Behavioral Health

550 E. Hospitality Way San Bernardino | (909) 388-0900
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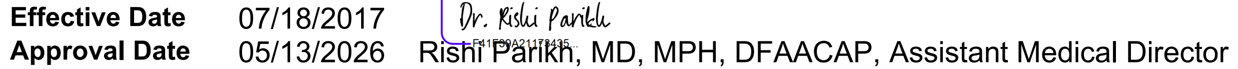
Clinical Practice Guideline: Clozapine



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Introduction

The San Bernardino County Department of Behavioral Health (DBH) Medical Services Division established the Clozapine Guidelines 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 Guidelines 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.

Definitions

Myeloproliferative disorder: A rare blood cancer that occurs when an individual's body makes too many red blood cells, white blood cells or platelets.

Agranulocytosis: A severe and potentially life-threatening condition characterized by extremely low levels of neutrophils, a type of white blood cell essential for fighting infections.

Paralytic Ileus: Occurs when the muscle contractions that move food through your intestines are temporarily paralyzed.

Benign Ethnic Neutropenia (BEN): Persistently low neutrophil counts in certain ethnic groups, particularly those of African or Middle Eastern descent, without an increased risk of infection.

Leukopenia: A medical condition characterized by an abnormally low white blood cell count, which can increase the risk of infections and indicate underlying health issues.

Cholinergic rebound: A withdrawal phenomenon that occurs after the abrupt cessation of a medication with anticholinergic properties.

Ameliorate: Lessened signs or symptoms of a disease.

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New DBH member already taking Clozapine

New DBH member already taking Clozapine

A new DBH member who is already taking Clozapine shall begin his/her treatment with the Clozapine Checklist (MDS024) (available on the DBH website) 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 restudied 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, or
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, and/or
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, or
- 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, and
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, and
2. Clozapine demonstrated the greatest reduction in symptoms.

Clozapine Clinic Treatment Team – Roles and Responsibilities

DBH Psychiatrist Duties

The DBH Psychiatrist duties are to:

1. Complete the clinical evaluation of the newly referred patient
2. Complete regular clinical evaluations and treatment of patients that currently use clozapine;
3. Coordinate, refer, and compile the comprehensive medical care of patients That use clozapine with the help of the Clozapine trained Nurse, and
4. Provide clinical supervision to the Clozapine trained Nurse.

DBH Child Psychiatrist

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

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Clozapine Trained Nurse Duties

The DBH Clozapine trained Nurse must be a Registered Nurse (RN), Licensed Vocational Nurse (LVN), or a Licensed Psychiatric Technician (LPT), whose duties are to:

1. Receive referrals for the use of clozapine 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. 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;
6. Assist the Psychiatrist in the blood-monitoring guide and document the results;
7. Act as the first line in receiving, collecting, and compiling information from the Clozapine patient and their support systems;
8. Receive and document medications for the Clozapine;
9. Distribute medications, per the Psychiatrist's order, with the use of bubble packs to improve compliance;
10. Call the medication changes in to the pharmacy as ordered by the Psychiatrist, and
11. Assist the Psychiatrist with any other vital functions of the use of Clozapine as they become more apparent.

Clinician/ Case Manager/ Medical Assistant Duties

The DBH Clinician, Case Manager, or Medical Assistant duties are as follows:

1. Upon receipt of the referral from the Psychiatrist and/or Clozapine trained Nurse, qualified staff will provide the patient individual or group therapy as seen fit by the Clozapine Treatment Team;
2. Case Manager will provide essential case management regarding issues brought forth by the patient and/or their support system;
3. Medical Assistant will assist in reminding the patient and/or their support system of their scheduled appointments and blood tests, and
4. Medical Assistant assists the Clozapine trained Nurse in obtaining laboratory results and other workups requested by the patients' primary care physician.

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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;
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, and
9. If any of the above criteria is not included, he/she shall receive a denial for an initial evaluation for Clozapine.

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

Titrations 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.

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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.

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

Week 2	
Day	**Daily Dose (mg)***
8	150
9	175
10	200
11	225
12	250
13	275
14	300

*In divided doses

Initiation of Clozapine Treatment

Initiating Clozapine Treatment

The DBH Psychiatrist and Clozapine trained Nurse shall:

1. Follow the Clozapine Checklist (available on the DBH website);
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) for Clozapine;
4. The Psychiatrist will order the titration of the Clozapine;
5. The Clozapine trained Nurse will educate the patient and his/her support system about the blood monitoring process with emphasis on adherence, and
6. The Clozapine trained Nurse will educate the patient and his/her support system about the requirements and treatment for Clozapine patients.

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Ongoing Monitoring

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

1. Titration Guide for Patients;
2. Clozapine Side Effects Checklist, and
3. Frequency of the Monitoring Base on Results of Absolute Neutrophil Count (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.

Agranulocytosis

Agranulocytosis effects generally include:

- Granulocytes of less than 500/mcL;
- Higher readings in the first three month;
- Ninety-five percent of cases occur within the first six months, and
- 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)

Symptom 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, and
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.

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Cardiac Toxicity and Myocarditis

Cardiac Toxicity and Myocarditis may develop 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.

Symptom 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, and
5. More recently, request a Cardiac echo every six months to rule out Cardiomyopathy.

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.

Symptom 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. Obtaining a neurology consultation and make sure an EEG is complete. Ongoing collaboration is essential, and
4. Proceed with slower titration.

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

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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.

Symptom 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, and
5. If there is suspicion of a gastrointestinal hypomotility, request a gastroenterology consultation ASAP.

Common, Less Dangerous, Side Effects

Sedation

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

Symptom 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, and
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.

Weight Gain

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

Symptom 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.
Related Policy or Procedure	DBH Standard Practice Manual and Departmental Forms • Clozapine Side Effect Checklist (MDS024) • Control, Access and Accountability of Medications and Medical Supplies Policy (MDS2008) • Control, Access and Accountability of Medications and Medical Supplies Procedure (MDS2008-1) • Medication Disposal Procedure (MDS2023)
Reference(s)	• US Food and Drug Drug Safety and Availability Highlights of Prescribing Information