

**San Bernardino County
Department of Behavioral Health**

Clinical Practice Guideline: Clozapine

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Introduction The San Bernardino County Department of Behavioral Health (DBH) Medical Services Division established the Clozapine Clinic with the purpose of ensuring coordination of treatment and discharge planning between State Hospitals, Community Hospitals, patients on Clozapine, and local practitioners' referrals.

Goals The goals of DBH for the Clozapine Clinic are to:

- Decrease recidivism to the acute inpatient hospitals by closer monitoring and treatment of these most "fragile" patients.
- Educate patients and their support system of the side effects, response to treatment, and possible signs and symptoms of impending relapse.

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Clinical Practice Guideline: Clozapine, Continued

New DBH client already taking Clozapine

**New DBH client
already taking
Clozapine**

A new DBH client who is already taking Clozapine shall begin his/her treatment at the [Clozapine Checklist](#) with immediate notification to the Clozapine Treatment Team to avoid treatment interruptions.

Clozapine Treatment

Background

Clozapine was the first atypical antipsychotic drug to be developed. Sandoz Pharmaceuticals developed Clozapine in 1961, and the drug underwent human trials from 1962 through 1996. In 1972, Sandoz Pharmaceuticals released the drug in Switzerland and Austria, but the manufacturer voluntarily withdrew the drug in 1975 due to agranulocytosis.

In 1989, the drug was re-studied and it was determined to be more effective than the other antipsychotic medications that were on the market to treat schizophrenia. Although the Food and Drug Administration (FDA) approved Clozapine use, it requires regular blood testing and ongoing monitoring due to agranulocytosis risks.

In 2002, the FDA approved Clozapine for reducing the risks of suicidal behavior for patients with schizophrenia.

Indications

Clozapine treatment is for patients who are experiencing treatment resistant schizophrenia. It may reduce the risk of suicidal behavior for patients with schizophrenia.

A patient that will be on Clozapine must be able to comply with a stringent laboratory and medication regimen, and have a stable support system.

Off Label Use

Patients suffering of the following conditions have substantially less aggression with Clozapine treatment:

1. Psychosis with L-Dopa treatment patients
 2. Lewy body Dementia
 3. Resistant acute mania
 4. Schizoid personality disorder
 5. Intractable chronic insomnia
 6. Bipolar disorder
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- Contraindications** Patients suffering with the following conditions shall not take Clozapine:
1. Uncontrolled seizure disorder
 2. Myeloproliferative disorder
 3. History of agranulocytosis
 4. Paralytic Ileus
 5. Severe Central Nervous System Depression or Comatose State from any cause
 6. Inability to maintain compliance with stringent laboratory, medication and communication requirements of Clozapine treatment

Note: *According to the guidelines noted on page 8, Patients with Benign Ethnic Neutropenia (BEN) may be on Clozapine.*

Toxicity Approximately 3 percent of patients on Clozapine experience Leukopenia, and 1 percent of patients on Clozapine will experience the life threatening agranulocytosis.

- Breaks in Treatment** If the period of interruption is:
- Two days or less, the patient must resume the drug at the previous dose.
 - Between two days and four days, the patient must reduce the Clozapine dose to one-half of the dose before titrating it to the previous dose.
 - More than four days, the patient shall treat Clozapine as if it were a newly introduced medication by titrating it.

Note: *The principal risk of reintroduction to Clozapine is orthostatic hypotension.*

Discontinuation Tapering is the preferred method of discontinuation for Clozapine. If the patient requires the Clozapine to stop abruptly due to agranulocytosis, there is a risk of cholinergic rebound, which may ameliorate by taper with Benztropine (beginning at 2 mg twice per day and discontinuing it to zero over a period of 5-10 days).

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**Cost and
Benefits**

The cost and savings of Clozapine treatment include:

1. Treatment resistance is at about 3 percent for patients with schizophrenia.
 2. In 1995, the annual hospitalization cost estimates were close to \$2.5 billion. It is a real economic burden.
 3. Less than 4 percent of treatment resistant schizophrenia receives Clozapine.
 4. Suicide is a serious and significant lifetime risk. There is a high prevalence of suicidal behavior in patients with schizophrenia. Up to 10 percent of patients with schizophrenia die from suicide.
 5. Clozapine therapy has reduced both recurrent hospitalization and suicidal behavior.
-

**Clinical
Effectiveness
(CATIE) II**

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) II study was a nationwide public health-focused clinical trial that compared the effectiveness of older (first available in the 1950s) and newer (available since the 1990s) antipsychotic medications used to treat schizophrenia.

The lessons learned from CATIE II ABOUT CLOZAPINE supported that:

1. Treatment discontinuation was lower with Clozapine due to a lack of efficacy compared to Olanzapine, Quetiapine, and Risperidone.
 2. Clozapine demonstrated the greatest reduction in symptoms.
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Clozapine Clinic Treatment Team – Roles and Responsibilities

DBH Psychiatrist Duties

The DBH Psychiatrist duties are to:

1. Enroll with the Patient Monitoring Registry Clozapine Risk Evaluation and Mitigation Strategy (REMS) program in order to obtain the pre-dispense authorization (PDA) for patients on Clozapine. The web address for Clozapine REMS is www.clozapinerems.com.
 2. Complete the clinical evaluation of the newly referred patient or possible acceptance to the Clozapine Clinic.
 3. Complete regular clinical evaluations and treatment of patients already with the Clozapine Clinic.
 4. Coordinate, refer, and compile the comprehensive medical care of patients in the Clozapine Clinic with the help of the Clozapine trained Nurse.
 5. Provide clinical supervision to the Clozapine trained Nurse.
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DBH Child Psychiatrist

In the event a minor, under the age of 18, requires Clozapine treatment, a Child Psychiatrist shall provide said treatment.

Clozapine Trained Nurse Duties

The DBH Clozapine trained Nurse must be a Mental Health Nurse II or Nurse Practitioner, whose duties are to:

1. Receive referrals to the Clozapine Clinic from the DBH, Arrowhead Regional Medical Center-Behavioral Health (ARMC-BH), area Hospitals and active practitioners in the community.
 2. Gather all components and data of the Clozapine chart prior to the clinical evaluation by the Clozapine Psychiatrist.
 3. Instruct the patient and support system about the blood monitoring process with emphasis on adherence.
 4. Educate the patient and support system about the requirements and treatment for Clozapine patients.
 5. Assist the Clozapine Psychiatrist in Clozapine REMS registry as a designee to enroll and update patient information and results.
 6. Obtain the results of all laboratory tests ordered by the Psychiatrist and file the hard copy in the chart, which includes the regular comprehensive metabolic profile tests.
 7. Assist the Psychiatrist in the blood-monitoring guide and document the results.
 8. Act as the first line in receiving, collecting, and compiling information from the Clozapine patient and their support systems.
 9. Receive and document medications for the Clozapine Clinic.
 10. Dispense medications, per the Psychiatrist's order, with the use of bubble packs to improve compliance.
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Clozapine Trained Nurse Duties, continued

11. Call the medication changes in to the pharmacy as ordered by the Psychiatrist.
 12. Assist the Psychiatrist with any other vital functions of the Clozapine Clinic as they become more apparent.
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Clinician/ Case Manager/ Clinic Assistant Duties

- The DBH Clinician, Case Manager, or Clinic Assistant duties are as follows:
1. Upon receipt of the referral from the Psychiatrist and/or Clozapine trained Nurse, staff will provide the patient individual or group therapy as seen fit by the Clozapine Treatment Team.
 2. Provide essential case management regarding issues brought forth by the patient and/or their support system.
 3. Assist in reminding the patient and/or their support system of their scheduled appointments and blood tests.
 4. Assist the Clozapine trained Nurse in obtaining laboratory results and other work-ups requested by the patients' primary care physician.
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Clozapine Checklist

DBH Clozapine trained Nurse Duties Regarding Documentation of Clozapine Referrals

- The DBH Clozapine trained Nurse duties with regard to processing the documentation of Clozapine referrals are to:
1. Identify the name of the referring Psychiatrist.
 2. Ensure the referral packet includes a copy of the patient's current medications.
 3. Ensure the referral packet includes a copy of the patient's psychiatric history and mental status examination.
 4. Ensure the referral packet includes a copy of the patient's most recent laboratory test results is attached, such as complete blood count (CBC) with differential, comprehensive metabolic profile, urinalysis, lab levels for Valproate Acid, Carbamazepine, Clozapine, Lithium, etc., if applicable.
 5. Ensure the referral packet includes a copy of the patient's most recent electrocardiogram (EKG) is attached.
 6. Ensure the referral packet includes the most recent pregnancy test of the patient is attached, if the patient is a female and of reproductive age.
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**DBH Clozapine
trained Nurse
Duties
Regarding
Documentation
of Clozapine
Referrals,
continued**

7. Ensure the referral packet includes a copy of the patient's most recent physical examination by his/her primary care physician.
 8. Ensure the referral packet includes a copy of the patient's insurance card.
 9. If any of the above criteria is not included, he/she shall receive a denial for an initial evaluation at the Clozapine Clinic.
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Titration Guide for New Patients

**Recommended
Titration**

The titration schedule depicted below reflects a daily dose of 300 mg, which is, generally, the accepted lower dose of the therapeutic range. The recommended titration is that the:

- Daily dosage increment does not exceed 25 mg during the initial titration.
- Subsequent daily dosage increment (if needed), does not exceed 100 mg and that the frequency is limited to twice weekly.

Titration shall be dependent on tolerance and therapeutic response of the patient. The maximum daily dose is 900 mg daily and generally provided in divided doses. The clinical response and urgency of need shall determine the length of the titration period.

Week 1 Titration

The recommended titration allows the attainment of a target daily dose of 300 mg in a two week period as specified in the product labeling.

Day	Daily Dose (mg)*
1	25
2	25
3	50
4	75
5	100
6	125
7	150

*In divided doses

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Frequency of Monitoring

Recommended Monitoring Frequency and Clinical Decisions by ANC Level

The table provided below depicts the recommended monitoring frequency according to [Absolut Neutrophil Count \(ANC\) Standards](#):

Clozapine and the Risk of Neutropenia:
A Guide for Healthcare Providers

CLOZAPINE REMS
The Single Shared System for Clozapine
Risk Mitigation

Table 1: Recommended Monitoring Frequency and Clinical Decisions by ANC Level

ANC Level	Recommended Monitoring/Follow-up	ANC Monitoring
<p>Normal Range for a New Patient GENERAL POPULATION - ANC > 1500/cuL</p> <p>SENIOR POPULATION - ANC > 1000/cuL - Clozapine should not be started until ANC is stable on the following treatment</p> <p>ADULT POPULATION (1000 - 1500/cuL)</p>	<ul style="list-style-type: none"> Initial treatment If treatment interrupted: <ul style="list-style-type: none"> > 30 days: continue monitoring as before > 30 days: monitor as first episode Discontinuation for reasons other than neutropenia 	<ul style="list-style-type: none"> Weekly from initiation to 6th month Every 2 weeks from 6 to 12 months Weekly after 12 months <p>- See Section 2.4 of the Full Prescribing Information</p>
<p>Modifiable Neutropenia (500 - 1000/cuL)</p>	<p>GENERAL POPULATION - Continue treatment</p> <p>SENIOR POPULATION - ANC less than 1000 is normal range for SENIOR population - ANC 1000-1500: continue monitoring as above - ANC 500-1000: continue monitoring as above - ANC < 500: discontinue monitoring as above</p> <p>- Discontinuation for reasons other than neutropenia</p>	<p>GENERAL POPULATION - Every 1000 weekly until ANC > 1000/cuL - Once ANC > 1000/cuL return to normal range of ANC monitoring interval</p> <p>SENIOR POPULATION - Weekly from initiation to 6th month - Every 2 weeks from 6 to 12 months - Weekly after 12 months</p> <p>- See Section 2.4 of the Full Prescribing Information</p>
<p>Severe Neutropenia (200 - 500/cuL)</p>	<p>GENERAL POPULATION - Patients who have history of neutropenia - Interrupt treatment for suspected or confirmed neutropenia - Resume treatment once ANC returns to > 1000/cuL</p> <p>SENIOR POPULATION - Neutropenia secondary to neutropenia - Continue treatment</p>	<p>GENERAL POPULATION - Every 1000 ANC until ANC > 1000/cuL - Once ANC > 1000/cuL return to normal range of ANC monitoring interval</p> <p>SENIOR POPULATION - Every 1000 weekly until ANC > 1000/cuL - Once ANC > 1000/cuL return to normal range of ANC monitoring interval</p>
<p>Severe Neutropenia (< 200/cuL)</p>	<p>GENERAL POPULATION - Resumption of treatment for suspected or confirmed neutropenia - Do not resume clozapine treatment until ANC returns to > 1000/cuL</p> <p>SENIOR POPULATION - Resumption of treatment for suspected or confirmed neutropenia - Do not resume clozapine treatment until ANC returns to > 1000/cuL</p>	<p>GENERAL POPULATION - Daily until ANC > 1000/cuL - Every 1000 weekly until ANC > 1000/cuL - If patient has had a severe neutropenia, resume treatment as a new patient under normal range monitoring once ANC > 1000/cuL</p> <p>SENIOR POPULATION - Daily until ANC > 1000/cuL - Every 1000 weekly until ANC > 1000/cuL - If patient has had a severe neutropenia, resume treatment as a new patient under normal range monitoring once ANC > 1000/cuL</p>

Note: Please check the Clozapine REMS website regularly for updates to ANC standards:
https://www.clozapinerems.com/CpmgClozapineUI/remis/pdf/resources/Clozapine_REMS_A_Guide_for_Healthcare_Providers.pdf

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Initiation of Clozapine Treatment

**Initiating
Clozapine
Treatment**

The DBH Psychiatrist and Clozapine trained Nurse shall:

1. Follow the Clozapine Checklist on page 6.
 2. The Clozapine trained Nurse will compile and make sure that the chart is in order prior to presenting it to the psychiatrist.
 3. The Psychiatrist will evaluate and decide the appropriateness of referral, and schedule a patient for a face-to-face assessment to determine the patient admission status (accept or deny) to the Clozapine Clinic.
 4. After accepting the patient to the Clozapine Clinic, the Psychiatrist will register the patient to the Clozapine REMS registry.
 5. The Psychiatrist will order the titration of the Clozapine.
 6. The Clozapine trained Nurse will educate the patient and his/her support system about the blood monitoring process with emphasis on adherence.
 7. The Clozapine trained Nurse will educate the patient and his/her support system about the requirements and treatment for Clozapine patients.
-

**Ongoing
Monitoring**

Clozapine treatment requires ongoing monitoring, which shall follow the general principles by:

1. Titration Guide for Patients
 2. Clozapine Side Effects Checklist
 3. Frequency of the Monitoring Base on Results of ANC
-

Adverse Events and Possible Management

**Medication
Interactions**

Clozapine is potentially life threatening and/or may cause serious side effects. Always use Clozapine with precaution when used in combination with carbamazepine, antiretroviral medications, and Type 1C antiarrhythmic medications.

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- Agranulocytosis** Agranulocytosis effects generally include:
- Granulocytes of less than 500/mcL
 - Higher readings in the first three months
 - Ninety-five percent of cases occur within the first six months
 - Evidence of immunological basis, direct toxicity of metabolites and genetic risk factors histocompatibility complex, class I, B (HLA-B), histocompatibility complex, class II, DQ beta 1(HLA-DQB1)
-

- Agranulocytosis Management** Agranulocytosis effects shall be managed as follows:
1. Interrupt the treatment with Clozapine immediately.
 2. Refer the patient to the Emergency Room for assessment and treatment of any infections and possible administration of a granulocyte colony-stimulating factor.
 3. For the general population, obtain daily CBC until the ANC is greater than 1,000 proceeded by three times of weekly CBC until the ANC is greater than 1,500.
 4. Consider re-challenging the patient with Clozapine when benefits outweigh the risks; Medical staff should have clear documentation of this in the chart. If so, monitor the CBC as if the patient were new to Clozapine with a weekly CBC for six months, etc.

Note: *Confirm all of the CBC results with ANC are less than 1,500 with a repeat of the CBC within 24 hours.*

Cardiac Toxicity and Myocarditis Cardiac Toxicity and Myocarditis develops in the first month of therapy and is sometimes fatal. The fatality incidence is about 2 percent, and thought to be a drug sensitivity reaction. Staff must be aware of signs and symptoms of heart failure: **Fever, Tachycardia, Tachypnea, Eosinophilia, Chest Pain, Fatigue, Palpitation (Arrhythmias).**

**Monitor for possible Cardiomyopathy, which is less acute but potentially fatal.*

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Clinical Practice Guideline: Clozapine, Continued

Cardiac Toxicity and Myocarditis Management

Cardiac Toxicity and Myocarditis effects shall be managed as follows:

1. Promptly discontinue the Clozapine treatment, and do not rechallenge the patient if myocarditis has developed.
 2. Tachycardia may be the first presenting sign, which requires a Cardiology consultation immediately.
 3. Monitor for eosinophilia.
 4. Request a Troponin I protein, Troponin T protein, C-reactive protein (CRP), Cardiac echo.
 5. More recently, request a Cardiac echo every six months to rule out Cardiomyopathy.
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Seizures

Seizures occur during the upward titration phase of treatment at doses greater than 600 mg per day. The risk at the low dose is 1-3 percent, but the risk increases to 5 percent when the dose is 600 mg per day to 900 mg per day.

Note: Monitor for a patient with a history of seizures or head trauma. A seizure is not an absolute contraindication for Clozapine treatment, but collaboration and/or consultation with the patient's neurologist is essential before accepting a patient to the Clozapine clinic. A neurology clearance may be needed as well.

Seizures Management

Seizure effects shall be managed as follows:

1. Cut the current dose to one-half.
2. Add an anti-seizure medication of your choice (e.g. Depakote because research supports that Depakote augments Clozapine).
3. Obtain a neurology consultation and make sure an EEG is complete. Ongoing collaboration is essential.
4. Proceed with slower titration.

Note: Remember that patients who have seizures require close monitoring when taking Clozapine treatment.

Gastrointestinal Hypomotility

Gastrointestinal Hypomotility is usually under-recognized and potentially fatal. This may present as severe constipation initially but progress to fecal impaction, bowel obstruction, paralytic ileus, acute mega colon, ischemia, or necrosis.

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**Gastrointestinal
Hypomotility
Management**

- Gastrointestinal Hypomotility effects shall be managed as follows:
1. Close monitoring of bowel function is essential and requires an examination at every clinic visit.
 2. Most patients using Clozapine may require stool softeners added to their medication regimen.
 3. Treat constipation aggressively. Clozapine is very anticholinergic.
 4. Remember that a normal bowel movement occurs at least three times per week. The patient must always document the bowel movement. Elderly patients require extra precautions because bowel rupture is more common.
 5. If there is suspicion of a gastrointestinal hypomotility, request a gastroenterology consultation ASAP.
-

Less Life Threatening Side Effects but Still Common

Sedation

Sedation is a common side effect that can be reported as drowsiness or tiredness.

**Sedation
Management**

- Sedation effects shall be managed as follows:
1. Prescribe these medications at night. If the patient has side effects, he/she may not notice them as he/she may be sleeping anyway.
 2. If the patient remains sedated during the day after switching the medication to the evening time, try lowering the dose.
 3. If the patient shows more symptoms after the reduction, augment the medication with another less sedating antipsychotic. Since these are difficult and treatment resistant patients, he/she may require a polypharmacy to prevent decompensation or rehospitalization.
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Weight Gain

The average weight gain for a patient receiving Clozapine is 60 pounds over the first four years.

**Weight Gain
Management**

The recommendation is for medical staff to provide Topiramate or Metformin. Metformin also helps to reduce Clozapine-induced metabolic syndrome.

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Hypersalivation Drooling Hypersalivation Drooling, also known as "Wet Pillow Syndrome" is a very embarrassing side effect. It happens in about 30 percent of patients on Clozapine because Clozapine is a full agonist at M4 subset but a muscarinic antagonist at M1, M2, M3 and M5 receptors. M4 receptors are highly expressed in the salivary glands.

Hypersalivation Drooling Management Hypersalivation Drooling effects shall be managed as follows:

1. Wrap the pillow with a towel and assure the patient that the drooling is transient and may go away without taking another medication for it.
2. If the drooling continues or is really bothering the patient, an anticholinergic medication may be used.
3. If the anticholinergic is ineffective, use Clonidine.
4. If Clonidine is ineffective, use Glycopyrrolate.
5. Always keep in mind that all of these medications can cause or aggravate constipation.

Tachycardia Tachycardia is a resting heart rate of over 100 beats per minute.

Tachycardia Management Tachycardia effects shall be managed as follows:

1. Repeat the EKG to determine if it is a plain anticholinergic effect or part of more serious side effect.
2. Monitor for possible comorbid substance abuse.
3. If tachycardia is persistent, use a selective beta-blocker such as Atenolol.
4. Use propranolol if the patient has akathisia or anxiety, but not if the patient has bronchial asthma.

Hypotension Hypotension is Blood Pressure that is less than 90/60.

Hypotension Management Hypotension effects shall be managed as follows:

1. Repeat the EKG to determine if it is part of a substantial cardiac event.
2. Obtain orthostatic Blood Pressure.
3. Test for a fluid and electrolyte balance.

Hypertension Hypertension is a mentioned side effect, but is uncommon. Hypertension is Blood Pressure more than 130/90.

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**Hypertension
Management**

Hypertension effects shall be managed as follows:

1. Blood Pressure is part of the regular monitoring.
 2. Refer to the patient's primary care physician for further evaluation and treatment.
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**Weight Gain and
Diabetes**

The FDA has warnings about risks of hyperglycemia and Diabetes with the use of atypical antipsychotic medications. Clozapine can decrease the insulin sensitivity and induce ketoacidosis.

**Weight Gain and
Diabetes
Management**

Weight gain and diabetes effects shall be managed as follows:

1. Always monitor for metabolic syndrome.
 2. Obtain a comprehensive metabolic profile every six months.
 3. Refer to the patient's primary care physician if diabetes develops. High risks with family history of diabetes and their mental illness may put them at high risk.
 4. Always refer for diabetic teaching classes when diagnosed.
-

Constipation

Either increased hardness or decreased frequency may be a part of hypomotility syndrome.

**Constipation
Management**

Constipation effects shall be managed as follows:

1. Always treat constipation aggressively.
 2. Monitor bowel movement with every office visit and document the findings.
 3. Prevent constipation by making stool softeners/gentle laxatives available to the patient before the onset of the problem.
 4. Monitor the patients' medications: iron, calcium blockers, and other drugs that can cause constipation.
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Medications for Constipation

Constipation effects may be managed with the following medications:

- Docusate (Colace) (stool softener)
- Senna (Senokot) (softener/gentle laxative)
- Bisacodyl (Dulcolax) suppository
- Milk of Magnesia (laxative)
- Cascara (laxative)
- Sorbitol (osmotic)
- Magnesium Citrate (osmotic)
- Fleet Enema
- Tap water enema
- High colonic enema
- Do not be afraid to use a combination of medications for constipation (i.e. black and white milk of magnesia and cascara, or cascara and sorbitol)

Note: *Do not give cathartics if there is a possibility of obstruction.*

Hepatic

Clozaril can affect the functioning of the liver.

Hepatic Management

Hepatic effects shall be managed as follows:

1. Monitor liver function by testing every six months as part of the comprehensive metabolic profile.
 2. Refer to the patients' primary care physician if liver enzymes are elevated to rule out different causes including non-alcoholic fatty liver disease (NAFLD).
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Urinary Incontinence

Urinary incontinence is the inability to control urinary bladder function.

Urinary Incontinence Management

Urinary Incontinence effects shall be managed as follows:

1. Repeat the urinalysis for possible urinary tract infection.
2. Try reducing the dose of Clozapine.
3. Ask the patient to stop the fluid intake by 5:00 p.m. and to try to urinate before going to bed.
4. May try Desmopressin, which is a hormone that reduces urine production.

Note: *Urinary incontinence can occur because the patient is too highly sedated to feel the urge in the middle of the night.*

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Withdrawal

Withdrawal effects can occur from abrupt cessation of Clozapine due to non-compliance. This can present as a cholinergic rebound, psychotic decompensation, and severe movement disorder.

Withdrawal Management

Withdrawal effects shall be managed as follows:

1. Always explore and monitor the medication compliance by asking the patient questions such as: "How many times have you missed taking your medicine?" and not "Are you taking your medicine?"
 2. Educate the caregiver or support system about the signs and symptoms of withdrawal and the risk of decompensation with poor compliance.
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Lessons Learned

Treatment Considerations

Consider the following when administering Clozapine:

1. Monotherapy with Clozapine is possible, but rare, and this could be due to treatment resistance.
 2. Augmentation is helpful for more severe symptoms.
 3. Current treatment algorithms suggest a Clozapine trial after 2-3 treatment failures.
 4. Always pay attention to metabolic syndrome and provide an early referral to the patient's primary care physician to prevent complications.
 5. Adding a long acting injectable helps with patients who are still symptomatic even with adequate trial.
 6. Genetic testing will be available soon for the patients who might be at risk of developing agranulocytosis. (HLA-B, HLA- DQB1)
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Reference

California Department of Health Care Services, Special Order No. DSH-162, February 18, 1992

Clozapine Risk Evaluation and Mitigation Strategy (REMS):

- <https://www.clozapinerems.com/CpmgClozapineUI/home.u>
- https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/resources/Clozapine_REMS_ISI.pdf, and
- https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/resources/Clozapine_REMS_A_Guide_for_Healthcare_Providers.pdf.

Food and Drug Administration:

- http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019758s062lbl.pdf.
-