



Document allergies on approved form and ensure medication reconciliation has been reviewed as per organizational process

Clozapine Initiation Order Set

ACTION

Administration

Document Purpose

This order set may be used for adult patients in both inpatient and outpatient settings.

Clozapine should be considered for patients with a diagnosis of schizophrenia who have not responded to adequate trials of at least 2 antipsychotic medications.¹⁻³

Rationale for Use

Select one:

- Treatment-resistant schizophrenia
 Other (specify): _____

Medication Review

- Document known current/prior antipsychotic trials and details (include any previous clozapine trial):
- Current medication (name, dose, duration): _____
 Response: full partial none Comments: _____
 Clinical Global Impression Severity (CGI-S) Scale: _____
 - Side effects: _____
 - Rationale for discontinuation: _____
 - Previous medication (name, dose, duration): _____
 Response: full partial none Comments: _____
 Side effects: _____
 - Rationale for discontinuation: _____
 - Previous medication (name, dose, duration): _____
 Response: full partial none Comments: _____
 Side effects: _____
 - Rationale for discontinuation: _____
 - Other antipsychotics previously tried: _____

Smoking Status Screening

****Smoking can induce enzymes responsible for the metabolism of clozapine; changes in smoking could lead to changes in the plasma clozapine levels and potentially impact medication efficacy, adverse events and toxicity**^{4,5}**

- Screen for smoking status
 Refer for further smoking cessation assessment/treatment

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Assessments

Parameters and frequency of monitoring for adverse effects to be determined based on review of current guidelines⁵⁻⁷ and individual patient characteristics

Medical History

Document presence of personal and/or family history of the following:

- Seizure disorder: _____
- Cardiovascular disease: _____
- Metabolic disorders (e.g. diabetes, dyslipidemia, obesity): _____
- Hypertension: _____
- Hematologic disorders (e.g. blood dyscrasias): _____
- Other (specify): _____

Vitals/Monitoring

Baseline Vitals/Monitoring

- Weigh patient, measure height^{6,7}:
 - Weight: _____ kg Height: _____ m BMI: _____ kg/m² **Formula⁸:** weight (kg)/[height (m)]²
- Waist circumference^{6,7}: _____ cm
- Baseline T⁹: _____ °C
- Baseline BP, HR⁹:
 - Supine BP¹⁰: _____ mmHg Supine HR: _____ beats/minute
 - Standing BP¹⁰: _____ mmHg Standing HR: _____ beats/minute
- _____

Vitals/Monitoring Post Day 1 Dose(s)

- T, HR, RR, BP, Orthostatic BP _____ (frequency)

Ongoing Vitals/Monitoring

- Orthostatic BP with clozapine dose changes¹⁰
- BP at 3 months and annually⁷
- Weigh patient, calculate BMI at 1, 2 and 3 months and then every 3 to 6 months⁷
- Waist circumference at 3 months and then annually⁷
- Assess bowel function regularly¹⁰

Side Effect Monitoring Assessment Tools

- Tool for Monitoring Antipsychotic Side Effects (TMAS) available at:
<http://epicanada.org/project/tool-for-monitoring-antipsychotic-side-effects/>
- Abnormal Involuntary Movement Scale (AIMS) available at:
<http://imaging.ubmmedica.com/all/editorial/psychiatrictimes/pdfs/clinical-scales-aims-form.pdf>
- Extrapryramidal Symptom Rating Scale (ESRS)
- _____

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Assessments Continued...

Parameters and frequency of monitoring for adverse effects to be determined based on review of current guidelines⁵⁻⁷ and individual patient characteristics

Lab Investigations

Baseline Lab Investigations

Hematology

CBC with differential⁵

Chemistry

- | | | |
|--|---|--|
| <input type="checkbox"/> Electrolytes ⁹ | <input type="checkbox"/> ALT, ALP, Bilirubin ⁹ | <input type="checkbox"/> A1C ^{6,7} |
| <input type="checkbox"/> Creatinine ⁹ | <input type="checkbox"/> AST ⁹ | <input type="checkbox"/> Fasting Glucose ^{6,7} |
| <input type="checkbox"/> Urine β HCG | <input type="checkbox"/> Albumin ⁹ | <input type="checkbox"/> HDL, LDL, Total Cholesterol, Triglycerides ^{6,7} |
| <input type="checkbox"/> _____ | | |

Cardiac Biomarkers

C-Reactive Protein¹¹ Troponin¹¹

Ongoing Lab Investigations

Monitoring plasma clozapine levels may be helpful in establishing optimal dosing or verifying adherence to clozapine⁴

CBC weekly for 26 weeks and PRN, then prescriber to reassess frequency of CBC after 26 weeks⁵

Additional Ongoing Lab Investigations Guidance

- Fasting lipid profile, fasting glucose and/or A1C at 3 months and then every 3 to 6 months⁷
- Consider ongoing monitoring for myocarditis, including ECG, and serum troponin and C-reactive protein¹¹

Diagnostics

ECG⁴ Reason: _____

_____ Reason: _____

Allergies

Allergies (list allergen and reaction): _____

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Clozapine

Treatment Consent/Registration

- Obtain and document patient/Substitute Decision-maker consent per policy/procedure
- Register patient in monitoring program and provide Registration #: _____
Specify program: P^rCLOZARIL (clozapine) Support and Assistance Network (CSAN)
http://csan.ca/enrollment_form_en
- Gen-Clozapine ACCESS Network (GenCan)
https://www.gencan.ca/PDFs/Patient_Eng.pdf
- AA-Clozapine Patient Care Network (AASPIRE)
http://www.aaclozapine.ca/downloads/hcp/AASPIRE-Pt-Registration_EN.pdf

Clozapine Dosing

The dosage of clozapine should be adjusted individually and the lowest effective dose should be used⁵; slower titration may help reduce the risks of hypotension, seizure and sedation^{10}

In the outpatient setting, prescriber should consider a slower titration of clozapine

Product Monograph Guidance⁵

- On Day 1, clozapine should be given at a 12.5 mg dose (one-half of a 25 mg tablet) once or twice
- On Day 2, one or two 25 mg tablets are recommended
- Post Day 2, if well tolerated, the dosage may be increased in daily increments of 25 mg to 50 mg, achieving a target dose of 300 – 450 mg/day by the end of two weeks

Day 1

- Clozaril _____ mg PO _____ (frequency) on _____ (yyyy-mm-dd) [caution-geriatric,hepatic,renal]
- GEN-Clozapine _____ mg PO _____ (frequency) on _____ (yyyy-mm-dd) [caution-geriatric,hepatic,renal]
- AA-Clozapine _____ mg PO _____ (frequency) on _____ (yyyy-mm-dd) [caution-geriatric,hepatic,renal]

Day 2

- Clozaril _____ mg PO _____ (frequency) on _____ (yyyy-mm-dd) [caution-geriatric,hepatic,renal]
- GEN-Clozapine _____ mg PO _____ (frequency) on _____ (yyyy-mm-dd) [caution-geriatric,hepatic,renal]
- AA-Clozapine _____ mg PO _____ (frequency) on _____ (yyyy-mm-dd) [caution-geriatric,hepatic,renal]

Day 3 to Day 7

- _____
- _____
- _____
- _____
- _____

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Psychoeducation and Health Lifestyle Information

- Provide education to patient, and Substitute Decision-maker where appropriate, on the following topics verbally, in writing, and electronically, as applicable:
- Risk of adverse events from clozapine treatment as highlighted in the product monograph and required monitoring⁵
 - Impact of substance use (e.g. cigarette smoking) on clozapine treatment efficacy and toxicity^{4,5}
 - Importance of healthy eating and physical activity⁴

Additional Orders

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Order Set Development and Implementation Considerations

The recommendations in this document are intended as general guidance, and do not replace clinical judgement. Physicians must consider relative risks and benefits in each patient when applying these recommendations

- **Adequate Trial of Antipsychotic Medication:** An 'adequate trial of antipsychotic medication' for the purpose of this document considers adequacy in terms of dose, duration and adherence.^{1,4} These terms have been defined in this order set according to review of current treatment guidelines^{1,9,12} and expert consensus:
 - Duration: oral antipsychotic medication trial for a minimum of 6 weeks,^{1,9,12} or long acting injectable (LAI) antipsychotic for at least 4 injection cycles
 - Estimated adherence: at least 75% of the time
- **Adverse Events:** Clozapine is associated with a range of adverse events of varying prevalence and potential danger to the patient, e.g. agranulocytosis.¹⁰ Prescribers should refer to the clozapine product monograph for a comprehensive list of possible adverse events.
- **Clinical Global Impression-Severity (CGI-S) Scale¹³:**

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

 - 1 = Normal
 - 2 = Borderline mentally ill
 - 3 = Mildly ill
 - 4 = Moderately ill
 - 5 = Markedly ill
 - 6 = Severely ill
 - 7 = Among the most extremely ill patients
- **Drug-specific Reminders:** Drug-specific reminders are intended to alert prescribers to potentially harmful drug properties for certain susceptible patients. The following caution flags are for the organization's consideration when developing an order set: [caution-geriatric,hepatic,renal]. For a comprehensive list of drug cautions and contraindications, consult product monographs and/or alternative resources.

References

Key references¹⁻¹³

All medications have been reviewed using Lexicomp and Compendium of Pharmaceuticals and Specialties (eCPS).

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