Clozapine Monitoring and Management in Community

Site Applicability

Vancouver Community:

- Adult Mental Health Teams
- Assertive Community Treatment Teams
- Early Psychosis Intervention
- Mental Health within Primary Care (Integrated Care teams)

Practice Level

Advanced Competency (requires additional education)

- Nurse (RN/RPN)
- Social Worker
- Clinical Counsellor
- Occupational Therapist
- Physician

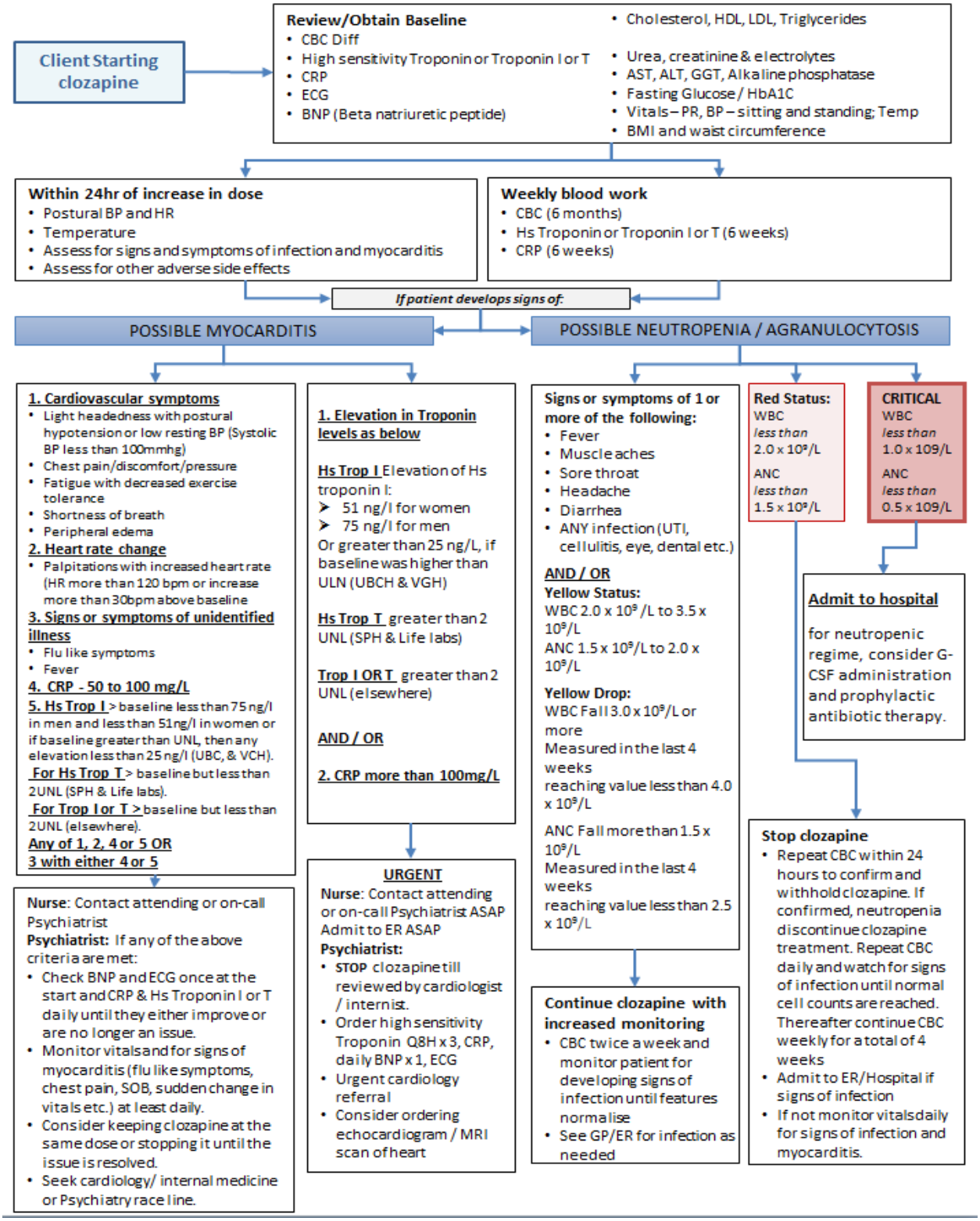
Additional Education

- *Training provided by Treatment Optimization of Psychosis Collaborative*

Requirements

Clozapine monitoring bloodwork requires a Provider's Order

Clozapine Initiation Monitoring and Management Algorithm for Physicians and Nurses



Need to Know

Clozapine is typically reserved for treatment-resistant or treatment-intolerant schizophrenia. Although an effective antipsychotic agent, the use of clozapine has been associated with severe adverse effects, including myocarditis and agranulocytosis. The literature demonstrates a clear need to implement close and structured monitoring of patients on clozapine to prevent the development of serious adverse outcomes.

Protocol

Client Criteria for Clozapine Initiation

The physician reviews criteria to help determine if the client is appropriate to be started on Clozapine:

- Has a primary care provider
- Stable housing or documented evidence that client has regularly attended appointments in prior 6 months
- Family support or highly reliable and adherent
- No medical complications e.g. diabetes, active liver disease, active seizure disorder, cardiovascular disease, hematological disorders and diseases, pregnancy, history of clozapine-induced cardiac or hematologic complication

Clozapine Registration

The physician is responsible for assessment, determining if a client is appropriate for a clozapine start or restart and select drug manufacturer. The case manager/care coordinator completes the clozapine registration form under the direction of the physician and is an administrative process.

Clozapine New Start (Appendix A)

- Registration forms can be obtained from (Gen-Clozapine/GenCAN), (AA-Clozapine/AAspire), or (Clozaril/CSAN).
- Case manager/care coordinator completes, signs, and faxes a clozapine registration form to the drug manufacturer monitoring program. The case manager/care coordinator sends a copy of clozapine registration form (with client demographics, case manager information) to community pharmacy.
- Physician completes, signs, and faxes a clozapine registration form with preliminary complete blood count with differential (CBC Diff) results to one of the drug manufacturer monitoring program. The physician completes the laboratory requisition and copies the respective manufacturer on all standing lab results.
- Community pharmacy completes the pharmacy section of clozapine registration form and faxes to the clozapine manufacturer/monitoring program.
- Drug manufacturer provides a registration number within 48 business hours.

Clozapine Restart

- For restarts, the physician determines which drug manufacturer the client was previously registered with and completes the corresponding registration form (see above).
- If the client is still registered with the drug manufacturer, the physician then checks off the "modify/modification" box on the form and updates the Most Responsible Physician (MRP) information.
- If the client has not been receiving clozapine for a prolonged period of time and is no longer enrolled with the drug manufacturer, the physician follows the same steps as for a "new start"
- The physician completes laboratory requisition and copies the respective manufacturer and primary care provider on all standing lab results.
- If the case manager/care coordinator or community pharmacy has changed, each completes, signs, and faxes a clozapine registration form to the drug manufacturer monitoring program.

Clozapine Continuation (Appendix A)

- For continuations between teams, transitions from hospital to community and on admission to the hospital, the physician is to determine the drug manufacturer the client was previously registered with and complete the corresponding registration form.
- The physician or case manager/care coordinator can check off the "modify/modification" box on the form and update the Most Responsible Physician (MRP) information. The form is sent to the community pharmacy to complete.
- The physician completes the laboratory requisition and copies the respective manufacturer and primary care provider on all standing lab results.
- If the case manager/care coordinator or community pharmacy has changed, each one completes, signs, and faxes a clozapine registration form to the drug manufacturer monitoring program.

Drug Manufacturer Information

	Website	Telephone	Fax
Genpharm (GenCan)	www.gencan.ca	1-866-501-3338	1-800-497-9592
AA Pharma (AASPIRE)	www.aaclozapine.ca	1-877-276-2569	1-866-836-6778
Clozaril (CSAN)	www.csan.ca	1-800-267-2726	604-689-1262 (BC only) OR 1-800-465-1312

Assessment and Interventions

The physician and nurse are responsible for any medical assessments as it is within their scope of practice.

Baseline Assessment

As outlined in the Clozapine Initiation Monitoring and Management Algorithm the physician orders and reviews #1-10 below. The physician or nurse can assess #11 and #12 below:

Review/Obtain Baseline

1) CBC Diff
2) High sensitivity Troponin T
3) C-Reactive Protein (CRP)
4) Electrocardiogram (ECG)
5) Fasting Glucose / HbA1C
6) Cholesterol, HDL, LDL, Triglycerides
7) BNP (Beta natriuretic peptide)
8) Urea, creatinine & electrolytes
9) Creatinine
10) AST, ALT, GGT, Alkaline phosphatase
11) Vital signs including postural blood pressure
12) BMI and waist circumference

Ongoing Assessment

As outlined in the Clozapine Vital and Adverse Effects Monitoring Sheet Flowsheet (Appendix B):

- **The day after increase in dose,** the client is assessed by the nurse as per below. For example, client's clozapine dose increased this evening and tomorrow the client is to have their vital signs checked and adverse effects monitored by nurse. If there are questions or concerns, the nurse informs the physician.
    - Vital signs including postural BP
    - Assess for signs and symptoms of infection and myocarditis (as outlined in ongoing assessment, see Algorithm)
    - Assess for other adverse side effects
        - Sedation
        - Dizziness
        - Hypersalivation
        - Constipation
        - Nocturnal enuresis

- **Weekly blood work** is ordered by the physician. The bloodwork is reviewed by the physician and nurse.
    - CBC (6 months)
    - High sensitivity Troponin T (6 weeks)
    - CRP (6 weeks)

The monitoring of increase in dose is from 2-12 weeks as the schedule is dependent on the physician's order for clozapine titration.

Each site should have a documented workflow for nursing coverage to support clients on clozapine in the event that the case manager/primary nurse is off.

1) Interventions

The nurse should report the following findings to the physician:

- Signs and symptoms of myocarditis (as outlined in ongoing assessment, see Algorithm)
- Signs and symptoms of infection as outlined in ongoing assessment, see Algorithm)
- WBC and ANC results in the yellow, yellow drop or red zones
- CRP greater or equal to 50 mg/L
- Hs Troponin T elevation – any elevation

If the client misses their bloodwork, the drug manufacturer notifies the physician and case manager/care coordinator. The case manager/care coordinator or covering case manager/care coordinator is to contact the client to complete bloodwork as soon as possible. Community pharmacy cannot dispense medication unless bloodwork is done.

In the event of the client missing 2 doses of clozapine, the client needs to be re-titrated from the start again unless the client has been on clozapine for a long time with no major side effects, in which case the physician can determine to start from half the original dose and titrate up to the original dose. The physician is to check for the latest missed doses protocol from the drug manufacturer.

Documentation

1) All documentation is completed in PARIS or Profile EMR. For sites using PARIS, the Clozapine Vital and Adverse Effects Monitoring Sheet Flowsheet (Appendix B) is to be kept in the client's paper chart and is completed by physician or nurse. For sites using Profile EMR, the Clozapine Vital and Adverse Effects Monitoring Sheet Flowsheet (Appendix B) is completed in the electronic health record.
2) Metabolic monitoring tool (1st and yearly) is completed by physician or nurse, and documented on a paper form in client's paper chart (Appendix C).
3) During the clozapine titration process, after each appointment a copy of the PARIS casenote or Profile EMR encounter note is documented by the physician and sent to the client's primary care provider by the administrative staff.
4) When the client has been successfully initiated on clozapine and later is discharged from the team to follow up with another provider i.e., primary care provider, mental health team, etc., a termination summary is to be completed by physician and case manager/care coordinator. It should include when the client was started on clozapine, the client's clozapine drug manufacturer, client's clozapine registration number, frequency of bloodwork, any altered parameters for blood work monitoring, most recent clozapine level, last day of bloodwork and any noticeable side effects the client may have experienced. (Appendix A)

Related Documents

1. Lexicomp Online Drug Reference

References

Ballon, J.S., Ashfar, H., & Noordsy. (2018). Clozapine Titration for People in Early Psychosis- A Chart Review and Treatment Guideline. Journal of Clinical Psychopharmacology, 38(3), 234-238.

CItrome L, McEvoy JP, Saklad SR. (2016). Guide to the management of clozapine-related tolerability and safety concerns. Clin Schizophr Relat Psychoses, 10(3):163-177

Meyer, J.M., & Stahl S. (2020). The Clozapine Handbook. Cambridge University Press.

Taylor, D., Barnes, T.R.E., & Young, A.H. (2018). The Maudsley Prescribing Guidelines in Psychiatry, 13th Edition. Wiley-Blackwell.

Definitions

Case manager/care coordinator: nurse, social worker, occupational therapist, clinical counsellor or other discipline

Continuation: ordering clozapine consistent with treatment prior to hospitalization or team transfer

New Start: ordering clozapine for a client never prescribed clozapine in the past

Restart: re-ordering clozapine for a client who has missed doses for two or more days OR if medication compliance is unknown

Appendix A: Clozapine Start, Transfer and Discharge Guideline

1. The physician obtains **informed consent** from client and share information with their family/support.

   If clozapine is **started at Mental Health Team (MHT)/ Early Psychosis Intervention (EPI)/ Assertive Community Treatment team (ACT)/ Mental Health within Primary Care (Integrated Care teams)** go to step 2.
   If started in **hospital or by a previous team,** go to step 3.
   If clozapine is started in **collaboration with Richmond At Home Based Treatment (AHBT) for EPI only,** go to step 4.

2. **Clozapine initiation at MHT/EPI/ACT/ Mental Health within Primary Care (Integrated Care teams)**

Tasks	Role	Completed ✓
Clozapine registration (complete physician section)	Case manager/care coordinator Physician	☐
Complete lab requisition or order pre-signed lab requisition	Physician	☐
Complete TOP Screen & Manage Tool	Physician + case manager/care coordinator	☐
Plan monitoring scheduling for Clozapine Vital and Adverse Effects Monitoring Sheet (Appendix B)	Physician + nurse	☐
Fax lab requisition to LifeLabs, fax/finalize clozapine registration form to clozapine company, send Primary Care Provider the Clozapine Vital and Adverse Effects Monitoring Sheet (Appendix B) and Important Information Regarding Your Client on Clozapine Titration (Appendix D).	Any role	☐

3. **Clozapine transfer to MHT/EPI/ACT/Mental Health within Primary Care (Integrated Care teams)**

Tasks	Role	Completed ✓
Clozapine registration (complete physician section)	Case manager/care coordinator Physician	☐
Complete lab requisition or order pre-signed lab requisition	Physician	☐
Fax lab requisition to LifeLabs + fax/finalize clozapine registration form to clozapine company	Case manager/care coordinator	☐

4. **Clozapine introduction with Richmond AHBT (as per AHBT checklist) for EPI only**

Tasks	Role	Completed ✓
Contact AHBT to assess wait time	Case manager	☐
Contact the AHBT team to discuss targeted clozapine dose + recommendations	Physician	☐
Have the client complete the initial laboratory investigations (hematology profile, BUN, creatine, electrolytes, AST, ALT, GGT, Alkaline Phosphatase, random blood glucose, ECG) + include weekly CBC, CRP and troponin levels	Physician	☐
AHBT referral form completed and faxed	Case manager	☐
Contact the AHBT team to discuss the referral and send Primary Care Provider the Clozapine Vital and Adverse Effects Monitoring Sheet (Appendix B) and Important Information Regarding Your Client on Clozapine Titration (Appendix D).	Case manager	☐

5. **Discharge of client on clozapine to their Primary Care Provider, new MHT or ACT**

Tasks	Role	Completed ✓
Phone call between EPI physician and MHT/ACT physician or primary care provider	Physician	☐
Initiate the registration form (complete physician section)	Case manager/care coordinator Physician	☐
Send the primary care provider/ new MHT or ACT: - termination summary (completed by physician and case manager) -med reconciliation - clozapine registration form - information for what to do if a consult is needed + provide Important Information Regarding Your Client on Clozapine Titration (Appendix D).	Case manager/care coordinator	☐

Appendix B: Clozapine Vital and Adverse Effects Monitoring Sheet to be Completed by Physician or Nurse

Seek medical advice if systolic BP drops by 20mmgs Hg or diastolic by 10mgs Hg or Pulse over 100 bpm or Temperature over 37.0 C

Date (dd/mm/yy)							
Time (hours)							
Note(s)							
BP (Sitting & Standing)							
Pulse rate (Sitting & Standing)							
Temperature							
Monthly weight							
MONITORING – Tick ✓ or ✗							
Signs of Infection: Fever							
Signs of Infection: Muscle Aches							
Signs of Infection: Headache							
Signs of Infection: Respiratory signs							
Signs of Infection: Urinary infection signs							
Signs of Infection: GE signs: diarrhoea, nausea, vomiting							
Signs of Infection: Other infections (eye, teeth)							
Signs of myocarditis: Chest Pain							
Signs of myocarditis: HR above 100 bpm							
Signs of myocarditis: Baseline HR increases More than 30 bpm							
Signs of myocarditis: Peripheral edema							
Signs of myocarditis: Fatigue							
Signs of myocarditis: Dizziness 0-3 scale							
Signs of myocarditis: Sedation 0-3 scale							
Other symptoms: Constipation Frequency per week							
Other symptoms: Akathisia 0-3							
Other symptoms: Hypersalivation 0-3							
Other symptoms: Initials							

NAME: DOB: PARIS ID PHN

Appendix C: Metabolic Monitoring Tool to be Completed by Physician and Nurse

METABOLIC MONITORING TOOL* (1st Year)

Please complete whenever a client begins a first trial of an antipsychotic or when switching antipsychotics

Client Name (last, first)	DOB (dd/mm/yyyy)	PARIS ID:	PHN:

Atypical:	Start Date (d/m/y):	Stop Date (d/m/y):
Atypical:	Start Date (d/m/y):	Stop Date (d/m/y):
Atypical:	Start Date (d/m/y):	Stop Date (d/m/y):

Risks: ☐ smoking ☐ increased lipids ☐ obesity ☐ high blood pressure ☐ physical inactivity ☐ history of gestational diabetes
☐ male ☐ Aboriginal, Hispanic, Asian, African or South Asian descent
☐ history diabetes ☐ cardiovascular disease ☐ family history of diabetes or cardiovascular disease ☐ schizophrenia or mood Disorder
☐ Other (list) _____

Comments:

Metabolic Parameters

Parameter (Normal Values)		True Pre-treatment Baseline*	Current Baseline	1 month	2 month	3 month	6 month	9 month	12 month
Test Date (dd/mm/yyyy): →									
Height (cm):	---								
Weight (kg):	---								
Waist Circumference: (At the level of the umbilicus)	*(See ethnic specific values on reverse)*								
Blood Pressure:	< 130/85								
Fasting Plasma Glucose:	< 5.6 mmol/L								
Fasting Total Cholesterol:	< 5.2 mmol/L								
Fasting LDL-C:	< 3.4 mmol/L								
Fasting HDL-C:	M: > 1.0 mmol/L F: > 1.3 mmol/L								
Total Cholesterol/ HDL-C Ratio:	< 5.0								
Fasting Triglycerides:	< 1.7 mmol/L								
Other_____: (eg. HgbA1C, OGTT etc.)									
Physician Initials: →									

Interventions: (continue checking as conducted throughout the year)			
	☐ Discuss metabolic risks	☐ Discuss diet	☐ Risk/benefit assessment
	☐ Discuss signs and symptoms of diabetes	☐ Refer to dietician	☐ Switch antipsychotic medication
	☐ Discuss signs and symptoms of DKA	☐ Discuss physical activity	☐ Liaise with GP re: abnormal lab.
	☐ Discuss smoking cessation	☐ Refer to rehab/groups for lifestyle management	☐ Refer to specialized services (via GP) e.g. lipid clinic, diabetes clinic
	☐ Other _____		

Comments:

* See ***Guidelines For Metabolic Monitoring***

VCHA, Vancouver Community Mental Health Services
HR-80a c-3-08

WAIST CIRCUMFERENCE: Ethnic Specific Values

Central obesity is most easily measured by waist circumference using the guidelines in the following table which are gender and ethnic-group (not country of residence) specific. The consensus group acknowledges that there are pragmatic cut-points taken from various different data sources and that better data will be needed to link these to risk.

Ethnic Group		Waist Circumference *
Europids *In USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes*	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians *Based on a Chinese, Malay and Asian-Indian population*	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese	Male	≥ 85 cm
	Female	≥ 90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

** In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut-points to allow better comparisons.*

Although a higher cut-point is currently used for all ethnic groups in the USA for clinical diagnosis, it is strongly recommended that for epidemiological studies and, whatever possible, for case detection, ethnic group specific cut-points should be used for people of the same ethnic group wherever they are found. Thus the criteria recommended for Japan would also be used in expatriate Japanese communities, as would those for South Asian males and females regardless of place and country of residence.

Note: For Indigenous ethnic group, they will follow the same cut-points as South Asians.

Appendix D: Important Information Regarding Your Client on Clozapine Titration

Important Information Regarding Your Client on Clozapine Titration

Why clozapine now?

- Evidence suggests that when two different antipsychotic medications have failed to help with psychosis despite an adequate dosage for at least 6 weeks, clozapine should be tried as the third trial. clozapine is more likely to help as a third trial than any other antipsychotic medication.
- clozapine, when effective, reduces mortality from physical health conditions and self-harm behaviors compared to any other antipsychotic medication in treatment resistant psychosis.

Common side effects & their management

Benign Tachycardia: Usually occurs within the first 4 weeks. R/O myocarditis or other causes. Consider adding bisoprolol, atenolol, metoprolol, or propranolol.

Postural Hypotension: Usually occurs within the first 4 weeks. R/O myocarditis. Advise getting up in slow stages, have a large glass of water by bedside and drink it before getting up from bed, increase fluid intake to 2L/day. Consider adding fludrocortisone.

Hypersalivation: Consider atropine 1% or hyoscine hydrobromide 1% sol 1-2 drops s/l HS. Alternatives include ipratropium bromide inhaler 1-2 puffs s/l HS, benztropine po HS or Hyoscine 300 mcg s/l po TID.

Hypertension: Usually occurs within the first 4 weeks. Slow the rate of increasing clozapine. Hypotensive therapy may be necessary.

Benign Pyrexia: R/O myocarditis, NMS, neutropenia, and other causes. It is thought to be due to inflammatory process and may be associated with elevated CRP and interleukin-6 levels. Slow the rate of increasing clozapine. Consider anti-inflammatory foods/spices (www.health.harvard.edu/staying-healthy/food-that-fight-inflammation).

Constipation: Advise fluid, fiber and exercise. Consider prunes, soaked chia seeds. Use magnesium up to 400 mgs/day (milk of magnesia, magnesium citrate or glycerinate). Keep diary if <3 BMs/week or < baseline BMs. For drug induced constipation, R/O alarm features like weight loss, GI bleeding, Fe deficiency, severe abdominal discomfort, fever/rigors/chills or family h/o colorectal cancers and IBD. For clients >50 years of age, screen for colorectal cancer. Exclude endocrinal, neurological, mechanical obstruction and functional causes before diagnosing clozapine induced constipation. Bulk forming laxatives are not effective in clozapine induced slow transit constipation, instead use stimulants and softeners such as Senna and Docusate once intestinal obstruction is ruled out. Use PEG and lactulose as second choice.

Weight Gain/ Metabolic Syndrome: Dietary advice and exercise. Monitor weight weekly for 3 months. Weight gain of >5% in first month indicates high risk. There is a substantial evidence for use of Metformin in non-diabetic clients in reducing antipsychotic weight gain.

Nocturnal Enuresis: May resolve spontaneously over months. Consider oxybutynin PO or desmopressin nasal spray 10-20 mcg. Monitor for signs of fluid overload.

Myoclonus: May lead to tonic-clonic seizures. Do an EEG. Consider valproate as first choice and lamotrigine as second choice but note that lamotrigine may worsen some types of myoclonus.

Investigations Scheduled

CBC weekly for 6 months, CRP, High Sensitivity Troponin T levels weekly for 6 weeks, 3 months and 9 months.

Potentially Life-Threatening Adverse Effects the Need Treatment

Agranulocytosis, Myocarditis, Thromboembolism example: DVT, stroke etc.; Fulminant hepatitis; Paralytic Ileus

Special Requests for Primary Care Provider

- Please prioritize your client for the duration if the titration
- Please review the latest physician note from our team when reviewing side effects or complications
- Please refer to side effects management attached or consult our team if you have questions
- Please feel free to call the case manager or physician at the team to discuss your client

Clozapine Collaborative. Important information regarding your client on clozapine titration. 2018.

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Approved By: *(committee or position)*	VCH **Endorsed By:** • VCH Regional SharePoint 2nd Reading • Regional P&T • Medical Advisory Council • VCH Operations Directors • VCH Professional Practice Directors **Final Sign Off:** Vice President, Professional Practice & Chief Clinical Information Officer, VCH
Owners: *(optional)*	VCH • Clinical Nurse Specialist, Vancouver Community MHSU • Psychiatrist and Medical Manager, Urban Vancouver Community Mental Health • Psychiatrist and Medical Director, Vancouver Community • Clinical Pharmacist, Tertiary MHSU • Clinical Nurse Educator, Treatment of Psychosis Collaborative • Operations Manager, Kitsilano-Fairview Mental Health Team **Clozapine Collaborative Working Group:** • Clinical Supervisor, Raven Song MHSU • Psychiatrist, Early Intervention in Psychosis • Clinical Supervisor, Early Intervention in Psychosis • Clinical Resource Nurse, Raven Song MHSU • Case Manager/Intake Nurse, Raven Song MH • Case Manager, Early Psychosis Intervention • Physician Lead Quality Improvement • Team Based Quality Improvement • Team Based Quality Improvement • Director, Special Projects, VC • Manager, Raven Song MHSU and Primary Care **Consultation with:** • Cardiologist, GENCAN reviewed advice on HS Troponin monitoring for myocarditis. • Clinical Pharmacist, BC Psychosis Program