Alberta Health Services

PROTOCOL

TITLE
CLOZAPINE INITIATION AND MAINTENANCE

SCOPE
Provincial: Addiction and Mental Health

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NOTE: The first appearance of terms in bold in the body of this document (except titles) are defined terms – please refer to the Definitions section.

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OBJECTIVES

- To support safe initiation of clozapine therapy by outlining clinical responsibilities for therapeutic monitoring.

APPLICABILITY

Compliance with this document is required by all Alberta Health Services employees, members of the medical and midwifery staffs, Students, Volunteers, and other persons acting on behalf of Alberta Health Services (including contracted service providers as necessary).

ELEMENTS

1. Points of Emphasis

1.1 As with all medications, use of clozapine requires detailed discussion and education with the **patient** or **alternate decision-maker** of the risks and benefits as well as ongoing assessments of the patient's clinical condition and side effects or adverse effects. A baseline status assessment must be completed prior to initiation.

1.2 The **authorized prescriber** (subsequently referred to as prescriber) shall only prescribe clozapine in conjunction with regular hematological examinations.

1.3 Prescribers shall ensure that all patients receiving clozapine are registered with a manufacturer-approved monitoring service.

2. Consent

2.1 The prescriber shall:

a) inform the patient or alternate decision-maker of the following:

(i) risks, benefits, and alternatives associated with clozapine use;

(ii) possible side effects and adverse effects (see Appendix A: *Possible Adverse Effects*);

(iii) regular blood tests are required to monitor for the occurrence of agranulocytosis and shall be performed according to a monitoring schedule;

(iv) clozapine tablets are made available only through a manufacturer-approved monitoring service;

(v) that their minimum personal health information is being disclosed to the manufacturer-monitoring service for the purpose of monitoring; and

(vi) information related to the privacy policy of this manufacturer;

b) provide medication information and teaching; and

c) obtain consent from the patient or patient's alternate decision-maker:

(i) as required per the Alberta Health Services (AHS) *Consent to Treatment/Procedure(s)* Policy Suite and by completing and signing the AHS *Consent to Disclose Health Information* Form.

2.2 Document the above in the patient's health record.

3. Patient Enrolment Process

3.1 Enrolment of a patient in clozapine intervention involves the following steps:

a) The prescriber or delegate shall:

(i) complete the necessary sections of the manufacturer's approved registration forms (e.g., including complete blood count and differential [CBCD] within the last 28 days);

(ii) send the manufacturer's approved registration forms and laboratory report to the hospital or local Pharmacy; and

(iii) order/perform and review baseline assessments as required in Section 4.1 below and consider completing the recommended assessments in Section 4.2 below.

b) The Pharmacist or delegate shall:

(i) complete the necessary sections of the manufacturer's approved registration forms;

(ii) fax the completed approved registration forms and laboratory report (if not already done) to the appropriate manufacturer-approved monitoring service;

(iii) receive the manufacturer's approved registration number; and

(iv) inform the patient care team of the patient's enrolment number with the manufacturer-approved monitoring service.

4. Pre-initiation (Baseline Status Assessment)

4.1 Prior to initiating clozapine treatment, the prescriber shall ensure the following assessments are completed:

a) ensure the patient has no contraindications to clozapine;

b) comprehensive medical and physical assessment;

c) mental status examination;

d) CBCD within the last 28 days, prior to the first dose (hematology measures are required by the manufacturer's approved monitoring service to initiate treatment; see Appendix B: *Hematological Guidelines*);

e) baseline electrocardiogram (ECG) evaluation;

f) baseline vital signs measurements of temperature (T), pulse (P), respirations (R), and blood pressure (BP, postural); and

g) height and weight measurement (body mass index [BMI]) and waist circumference.

4.2 The prescriber shall consider completing the following assessments:

a) laboratory measures:

(i) lipid panel;

(ii) hemoglobin A1C (glycosylated hemoglobin) and fasting or random blood glucose;

(iii) liver function testing; and

(iv) C-reactive protein (CRP) and high-sensitivity troponin-T.

b) electroencephalogram (EEG), if clinically indicated.

5. Initiation of Clozapine

5.1 The prescriber shall:

a) approve initiation of treatment upon satisfactory baseline status assessment;

b) order clozapine;

(i) a non-psychiatric prescriber shall obtain psychiatric consultation and approval prior to initiation of clozapine; and

c) document the patient's height and weight measurement (body mass index [BMI]) and waist circumference.

5.2 The Nurse shall:

a) ensure blood samples are drawn and sent to the laboratory for testing and results reviewed;

b) ensure patient registration is completed and the patient's enrolment number is obtained; and

c) complete vital signs monitoring (refer to Appendix C: *Vital Signs Monitoring*).

5.3 Pharmacy shall only dispense the clozapine once the patient registration is completed and the patient's enrolment number is obtained.

5.4 Based on the setting, the assigned prescriber, Pharmacist, or Nurse shall:

a) monitor and assess for any possible side effects or adverse effects (see Appendix A: *Possible Adverse Effects*);

b) assess for possible medication interactions; and

c) provide education to the patient or alternate decision-maker.

6. Patient Education

6.1 The **health care professional** shall discuss with the patient or alternate decision-maker:

a) the benefits and risks of clozapine therapy;

(i) Attention should also be given to interactions between clozapine and caffeine, smoking, prescribed medications, alternative therapies, and other substances.

b) the importance of monitoring (see Appendix A, B, and C below);

c) possible side effects and adverse effects (e.g., the most likely side effects and adverse effects, what the patient might experience, and how to manage them or when to call for help); and

d) supportive activities (e.g., diet, exercise, smoking cessation) and possible interventions to reduce metabolic risk.

6.2 The patient or alternate decision-maker shall be provided with instructions to monitor for signs of infection and the need for follow-up blood work.

7. Ongoing Assessment

7.1 Based on the setting, the assigned health care professional shall ensure that the following monitoring steps are completed:

a) mental status examination or assessment of medication efficacy, assessment of medication side effects, and assessment of compliance (if treatment is interrupted, refer to Appendix D: *Clozapine Treatment Interruption*);

b) CBCD (to be drawn and reported at the frequency required by the manufacturer's approved monitoring service). Subsequent dispensing and administration of clozapine requires assessment of CBCD results as outlined in Appendix B: *Hematological Guideline*s;

c) vital signs monitoring (see Appendix C: *Vital Signs Monitoring*);

d) repeat ECG as clinically indicated (based on vital signs monitoring or changes in patient's clinical status);

e) repeat laboratory measures as clinically indicated (e.g., CRP and High Sensitivity Troponin); and

f) any further monitoring, per the applicable antipsychotic monitoring guidelines.

7.2 Based on the setting, the assigned health care professional shall notify the prescriber if the patient has:

a) a temperature greater than 38.5 degrees Celsius (°C) (if fever is present, CBCD is to be done twice weekly until fever is resolved);

b) persistent tachycardia at rest;

c) a fall in systolic blood pressure of at least 20 millimetres of mercury (mm Hg) or diastolic blood pressure of at least 10 mm Hg when a person assumes a standing position within three (3) minutes;

d) flu-like symptoms or other symptoms which might suggest infection (if symptoms are present, CBCD is to be done twice weekly until symptoms are resolved);

e) dystonia (involuntary muscle contraction); or

f) other adverse effects that could impact the patient's health.

7.3 Abnormal findings should be managed as described by the manufacturer.

8. Transfer of Care

8.1 The referring health care provider responsible for planning transitions of care shall:

a) communicate with the patient's health care professional from the receiving program prior to the transfer of the patient between the programs, and include but not be limited to information about the patient's condition and risk level; and

b) notify the primary care Physician, as appropriate.

8.2 Ambulatory and inpatient programs shall also provide to the patient or alternate decision-maker and the receiving health care provider, referral information required by the receiving service provider per the AHS *Safe and Supportive Transfers and Discharges* Procedure (Addiction and Mental Health) and if not already acquired:

a) the community pharmacy (name and contact information);

b) frequency of lab work; and

c) frequency of medical follow-up if required.

8.3 The receiving health care provider, or other staff member as appropriate, shall:

a) complete the necessary sections of the manufacturer's approved registration forms for modification of the patient's registration;

b) arrange for scheduled follow-up for assessment regarding medication efficacy, vital signs or other assessment, management of side or adverse effects, and other therapy, outreach or rehabilitation support;

c) arrange for follow-up mandatory CBCD and report to the manufacturer and the prescribing Physician;

d) ensure continuity of medication supply; and

e) monitor for arising issues if a different manufacturer's clozapine is substituted, or if there is an interruption in doses during transition.

9. Documentation

9.1 Documentation in the patient's health record shall include, but is not limited to, the following aspects of care:

a) discussion of risks, benefits, possible side effects or adverse effects, and alternatives;

b) consent for medication use;

c) patient teaching;

d) vital signs, monitoring values, and interventions;

e) results of all laboratory testing (e.g., blood, ECG, EEG);

f) mental status examination or medication efficacy;

g) any sign, symptom, or voiced complaints of side effects or adverse effects, along with any interventions taken by the health care provider;

h) manufacturer registration documents, hematological monitoring status changes (e.g., Red, Yellow, Green), blood monitoring interval changes, and special consideration; and

i) communication between referring and receiving health care teams if patient's care is transferred.

DEFINITIONS

Alternate decision-maker means a person who is authorized to make decisions with or on behalf of the patient. These may include, specific decision-maker, a minor's legal representative, a guardian, a 'nearest relative' in accordance with the *Mental Health Act* (Alberta), an agent in accordance with a Personal Directive, or a person designated in accordance with the *Human Tissue and Organ Donation Act* (Alberta).

Authorized prescriber means a health care professional who is permitted by Federal and Provincial legislation, their regulatory college, Alberta Health Services, and practice setting (where applicable) to prescribe medications.

Health care professional means an individual who is a member of a regulated health discipline, as defined by the *Health Disciplines Act* (Alberta) or the *Health Professions Act* (Alberta), and who practises within scope and role.

Patient means all persons, inclusive of residents and clients, who receive or have requested health care or services from Alberta Health Services and its health care providers and also means, where applicable:

a) a co-decision-maker with the person; or
b) an alternate decision-maker on behalf of the person.

REFERENCES

- Appendix A: *Possible Adverse Effects*
- Appendix B: *Hematological Guidelines*
- Appendix C: *Vital Signs Monitoring*
- Appendix D: *Clozapine Treatment Interruption*
- Alberta Health Services Governance Documents:
  - *Consent to Treatment/Procedure(s)* (#PRR-01)
  - *Safe and Supportive Transfers and Discharges* Procedure (Addiction and Mental Health) (#AMH-03-03)
- Alberta Health Services Forms:
  - *Consent to Disclose Health Information* Form (#18028)
- Non-Alberta Health Services Documents:
  - *CCHCH/DHCS Care Guide: Clozapine*
  - *Clinical Handbook of Psychotropic Drugs (18th edition)*

VERSION HISTORY

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July 31, 2019	Rescinded
August 1, 2019	Revised
October 10, 2019	Revised
Click here to enter a date	Optional: Choose an item

APPENDIX A

Possible Adverse Effects

Serious

Problem	Symptomatology	Management
Agranulocytosis/neutropenia (first 18 weeks but may occur at any time)	Sore throat Mouth ulcers Reduced immune response proneness to infections	Follow Appendix B
Myocarditis (within 6 – 8 weeks but may occur later in treatment)	Persistent tachycardia at rest, fever, chest pain, tachypnea, fatigue, hypotension, raised jugular venous pressure, sore throat, diarrhea, vomiting, headache, sweating, urinary discomfort/frequency	Hold clozapine doses until urgent diagnostic evaluation by a cardiologist
Seizures (may occur at any time, correlated with dose and rapidity of titration)	Seizures may be preceded by myoclonus or drop attacks	Cautious titration and/or dose reduction can help prevent further seizures
Fever, peak incidence within 3 weeks	Patients may experience transient temperature elevations, this fever is generally benign	Patients should be carefully evaluated to rule out possibility of infection, blood dyscrasias
Gastrointestinal (GI)	Constipation (monitor weekly during the first four [4] months of therapy). Clozapine has been associated with fatal bowel obstruction. Nausea (first six [6] weeks)	Therapy goal should be to maintain normal bowel function Adequate fluids, high fiber diet, exercise and laxatives if necessary Eliminate concomitant anticholinergic medications
Neuroleptic malignant syndrome (NMS)	Altered mental status; High fever - greater than 38.5 degrees Celsius;	The management of NMS should include:

Problem	Symptomatology	Management
	Dystonia or muscle rigidity; Irregular pulse and blood pressure; or Diaphoresis (excess perspiration or sweating).	(1) Hold clozapine and contact authorized prescriber; (2) Intensive symptomatic treatment and medical monitoring; and (3) Treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported *Further strategies on management of NMS shall be discussed with the treatment team

APPENDIX A: CONTINUED

Possible Adverse Effects

Common

Area of concern	Symptomatology	Management
Metabolic	Hyperglycemia, weight gain, dyslipidemia	Education re: fitness and nutrition Monitoring based on applicable antipsychotic monitoring guidelines
Autonomic nervous system (ANS)	Hypersalivation (first few months)	Towel on pillow at night. Sugarless gum to reduce daytime symptoms
Central nervous system (CNS)	Drowsiness, sedation, dizziness (first few months, correlated with dose and rapidity of titration)	Slow down rate of titration or reduce the dose; assess for drug interaction; education to clients (not to stand up too quickly)
Cardiovascular system (CVS)	Tachycardia, orthostatic hypotension (first four [4] weeks) can be related to rapidity of titration QT prolongation	Slow down rate of titration or reduce the dose; referral to cardiology Monitor QT prolongation
Abnormal involuntary movement	Abnormal movements caused by clozapine are rare, however baseline assessments should be completed and regular follow up is encouraged	Strategies on management shall be discussed with the treatment team
Enuresis (1%)	Occurs at any time	Reduce fluid intake at bedtime and review other medications

Note: Please note that this is not an exhaustive list, check product monograph for a more complete list.

APPENDIX B

Hematological Guidelines

Status	Action
Green Status WBC $\geq 3.5x10^{9/}L$ ANC $\geq 2.0x10^{9}/L$	Continue clozapine treatment. CBC and Differential lab work once weekly, every 2 weeks or every 4 weeks. Pharmacy continues to dispense clozapine once weekly, every 2 weeks or every 4 weeks.
Yellow Status Low Values: $2.0x10^{9}/L \leq$ WBC $< 3.5x10^{9}/L$ $1.5x10^{9}/L \leq$ ANC $< 2.0x10^{9}/L$ Falling Values: WBC Fall $\geq 3.0x10^{9}/L$ Measured in the last 4 weeks reaching a value of $< 4.0x10^{9}/L$ ANC Fall $\geq 1.5x\ 10^{9}/L$ Measured in the last 4 weeks, reaching a value $< 2.5x10^{9}/L$ Physical Symptoms: Flu-like complaints, fever or other symptoms which might suggest infection	Continue clozapine treatment. CBC and Differential lab work twice weekly. Evaluate for flu-like complaints, fever, signs and symptoms of infection.

Status	Action
<u>Red Status</u>: WBC < $2.0x10^9$/L ANC < $1.5x10^9$/L	Clozapine therapy must be immediately withheld and the patient closely monitored. Pharmacy consults physician. Confirm results within 24 hours. Results confirmed = STOP clozapine treatment. Evaluate for flu-like complaints, fever, signs and symptoms of infection. CBC and Differential lab work continue weekly x 4 weeks. CLOZAPINE TX MUST NOT BE RESUMED: PATIENT NON-RECHALLENGEABLE
Note: WBC < $1.0 x10^9$/L ANC < $0.5 x 10^9$/L	Protective isolation is recommended, if evidence of infection develops, appropriate cultures and antibiotic regime should be performed.

APPENDIX C

Vital Signs Monitoring

Inpatient

Day One - Two	Take Temperature, Pulse, Respiration (T, P, R) and orthostatic Blood Pressure (BP): prior to administration and then post-dose. Vital signs shall be completed 6-8 hours post-dose or at prescriber's discretion.
Day Three - until maintenance dose achieved	Take (T, P, R and orthostatic BP): BID (twice a day or at prescriber's discretion).
Once maintenance dose achieved and ongoing until discharge	Take (T, P, R and orthostatic BP) daily or at prescriber's discretion.

Note: More frequent monitoring may be necessary.

Ambulatory

Day One - Two	Take Temperature, Pulse, Respiration (T, P, R) and orthostatic Blood Pressure (BP): prior to administration and then 1 hour post dose. If stable, and at the clinician's discretion, the patient may leave the clinic but is asked to return in 2-3 hours for vital signs measurement. If stable, and at the clinician's discretion, the patient may leave the clinic a second time but is asked to return in 2-3 hours for vital signs measurement. (Patient should be accompanied by a family member/friend when leaving the clinic/office and is asked not to drive or participate in activities that require concentration.)
Day Three – until maintenance dose achieved	Take (T, P, R and orthostatic BP) at discretion of clinician. (Patient should be seen regularly by the treatment team until maintenance dose is achieved.)
Once maintenance dose achieved	Take (T, P, R and orthostatic BP) at discretion of clinician.

Note: More frequent monitoring may be necessary.

APPENDIX D

Clozapine Treatment Interruption

Due to clozapine's unique monitoring requirements and pharmacological profile, special consideration needs to be taken when restarting clozapine after treatment interruption.

If clozapine treatment is interrupted for greater than 48 hours but less than 72 hours, it is recommended that the patient's clozapine dose return to the initial starting dose and be re-titrated. The CBC monitoring frequency may remain the same.

If clozapine treatment is interrupted for more than 72 hours but less than or equal to 4 weeks, it is recommended that the patient's dose return to the starting dose and be re-titrated. Additionally it is recommended that CBCs are done weekly for 6 weeks, then may return to their regular frequency. The manufacturer's approved monitoring service should be notified of the interruption.

If clozapine treatment is interrupted for more than 4 weeks, then patient should be treated as a new start. The manufacturer's approved monitoring service should be notified of the interruption.

Summary of CBC monitoring frequency changes following treatment interruption