by CYP 1A2</li> <li>• Concomitant use of strong CYP 1A2 inhibitors increases total clozapine exposure by <math>\geq 5</math>-fold, resulting in toxicity</li> <li>• It is recommended that strong CYP 1A2 inhibitors be discontinued prior to starting clozapine</li> <li>• Closely monitor patients if prescribed moderate or weak CYP 1A2 inhibitors (e.g., caffeine, oral contraceptives)</li> </ul>
CYP 2D6 inhibitors (e.g., paroxetine, fluoxetine, bupropion, quinidine) CYP 3A4 inhibitors (e.g., itraconazole, ketoconazole, clathromycin, ritonavir)	<ul style="list-style-type: none"> <li>• CYP 2D6 and 3A4 are secondary routes of clozapine metabolism</li> <li>• Potent CYP 2D6 and 3A4 inhibitors may increase clozapine plasma levels by up to 100%</li> <li>• Monitor clozapine plasma levels as the clozapine dose is increased</li> <li>• The greatest risk occurs when the CYP inhibitor is tapered rapidly or stopped as clozapine plasma levels will fall resulting in a relapse of psychosis.</li> </ul>
CYP 1A2 inducers (e.g., omeprazole)  CYP 3A4 inducers (e.g., carbamazepine, phenytoin, rifampin)	<ul style="list-style-type: none"> <li>• Concomitant use with clozapine is not recommended</li> <li>• If the inducer cannot be switched to an alternate medication, a larger dose of clozapine may be necessary</li> </ul>

## PREPARING FOR CLOZAPINE INITIATION

Informed consent for treatment with clozapine is required prior to the start of treatment and renewed annually unless the court has granted an involuntary medication order. A baseline work-up must be performed for all patients prior to initiation of clozapine. For clozapine use, baseline assessment should be completed no longer than 30 calendar days prior to the initiation of clozapine

BASELINE VITAL SIGNS AND EXAMINATIONS <sup>10</sup>	
Measure	Rationale and Recommendations
Temperature	<ul style="list-style-type: none"> <li>• Benign fever during clozapine initiation is common, with an incidence of up to 20%</li> <li>• If temperature is <math>&gt; 38^\circ \text{C}</math>, work-up etiology</li> <li>• Hold clozapine initiation until resolved</li> </ul>
Resting heart rate	<ul style="list-style-type: none"> <li>• Tachycardia is a common adverse effect from clozapine</li> <li>• If tachycardia is present, work-up the etiology (e.g., dehydration, orthostasis, medication effect, etc.)</li> <li>• Hold clozapine initiation until resolved</li> </ul>
Blood pressure*	<ul style="list-style-type: none"> <li>• Orthostasis is common, particularly during the early weeks of the clozapine titration</li> <li>• Rule-out pre-existing orthostasis by measuring orthostatic blood pressures</li> <li>• If orthostatic changes are present, work-up the etiology (e.g., hypovolemia, medication-related, etc.)</li> <li>• Hold clozapine initiation until resolved</li> </ul>

\*MAPIP Requirement

## Preparing for Clozapine Initiation, cont'd

BASELINE VITAL SIGNS AND EXAMINATIONS, cont'd	
Measure	Rationale and Recommendations
Weight, abdominal circumference, and Body Mass Index (BMI)*	<ul style="list-style-type: none"> <li>Weight gain is a very common adverse effect of clozapine</li> <li>In patients who are overweight or obese at baseline, consider more aggressive measures (metformin) to reduce weight gain at the start of clozapine treatment</li> </ul>
History and physical examination*	<ul style="list-style-type: none"> <li>Areas of investigation include cardiovascular history, history of bowel dysfunction, history of seizures and physical findings suggesting active disease</li> <li>It is recommended that constipation, poorly controlled seizure disorder, and congestive heart failure be addressed prior to clozapine initiation</li> <li>Managing constipation (See pages <a href="#">23-25</a>)</li> </ul>
Abnormal involuntary movement scale (AIMS)*	<ul style="list-style-type: none"> <li>Clozapine tends not to worsen tardive syndromes and may reduce involuntary movements related to psychotropic medications</li> </ul>

BASELINE LABORATORY MEASURES, PROCEDURES, AND IMAGING <sup>10</sup>	
Measure	Rationale and Recommendations
Complete blood count (CBC) with differential*	<ul style="list-style-type: none"> <li>Baseline ANC is required to start clozapine</li> <li>Investigate potential causes of subthreshold ANC or neutropenia, e.g., medication-related, BEN. (See next page)</li> <li>Eosinophilia may occur during treatment with clozapine</li> </ul>
Complete metabolic panel (CMP)*	<ul style="list-style-type: none"> <li>Rule-out undiagnosed electrolyte abnormalities or organ pathology</li> <li>Baseline creatinine and estimated glomerular filtration rate (eGFR) are necessary in case the patient develops interstitial nephritis</li> </ul>
Hemoglobin A1C*	<ul style="list-style-type: none"> <li>A1C values of <math>\geq 5.7\%</math> are consistent with prediabetes. Treatment with metformin is a consideration</li> <li>A1C values of <math>\geq 6.5\%</math> are diagnostic of diabetes and treatment is warranted</li> <li>A1C values <math>&gt; 7.0\%</math> suggest suboptimum control and assessment is warranted</li> </ul>
Fasting lipid panel*	<ul style="list-style-type: none"> <li>Rule out undiagnosed or undertreated dyslipidemia</li> <li>Address elevated triglycerides given clozapine's effects on insulin resistance</li> </ul>
Human chorionic gonadotropin (hCG)*	<ul style="list-style-type: none"> <li>Rule out pregnancy in people with a uterus of childbearing age</li> </ul>
Troponin I/T and C-Reactive Protein (CRP)	<ul style="list-style-type: none"> <li>Myocarditis is a rare but potentially fatal adverse effect seen within the first six weeks of clozapine treatment</li> <li>Baseline troponin I/T and CRP with weekly measurements for the first six weeks of treatment may be useful to screen for myocarditis</li> </ul>
EKG	<ul style="list-style-type: none"> <li>Rule out untreated conduction or other cardiac issues</li> <li>Consult with PCP for any EKG concerns</li> <li>Use the appropriate QT correction formula if the resting heart rate is <math>&gt; 60</math> bpm. (See next page)</li> </ul>
Abdominal X-ray	<ul style="list-style-type: none"> <li>Consider obtaining abdominal X-ray or kidney, ureter, and bladder (KUB) in patients who are limited or poor historians to rule out constipation</li> <li>If there is X-ray evidence of significant stool burden, address constipation before commencing clozapine. (See pages <a href="#">23-25</a>)</li> </ul>

\*MAPIP Requirement

## Evaluation of Pretreatment Neutropenia

The most common etiologies of neutropenia in patients who are incarcerated and have mental health comorbidities are:

- Medication-induced neutropenia
  - A wide variety of drugs are associated with neutropenia including non-steroidal anti-inflammatory drugs (NSAIDs)/analgesics, antithyroid drugs, cardiovascular drugs, chemotherapeutic agents, antimicrobials, antiepileptics, and antipsychotics
  - All antipsychotics carry a class warning regarding neutropenia although it is uncommon outside of clozapine treatment
    - Ongoing neutropenia despite changes in antipsychotic treatment suggests another cause
  - Valproic acid (divalproex) has a reported incidence of neutropenia up to 26%
- Benign ethnic neutropenia
  - BEN is the most common form of neutropenia worldwide when defined as an ANC of < 1500 cells/mcL and occurring in the absence of frequent infections. If BEN is suspected, further evaluation to confirm the diagnosis is advised.
  - BEN is common in people of African or Eastern Mediterranean heritage with a prevalence of up to 50%
    - Suspect BEN in patients with an ANC in the 1000-1500/mcL range without evidence of pancytopenia or frequent infections
  - Genetic testing definitively diagnoses BEN
    - Order Duffy Antigen/Chemokine Receptor (DARC) genetic testing (Red Blood Cell Antigen Typing)
    - Lab results showing the absence of the Duffy antigen Negative for FYA, Negative for FYB, (see below) confirms BEN. Duffy null/null is the ONLY genotype that is seen in BEN patients
    - It is still unclear how the DARC null genotype is related to neutropenia
    - Importantly, neutropenia is a laboratory finding only. Patients with BEN have normal circulating neutrophils and are not at increased risk of infection
    - The patient can be registered in the Clozapine REMS system as a BEN patient
  - Pretreatment neutropenia due to BEN or persisting neutropenia despite measures to eliminate reversible causes can be managed with lithium<sup>†</sup> or filgrastim. (See page [13](#))

### DARC Genetic Testing confirming BEN

Test Name	In Range	Out Of Range	Reference Range	Lab
RED BLOOD CELL ANTIGEN TYPING				QAW
ANTIGEN:	ANTI-FY (A), ANTI-FY (B)			
ANTIGEN TYPE:	NEGATIVE FOR FYA			
ANTIGEN TYPE:	NEGATIVE FOR FYB			

<sup>†</sup>Heat Drug: May disrupt the body's ability to reduce core body temperature and could result in hyperthermia with exposure to extreme heat, strenuous exercise, etc.

## QT Correction – The Importance of Using the Correct Formula

- Most CCHCS ECG machines use the Bazett formula to correct the QT interval
- The Bazett formula overcorrects the QT when the heart rate is elevated
- The American Heart Association recommends against using the Bazett formula. Evidence supports using either the Fridericia or the Framingham correction formula, which demonstrate the best rate correction of the QT interval<sup>15</sup>
- An online calculator that will correct the QT interval using the Fridericia or Framingham formula can be found here: <https://www.thecalculator.co/health/QTc-Calculator-385.html>. Consult with the PCP for any EKG abnormalities.



### Clozapine Initiation and Titration

- There are a number of patient and environmental factors that can impact tolerability and safety. These include age, medical comorbidities, current medications/drug-drug interactions, illness acuity, treatment setting, etc.
- The clozapine titration ought to be individualized based on patient and clinical factors
- Below is a **sample** titration schedule
  - This is a conservative titration schedule with arrival at a dose of 200 mg at the end of week 4
    - The benefit of a conservative titration is that it allows time for the patient to adapt to  $\alpha_1$ , H1, and muscarinic antagonism resulting in decreased risk of severe orthostasis and sedation
  - The speed of the sample titration can be increased or decreased based on tolerability and the ability to monitor the patient
    - For example, in a healthy young patient who is tolerating the clozapine well and who participates readily in daily nursing assessments, the speed of the titration can be increased to arrive at 200 mg/day at the end of week 2 or 3
      - Dose increases > 25 mg/day or 50 mg total dose/week are not recommended
    - Conversely, an older patient with orthostasis at baseline who intermittently refuses to leave the cell for nursing assessments, may require an even more conservative titration than the sample, starting with 6.25 mg/day and titrating by 6.25 mg increments every 1-2 weeks
- Obtain a clozapine plasma level after reaching a total dose of 200 mg/day or 100 mg/day in elderly patients. See page 15 on interpreting plasma levels
- After completing the titration and after the medication has been titrated to a stable maintenance dose, the clozapine dose can be slowly consolidated to a single dose at bedtime to reduce daytime sedation. If a split dose is required, give the majority of the dose in the evening.

**Sample Clozapine Titration Schedule (With Dose Increases Every 3 Days)**

Week 1	AM Dose (mg)	PM Dose (mg)	Week 3	AM Dose (mg)	PM Dose (mg)
Day 1 Initiate	0	12.5	Day 15	25	50
Day 2	0	12.5	Day 16	50	50
Day 3	0	12.5	Day 17	50	50
Day 4	12.5	12.5	Day 18	50	50
Day 5	12.5	12.5	Day 19	50	75
Day 6	12.5	12.5	Day 20	50	75
Day 7	12.5	25	Day 21	50	75
Week 2	AM Dose (mg)	PM Dose (mg)	Week 4	AM Dose (mg)	PM Dose (mg)
Day 8	12.5	25	Day 22	50	100
Day 9	12.5	25	Day 23	50	100
Day 10	25	25	Day 24	50	100
Day 11	25	25	Day 25	50	150
Day 12	25	25	Day 26	50	150
Day 13	25	50	Day 27	50	150
Day 14	25	50	Day 28	50	150

### Clozapine Titration in Patients with Parkinson’s Disease Psychosis

- The recommended starting dose is 6.25 mg at bedtime
  - This dose may be an effective maintenance dose for some patients
- Titrate by 6.25 mg increments every 3-4 days.
- The mean daily dose in clinical trials has ranged from 25 to 36 mg/day.

Medication: Clozapine		
Medication	Dosing	Comments
<p><b>Clozapine*</b></p> <p>Brand names Clozaril®, Versaclo® (oral suspension) Fazaclo® (oral disintegrating tablet)</p>	<p>Titration (See below)</p> <ul style="list-style-type: none"> <li>Maintenance dose is highly variable</li> <li><b>Half-life is 5-16 hours</b></li> <li>Literature supports once daily dosing</li> <li>Dose can also be split 1/3 during the day and 2/3 at bedtime</li> <li>Dose range: 300-900 mg/day in treatment-resistant schizophrenia</li> <li>Dose range: 6.25-50 mg/day in Parkinson's disease psychosis</li> </ul> <p><b>Lower dose range:</b></p> <ul style="list-style-type: none"> <li>Elderly patients</li> <li>Medically fragile patients</li> <li>Patients with neurodevelopmental disorders</li> <li>Personality disordered patients</li> </ul>	<ul style="list-style-type: none"> <li>Tablets are equally bioavailable to solution</li> <li>Bioavailability is not affected by food. Administer with or without food</li> <li>Monitor clozapine plasma levels regularly</li> <li>Drug-drug interactions (See pages <a href="#">4-5</a>)</li> <li>Use with caution in patients with significant renal and/or hepatic impairment <ul style="list-style-type: none"> <li>Due to clozapine's extensive hepatic impairment, consider dose reduction in patients with severe hepatic impairment (as evidenced by hyperbilirubinemia, hypoalbuminemia, coagulopathy, ascites, and/or encephalopathy)</li> </ul> </li> <li>Pregnancy <ul style="list-style-type: none"> <li>Data does not support increased risk of fetal malformations<sup>8</sup></li> <li>Clozapine crosses placenta and accumulation in fetal blood may contribute to increased rates of floppy infant syndrome at delivery and neonatal seizures</li> <li>Consider decreasing dose 48 hours before delivery to minimize effects in infant</li> </ul> </li> <li>Elderly patients may be more susceptible to orthostasis, tachycardia, anticholinergic effects (constipation, urinary retention), and sedation <ul style="list-style-type: none"> <li>Decrease starting dose, titrate more slowly, and observe carefully</li> <li>Efficacy in elderly patients may be achieved with lower doses</li> </ul> </li> <li>Elderly patients with dementia-related psychosis are at an increased risk of death. Clozapine is contraindicated in this group</li> </ul>

\* See clozapine prescribing information for complete description of adverse effects and drug interaction

### Patient Housing and Mental Health Level of Care

- Patients in the PIP may be initiated on clozapine. Patients may be initiated on clozapine in alternative settings pending the approval of the Statewide Chief of Psychiatry or designee.
- Patients in the Mental Health Crisis Bed (MHCB) undergoing clozapine initiation, will remain in the MHCB until such time as they are stable for transfer, which may be a longer period than average MHCB admission for alternative reasons.
- If initiation was conducted in a Mental Health Crisis Bed (MHCB) the patient will be discharged to a PIP to complete initiation. Once stable after initiation, the patient may be transferred to a designated clozapine maintenance institution. The patient may not be transferred to a level of care (LOC) lower than the Enhanced Outpatient Program (EOP) LOC for at least 6 months thereafter. Please refer to the most recent memorandum for a list of clozapine maintenance locations.

### Clozapine Response, Non-Response, and Discontinuing Clozapine

- Studies have determined that a clozapine plasma level of 350 ng/ml is the threshold for response
  - Patients with schizophrenia are less likely to respond at levels < 350 ng/ml. Many patients require levels well above 350 ng/ml
  - Elderly patients, patients with personality disorders, and patients with primary polydipsia tend to respond to lower plasma levels
- Some patients demonstrate an early response occurring at 4-6 weeks. Response continues to be observed up to 24 weeks. If there is absolutely no response by 24 weeks, it is unlikely that the patient will respond
- If a patient is not responding and the plasma level is at least 350 ng/ml, slowly titrate the dose. Continue current dose for three weeks between increases to observe for response
  - Studies indicate that it is worthwhile to titrate to 1000 ng/ml as long as it is tolerated by the patient to assess for response. Certain forensic patients require and tolerate higher doses/plasma levels
- At least 40% of patients with schizophrenia are clozapine partial-responders or non-responders with an ultra-treatment-resistant illness. There are two options for these patients:
  - Augment clozapine with a strong D2 antagonist such as haloperidol or risperidone
  - Augment clozapine with ECT. ECT tends to be more effective when combined with clozapine than with other antipsychotics
- Discontinuation of clozapine may be necessary in medical situations or in cases of treatment failure
  - Urgent discontinuation: When clozapine needs to be abruptly stopped, the patient is at risk for cholinergic rebound and clozapine withdrawal catatonia
    - To reduce risk of cholinergic rebound, replace the anticholinergic activity of clozapine with an equivalent amount of benztropine, i.e., 50 mg (for patients who do not smoke) to 100 mg (for patients who smoke) of clozapine = 1 mg benztropine
    - For example, 200 mg of clozapine would be replaced with 2 mg of benztropine.
    - Non-urgent discontinuation: Taper clozapine slowly while replacing with an alternate antipsychotic

### Hematological Monitoring

- The incidence of severe neutropenia (ANC < 500 cells/mcL) is 0.9% with the highest period of risk occurring in the first six months of treatment
  - Patients with BEN who are treated with clozapine are less likely to develop severe neutropenia than the general population
- Routine monitoring is essential to decrease risk of morbidity and mortality
- The table on next page contain the US treatment recommendations based on ANC monitoring
  - See page [12](#) for Clinical Management of ANC Abnormalities

**Hematological Monitoring, cont'd**

US Treatment Recommendations Based on ANC Monitoring		
ANC Level	Treatment Recommendation	ANC Monitoring Frequency
<b>General Population</b>		
Normal (≥ 1500/mcL)	<ul style="list-style-type: none"> <li>Initiate treatment</li> <li>If treatment is interrupted:                             <ul style="list-style-type: none"> <li>&lt; 30 days, continue monitoring as before</li> <li>≥ 30 days, monitor as if new patient</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Weekly from initiation to 6 months</li> <li>Every 2 weeks from 6 to 12 months</li> <li>Monthly after 12 months</li> </ul>
Mild neutropenia (1000-1499/mcL)*	<ul style="list-style-type: none"> <li>Continue treatment</li> </ul>	<ul style="list-style-type: none"> <li>Three times weekly until ANC ≥ 1500/μl</li> <li>Once ANC ≥ 1500/μl, return to patient's last "Normal Range" ANC monitoring interval**</li> </ul>
Moderate neutropenia (500-999/mcL)*	<ul style="list-style-type: none"> <li>Interrupt treatment for suspected clozapine induced neutropenia</li> <li>Resume treatment once ANC normalizes to ≥ 1000/mcL</li> </ul>	<ul style="list-style-type: none"> <li>Daily until ANC ≥ 1000/μl then,</li> <li>Three times weekly until ANC ≥ 1500/μl</li> <li>Once ANC ≥ 1500/μl, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**</li> </ul>
Severe neutropenia (<500/mcL)*	<ul style="list-style-type: none"> <li>Recommend hematology consultation.</li> <li>Interrupt treatment for suspected clozapine induced neutropenia</li> <li>Caution as patient may be at increased risk of infection at this time</li> <li>Do not rechallenge unless prescriber determines benefits outweigh risks and documents discussion with patient</li> </ul>	<ul style="list-style-type: none"> <li>Daily until ANC ≥ 1000/μl then,</li> <li>Three times weekly until ANC ≥ 1500/μl</li> <li>If patient is rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/μl.</li> </ul>
<b>Patients with Benign Ethnic Neutropenia</b>		
Normal BEN range (≥ 1000/mcL)	<ul style="list-style-type: none"> <li>Obtain at least 2 baseline ANC levels before initiating treatment</li> <li>If treatment interrupted:                             <ul style="list-style-type: none"> <li>&lt; 30 days, continue monitoring as before</li> <li>≥ 30 days, monitor as if new patient</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Weekly from initiation to 6 months</li> <li>Every 2 weeks from 6 to 12 months</li> <li>Monthly after 12 months</li> </ul>
BEN neutropenia (500-999/mcL)*	<ul style="list-style-type: none"> <li>Continue treatment</li> <li>Recommend hematology consultation†</li> </ul>	<ul style="list-style-type: none"> <li>Three times weekly until ANC ≥ 1000/μl or ≥ patient's known baseline</li> <li>Once ANC ≥ 1000/μl or at patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval**</li> </ul>

\* The package insert recommends confirming initial ANC < 1500/mcL with repeat ANC within 24 hours for general population patients. Patients with BEN and ANC of < 1000/mcL ought to be confirmed with a repeat ANC within 24 hours

\*\*If clinically appropriate

† Consider DARC genetic testing if not performed at baseline

Clinical Management of ANC Abnormalities	
Severity	Monitoring and Treatment Interventions
Mild Neutropenia GP ANC <1500/mcL	<ul style="list-style-type: none"> <li>• Adjust ANC monitoring. (See table on previous page)</li> <li>• Monitor vital signs once or twice daily until ANC has recovered</li> <li>• Infection is rare in this context</li> </ul>
Moderate neutropenia General Population ANC 500-999/mcL BEN ANC 500-999/mcL	<p>General Population</p> <ul style="list-style-type: none"> <li>• Adjust ANC monitoring. (See table on previous page)</li> <li>• Interrupt clozapine treatment                             <ul style="list-style-type: none"> <li>○ Interruption of clozapine for &gt; 24 hours requires benztropine taper to avert cholinergic rebound.</li> </ul> </li> <li>• Monitor vital signs once or twice daily</li> <li>• Aggressive work-up of any signs or symptoms of infection, including chest X-ray and cultures (throat, blood, urine). Treat infection as indicated</li> <li>• Resuming clozapine once ANC has recovered is at the discretion of the treating physician</li> <li>• If clozapine is discontinued, check the ANC weekly for four weeks or until ANC recovery has occurred</li> </ul>
Severe Neutropenia ANC <500/mcL	<ul style="list-style-type: none"> <li>• Adjust ANC monitoring. (See table on previous page)</li> <li>• Severe neutropenia and impending agranulocytosis (literally ANC of 0) are medical emergencies                             <ul style="list-style-type: none"> <li>○ Autoimmune destruction of neutrophil progenitor cells includes loss of eosinophils and basophils and continues beyond the discontinuation of clozapine</li> <li>○ Infections occur once neutrophils persistently decline to &lt; 100/mcL and infections (bacteremia, meningitis) are rapidly progressive and overwhelming</li> <li>○ The mean duration of clozapine-associated severe neutropenia is 12 days, although it may last up to 3 weeks.</li> </ul> </li> </ul> <p><b>IMMEDIATE INTERVENTIONS</b></p> <ul style="list-style-type: none"> <li>• Stop clozapine (with a benztropine taper to prevent cholinergic rebound)</li> <li>• Administer filgrastim 480 mcg subcutaneous (SQ) as soon as possible (filgrastim in a non-formulary medication and will require review and approval per the non-formulary approval process)</li> <li>• Transfer to an acute care hospital                             <ul style="list-style-type: none"> <li>○ Daily filgrastim (average time to response is 12 days)</li> <li>○ Reverse isolation or other precautions to decrease risk of infection</li> <li>○ Work-up signs/symptoms of infection with aggressive treatment</li> <li>○ Daily monitoring of ANC and vitals until ANC is &gt; 1000/mcL or at the characteristic baseline in BEN patients</li> <li>○ Thrice weekly monitoring of ANC until ANC is &gt; 1500/mcL or greater than the characteristic baseline in BEN patients</li> </ul> </li> <li>• The patient’s case must be reported to the Clozapine REMS</li> <li>• Re-challenge with clozapine is not indicated unless it is determined that benefits of clozapine treatment clearly outweigh risks</li> <li>• Due to immune memory, rechallenge may result in a rapid relapse of severe neutropenia, infection, and death unless careful ANC monitoring and ongoing filgrastim supports are provided</li> </ul>

### Treatment Interruptions

- For treatment that is interrupted for 2-29 days, restart clozapine at no more than 12.5 mg two times a day (BID) on the first day. Re-initiation after interruption for less than 30 days can be considered for evaluation on a case-by-case basis and discussed with the local Chief Psychiatrist and Statewide Chief of Psychiatry to determine the most appropriate setting for re-initiation.
  - If the interruption has been short, the titration may progress fairly rapidly. If the interruption has been 2-4 weeks, the patient’s tolerance to  $\alpha$ 1 and H1 antagonism has diminished, and a slower titration is required to decrease the risk of orthostasis and sedation. ANC monitoring continues at the previous interval.
- Treatment interruptions of > 30 days require the patient to be treated as patient who is newly prescribed clozapine, with the appropriate titration and monitoring weekly for the first 6 months. Re-initiation must occur at an approved initiation facility or inpatient unit

### Management of Frequent Treatment Interruptions

- There may be some variability in ANC, with dips into mild neutropenia
- Certain patients with BEN will routinely have ANC measurements that dip to < 1000/mcL and a subset of patients with BEN will consistently have an ANC < 1000/mcL
- The need to increase monitoring or interrupt treatment is problematic for all (patients, staff, prescribers) and may interfere with the patient’s willingness to continue clozapine treatment
- While hematology consult may be indicated, the clozapine provider ought to be independently familiar with monitoring requirements for ANC value changes
- For patients with persistent neutropenia in the absence of reversible causes or whose ANC frequently dips below thresholds resulting in increased monitoring or treatment interruptions, lithium and filgrastim are two medically appropriate, off-label strategies to increase the ANC

Medication	Considerations	Dosing
Lithium	<ul style="list-style-type: none"> <li>• Increases the production of granulocyte colony stimulating factor (G-CSF) and directly stimulates the proliferation of pluripotent stem cells<sup>3</sup></li> <li>• The patient should not have any contraindications to lithium and medications that may interact with lithium should be addressed (e.g., HCTZ, lisinopril, etc.)</li> </ul>	<ul style="list-style-type: none"> <li>• Dosing:                             <ul style="list-style-type: none"> <li>○ Lithium has a 24-hour brain half-life, dosed once daily at bedtime</li> <li>○ The instant release formula provides a more accurate trough level</li> <li>○ Begin with a starting dose of lithium IR 150 mg or 300 mg</li> <li>○ Refrain from titrating rapidly as the hematopoietic effect may take 2-3 weeks</li> <li>○ The effect on ANC is dose dependent with some patients responding at lower doses/serum levels, while others require higher doses/serum levels. No benefit is seen at serum levels &gt; 1.0 meq/L</li> <li>○ Monitor serum trough levels, renal function, and thyroid function per MAPIP guidelines</li> </ul> </li> </ul>

Medication	Considerations	Dosing
Filgrastim	<ul style="list-style-type: none"> <li>• Recombinant G-CSF used to treat neutropenia due to cancers, bone marrow transplant, chemotherapy as well as neutropenia associated with clozapine<sup>5</sup></li> <li>• Patient must not have an allergy to human G-CSFs</li> <li>• Possible side effects can include but are not limited to thrombocytopenia, alveolar hemorrhage with hemoptysis, glomerulonephritis, leukocytosis, and cutaneous vasculitis. May lead to an exacerbation in patients with sickle cell disorders</li> <li>• May require consult with hematologist</li> </ul>	<ul style="list-style-type: none"> <li>• Dosing:                             <ul style="list-style-type: none"> <li>○ Begin with a single test dose of 300 µg SQ and measure the ANC twice weekly for 2 weeks, then weekly for 2 more weeks to determine if the ANC values are above thresholds</li> <li>○ The hematopoietic effect emerges within 24-48 hours and the duration of the effect varies between patients</li> <li>○ For example, some patients may require 300 µ SQ twice weekly while others may require a weekly dose</li> <li>○ ANC values can peak at &gt; 15,000-20,000/mcL due to filgrastim’s stimulation. This is expected and is not cause for alarm. The value will decline</li> <li>○ Do not give filgrastim when the ANC &gt; 10,000/mcL</li> <li>○ Filgrastim has not been found to cause any form of bone marrow malignancy, e.g., leukemia (of note, in patients undergoing certain cancer treatment including chemotherapy and radiation, there has been evidence of risk of bone marrow malignancy)</li> </ul> </li> </ul>

General Monitoring During Clozapine Treatment			
Parameter	Baseline or As Indicated	3 months	Annual or As Indicated
<b>Vital Signs and Examinations</b>			
Height/Weight/BMI	✓	✓	✓
Orthostatic Blood Pressure, Heart Rate, and Temperature	<ul style="list-style-type: none"> <li>• Daily for first two weeks of initiation</li> <li>• For 2-3 days after each dose increase</li> </ul>	✓	✓
Physical Examination	✓		✓
Bowel function	<ul style="list-style-type: none"> <li>• Daily for first months of treatment</li> <li>• At every physician visit</li> <li>• <b>As clinically indicated</b></li> </ul>		✓
AIMS	✓		✓
Nursing assessments	• <b>As ordered by the provider</b>		
<b>Laboratory Analysis and Procedures</b>			
ANC or CBC with differential	<ul style="list-style-type: none"> <li>• Weekly for first 6 months THEN</li> <li>• Every two weeks for second 6 months THEN</li> <li>• Monthly</li> <li>• OR as indicated based on ANC</li> </ul> <p>If ANC is not measured as part of a CBC with differential, consider ordering CBC with differential monthly for the first several months to observe for other blood dyscrasias, e.g., eosinophilia</p>		

✓ Indicates mandatory monitoring per MAPIP

General Monitoring During Clozapine Treatment, cont'd			
Parameter	Baseline or As Indicated	3 months	Annual or As Indicated
<b>Laboratory Analysis and Procedures, cont'd</b>			
<b>CMP</b>	✓ • Creatinine and eGFR weekly for the first 8 weeks to screen for interstitial nephritis	✓	✓
<b>Hemoglobin A1c</b>	✓	✓	✓
<b>Fasting Lipid Panel</b>	✓	✓	✓
<b>hCG/Pregnancy Test</b>	✓		As indicated
<b>Thyroid Stimulating Hormone</b>	✓		Every 5 years
<b>Troponin I/T, CRP</b>	✓ • Weekly for the first 6 weeks to screen for myocarditis		
<b>Clozapine plasma level</b>	• Obtain after clozapine dose reaches 200 mg/day in adults or after 100 mg/day in the elderly • Check monthly or more frequently if indicated		
<b>ECG</b>	✓		✓
<b>Abdominal X-ray/KUB</b>	Obtain in patients who are poor historians or who have risk factors* for constipation		As indicated

✓ Indicates mandatory monitoring per MAPIP

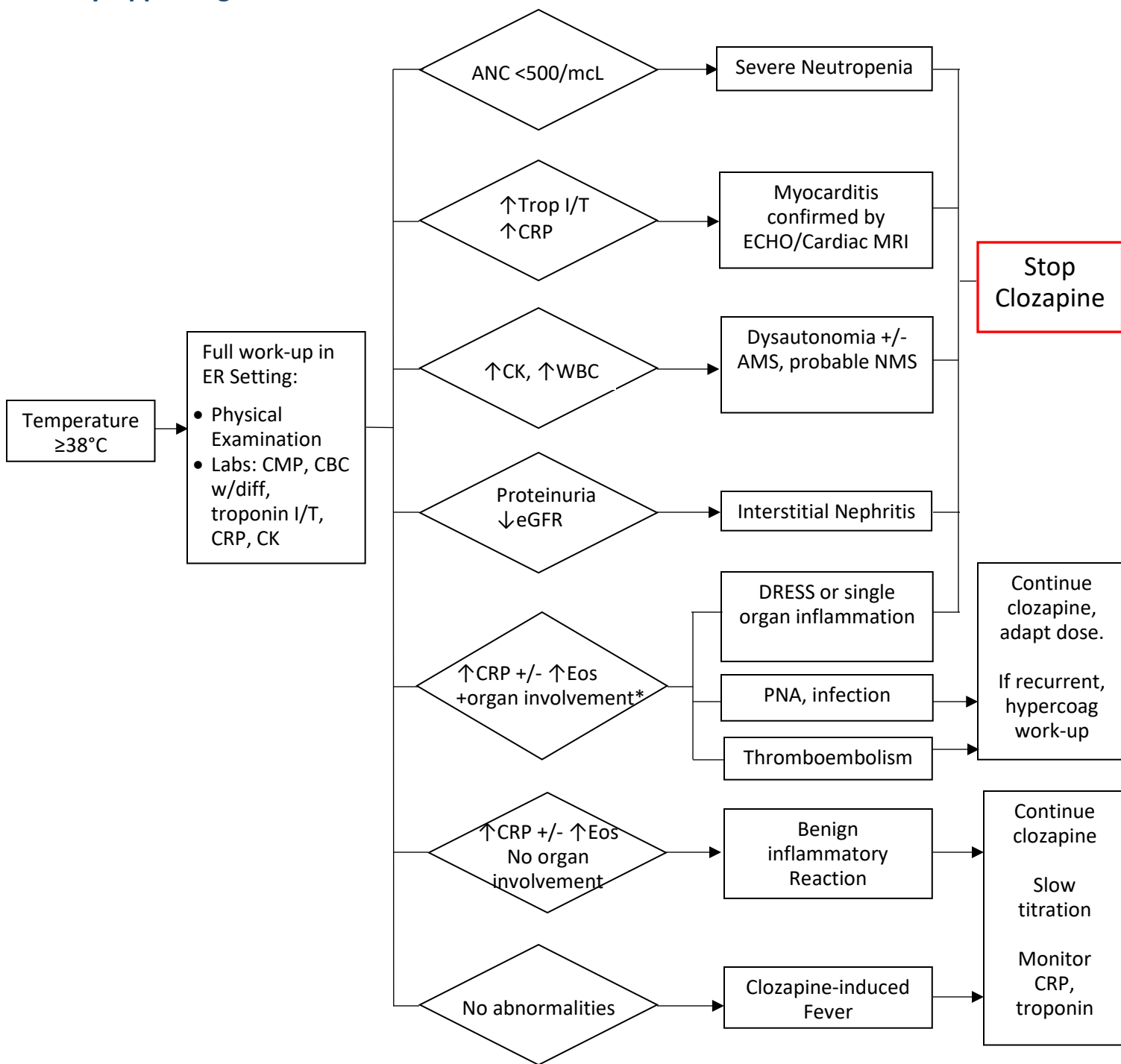
\*Risk factors include, but are not limited to, certain medical conditions or medications.

### Workup of Early Appearing Fever

- The incidence of clozapine-induced fever is about 20% when using a temperature threshold of 38°C
- Nearly all cases present in the first 6 weeks – fourteen days is mean time to onset with 4.5 day mean duration
- In 80% of cases, no cause will be found
- General principles for approaching early fever:
  - Work-up any fever (temp > 38°C; 100.4°F) in the first 8 weeks of clozapine treatment:
    - Evaluate in an emergency room (ER) or correctional treatment center (CTC) setting
    - Perform physical exam and order full set of basic labs including troponin I/T, CRP, creatinine, and a urinalysis (UA)
    - Perform confirmatory studies based on exam/lab data
    - Hold clozapine during fever work-up. Cover for cholinergic rebound at doses greater than 50 mg/day
    - If fever occurs after 3 months of clozapine, focus treatment on bacterial/viral etiology and evidence of neutropenia



### Algorithm for Fever Work-Up and Determination of Main Medical Causes of Early-Appearing Fever



\*Organ involvement assessed with hepatic panel, lipase, chest X-ray, erythrocyte sedimentation rate (ESR), D-dimer<sup>16</sup>

Clozapine Adverse Effects and Suggested Management	
Adverse Effect	Action/Comments
<b>BENIGN EOSINOPHILIA</b>	<ul style="list-style-type: none"> <li>• Is defined as a blood eosinophil count greater than 700/mcL</li> <li>• Eosinophilia has been seen in almost 1 to 6% of clozapine-treated patients, usually early in treatment, and in the absence of systemic involvement, e.g., not vital sign abnormalities, no organ involvement</li> <li>• Eosinophilia is graded as mild (351-1500/mcL), moderate (&gt;1500-5000/mcL), and severe (&gt;5000/mcL)</li> <li>• The differential diagnosis of eosinophilia includes medications (antipsychotics, antibiotics, antiretrovirals, antiepileptics, and others), infections, parasites, allergic disease, and malignancy. Drug-induced eosinophilia is a diagnosis of exclusion. Clozapine does not need to be discontinued in cases of mild eosinophilia. If the eosinophil count continues to rise in the absence of organ involvement or systemic disease, a hematology consultation is warranted</li> <li>• Note that there is a mandatory treatment interruption in the UK when eosinophils reach &gt;3000/mcL. There is no similar requirement in the US.</li> </ul>
<b>CARDIOMYOPATHY</b>	<ul style="list-style-type: none"> <li>• Is very rare, occurring in &lt; 0.1% of patients</li> <li>• Untreated, sustained tachycardia is a risk factor</li> <li>• The onset is insidious, occurring after ≥ 1 year of clozapine treatment</li> <li>• Suspect when a patient complains of fatigue, shortness of breath, and has peripheral edema</li> <li>• Work-up included brain natriuretic peptide (BNP), N-terminal pro BNP, CMP, CBC, iron panel, TSH, urine toxicology, and transthoracic echocardiogram (ECHO). Clozapine-induced myocarditis is a diagnosis of exclusion</li> <li>• Treat heart failure with salt restriction and heart failure medications</li> <li>• Continue clozapine during work-up. If heart failure responds to medication, clozapine may be able to be continued. If not, clozapine can be slowly tapered</li> <li>• Heart transplantation is a consideration for stable, high-functioning patients</li> </ul>
<b>CONSTIPATION</b>	<ul style="list-style-type: none"> <li>• See section on constipation (<a href="#">page 22</a>)</li> </ul>
<b>DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)</b>	<ul style="list-style-type: none"> <li>• Very rare</li> <li>• Severe cutaneous adverse drug reactions akin to Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Many more common drug culprits than clozapine, e.g., allopurinol, phenytoin, carbamazepine</li> <li>• Prodrome includes itching, fever, and symptoms of organ involvement. The liver is involved in 80-90% of cases</li> <li>• DRESS is classified as definite, probably, possible or no case via the RegisCAR DRESS Criteria. An online calculator can be found here: <a href="http://tools.farmacologiaclinica.info/index.php?sid=10001">http://tools.farmacologiaclinica.info/index.php?sid=10001</a></li> <li>• The mainstay of treatment is withdrawal of the culprit drug and corticosteroid treatment</li> </ul>

Clozapine Adverse Effects and Suggested Management, Cont'd	
Adverse Effect	Action/Comments
<b>ENURESIS</b>	<ul style="list-style-type: none"> <li>• Prevalence appears to be at least 20% for patients treated with clozapine</li> <li>• Important to ask about the patient's symptoms prior to clozapine initiation</li> <li>• If nocturnal enuresis develops, consider slowing titration, reducing fluid intake the afternoon/evening, avoid bedtime diuretics</li> <li>• For daytime symptoms, discuss urinary patterns with the patient. May consider evaluation of bladder function and anatomy</li> <li>• Consider options to target overactive bladder, such as selective <math>\alpha</math>1A-adrenergic receptor antagonist (tamsulosin) or <math>\beta</math>3-adrenergic receptor agonist mirabegron</li> <li>• Anticholinergics are not recommended</li> </ul>
<b>ILEUS</b>	<ul style="list-style-type: none"> <li>• Suspect ileus in a patient who reports abdominal discomfort or pain of moderate to severe intensity lasting &gt; 1 hours or pain/discomfort lasting &gt; one hour with associated distention, diarrhea, vomiting, lack of or high-pitched bowel sounds or signs/symptoms of sepsis</li> <li>• Some patients may not or may be unable to report pain/discomfort. Close monitoring and assessment are indicated</li> <li>• If the level of suspicion is high, transfer to outside hospital for evaluation/management</li> <li>• Associated with fatality rates &gt; than those associated with neutropenia</li> <li>• If rechallenging a patient on clozapine with a history of ileus, initiate a secretagogue alongside clozapine</li> <li>• In a patient who develops diarrhea, hold the secretagogue for 7 to 10 days, then re-start (See pages <a href="#">23-24</a>)</li> </ul>
<b>INTERSTITIAL NEPHRITIS</b>	<ul style="list-style-type: none"> <li>• Very rare with a handful of published case reports</li> <li>• Drug hypersensitivity reaction, occurring during the first 8 weeks of treatment</li> <li>• Presenting features overlap with myocarditis – fever, tachycardia, nausea/vomiting, diarrhea.</li> <li>• Fever work-up (See page <a href="#">17</a>)</li> <li>• While renal biopsy provides definitive diagnosis, if UA shows protein, +/- RBCs or leukocytes, plasma creatinine is elevated and eGFR is decreased, acute interstitial nephritis is likely, it is strongly recommended that clozapine be stopped</li> <li>• Consider serum creatinine and eGFR at baseline and weekly x 8 weeks to screen for abnormalities</li> </ul>
<b>METABOLIC CHANGES</b>	<ul style="list-style-type: none"> <li>• 60 to 75% of patients experience weight gain</li> <li>• Insulin resistance and DM are common with over 40% of patients suffering from DM and over 60% with metabolic syndrome. Coordinate management with primary care. Clozapine does not need to be discontinued</li> <li>• The prevalence of dyslipidemia in clozapine patients is &gt;30%. Coordinate management with primary care. Clozapine does not need to be discontinued.</li> <li>• Exercise is evidence-based to benefit patients with mental illness. Prescribe exercise early and track physical activity</li> <li>• Involve the dietitian as early as possible</li> <li>• Consider metformin which results an average weight loss of &gt;3 kg while improving insulin resistance and triglycerides</li> </ul>

<b>Clozapine Adverse Effects and Suggested Management, Cont'd</b>	
<b>Adverse Effect</b>	<b>Action/Comments</b>
<b>MYOCARDITIS</b>	<ul style="list-style-type: none"> <li>Occurs in &lt; 0.1 -3% of cases within the first 6 weeks of clozapine treatment with 83% of cases occurring between week 2 and week 3</li> <li>The first indications of onset are non-specific symptoms such as fever and flu-like symptoms (fatigue, myalgias, shortness of breath). This is followed by significant tachycardia (20-30 bpm greater than baseline) and chest pain/respiratory symptoms</li> <li>Fever work-up (See page x)</li> <li>Labs will show troponin I or T &gt; 2x ULN and/or CRP &gt; 100 mg/L</li> <li>Eosinophil counts and ECG are neither sensitive nor specific</li> <li>Cardiac imaging (transthoracic ECHO or cardiac MRI) is warranted if there are signs/symptoms of myocarditis and troponins or CRP are normal</li> <li>Discontinue clozapine if myocarditis is confirmed by ECHO or cardiac MRI</li> <li>Consider troponin I/T and CRP at baseline and weekly x 6 weeks to screen for abnormalities</li> </ul>
<b>NEUROLEPTIC MALIGNANT SYNDROME (NMS)</b>	<ul style="list-style-type: none"> <li>Uncommon with clozapine monotherapy due to clozapine's weak D2 antagonism. However, may be seen if clozapine is combined with other antipsychotics</li> <li>Evolves over 1-3 days with mental status changes, muscular rigidity/CK elevation, hyperthermia, and autonomic dysfunction</li> <li>Discontinue all dopamine receptor antagonists. It is imperative to cover the patient for cholinergic rebound with an equivalent dose of benztropine (clozapine 50 mg (for patients who do not smoke) to 100 mg (for patients who smoke) of clozapine = benztropine 1 mg). Cholinergic rebound can worsen delirium and it will exacerbate extrapyramidal symptoms</li> <li>Fever work-up (See page x). NMS is a diagnosis of exclusion</li> <li>Moderate to severe cases will likely be managed at an outside acute care facility with supportive treatment, dopamine agonists and/or bromocriptine</li> <li>Rechallenge with clozapine has enjoyed a 100% success rate to date</li> </ul>
<b>NEUTROPENIA</b>	<ul style="list-style-type: none"> <li>See section on Hematological Monitoring above (Page <a href="#">10</a>)</li> </ul>
<b>OBSESSIVE COMPULSIVE DISORDER (OCD)</b>	<ul style="list-style-type: none"> <li>New onset OCD is rare with atypical antipsychotics but more common with clozapine than other drugs. May be related to dose</li> <li>OCD will resolve if clozapine is discontinued</li> <li>If clozapine discontinuation is unacceptable: <ul style="list-style-type: none"> <li>Check the plasma level and consider reducing the dose by 5%/month provided that the patient is stable</li> <li>Treat OCD with a selective serotonin reuptake inhibitor (SSRI) such as sertraline. Do not use fluvoxamine, paroxetine, or fluoxetine due to CYP P450 interactions</li> <li>Behavioral therapies such as exposure and response prevention are a consideration</li> </ul> </li> </ul>

<b>Clozapine Adverse Effects and Suggested Management, Cont'd</b>	
<b>Adverse Effect</b>	<b>Action/Comments</b>
<b>ORTHOSTATIC HYPOTENSION</b>	<ul style="list-style-type: none"> <li>• Seen in about 9% of patients, often early in treatment, and is related to the dose and speed of titration</li> <li>• Definition: sustained reduction in systolic BP of &gt; 20 mm Hg or diastolic BP of &gt; 10 mm Hg within 3 minutes of standing</li> <li>• Slow the titration in the elderly, patients with orthostasis at baseline, those treated with antihypertensives</li> <li>• For antipsychotics with alpha1 antagonist activity (chlorpromazine) that cannot be withdrawn, cross taper with clozapine</li> <li>• If a patient experiences orthostatic drops in BP, return to the last clozapine dose and hold there so that the patient has time to adapt. Encourage hydration</li> <li>• For persistent orthostasis, fludrocortisone is the preferred medication and can be started at 0.1 mg po daily</li> </ul>
<b>SEDATION</b>	<ul style="list-style-type: none"> <li>• Experienced by more than 40% of patients</li> <li>• Appears early on in treatment, prior to tolerance to antagonism of muscarinic and histamine receptors.</li> <li>• Most common reason cited for medication discontinuation by patients</li> <li>• To manage: <ul style="list-style-type: none"> <li>○ Taper doses of other sedating medications if possible</li> <li>○ Consolidate dose to a single bedtime dose</li> <li>○ Consider slowing titration</li> <li>○ Consider checking a plasma clozapine level. The patient may be a slow metabolizer at CYP 1A2</li> </ul> </li> </ul>
<b>SIALORRHEA</b>	<ul style="list-style-type: none"> <li>• Prevalence ranges from 30 to 80 %</li> <li>• Third most common reason patients cite for discontinuing clozapine</li> <li>• Mechanism appears to be related to norclozapine's muscarinic agonist effects. Decreasing the dose does not appear to reduce symptoms</li> <li>• Topical anticholinergics are the mainstay of treatment; however, they need to be dosed frequently and administered appropriately to be effective. <ul style="list-style-type: none"> <li>○ Atropine 1% drops can be started at 1-2 drops sublingually QHS. Maximum dose is 3 drops sublingually TID. Place the drop(s) under the tongue, swish with a very small amount of water (&lt;5 mg) for 30 seconds, then spit out. Using too much water will dilute the medication rendering it ineffective. Eating or drinking too soon afterwards may impact absorption and efficacy.</li> <li>○ Ipratropium 0.06% spray can be started at 1-3 sprays intraorally QHS, swishing with &lt;5 ml of water for 30 seconds, and spitting out. Using too much water will dilute the medication rendering it ineffective. Eating or drinking too soon afterwards may impact absorption and efficacy.</li> </ul> </li> <li>• If the patient does not respond to one medication, try the other.</li> </ul>

<b>Clozapine Adverse Effects and Suggested Management, Cont'd</b>	
<b>Adverse Effect</b>	<b>Action/Comments</b>
<b>SEIZURE</b>	<ul style="list-style-type: none"> <li>• Incident is about 5%, though literature varies. Most common type is tonic-clonic.</li> <li>• Occurrence of a seizure is not a reason to discontinue clozapine or use a subtherapeutic dose. See management below.</li> <li>• Does not appear to be related to dose or rapid titration (Meyer and Stahl, 2019).</li> <li>• Management: <ul style="list-style-type: none"> <li>○ Obtain a plasma clozapine level, electrolytes, renal/hepatic function, urine toxicology, and plasma level of anticonvulsant (if prescribed)</li> <li>○ Review medication history for recent changes, i.e. dose adjustment, addition of CYP inhibitors, discontinuation of CYP inducers, inconsistent medication adherence, etc.</li> <li>○ Hold clozapine x24 hours</li> <li>○ If medication related: Adjust clozapine dose and recheck level. If a higher dose is required or if a second seizure occurs, add divalproex</li> <li>○ If no cause can be found and the level is &gt;30% above prior stable levels, adjust the dose and recheck the level</li> <li>○ If no cause can be found and the level is consistent with prior levels, add divalproex</li> </ul> </li> <li>• Divalproex is the preferred agent for treating clozapine related seizures</li> <li>• Asymptomatic EEG abnormalities are common in clozapine-treated patients without preexisting seizure disorders and are dose related. It is recommended that EEGs not be routinely performed in asymptomatic patients</li> </ul>
<b>TACHYCARDIA</b>	<ul style="list-style-type: none"> <li>• Persistent or sustained tachycardia is a heart rate &gt; 100 bpm</li> <li>• Rates of tachycardia range from 25-50%</li> <li>• Prior to diagnosing clozapine-induced tachycardia, rule out: reflex tachycardia due to orthostasis, contributions from anticholinergic or adrenergic agonist medications, pain, or infection, and if occurring during the first 6 weeks of treatment, myocarditis</li> <li>• Treat clozapine-induced tachycardia with atenolol, starting at 12.5 mg po QD. Atenolol can be titrated by 12.5 mg increments weekly.</li> <li>• The goal is HR &lt;100 bpm and preferably &lt; 80 bpm.</li> <li>• Untreated or undertreated, sustained tachycardia increases the risk for cardiomyopathy</li> </ul>
<b>TARDIVE DYSKINESIA</b>	<ul style="list-style-type: none"> <li>• The development of tardive dyskinesia in a patient prescribed clozapine is rare and is usually due to prior antipsychotic exposure or treatment with metoclopramide</li> <li>• Clozapine has been shown to improve tardive dyskinesia as well as drug-induced parkinsonism and chronic akathisia<sup>13</sup></li> </ul>
<b>VENOUS THROMBOEMBOLISM (VTE) AND PULMONARY EMBOLISM (PE)</b>	<ul style="list-style-type: none"> <li>• Antipsychotics as a class are associated with an increased risk for VTE</li> <li>• Clozapine's risk is not significantly different from other agents</li> <li>• Prophylaxis is recommended for patients with VTE. Clozapine may not need to be discontinued for a single episode</li> <li>• It is strongly recommended that recurrent VTE prompt work-up for a hypercoagulable state and risk-benefit discussion regarding discontinuation of clozapine with relapse of psychosis vs continuation of clozapine with lifetime anticoagulant therapy</li> </ul>

## Constipation

- Clozapine-induced gastrointestinal hypomotility is one of the most common and most serious adverse effect resulting in constipation that progresses to ileus, bowel obstruction toxic megacolon and death. The incidence of clozapine induced constipation per the literature ranges from 32 to 60%. In 2020 the FDA issued a statement increasing the strength of the warning related to the impact of clozapine, stating “FDA is strengthening an existing warning that constipation caused by the schizophrenia medicine clozapine (Clozaril, Fazacllo ODT, Versacloz, generics) can, uncommonly, progress to serious bowel complications. This can lead to hospitalization or even death if constipation is not diagnosed and treated quickly.”
- The average colonic transit time (CTT) in adults is 24 hours. For patients who are treated with clozapine and are not on laxatives, the median CTT is 110 hours (over 4 times longer)
  - Even with maximal doses of the three types of laxatives (softener, osmotic, stimulant) the CTT was still 62 hours<sup>2</sup>
- Although the majority of patients on clozapine have gut hypomotility, only about 25% self-reported constipation. Variations in pain tolerance, presentation of somatic symptoms, facial affect, amongst other clinical factors may impact a patient’s reporting of constipation symptoms. Careful and close monitoring and assessment is warranted.
- Perform a thorough bowel function evaluation prior to initiation of clozapine and regularly during treatment. This includes:
  - Document the following:
    - Baseline bowel function, stool frequency and consistency
    - Comorbid medical conditions and medications affecting bowel function
    - Encourage patients to notify staff if they find that they are having difficulty passing gas, have not had at least three bowel movements in a week, have experienced hard/dry stool or have noticed a decrease in their regular bowel habits.
  - Elicit history of:
    - Changes in stool frequency and consistency
    - Straining, pain, or bloating
    - The sensation of incomplete evacuation
    - Use of manual efforts for successful defecation
  - Assessment of:
    - Abdominal tone, bowel sounds, tenderness, or masses
    - Gastrointestinal symptoms associated with gastrointestinal hypomotility, such as abdominal distention, nausea, vomiting, abdominal pain
    - The peritoneum and rectal cavity (via digital rectal examination)
    - Other treatable causes of constipation via labs, e.g., hypothyroidism
    - Stool burden or anatomical issues affecting the gastrointestinal (GI) tract via imaging
  - Consider further evaluation and/or consultation for alarm symptoms of colon cancer or other GI pathologies
- The following is an evidence-based constipation management protocol for patients taking clozapine
  - Nonpharmacological Interventions
    - Normalize reporting/discussion of bowel habits
      - Train health care staff to use open ended questions and to ask regularly
      - Encourage patients to report any changes in bowel habits including stool consistency or color, blood in stool, straining, incomplete evacuation, hard stool, or abdominal pain
      - Encourage regular toilet time after meals where possible
    - Encourage physical activity
      - Being sedentary promotes constipation
      - Daily moderate exercise, e.g., walking for at least 20 minutes, has shown benefit
    - Encourage adequate fluid intake and intake of fruits and vegetables
      - Dehydration increases water resorption from the bowel, hardening the stool further
      - Dietary fiber promotes bowel regularity
  - Minimize Medication Related Causes of Constipation
    - Minimize or discontinue anticholinergic medications
      - Anticholinergic medications prolong stool transit time, promote drying of stool, and increase risk of constipation, impaction, and bowel obstruction

## Constipation, Cont'd

- These include:
  1. Antiparkinsonian agents: benztropine, diphenhydramine, trihexyphenidyl
  2. Antidepressants: tricyclic antidepressants (TCAs) and paroxetine
  3. Antipsychotics: chlorpromazine, olanzapine, quetiapine
  4. Antihistamines: chlorpheniramine, meclizine, cetirizine, fexofenadine, loratadine
  5. Overactive bladder agents: oxybutynin, tolteridine
  6. Others: darifenacin, solifenacin, trospium, glycopyrrolate
- Discontinue bulk-forming laxatives (psyllium, polycarbophil)
  - When colonic transit time is slowed, these medications add to stool mass increasing the risk of fecal impaction and bowel obstruction
- Minimize or discontinue iron and opioids
  - In patients with iron-deficiency anemia, hold iron during the initial 4-6 weeks of clozapine titration. Add back slowly while monitoring bowel habits
  - Where feasible, stop opioids prior to starting clozapine as these agents are profoundly constipating
  - Patients treated with buprenorphine or methadone as part of medication assisted treatment (MAT) will require special vigilance
- Other medications associated with constipation include antiepileptics, diuretics, calcium channel blockers, cholinolytics, and serotonin antagonists (e.g., antiemetics), and antidiarrheal medications (loperamide). While the constipating effects may not be as great as the anticholinergics, iron, or opioids, it is recommended to minimize, discontinue, or switch these medications when possible
- Recommended bowel regimen
  - Step 1:** When commencing clozapine, start medication(s) to treat constipation, even if constipation is not an issue. Since there is limited evidence for docusate and high-quality evidence for PEG-3350 (Miralax), strongly consider starting both simultaneously upon initiation of clozapine. Also start a PRN rescue agent such as magnesium citrate or magnesium hydroxide (use with caution in patients with renal insufficiency)
  - Step 2:** If docusate and PEG are not adequate, add a stimulant laxative such as bisacodyl q 2 to 3 days, and decrease the frequency of PEG to 8.5 g/day
  - Step 3:** If the combination of softener, osmotic, and stimulant laxatives are insufficient, add one secretagogue. If the secretory agent is effective, it may be possible to taper off the stimulant laxative and then the osmotic laxative

Urgent evaluation of the patient is warranted if there are reports of any of the following symptoms: moderate to severe abdominal pain that lasts for greater than an hour, abdominal distention, lack of or high-pitched bowel sounds, bloody diarrhea, signs of sepsis, hemodynamic instability, metabolic acidosis, or leukocytosis.

Medications for Constipation		
Medication	Dose	Comments
Docusate (Colace®) Softgel: 100 mg \$	<ul style="list-style-type: none"> <li>• Starting dose: 200 mg QHS</li> <li>• Maximum dose: 200 mg BID</li> <li>• Action onset: 24-72 hours</li> </ul>	<ul style="list-style-type: none"> <li>• Stool softener</li> <li>• Commonly used despite little evidence of efficacy (see above)</li> <li>• No laxative effect alone, use with another laxative</li> <li>• Ineffective with long term use</li> <li>• Not useful in patients with mushy or soft stools</li> <li>• Rarely causes nausea, abnormal taste in mouth, cramping</li> </ul>
Polyethylene glycol 3350 (PEG-3350) (Miralax®) Powder \$	<ul style="list-style-type: none"> <li>• Starting dose: 17 g QD</li> <li>• Maximum dose: 17 g BID</li> <li>• Action onset: 1-4 days</li> </ul> <p>Mix in 8 ounces of liquid</p>	<ul style="list-style-type: none"> <li>• Osmotic agent that causes water to be retained in the stool</li> <li>• Strong evidence of efficacy*</li> <li>• Preferred over lactulose</li> <li>• Contraindicated in patients with bowel obstruction</li> <li>• May cause nausea, bloating, cramping</li> </ul>



Medications for Constipation		
Medication	Dose	Comments
		<ul style="list-style-type: none"> <li>Elderly patients may have higher rates of diarrhea</li> </ul>
Lactulose (Enulose®) Oral solution: 10 g/15 ml \$	<ul style="list-style-type: none"> <li>Starting dose: 30 ml QD</li> <li>Maximum dose: 30 ml BID</li> <li>Action onset: 24-48 hours</li> </ul>	<ul style="list-style-type: none"> <li>Osmotic agent</li> <li>Broken down by colonic bacteria to lactic acid which increases osmotic pressure and acidifies contents resulting in increase in stool water content</li> <li>Poorly absorbed with only small amounts reaching the blood</li> <li>Avoid if intolerant to galactose or lactose</li> <li>Use with caution in patients with diabetes</li> <li>Check serum electrolytes in elderly patients treated for more than 6 months</li> <li>Gaseous distention or belching and abdominal discomfort in 20% of patients</li> </ul>
Bisacodyl (Dulcolax®) Tablet: 5 mg	<ul style="list-style-type: none"> <li>Starting dose: 5 mg QHS</li> <li>Maximum dose: 15 mg BID</li> <li>Action onset: 6-10 hours</li> </ul>	<ul style="list-style-type: none"> <li>Stimulant laxative</li> <li>Strong evidence of efficacy</li> </ul>
Sennosides	<ul style="list-style-type: none"> <li>Starting dose: 8.6 mg QHS</li> <li>Maximum dose: 17.2 mg BID</li> <li>Action onset: 6-12 hours</li> </ul>	<ul style="list-style-type: none"> <li>Stimulant laxative</li> <li>Absence of controlled data</li> <li>Abdominal cramps, diarrhea, nausea, vomiting</li> <li>Contraindications: intestinal obstruction, nausea/vomiting, abdominal pain of unknown origin, appendicitis, Crohn's disease</li> </ul>

\*From the American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Constipation

Management of Constipation and Risk Factors			
Status		Low risk (less than three risk factors)	High risk (three or more risk factors)*
Prevention		Encourage healthy diet, adequate fluid intake and regular exercise.	Encourage healthy diet, adequate fluid intake and regular exercise Add PEG3350 17 g, dissolved in 240ml (8oz) daily, hold if diarrhea
Bowel not open (BNO) 2-3 days	1 <sup>st</sup> Line	Add PEG3350 17 g, dissolved in 240ml (8oz) daily	Add Senna 17.2mg daily
BNO 3 days	2 <sup>nd</sup> Line	Add senna 17.2mg daily	Add lactulose 10g (15ml) daily
BNO 4 days	3 <sup>rd</sup> Line	Use lactulose 10g (15ml) daily	Lubiprostone** 24mcg twice daily
BNO 5 days	4 <sup>th</sup> Line	Mineral oil suppository or tap water enema	Mineral oil suppository or tap water enema

\*Risk Factors: Age > 60, low fiber, lack of exercise/immobility, dehydration, history of constipation

Medical Comorbidities: Parkinsons, Stroke, multiple sclerosis, Hypothyroid, DM, IBS, diverticular disease, scleroderma, previous abdominal surgery

On medication: opioids, anticholinergics, calcium channel blockers, antipsychotics, iron, calcium supplement

\*\*Alternative secretagogues can be used if the patient has previously been non-responsive to lubiprostone

If not responsive to 4th line treatment, consider digital disimpaction, obtain abdominal x-ray, put patient on NPO, and urgent medical review (call GI consult if available. Seek HLOC for certain patients with "red flags": Moderate to severe abdominal pain or any abdominal pain/discomfort lasting over an hour AND one or more of the following: abdominal distension, vomiting, diarrhea (particularly if bloody), absent or high-pitched bowel sounds, signs of sepsis, leukocytosis, and/or hemodynamic instability.

Once constipation is resolved, progress backwards from the progression listed above for additional medications as clinically indicated.

## Making Sense of Clozapine Plasma Levels

- Clozapine plasma levels\* can be used to monitor adherence, adequacy of trial, and the effects of CYP P450 inhibitors or inducers
  - The presence of clozapine in the urine ONLY monitors adherence
- The plasma clozapine level alone (not clozapine + norclozapine) correlates with therapeutic effect
- At steady-state conditions, clozapine demonstrates linear pharmacokinetics, i.e. if the dose is doubled, the plasma level doubles
- Clozapine is metabolized to its active metabolite (norclozapine) by multiple cytochrome P450 enzymes with CYP 1A2 playing a primary role, especially at lower doses
- The primary use of norclozapine is to understand activity of the CYP isoenzymes involved in clozapine metabolism
  - The ratio of the clozapine plasma level to the norclozapine plasma level (clozapine: norclozapine) is the metabolic ratio (MR)
  - The table below explains the role of the MR in understanding clozapine metabolism
- Responding to the spectrum of clozapine plasma levels
  - Level lower than expected
    - For example, a patient on a dose of 300 mg QHS has a clozapine plasma level of 75 ng/ml
    - Next steps:
      - Check previous levels. Is this level consistent or an outlier?
      - Check the Medication Administration Record (MAR) – Has the patient accepted all clozapine doses? Does the patient have a history of medication diversion (cheeking)?
      - Calculate the MR and check the medication list. Is the patient on an inducer?
    - For patients on a stable dose with previous levels, up to 30% variability is acceptable. When variation approaches 50%, suspect medication nonadherence
    - The MAR only reports that the patient accepted the medication. It does not report adherence. Only plasma levels or urine levels can truly monitor adherence
  - Level higher than expected
    - For example: Patient treated with 200 mg/day has a plasma level of 700 ng/ml
    - Check previous levels. Is this level consistent or an outlier?
    - Check the MAR. Did the patient receive a dose prior to the blood draw? Or did the patient receive an extra dose?
    - Calculate the MR and check the medication list. Is the patient on an inhibitor? Was an inducer removed? Does the patient have a serious infection?
  - New “High” level (> 1000 ng/ml)
    - Evaluate the patient:
      - Is there evidence of toxicity such as sedation, orthostasis, tachycardia, sialorrhea, myoclonus or seizure?
      - Does the patient have a serious bacterial or viral infection?
    - Determine if the level was a true trough level
      - If a true trough with adverse effects, adjust clozapine dose
    - Recheck the level the next day to rule out a lab error
    - Certain patients tolerate and respond to levels of circa 1000 ng/ml and decompensate at lower levels. If the patient has been stable at a level of circa 1000 ng/ml, resist the urge to taper the medication based on a number

\* Plasma levels are steady state trough levels and assume a 12-hour trough

Clozapine: Norclozapine, Metabolic Ratio	Interpretation <sup>10</sup>
1.32	This is the expected value for healthy, non-smoking adults who are extensive metabolizers at CYP 1A2 (most patients)
Less than 1.32 (MR < 1.32)	Increased metabolism of clozapine Explanations: <ol style="list-style-type: none"> <li>1. Ultrarapid metabolizer status at CYP 1A2</li> <li>2. Exposure to an inducer (phenytoin, omeprazole, etc.) (See pages 4-5)</li> </ol>
Greater than 1.32 (MR > 1.32)	Values > 2.0 indicate decreased metabolism of clozapine Explanations: <ol style="list-style-type: none"> <li>1. Poor metabolizer status at CYP 1A2 or CYP 2D6</li> <li>2. Exposure to CYP inhibitor (See pages 2-3) <ul style="list-style-type: none"> <li>• CYP 1A2 inhibitors ↑ clozapine plasma level up to 10x (MR range &gt; 3)</li> <li>• CYP 2D6 or 3A4 inhibitors ↑ clozapine plasma level by 40-100% (MR range 1.880-2.60)</li> </ul> </li> </ol>
Greater than 3 during medical illness (MR > 3)	Values of 3 or more during serious infections (bacterial or viral) are thought to result from inhibitory effects of inflammatory cytokines on CYP P450 activity

### Rechallenging After an Adverse Related Event Discontinuation

- The discontinuation of clozapine is frequently followed by relapse of psychosis with deterioration in functional status and quality of life
- Careful rechallenge can be considered in certain situations and with specific precautions and supports

#### Guidance for Rechallenging Patients After Severe Adverse Events

Adverse Event	Comments
<b>Severe Neutropenia / Agranulocytosis</b>	<ul style="list-style-type: none"> <li>• Rechallenge not recommended</li> <li>• Of published cases, only 3 out of 17 have been able to be rechallenged successfully. In the remainder, severe neutropenia recurred<sup>7</sup></li> </ul>
<b>DRESS</b>	<ul style="list-style-type: none"> <li>• Rechallenge not recommended</li> </ul>
<b>Interstitial Nephritis</b>	<ul style="list-style-type: none"> <li>• Rechallenge not recommended</li> </ul>
<b>Myocarditis</b>	<ul style="list-style-type: none"> <li>• Rechallenge possible with support <ul style="list-style-type: none"> <li>○ Of published cases 11 out of 17 have been successful<sup>7</sup></li> <li>○ Consult with cardiologist, vigilant monitoring of labs and vital signs, slow titration</li> <li>○ Recurrence is rapid when it occurs</li> </ul> </li> </ul>
<b>Neutropenia</b>	<ul style="list-style-type: none"> <li>• Rechallenge possible with support <ul style="list-style-type: none"> <li>○ Of published cases, 78 out of 112 patients were successfully rechallenged and did not develop a blood dyscrasia<sup>7</sup></li> </ul> </li> <li>• Many successful patients were treated with lithium or filgrastim<sup>11</sup> (See page 13)</li> </ul>
<b>Neuroleptic Malignant Syndrome (NMS)</b>	<ul style="list-style-type: none"> <li>• Rechallenge possible with support <ul style="list-style-type: none"> <li>○ 7 out of 7 published cases with successful rechallenge<sup>7</sup></li> <li>○ Careful monitoring of vital signs, mental status, muscle tone/movement and creatine kinase</li> </ul> </li> </ul>
<b>Ileus</b>	<ul style="list-style-type: none"> <li>• Rechallenge possible with support, particularly if no secretagogue used previously <ul style="list-style-type: none"> <li>○ Start secretagogue when clozapine is started. Add other laxatives sequentially, if needed.<sup>10</sup> (See pages 23-25)</li> </ul> </li> </ul>

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**PATIENT EDUCATION/SELF MANAGEMENT****CLOZAPINE: WHAT YOU SHOULD KNOW****WHAT IS CLOZAPINE?**

Clozapine is a highly effective medicine used to treat people with some types of mental illness who have not responded to other treatments or cannot take other treatments.

**REQUIREMENTS FOR CLOZAPINE THERAPY**

- Clozapine is provided through a special program in CCHCS/DCHS to ensure patient safety because of the potential risks of this therapy.
- You must agree to have all blood tests required during clozapine therapy. These include:
  - Weekly blood tests for the first six months of treatment,
  - Blood tests every two weeks for the second 6 months, and
  - At least monthly blood tests after one year of therapy.

**WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS OF CLOZAPINE?**

- Constipation, which may be severe
- Seizures
- Weight gain
- Rapid heart rate
- Drowsiness
- Potentially serious or life-threatening infections
- Dizziness or fainting
- Inflammation of the heart (myocarditis)
- Heavy salivation
- Blood clot in the lungs (pulmonary embolism)
- Fever

**CLOZAPINE: WHAT YOU SHOULD DO**

- Take your medications as prescribed. DO NOT miss doses.
- Tell your health care professional about all medications that you are taking, including anything that you take without a prescription.
- Avoid the use of illicit drugs or alcohol.
- Exercise regularly, make healthy food choices, and drink an appropriate amount of water daily.
- Report any of the following symptoms to your treatment team right away:
  - Fever
  - Change in bowel pattern such difficulty passing gas or stool, change in frequency of bowel movements, or not having at least three bowel movements in a week.
  - Abdominal pain
  - Dizziness or fainting, especially when you stand
  - Fatigue/extreme tiredness
  - Seizures
  - Change in heartbeat
  - Shortness of breath
- Be sure you also report any other new symptom that you have while you are taking clozapine to your treatment team right away.

**EDUCACIÓN PARA EL PACIENTE/CONTROL PERSONAL DEL CASO****CLOZAPINA: LO QUE DEBE SABER****¿Qué es la clozapina?**

La clozapina es un medicamento muy eficaz utilizado para tratar a personas con ciertas enfermedades mentales cuando el individuo no ha respondido a otros tratamientos o no puede tomar otros tratamientos.

**Los requisitos para la terapia con clozapina**

- La clozapina se proporciona a través de un programa especial en la CCHCS/DCHS para garantizar la seguridad del paciente debido a los riesgos potenciales de esta terapia.
- Usted debe aceptar que se hagan todos los análisis de sangre necesarios mientras esté tomando la clozapina. Estos incluyen:
  - Un análisis de sangre cada semana durante los primeros seis meses de la terapia,
  - Un análisis de sangre cada dos semanas durante el segundo periodo de seis meses, y
  - Por lo menos un análisis de sangre cada mes después de un año de terapia con clozapina.

**¿Cuáles son los riesgos y efectos secundarios posibles cuando se toma la clozapina?**

- Estreñimiento (que podría ser grave)
- Convulsiones
- Aumento de peso
- Pulso rápido
- Somnolencia
- Infecciones que podrían poner en riesgo su vida
- Mareos o desmayos
- Inflamación del músculo del corazón (miocarditis)
- Aumento en la producción de saliva
- Fiebre

**CLOZAPINA: LO QUE DEBE HACER**

- Tome sus medicamentos según las indicaciones. **NO DEJE PASAR NINGUNA DOSIS.**
- Informe a su médico o enfermera si Ud. está tomando otros medicamentos, incluyendo aquellos que no son recetados.
- No usá drogas ni alcohol.
- Haga ejercicio regularmente, elija alimentos saludables y beba una cantidad adecuada de agua al día. Si tiene alguno de los siguientes síntomas dígaselo inmediatamente a un miembro de su elenco tratante:
  - Fiebre
  - Cambio en el patrón intestinal, como dificultad de pasar gases o deposiciones, cambio en la frecuencia de los deposiciones o no tener al menos tres deposiciones cada semana
  - Dolor de estómago
  - Cansancio
  - Cambio en el ritmo cardíaco
  - Falta de aliento
  - Mareos o desmayos (especialmente cuando se pone de pie)
  - Convulsiones
- Informe inmediatamente a un miembro de su elenco tratante si Ud. empieza a sentir cualquier otro síntoma nuevo mientras esté tomando la clozapina.