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Review Article

# Practical Aspect of Clozapine

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**Abstract**

Clozapine is an atypical antipsychotic which is considered a gold standard in treatment for treatment resistant schizophrenia. This drug is acting on multiple receptors like dopaminergic receptors, serotonergic receptors, adrenergic receptors, and muscarinic receptors. The action on dopaminergic and serotonergic receptors alleviates the positive and negative symptoms of schizophrenia but action on some other receptors explains its side effects. Though it is an outstanding drug in treatment resistant schizophrenia, treatment resistant mood disorder, co-morbid use of alcohol and other substances in schizophrenia, hostility, and suicidality of the patient with schizophrenia, due to its severe side effects among which some are fatal, it is of having limited use. Before starting the therapy, a proper history should be taken, thorough physical examination and review of the investigation to be done to get the baseline of the specific patient. During the therapy, the patient should be frequently checked for changes in different parameters like vital signs, absolute neutrophil counts, BMI, biological functions, etc by using clozapine assessment checklist. Proper assessment will help to prevent worsening of the side effects. If any adverse effect is observed, then the symptomatic management is required.

**Keywords:** Clozapine; Antipsychotic; Schizophrenia; Dopamine; Side-effect; Nursing Considerations; Treatment Regime; Assessment; Mood Disorders.

## Introduction

Around 0.32% population in the world is affected by a chronic and debilitating disorder that is schizophrenia.[1] Though the mwain treatment for this severe disorder is antipsychotics, around 20 to 60% of the population does not respond effectively to this conventional mode of treatment.[2] Clozapine isan atypical also known as a second generation antipsychotic drug widely recognized as the gold standard in treating schizophrenia, especially treatment resistant schizophrenia.[3]

Clozapinehas an outstanding effect when all other drugs fail, but due to its potential side effects some of which are life threatening, it is a concern of use. Because of this, therapeutic drug monitoring and proper management of the side effects is required to get optimum health benefit and adherence to medication.

## Why Clozapine?

Clozapinea typical antipsychotic is effective in treating various psychotic conditions:[4]

- It is effective in treatment resistant schizophrenia including both positive and negative symptoms.
- It helps to improve the quality of life of aperson with schizophrenia by improving his daily functioning.
- Reduces aggressiveness, hostility, and excitability in schizophrenia.
- There is an effective reduction in the intake of alcohol and other substances in a patient with schizophrenia by reducing the craving for that particular substance.
- It reduces suicidality in schizophrenia.
- It is also effective in treatment resistant mood disorders.
- There is a marked reduction in tardive dyskinesia.

**Mechanism of Action**: Clozapine is acting on multiple receptors.[5]

- ***Effect on dopamine receptors:***[4,5] There is a high affinity towards D1 and D4 receptors than D2 receptors. Clozapine is also showing a fast-off phenomenon in the D2 receptor in which there is rapid dissociation of clozapine from the D2 receptors which causes less occurrence of extrapyramidal symptoms and hyperprolactinemia.
- ***Effect on other receptors:***[5] It is having an affinity for various receptors like serotonergic receptors, histaminergic receptors, adrenergic receptors, and muscarinic receptors. Effects on the above mentioned receptors explain its efficacy as well as occurrences of various side effects.
- ***Immune-mediated action:***[6] Clozapine is acting asan immunomodulatory drug where there is an increase in pro-inflammatory cytokines and C reactive protein. This action is having efficacy in treating schizophrenia but also causes adverse effects like eosinophilia, hematological adverse effects, cardiovascular adverse effects and hyperthermia.

**Dose Regimen of Clozapine**[7]: clozapine is available in twoforms that are oral form and intramuscular injection.

- ***Oral form:*** It is available in tablet form and the most available doses are 25 mg and 100 mg. Most of the side effects are either dose related or with speedy titration so it is to be started with very slow doses and gradually reached the therapeutic dose. In the beginning, it is to be started with 12.5 mg at bedtime. On the second day, 25 mg of the tablet is given in divided doses that are twice daily. Now if the patient can tolerate the dose, then it can be increased to 25 to 50 mg per day until a dose of 300 mg a day is reached over 2 to 3 weeks. If required then further increase can be done in the rate of 50 to 100 mg increments each week.
- ***Intramuscular injection:*** It is unlicensed in different countries and considered as a last resort. Basically, the injection is advised for patients who refused to take oral medications and only respond to clozapine. It is preferable to give the injection in the gluteal region. Strict therapeutic monitoring is very much required when a patient is getting an injection of clozapine.

**Initial Assessment:** The initial assessment is required to rule out any risk factors and helps to provide baseline data.

- ***History taking:*** Proper history to be collected which includes the history of any medical disorder, treatment history, and smoking history.
- ***Physical examination:*** A thorough physical examination including checking weight and vital signs to be done.
- ***Laboratory investigation:*** Complete blood count, LFTs, urea and electrolytes, lipid profile, glucose/HbA1c, troponin, C reactive protein, beta natriuretic peptide, erythrocytesedimentation rate, ECG, and echocardiogram (if clinically indicated) to be performed before starting the medication.
- ***Assessment tools:*** There are numerous tools available that help to identify the side effects of clozapine. The most used tools are Glasgow antipsychotic side effects scalefor clozapine[8] and the clinician prompt checklist.

**Monitoring of a Patient With Clozapine**: The following parameters are to be checked at baseline and yearly and the further frequency of checking is described in the following table 9.

**Table 1:** Parameters

| Parameters | Frequency of testing |
|---|---|
| WBC Count, DC, and ANC | Every weekfor the first 18 weeks, fortnightly up to one year, and then monthly. |
| Complete blood count | To be done at baseline and then yearly once. |
| Liver Function Tests | To be done at baseline and then yearly once. |
| Urea and electrolytes | To be done at baseline and then yearly once. |
| Lipid profile | Every 3 months for the first yearand then yearly once. |
| Blood glucose fasting | Monthly once. |
| ECG | Afterthechangesin the dose. |
| Physical examination | Every weekly. |
| Temperature | Daily and frequent monitoring. |
| Pulse | Daily and frequent monitoring. |
| Blood pressure | Daily and frequent monitoring specifically to check for orthostatic hypotension. |
| Weight | Frequently for the first 3 months, then 3 monthly for the first year, and then yearly. |
| Body mass index | Monthly. |
| Waist circumference | Monthly. |
| Cardiovascular monitoring | Regularly at the time of follow-up. |
| Serum Clozapine | If necessary or if the doses are more than 600 mg. |
| EEG | If relevant |

***Side Effects of Clozapine:*** The most common reason for non-adherence to clozapine is its side effects. Among these side effects, few are life-threatening. If the common side effects are treated properly in time, then it helps to prevent the occurrence of uncommon and rare side effects. Here we will be discussing the side effects according to their occurrence.[4]

**Table 2.** Side effects

| Common side effects | Uncommon side effects | Rare side effects |
|---|---|---|
| Sedation | Agranulocytosis | Myocarditis |
| Hypertension | Diabetes mellitus | Cardiomyopathy |
| Weight gain | Diabetes ketoacidosis | Heat stroke |
| Seizures | Metabolic syndrome | Hepatic failure |
| Hypersalivation | Delirium | Paralytic ileus |
| Hyperthermia | Abnormalitiesin liver enzyme | Pancreatitis |
| Hypotension | Nephritis | Pneumonia |
| Nausea | Stuttering | Respiratory failure |
| Nocturnal enuresis | Thrombocytopenia | Skin rash |
| Gastroesophageal reflux disorder | Neuroleptic malignant syndrome | Ocular pigmentation |
| Constipation | – | Priapism |
| Tachycardia | – | QT prolongation |
| Dizziness | – | Sudden death |
| Blurred vision | – | – |
| Dysarthria | – | – |
| Blood dyscrasias such as leukopenia, neutropeniaeosinophilia, and leucocytosis | – | – |

***Management of the Side Effects:*** It is very important to manage the side effect accordingly so that we can prevent serious life-threatening conditions.[4,9-13]

***Nursing Considerations:***

**Table 3.** Side effects and its interventions

| Side effects | Interventions |
|---|---|
| Sedation | • Assure the patient that it will gradually diminish.<br>• The practice of good sleep hygiene (e.g. regular sleep-wake schedule, avoiding caffeine and nicotine during the evening and at night, relaxing before bed, keeping the bedroom quiet and cool.<br>• Avoid other's sedating medication.<br>• A smaller dose is preferred in the morning.<br>• The evening dose is to be provided earlier if it is difficult to wake up in the morning.<br>• If possible the dose may be reduced. |
| Hypersalivation | • Chewing gum to be provided to promote swallowing.<br>• The head endis to be elevated while sleeping.<br>• It is preferable to sleep in a sideline position to reduce the risk of aspiration andthus pneumonia.<br>• Provide towels over the pillow to soak saliva.<br>• Provide anticholinergic if required. |
| Constipation | • Take thorough GI history and perform an abdominal examination before starting clozapine.<br>• Explain the possible side effects before starting treatment.<br>• screen regularly.<br>• Ensure an adequate fiber rich diet.<br>• Maintain adequate hydration daily.<br>• Perform regular exercise.<br>• If constipated then the first line treatment is stimulant laxatives.<br>• Avoid bulk-forming laxatives because of gastric hypomotility. |
| Orthostatic hypotension | • Check the lying and standing BP regularly to monitor orthostatic hypotension.<br>• Dose titration to be done in moderation.<br>• Adviceto change the body position very slowly.<br>• Tilt upward the head end of the bed at night. |
| Tachycardia | • Monitorvital signs regularly.<br>• The clozapine doseis to be reduced if the plasma levels are high.<br>• Provide a beta-blocker (atenolol) if the dose reduction is not successful. Ivabradine can be given when there is a contraindication of atenolol.<br>• If there is persistent tachycardia at rest and if it is associated with fever, hypotension,or chest pain then it may indicate myocarditis. Prolonged tachycardia may lead to cardiomyopathy.<br>• If there is any sign of myocarditis or cardiomyopathy then the patient should be referred to the cardiologist.<br>• ECG evaluation to be done.<br>• Clozapineis to be stopped if tachycardia persistsfor a prolonged period. |
| Weight gain | • Measure weight, waist circumference, and BMI at baseline and regularly.<br>• Counsel the patient on the need fora balanced diet and regular exercise.<br>• Metformin may be provided for the prevention ofantipsychotic-induced weight gain. |
| Fever | • Provideparacetamol.<br>• Send the blood sample to check for neutropenia.<br>• Persistent fever with cardiac symptoms maybe indicative of myocarditis so if the symptoms are present then perform chest X-ray, ECG, CRP, creatinekinase MB,B-type natriuretic peptide, and WBC. |
| Seizures | • The dose titration is to be done very slowly and the lowest effective dose is to be maintained.<br>• If the patient is getting a very high dose(>500mg/day) or there isa high plasma level(.500mcg/L) then the prophylactic topiramate, lamotrigine, gabapentin, or valproate is to be considered.<br>• Withhold clozapine for one day after the seizure episode and then restart half of the previous dose.<br>• Anti-seizure medication to be given.<br>• Proper smoking history to be taken.<br>• EEG to be done. |

| | |
|---|---|
| Nausea | • Anti-emetic to be given.<br>• Ondansetronis the drug of choice. |
| Nocturnal enuresis | • Split the bedtime dose during the day.<br>• Avoid intake of diuretic substances like alcohol or caffeinated drink and excessive fluid intake at night.<br>• Emptythe bladder completely before sleep.<br>• Consider the night time toilet schedule.<br>• Desmopressin nasal spray may be given in severe cases. |
| Gastroesophageal reflux disease | • Provide proton pump inhibitor.<br>• Avoid spicy and oily food. |
| Agranulocytosis/neutropenia | • Stop the medicine immediately.<br>• Haematologist consultation.<br>• It is a medical emergency.<br>• Strict monitoring of the ANC before starting clozapine the initial ANC should be> 1500/ cubic mm. Monitor weekly for the first 6 months, then fortnightly for the next 6 months, and then monthly after one year. |
| Myocarditisand cardiomyopathy | • Instruct the patient to report immediately if there is persistent tachycardia palpitation unexplained chest pain fever Disney hypotension.<br>• monitor all the clinical symptoms weekly and check the laboratory investigation periodically.<br>• If suspected discontinue the treatment immediately.<br>• WBC count, troponin I or T, CRP, ECG, CKMB,and echocardiography to be performed.<br>• Consulta cardiologist. |
| Diabetes mellitus | • Measure waist circumference, weight, BP, blood glucose, and lipid profile at baseline and regularly thereafter.<br>• Counselthe patient regarding the need for proper diet and exercise.<br>• Start appropriate antidiabetic management if there is a very high level of fasting glucose and stop the clozapine.<br>• Diabetic ketoacidosis isa medical emergency so the patient needs to be transferred to the emergency department and clozapine should be discontinued. |

- Assess history of myocarditis: do not administer if suspected for myocarditis.
- Assess input and output ratio: collect baseline before administration; palpate bladder if decreased urinary output present.
- Assess complete urinalysis before and during, in the patient with long term therapy.
- Assess the mental status examination and mental health history: mood, suicidal thought, affect, memory, orientation, reflexes, gait, and sleep pattern.
- Assess extra pyramidal symptoms (EPS): Akathisia (not able to sit still), tardive dyskinesia (bizzare movement of body part like jaw, tongue, extremities), psuedo parkinsonism (rigidity, tremors, pill rolling).
- Assess the level of consciousness, sleep pattern, gait and reflexes.
- Assess the level of appetite, urinary retention, constipation during therapy; ask patient to increase fluid intake and bulk diet, sometimes there is a need to administer laxatives.
- Assess the diabetic status: check blood glucose level.
- Supervise and assist in ambulation during early stage of treatment until stabilisation.
- Educate to avoid sudden change in position (to prevent orthostatic / postural hypotension).
- Instruct not to change doses, brand or discontinue drug without physician's order; plan and teach patient and family members about tapering of doses gradually.
- Instruct patient NOT to involve in machinery or hazardous activities, such as driving and other activities which require alertness.
- Instruct the patient to avoid OTC drugs, alcohol.
- Assess vitals: pulse, BP (standing and lying position) every 4 hours, respiration; drop in BP and respiration should be informed to the treating consultant.
- Advise patient to report if he/she experiences any of the following; seizures, changes in vision, jaundice , muscle twitching, tremors, sore throat, malaise, nausea, vomiting, difficulty in breathing (bronchospasm), urinary retention.
- Overdose intervention: Monitor vital sign, activated charcoal and airway; restrict

on inducing of vomiting (always follow institutional policy).

## CONCLUSION

Clozapine an atypical antipsychotic is having numerous benefits in treating various psychotic conditions. Though some of it's side effects are fatal but it still remained the gold standard for treating the treatment resistant schizophrenia. Therefore, improving our knowledge of the adverse effects of clozapine and its management is essential to increase the possibility of prescribing it to those in need.

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