Safe and quality use of clozapine in Mental Health Alcohol and Other Drugs (MHAOD) Services

Developed by the Queensland Psychotropic Medication Advisory Committee

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An electronic version of this document is available at:
https://www.health.qld.gov.au/qhpolicy/html/index-m.asp

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1. Introduction

Clozapine, tradename Clozaril® or Clopine®, is a medication regulated by the Therapeutic Goods Administration (TGA) and subsidised under the Pharmaceutical Benefits Scheme (PBS) - Highly Specialised Drugs Program (PBS S100). It is used for the management of schizophrenia, treatment resistant to other antipsychotic medications. Patients may only be prescribed clozapine when mandatory blood testing, regular administration and other monitoring requirements can be achieved.

2. Purpose

This Guideline supports the safe and effective use of clozapine therapy in alignment with the need to:

- support decision making,
- minimise the risk of patients experiencing adverse events and
- standardise evidence-based practice.

This Guideline supports the National Safety and Quality in Health Service (second edition) Medication Safety Standard. It must be used with the clozapine patient monitoring services protocols, with consideration of the manufacturer's published guidance, state and local protocols and procedures. It complements these references and does not replace them.

3. Scope

This Guideline provides information for all Queensland public health system employees (permanent, temporary, and casual) and all organisations and individuals acting as its agents (including Visiting Medical Officers and other partners, contractors, consultants and volunteers). This Guideline provides guidance for private psychiatrists, general practitioners and community pharmacists working in partnership with Queensland Health employees.

4. Background

Clozapine is indicated for use in the management of treatment resistant schizophrenia where patients are non-responsive or intolerant of at least two antipsychotic agents other than clozapine. Its proven clinical benefits must be balanced against significant safety concerns due to serious side effects (particularly haematological, cardiac and gastroenterological) which require careful monitoring.

Individual Hospital and Health Services are responsible for their medication quality and safety governance processes in relation to the administration of clozapine.

5. Acknowledgements

This Guideline reflects and aligns with the recommendations of the Clozapine Management Clinical Guideline, Government of South Australia (2017).

6. Legislation and regulations

National and local legislation, regulation and policies apply to ensure safe prescription, supply, administration and monitoring.

6.1 Medicines and Poisons (Medicines) Regulation 2021

In Queensland, the Medicines and Poisons (Medicines) Regulation 2021 places controls on the supply and use of medicines to ensure that they are used safely and effectively. In the regulation, clozapine is classed as a Schedule 4, regulated restricted medicine. Only specialist medical practitioners in the speciality of psychiatry and registrars (in psychiatry) working directly under the supervision of a specialist medical practitioner in the speciality of psychiatry have the authority to initiate clozapine.

Continuation treatment can be ordered on a medication chart (paper or electronic) by any medical officer as this is not technically "a prescription" but an "instruction to administer". Any change (i.e. dose) to the original order must be authorised by a psychiatrist. Psychiatrists/registrars can prescribe on a prescription (i.e. outpatient or discharge) regardless if the treatment is new or continued.

Other prospective prescribers must apply for an approval from the Chief Executive Queensland Health. Further approvals and authorities information can be accessed through the link https://www.health.qld.gov.au/system-governance/licences/medicines-poisons/medicines/prescribing-approvals.

Queensland Health's Healthcare Approvals and Regulation Unit have produced fact sheets and supporting documents on the requirements for prescribing and dispensing regulated restricted drugs under the medicines, poisons and pest management regulatory framework. These resources can be accessed via the *Medicines and Poisons Act 2019* Fact sheets and supporting documents (Queensland Health) website.

All staff involved in the management of clozapine are required to comply with TGA and PBS requirements.

6.2 Human Rights Act 2019

The Queensland public sector must consider the impact on the human rights of individuals when making decisions and ensure that any decision is compatible with the *Human Rights Act 2019* (Queensland). This guideline must be implemented in a way that is consistent with the rights outlined in the Act. Queensland Health staff have obligations under the *Human Rights Act 2019* (Queensland) to make decisions and act in ways that are compatible with human rights.

6.3 Clozapine patient monitoring services

There are two brands of clozapine available in Australia, each with an associated clozapine patient monitoring service:

- Clozaril® (Mylan) – the Clozaril Patient Monitoring System (CPMS), and
- Clopine® (Pfizer) – Clopine Central™.

The two separate monitoring systems can be accessed at http:/www.ecpms.com.au/ for Clozaril® or https:/www.clopine.com.au/ for Clopine®.

Clozaril and Clopine branded tablets are NOT interchangeable.

These clozapine patient monitoring services require that all patients; prescribing doctors; dispensing pharmacists and pharmacists; centre coordinators and centres involved in the provision of clozapine, be registered with the specific service. A centre is defined as a hospital, clinic or other facility using clozapine. Clozapine will only be provided to centres that are registered in accordance with the relevant clozapine patient monitoring service protocols.

Each centre requires a centre specific clozapine coordinator to oversee adherence to clozapine protocols. Medical Officers who hold an approval to prescribe from the Chief Executive Queensland Health must also be registered with the monitoring system before prescribing. Patients are listed as 'belonging' to a specific centre through their registration at the centre. Pharmacists may only dispense prescriptions for clozapine written by an approved prescriber.

6.4 Pharmaceutical Benefits Scheme

For the purposes of initiation of treatment, clozapine is classified as a 'highly specialised drug' (section 100 HSD) under the PBS. The PBS has several administrative requirements in relation to the prescribing and dispensing of clozapine.

For the purposes of 'Initial treatment' of patients with clozapine the following clinical and treatment criteria must be met:

- the patient must be non-responsive to other anti-psychotic agents OR
- the patient must be intolerant of other anti-psychotic agents AND
- the patient must be treated by a psychiatrist or in consultation with a psychiatrist affiliated with the hospital or specialised unit managing the patient.

Patients must complete at least 18 weeks of initial treatment under this restriction before being able to qualify for treatment under the continuing restriction.

The name of the psychiatrist should be included in the patient's medical records.

Clozapine may be prescribed by psychiatrists, general practitioners or other authorised community prescribers and dispensed by community pharmacists, and in hospital settings.

For the purposes of PBS subsidy for clozapine 'Continuing/Maintenance therapy' the following criteria apply:

- the patient must have previously received PBS-subsidised therapy with this drug for this condition

- the patient must have completed at least 18 weeks initial treatment under a psychiatrist AND
- the treating psychiatrist agrees the patient is suitable for community-based management and prescribing AND
- the patient's clozapine dosage is considered stable by the treating psychiatrist AND
- treatment is under the supervision and direction of the psychiatrist reviewing the patient at regular intervals
- the patient must be treated by a psychiatrist OR the patient must be treated by an authorised medical practitioner with the agreement of the treating psychiatrist.

A medical practitioner should request a quantity for up to one month's supply. Up to five repeats are authorised when clozapine is prescribed in a community shared care arrangement.

6.5 Therapeutic Goods Administration

The TGA has mandatory haematological monitoring standards in Australia to minimise the risk of clozapine side effects. All authorised clozapine prescribers must comply with the following:

- a range of pre-treatment parameters including baseline haematological, metabolic and cardiac screening
- periodic haematological, metabolic and cardiac testing once treatment has commenced and/or following the cessation of treatment.

7. The administration, monitoring and prescribing of clozapine therapy

7.1 Prior to the commencement of clozapine

Assessment should include:

- history of medication and other past treatments
- height, weight, and waist measurements
- any possible history of drug-induced neutropenia or bone marrow disorders, or any other factors that might increase the risk of neutropenia or agranulocytosis on clozapine
- relevant family history including ethnic background of Afro-Caribbean or African ancestry, that infers a risk of benign ethnic neutropenia with naturally low absolute neutrophil counts (ANC)
- any history or family history of cardiac related disorders that could increase the risk of cardiac related side effects while on clozapine e.g. hypertension
- any history or family history of diabetes mellitus, dyslipidemia or other metabolic disorders

- any history or family history of epileptic activity
- any history or family history of thromboembolism
- current smoking status
- current bowel habits
- allergies and adverse drug reactions
- current medication history
- pregnancy and breastfeeding status. If the patient is pregnant specific consideration of risks and discussion with the patient and their family is required and should include consideration of a formal second opinion. Clozapine is excreted in breast milk therefore it is important to ensure that the patient is not breastfeeding prior to the initiation of clozapine.

Baseline measurements will include:

- full blood count, white blood cell count and ANC
- blood group
- urea / electrolytes
- fasting glucose and lipids
- liver function tests
- C-reactive protein (CRP)
- troponin
- creatine kinase (CK)
- echocardiogram (Echo)
- electrocardiogram (ECG)

Due to diurnal variation and white cell count being lowest in the morning, taking blood late in the day may avoid false lows that could prevent the patient starting (or continuing) clozapine. Afternoon blood testing should be individualised.

All registration requirements must be addressed along with necessary authority of the intended clozapine prescriber. The patient and family, where appropriate, must be provided with verbal and written information specific to clozapine, including benefits, alternatives, required monitoring, side effects and their management. A treatment plan is also necessary to enable informed consent.

The ability and willingness of the patient to adhere, and of their support system and care network to support adherence considering the requirements, should be assessed and documented. Adequate adherence to administration and monitoring must be achievable in the community.

7.2 The initiation of treatment with clozapine

Total white blood cell count (WBC) and absolute neutrophil count (ANC) results will determine the commencement of clozapine therapy.

A traffic light system is used to classify the blood results and guide further action as follows:

Table 1 Guidelines for evaluating the WBC and NC results

	Blood results	Recommended actions
Green range	WBC greater than 3.5 x 10^9/L and ANC greater than 2.0 x 10^9/L	Clozapine therapy may be commenced subject to assessment by the treating medical officer and successful registration.
Amber range	WBC 3.0 to 3.5 x 10^9/L and/or ANC 1.5 to 2.0 x 10^9/L	Repeat blood count after one week. If still within same range, clozapine therapy may commence subject to assessment by the treating medical officer and successful registration.
Red range	WBC less than 3.0 x 10^9/L and/or ANC less than 1.5 x 10^9/L	DO NOT START THERAPY. Seek haematologist advice if wish to commence clozapine therapy.

The National Adult Clozapine Titration Chart (CTC) provides guidance on clozapine titration. It is intended to be used as a record of the prescribing, monitoring and administration of clozapine titration for all patients in inpatient or outpatient settings. A Clozapine Titration Schedule has been included within the Clozapine Titration Chart to assist specifically with prescribing and dosing.

When clozapine is used for maintenance treatment in the inpatient setting, the National Inpatient Medication Chart (NIMC) is to be used. For services using an integrated electronic medical record (ieMR), clozapine initiation PowerPlans may be available to assist with clozapine titration dosing, testing and monitoring.

The CTC can be accessed at: Adult Clozapine Titration Chart (Queensland Government). When clozapine is used for maintenance treatment in the inpatient setting, the National Inpatient Medication Chart (NIMC) is to be used.

Clozapine should not be used in combination with other antipsychotics unless approved by a psychiatrist with appropriate consent and adequate clinical justification. Cross tapering is sometimes necessary when initiating clozapine therapy (when discontinuing the preceding antipsychotic preparation is not realistic) but this must be done with caution.

A clozapine medical alert should be made in relevant medical record/s.

To monitor for any adverse effects after the first clozapine dose, patients should be supervised for approximately six hours in an environment with appropriate resuscitation facilities. Monitoring of vital and neurological signs must take place; half hourly for two hours, and then hourly for four hours after the first dose, regardless of the setting. For subsequent titration doses, observations should be taken at least once daily, half an hour after a dose is administered. In inpatient settings, more frequent observations are appropriate.

Daily monitoring should continue for at least two weeks or until there are no unacceptable adverse effects, after which alternate day monitoring may be undertaken until a stable dose is reached, when further monitoring should take place at the time of blood testing. Blood tests should include the time of last dose and the time that the blood is taken.

7.3 Consideration for community initiation

Initiation of clozapine in an outpatient or community setting can be a practical and safe option for a group of eligible patients. This usually requires a lower starting dose (as little as 6.25 mg) and slower upward titration, in addition to increased community physical health monitoring.

Contraindications for Community Initiation:

- Significant medical comorbidities increasing the risk of significant adverse health effects.
- History of epilepsy, unstable diabetes, paralytic ileus, neuroleptic malignant syndrome, significant cardiovascular disease, hepatic or renal disorders and blood dyscrasias.
- History of respiratory, cardiac or seizure associated with previous clozapine initiation.
- Use of alcohol or other drugs, which may increase the risk of adverse events.
- Poor medication adherence and chaotic lifestyle that may affect adherence and monitoring.

7.4 Management and monitoring of clozapine therapy

The rate of clozapine titration will depend on symptom response, tolerability, gender, body mass index (BMI), ethnicity, smoking and serum clozapine levels.

Dose Optimisation

Clozapine dosing should be guided by clozapine therapeutic drug monitoring where possible. A guide for the Clozapine Titration Schedule is included on the Adult Clozapine Titration Chart.

If a patient has an inadequate response to clozapine, then clozapine trough levels should be optimised to between 350 ng/ml and 600 ng/ml. Trough levels above 600 ng/ml are associated with an increased risk of severe side effects including seizures and sedation. Where possible patients should be maintained at levels below 600 ng/ml, however some patients respond only at higher levels. The consensus maximum serum level is 1000 ng/ml. Where patients record serum levels above 1000 ng/ml, or above 600 ng/ml, where response is known below this value, a review of treatment should occur, to identify drug interactions, changes in substance use (e.g. tobacco), timing of clozapine level in respect to dose, or comorbid infection, liver or renal dysfunction.

The rate of dose reduction will depend on the risk as determined by the clozapine level, the presence of dose-related side effects, the stability of the patient, the clozapine level at which the patient is known to respond and the management of the cause of the level increase (e.g. drug interaction). Where risk is high due to severe side effects and/or very high levels, the dose can be held for up to 48 hours without interruption of therapy. If there are no contraindications, recommencement at a reduced dose should be considered before 48 hours to avoid an interruption in therapy.

Where the risk from clozapine levels or side effects is low, then a gradual down titration at 25-50mg increments until a safe tolerable level is achieved will reduce the risk of

relapse. Mental state should be monitored as clinically indicated during this period and clozapine levels can be reviewed from 5 days after the adjustment in dose.

A key strategy for use of clozapine medication is the use of the minimum effective dosage. After the maximum therapeutic benefit has been achieved, the minimum effective dosage should be used to maintain clinical remission.

A tactic for enabling use of minimum effective dosage and for minimising side effects is dose splitting. The total daily dose may be divided unevenly with the larger portion at bedtime. Clinicians should consider dose splitting where appropriate to minimise side effects while recognising adherence risks associated with increasing complexity of medications and dosing regimen.

NOTE: Blood testing samples for serum trough levels should be taken 12 hours after the last dose.

Patient monitoring and management

Mandatory patient monitoring includes assessment of test results and of physical health, mental state and function, to identify problems with efficacy, adverse events or comorbidity and intervene early to prevent further complications.

Patients should be regularly reminded of the signs and symptoms of infection and other high-risk adverse effects and given instructions in relation to notifying treating clinicians should symptoms emerge between consultations.

Haematological considerations

Severe neutropenia (ANC < 0.5 x 10^9/L) occurs in 0.9% of patients treated with clozapine, with 85% of neutropenia cases during the first 18 weeks of treatment (Myles, et al., 2018). Mild to moderate neutropenia (ANC < 1.5 x 10^9/L) can occur in 3-4% of people treated with clozapine.

Clozapine can be associated with a range of haematological side effects that include, but are not limited to, neutropenia and agranulocytosis.

White cell and absolute neutrophil counts must be performed for all patients on clozapine therapy at least weekly for the first 18 weeks of therapy and then at least every four weeks afterwards. A traffic light system is also used for this blood count monitoring and must be adhered to at all times during clozapine therapy (refer to Table 2).

- If a patient has a blood count result in the amber range, blood counts must be repeated twice a week until a green range result is obtained. Monitoring may then return to previous frequency.
- If a patient has a blood count result in the red range, clozapine should be ceased immediately and consultation will be required with a haematologist.

Haematological information sharing between the clozapine prescriber, pharmacy and clozapine coordinator is conducted using clozapine patient monitoring service specific blood count recording forms or according to local protocols.

Table 2 Clozapine blood count monitoring protocol

Blood count results		Recommended actions
Green range	WBC greater than 3.5 x 10^9/L and ANC greater than 2.0 x 10^9/L	Continue with clozapine therapy
Amber range	WBC 3.0 to 3.5 x 10^9/L and/or ANC 1.5 to 2.0 x 10^9/L	Increase monitoring to twice weekly until a green result is obtained
Red range	WBC less than 3.0 x 10^9/L and/or ANC less than 1.5 x 10^9/L	STOP IMMEDIATELY. Repeat test in 24 hours. Seek haematologist advice if wish to continue clozapine therapy.

If a patient on clozapine develops symptoms of infection (e.g. fever, sore throat, mouth ulcers or flu like symptoms), a white cell count and absolute neutrophil count should be performed immediately and a clinical assessment of the patient must take place. If both are normal, clozapine may continue with twice weekly haematological reviews until symptoms resolve.

If a patient on clozapine develops neutropenia, consideration must be given to switching to an alternate antipsychotic and reducing or ceasing other medications that decrease white cells (e.g. sodium valproate). Specialist haematology advice should be sought if this is being considered.

Rechallenge with clozapine may be possible in some patients who have previously experienced neutropenia if the potential benefits of treatment outweigh the risks associated with the rechallenge. Rechallenge must be approved by the clozapine manufacturer. Generally, they will only approve rechallenge if there is an alternative plausible explanation for the neutropenia. Haematology advice must be sought if this is to be considered and increased blood monitoring will be required. Clinicians must be aware that neutropenia on rechallenge with clozapine usually occurs sooner (typically within 10 weeks) and is frequently more severe than the first episode (Dunk, Annan & Andrews, 2006).

Cardiac considerations

Cardiac monitoring assesses for complications such as arrhythmias, hypotension, myocarditis and cardiomyopathy. Required investigations include: ECG, troponin and CRP and echocardiogram.

Cardiac monitoring through clozapine therapy includes:

- An ECG must be repeated at weeks one, two, three and four and every six months thereafter or sooner if clinically indicated.
- An echocardiogram should be repeated at six months and thereafter as clinically indicated or in line with local protocols (often annually).
- CRP, troponin – weekly for the first month, monthly to six months and then six-monthly unless clinically indicated. CRP, generally a nonspecific marker of

inflammation, is an early diagnostic indicator of the presence of myocarditis where other cardiac biomarkers are elevated.

- Regular monitoring of vital signs – blood pressure, pulse rate, temperature and respiratory rate – at least 4-weekly.

Tachycardia is a common side effect of clozapine in the initial period of treatment and will often settle and resolve within the first two months, or as tolerance develops. It is important not to dismiss it as an expected and unimportant side effect as it can also be an important sign of more serious cardiac complications such as myocarditis.

Tachycardia with other symptoms such as chest pain or heart failure require close attention to possible additional pathology, with a clinical assessment and ECG. Consideration should be given to ceasing clozapine until the exclusion of more serious cardiac complications. Clozapine related tachycardia, in the absence of additional cardiovascular complications, is sometimes treated with beta blockers but only once the patient has been on clozapine treatment for a sufficient period (to allow for tolerance to have developed) and once additional pathology has been excluded. Cardiology advice should be considered in this event. Tachycardia, without cardiac symptoms of orthostasis should not be a reason to stop clozapine (Nielsen, Correll, Manu & Kane, 2013).

A sudden or rapid rise in blood pressure may occur on initiation of treatment with clozapine or following a clozapine dose increase. Caution must be taken with the prescription of clozapine in patients with pre-existing hypertension. Clozapine induced hypertension is often best managed by a slow and gradual titration. Antihypertensives may be clinically useful and specialist advice may assist in its management.

Orthostatic hypotension may also be problematic for patients on clozapine therapy. Titrating clozapine slowly can help to minimise orthostasis, dizziness and faintness. Tolerance to the hypotensive effects of clozapine typically develops over days to weeks but may persist at higher doses. A slower-than-usual titration schedule may be required until tolerance develops. Intervention may be required to reduce risk of falls and injury. Patients must be provided with advice on managing postural dizziness and the modification of dietary salt and fluid intake. Specialist support may be needed if the symptom persists. Fludrocortisone is the most commonly used pharmacological intervention for management of orthostatic hypotension. Potassium levels should be monitored to prevent hyperkalaemia.

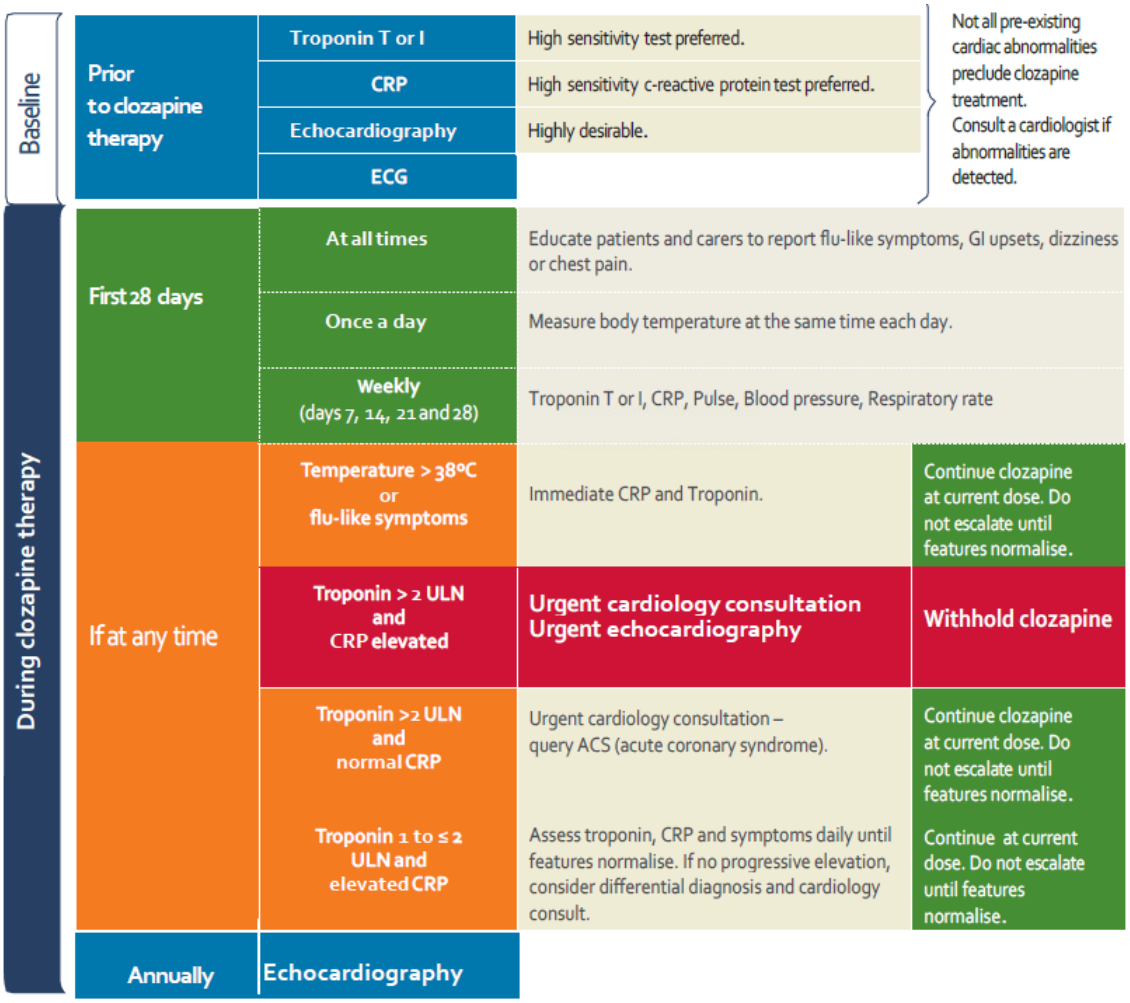
Clozapine induced myocarditis usually occurs within the first month of treatment, but the risk persists throughout treatment. The symptoms are generally non-specific and may present mildly so routine monitoring for myocarditis should occur during the first month of treatment.

Patients showing any of the following signs and symptoms should urgently undergo a diagnostic evaluation for myocarditis by a cardiologist:

- Symptoms of effort intolerance, persistent tachycardia (HR greater than 120 bpm or 30 bpm above the patient's normal range), significantly elevated CRP (greater than 100 mg/L) or troponin greater than 2 x upper limit of normal.
- Persistent tachycardia at rest, accompanied by other signs and symptoms of heart failure such as tachypnoea, shortness of breath, hypotension, and raised jugular venous pressure or arrhythmias.

- Fatigue, flu-like symptoms, chest pain or fever that is otherwise unexplained.

The flow chart below has been adapted from the Clozaril Patient Monitoring System Protocol (2018) and provides guidance for clinicians with patients on clozapine with suspected clozapine-induced myocarditis. It was developed by a panel of cardiologists, psychiatrists and other medical advisors and gives specific advice as to when monitoring should be escalated and at what point clozapine therapy should be with-held (when troponin is above >2 ULN *and* CRP is elevated).



Adapted from: Clozaril Patient Monitoring System (CPMS). (2018). *Clozaril Patient Monitoring System Protocol:* Version 3. Mylan: Sydney.

Given the potential benefits of clozapine, its continuation should be encouraged if it can occur safely. This is feasible in the presence of mild cardiac disease, with specialist monitoring and support which indicates that cardiac function is not at risk. Slow titration of clozapine in this situation is essential.

Cardiomyopathy usually develops later in clozapine treatment with a median duration of treatment of nine months. It tends to follow a more chronic course than clozapine related myocarditis. Patients usually develop a dilated cardiomyopathy with congestive heart failure. A high index of suspicion must be maintained as patients may be asymptomatic despite this cardiac involvement.

Venous thromboembolism is associated with clozapine. Preventative measures such as compression stockings or anticoagulation may be needed for patients at higher risk (Manu, et al., 2012).

Other uncommon cardiac adverse effects include prolongation of the QTc interval and sudden cardiac death.

Metabolic considerations

Weight gain is common in patients on clozapine therapy. It is most rapid in the first six months of treatment but may continue through the long term. Patients should be informed of, and supported in, lifestyle and dietary improvements particularly targeting exercise and a balanced diet. Referral to a dietician may be considered. Where lifestyle programs are available, referral and support of the patient's engagement in healthy lifestyle activities should be considered as part of the care plan.

There is increasing evidence for the use of pharmacological strategies for clozapine associated weight gain, including metformin and glucagon-like peptide receptor agonists (GLP1-RAs) such as semaglutide, exenatide and liraglutide (Siskind, et al., 2016; Siskind, et al., 2019). Co-commencement of clozapine and metformin can partially ameliorate clozapine induced weight gain (Spokes, et al., 2021).

- Weight, body mass index (BMI), and waist measurements should be repeated at monthly intervals.

For all people on clozapine:

- Fasting glucose should be repeated at one month and then every six months unless otherwise clinically indicated.
- Lipids and triglycerides should be repeated every six months unless otherwise clinically indicated.
- Abnormal results should be followed up as appropriate, involving primary care and endocrinology clinics.

Patients with diabetes mellitus commencing clozapine therapy should be monitored for worsening glucose control including symptoms of hyperglycaemia such as polydipsia, polyuria, polyphagia and weakness or the risk of diabetic ketoacidosis.

Elevation of liver enzymes may occur with clozapine treatment. It is usually clinically insignificant and spontaneously remits but cases of hepatitis and liver failure have been recorded.

- Liver function tests should be repeated every six months unless otherwise clinically indicated.

Gastrointestinal considerations

Clozapine related constipation and gastrointestinal hypomotility is very common and can have a significant impact on medication adherence in addition to the serious, more rare and potentially life threatening complications including bowel obstruction, paralytic ileus, toxic megacolon and death (Cohen, 2017). Unlike some other side effects of clozapine, constipation tends to persist and patients do not develop a tolerance for it. Clinicians should enquire routinely about patients' bowel habits and provide education

about the importance of adequate hydration, dietary fibre and exercise. Bowel monitoring (for example, using the Bristol stool chart), should be undertaken as routine practice, with questioning of bowel motion frequency, and presence of blood or pain on bowel movement. Physicians are encouraged to commence aperients alongside the first prescription of clozapine. Based on the Porirua protocol, first line treatment should involve stool softeners and a stimulant such as docusate and senna, and macrogol. Bulk-forming laxatives (for example; psyllium) should be avoided in clozapine-treated patients due to the slow colonic transit times and risk of inspissation. Symptoms of ileus including nausea and vomiting, cramps, bloating, and retention of stool and flatus should prompt consideration of urgency of further assessment and as appropriate referral for timely evaluation. Symptoms of ileus should prompt an immediate referral for evaluation.

Nausea and reflux are common with clozapine therapy, caused in part by anticholinergic effects, and may be compounded by hypersalivation, increased appetite and specific hypothalamic effects. It is usually worst on initiation of treatment and patients may develop tolerance for it. Patients may require specific treatment such as antiemetics if it is intolerable. Hyoscine hydrobromide has also been helpful. Many patients will require a proton pump inhibitor (PPI) or H2 antagonist for reflux.

Central Nervous System considerations

Sedation is common with many antipsychotic preparations but can be particularly pronounced with clozapine. It is usually more severe early in treatment and most patients will develop tolerance over a few months. It can impact on quality of life and contribute to poor adherence. It can be managed through slow dose titration, minimising other sedating medications, using the minimal effective dose and asymmetric dose splitting (with the largest dose in the evening). Plasma levels should be reviewed if over sedation is persistent and troubling. Aripiprazole in low doses is sometimes used to address clozapine related sedation. The use of stimulants is limited due to their potential to exacerbate psychotic effects. Up to 25% of men taking clozapine have obstructive sleep apnoea. If suspected, patients should be referred for investigation.

Clozapine is epileptogenic. The risk of seizures increases with clozapine blood levels above 1000 microgram/L. Clozapine related seizures occur more frequently in those with a prior head injury, a history of seizure activity or a lowered seizure threshold (which may be contributed to by other medications such as antidepressants, anticholinergics, lithium and other antipsychotics, electrolyte imbalances).

Clozapine patient electroencephalograms (EEGs) are frequently abnormal with diffuse slow wave changes, even in the absence of seizures. Patients can also experience myoclonic jerks which may indicate an increased seizure risk. Due to the low incidence of seizures and risk of further weight gain and neutropenia with valproate treatment, prophylactic anticonvulsant therapy is rarely necessary (Malik, et al., 2018). Lamotrigine may be used, however it may exacerbate myoclonic jerks. Carbamazepine and phenytoin should be avoided due to their impact on clozapine metabolism (increased clearance and reduced levels) and increased risk of agranulocytosis (Pisani 2002).

Other general monitoring and management

Benign and transient pyrexia is common in the early stages of treatment with clozapine and can be managed with simple antipyrexial agents. It can, however, also be a hallmark of more serious side effects of myocarditis, neuroleptic malignant syndrome, neutropenic sepsis and should be investigated accordingly.

There is emerging evidence that a normal response to infection inhibits cytochrome P450 enzymes resulting in significantly elevated serum clozapine levels which can lead to increased side effects including sedation and seizure activity. If there is evidence of an infection, the patient should be assessed for signs of clozapine toxicity and if indicated a serum clozapine levels taken and reviewed by a medical officer. In the event of a raised serum clozapine levels or clinical signs of clozapine toxicity then a medical review is required with consideration given to dose reduction if indicated. If the serum clozapine level is raised, consideration should be given to monitoring the serum clozapine levels weekly during the period of infection. Treatment with antibiotics that inhibit CYP enzymes associated with clozapine metabolism (e.g. CYP 1A2 - quinolones such as ciprofloxacin) will also increase the risk of toxicity.

Clozapine induced hypersalivation is a common side effect. It can be embarrassing and impact significantly on quality of life. It is often worse on initiation of treatment, may improve over several months and is likely to be dose related. It may be worse for patients at night-time. It may lead to aspiration pneumonia and must not be dismissed. In milder cases non-pharmacological strategies are usually of benefit. Pharmacological strategies for hypersalivation have limited evidence. First line treatments include locally applied therapies such as ipratropium bromide sublingually or atropine sublingual drops (Chen, et al., 2019). Atropine should be used with caution because of the risk of accidental or intentional overdose (TGA 2018). Anticholinergics, although sometimes effective for hypersalivation, are associated with an increased risk of ileus (Nielsen & Meyer, 2012). If anticholinergics are required, monitor bowel function closely and use alongside aggressive prophylactic treatment of constipation. Augmentation of clozapine with amisulpride may reduce sialorrhea.

Clozapine is frequently associated with urinary symptoms of nocturnal enuresis, urinary incontinence, urgency, and frequency. Direct questioning about the frequency and severity of symptoms should be undertaken routinely to ensure timely identification. They are often self-limiting and are most likely to occur during clozapine titration. Patients should be reminded that clozapine is sedating and may cause temporary bed wetting. Strategies to address enuresis include attention to limiting evening fluid intake, bedtime voiding, limiting the use of diuretic substances, and setting alarms for night-time voiding. If symptoms persist, pharmacological intervention options include aripiprazole, desmopressin, amitriptyline or imipramine, alpha-1 agonists. As with hypersalivation, anticholinergic agents should be used with caution and reserved for severe cases. Hyponatraemia is a common side effect of desmopressin; check sodium levels and screen patients for polydipsia prior to commencement. If pharmacological interventions are unsuccessful, treatment may be aided by transabdominal ultrasound or urodynamic testing. Medical issues such as benign prostatic hypertrophy and pelvic floor weaknesses should be considered.

Clozapine can be associated with an increase in obsessive compulsive symptoms, greater than that in schizophrenia generally. These symptoms may be transient but can also follow a more persistent and chronic course and can be disabling and impact on

quality of life. If symptoms persist treatment options include cognitive behavioural therapy or pharmacological agents such as selective serotonin reuptake inhibitors for patients without a history of mania. Caution must be applied as many antidepressants can affect clozapine levels.

Clozapine and Tobacco use

Changes in tobacco use can affect clozapine levels. Starting or increasing tobacco smoking may reduce clozapine levels, while tobacco smoking cessation may increase serum clozapine levels, with potential for clozapine toxicity and its associated adverse effects, including death.

Smoking patterns and changes should be reviewed at each visit, using the Queensland Health smoking cessation clinical pathway as appropriate. Patients should be encouraged to cease smoking and to advise staff if they cease, reduce or otherwise change or plan to change their smoking pattern. The potential effects of smoking and smoking cessation on clozapine levels should be explained to the patient and their carers.

For patients who smoke, the amount of inhaled smoke and serum clozapine levels should be monitored to assist with dose adjustments.

Factors to consider on an individual basis when determining impact of smoking cessation on clozapine levels include:

1. the number of cigarettes smoked.
2. for inpatients, the expected change in smoking on admission and on discharge (e.g. return to pre-admission levels, an increase from baseline).
3. medication adherence patterns in relevant settings.
4. clozapine metabolism, as measured by dose versus serum clozapine levels.
5. history of side effects on clozapine and the approximate associated serum clozapine levels; and
6. changes in caffeine intake, as increased caffeine levels can result in increasing serum clozapine levels.

If a patient reports starting or restarting regular smoking for longer than 1 week, then a clozapine level should be considered, particularly for patients with break-through symptoms, unstable illness or higher risk of relapse. Where clozapine levels are significantly reduced, then upward titration of dose should be considered to return to therapeutic levels, usually at 25 to 50mg increments depending on the drop in clozapine levels and illness and side effect related risks.

When a patient plans to stop smoking, measure serum clozapine level prior to smoking cessation.

Consider the patient's likely adherence to smoking cessation, establishing good communication to ensure that if not successful the clozapine dose is adequate to maintain therapeutic serum clozapine level for that patient. Patients with irregular smoking patterns will require closer monitoring of their serum clozapine levels.

Serum clozapine levels following smoking cessation or reduction should be measured at day 7, day 14, day 21 and day 28 or until stable, and can be synchronised with routine blood tests. Abrupt cessation of smoking may lead to clozapine toxicity. A

patient who abruptly ceases smoking may require a clozapine dose reduction of up to a third, if they maintain abstinent from smoking. Any planned cessation of smoking should be supervised and, where possible, tapered and accompanied by an immediate reduction in the clozapine dose with monitoring of clozapine levels.

Patients who cease smoking should be monitored closely for side effects of raised serum clozapine levels. The risk of sedation, hypotension and adverse neurological effects including myoclonus and seizures will be greater when serum clozapine levels are higher; however the occurrence of clozapine-induced agranulocytosis and many other adverse effects are not dose dependent. The clozapine dose may need to be reduced if the serum clozapine levels rises outside of the patient's base range, or above 1000 ng/ml, during smoking cessation.

Nicotine Replacement Therapy (NRT) or varenicline (Champix) does not affect serum clozapine levels. The clinical team should provide ongoing support and advice to the patient and care giver, regarding the possible impacts that may emerge with smoking cessation or reduction.

Clozapine and caffeine

Caffeine may significantly inhibit the metabolism of clozapine. Changes in caffeine intake (e.g. tea, coffee, cola and energy drinks) can lead to clinically significant changes in serum clozapine levels. Concurrent use of caffeine in moderate to high quantities with clozapine may result in an increased risk of clozapine toxicity. Clinicians should ensure that caffeine consumption levels are regularly assessed and monitored.

Patients should be encouraged to reduce their caffeine intake when stopping smoking. Caffeine toxicity may cause agitation, sleep disturbance and gastrointestinal symptoms all of which may be misinterpreted as nicotine withdrawal. NRT will not mitigate these effects.

Clozapine levels – therapeutic drug monitoring

Clozapine's metabolism is complex and there are significant inter and intra-individual variations in clozapine serum levels for a given dose. Additionally, there are many clinically significant interactions between clozapine and other substances – nicotine, caffeine and other prescribed medications. Therapeutic drug monitoring of clozapine is therefore frequently used.

Clinicians should be familiar with the adverse effects of clozapine that correlate with serum levels (particularly the central nervous system side effects) and those that are unrelated to serum levels (the haematological and cardiac events).

Overdose with clozapine is a medical emergency and should lead to hospital assessment as soon as possible.

A 'therapeutic' dose can, therefore, be associated with severe toxicity in a clozapine naive patient.

Levels are particularly helpful in the following circumstances:

- a poor clinical response
- suspected poor adherence
- side effects likely to be related to higher serum level (i.e. seizures)

- other signs of toxicity
- changes to other concurrent medications, including augmentation
- changes to caffeine or nicotine intake
- impaired liver function.

7.5 The transition to maintenance therapy

Once treatment has been initiated and stabilised, it can be described as progressing from the initiation phase to the maintenance phase or maintenance therapy (at least and may often be beyond 18 weeks post-commencement). This phase can occur at variable times in treatment for different patients. Definitions of maintenance therapy generally refer to a point in clozapine therapy when the patient's mental state and functional level, clozapine dosage and significant side effects of the medication are all considered to be at an optimal level.

8. Models of clozapine management for maintenance therapy

Community care for the patient receiving maintenance therapy with clozapine can occur through different arrangements, with models of care varying locally and depending on patient and service system characteristics.

Public MHAOD services only

When a patient's clinical needs require ongoing public MHAOD services service intervention, clozapine is prescribed by psychiatrists or other medical staff working within the Hospital and Health Service but can be obtained either at the hospital pharmacy or from a community pharmacy. The frequency of reviews will be determined by clinical need, including legislative and service requirements, and the involvement of other clinicians in multi-disciplinary teams.

General Practitioner prescribing shared care

The general practitioner assumes primary responsibility for prescribing and monitoring clozapine (including all necessary reviews of physical and mental health and cardiac, haematological and other monitoring required). The general practitioner should personally review the blood tests before prescribing clozapine and works under the supervision of a psychiatrist according to local shared care arrangements and individual patient needs.

In this model, the clozapine community prescriber must be designated and eligible in accordance with the HDPR and all other legislation, regulation and guidelines and the patient can have the clozapine dispensed either from the hospital or community-based pharmacy.

General Practitioner monitoring shared care

In this model community patients are reviewed regularly by both specialist mental health and primary care providers. A patient may be seen monthly by their general

practitioner for mental state monitoring, a review of physical health care needs and other specific monitoring required.

In this model the general practitioner does not prescribe the clozapine. The patient will also see at regular intervals a psychiatrist, or a medical officer supervised by a psychiatrist, who will prescribe the clozapine. These specialist medical reviews will be determined according to clinical need or policy but might entail two, three- or six-monthly reviews.

Under this model, the psychiatrist or registrar who prescribes the clozapine for the patient may prescribe five repeats that can be available at the nominated pharmacy (either public hospital or community based) for dispensing when the general practitioner is satisfied that the patient is stable, has ordered and reviewed the standard haematological and other monitoring results and has determined that a continuation of therapy is appropriate.

A psychiatrist must continue to provide supervision of the patient's care. Under this model, the patient will often retain contact with the specialist mental health provider for additional services such as case management. Local shared care models should support this model of care.

Private psychiatrist only care

In this model a private psychiatrist assumes responsibility for the patient's full care including the monitoring and prescribing of clozapine, all necessary physical health reviews, mental state reviews and all cardiac, haematological and other monitoring as required. The patient will usually not have additional legislative requirements, may or may not have case management (either in the public or private health system), will need to link in with a clozapine coordinator that may be based with the private psychiatrist or a private psychiatric hospital setting, and will usually receive their clozapine through a community pharmacy.

Considerations for clozapine shared care

Strong links should be established between all parties in clozapine shared care models. All models of shared care for clozapine management must ensure the safety of patients, in the transition to shared care. and that specialist oversight of the care remains. All the community professionals involved in the prescribing and dispensing of clozapine must be appropriately educated and registered and must have retained clear links with clozapine coordinators and shared care coordinators either in the public or private health systems.

Not all clozapine patients on maintenance therapy are suitable for community prescribing or dispensing. The characteristics of the patient receiving the clozapine rather than the duration of clozapine therapy which should be the determining factor in any transition of care considered.

Factors that may affect a patient's ability to move to community-based care:

- a patient's history of adherence to clozapine and other medication
- their ability to attend appointments, blood tests and other investigations independently or with long-term sustainable support
- their ability to access a suitable pharmacy

- their satisfaction with the transition to community care and
- their practical ability to access the community scheme.

Transition of a patient's clozapine management out of the traditional hospital or community clinic-based model requires careful planning, preparation and monitoring to ensure sustained success. All service providers should understand legislative, policy and clinical requirements before implementing new models of care for clozapine.

Clozapine coordinators, whilst all being required to meet a minimum number of tasks and role descriptors, are allowed some flexibility in scope and approach according to the specific clozapine centre's needs. Clozapine coordinators may be required to take the lead role in identifying, preparing and initiating the transition of patients into community care arrangements, may be the first line response for consultation and advice for community prescribers and dispensers, may take a lead role in education and training of these health professionals, will retain some shared understanding of the patients with the community clinicians and will provide a rapid response and facilitate re-entry to the specialist mental health system if required.

8.1 Managing complications

Should an adverse event occur as a result of clozapine therapy (for example cardiac complications, haematological or metabolic complications or any other side effects discussed above) the adverse incident must be reported in the local clinical incident management system, with the relevant clozapine patient monitoring system and with the TGA adverse event monitoring, within 24 hours of the event taking place or being first noted.

This guideline should be used in conjunction with local Hospital and Health Service clinical incident governance processes, and in alignment with the National Safety and Quality Health Service (second edition) Standards.

8.2 Restarting therapy after interruption

Interruption to clozapine therapy for whatever reason must initiate a review of the circumstances of the interruption and an assessment of the patient. If clozapine is stopped for more than 48 hours and then recommenced at full dosage there is a significant risk of severe side-effects similar to those that occur at initial titration including severe sedation, cardiovascular adverse effects and seizures. Subsequent action is guided by the period of interruption i.e. the time since last dose was taken.

Table 3. Restarting clozapine

Time since last clozapine dose	Action to re-start
Up to 48 hours	**Re-start at previous dose** – no re-titration required

48 – 72 hours	**Begin rapid re-titration as soon as possible** On day 1, re-start with half of the previously prescribed total daily dose given in divided doses 12 hours apart. Then give 75% of previous daily dose on day 2 and, if prior doses have been tolerated, the whole of the previous daily dose in the normal dosing schedule on day 3
72 hours to 1 week	**Begin re-titration with 12.5 mg or 25 mg clozapine** Try a second dose 12 hours later if the first is well tolerated. Increase to normal dose according to patient tolerability over at least 3 days.
More than 1 week	**Re-titrate as if new patient** Aim to reach previously prescribed dose within 2-4 weeks. Increase according to tolerability

Taken from: Taylor, D.M., Barnes, T.R.E. & Young, A.H. (2018). *The Maudsley Prescribing Guidelines* (13th Ed.). Wiley-Blackwell: New York.

Patients who experience an interruption in therapy are at risk of relapses of psychosis often of severe nature. Treating teams should provide close monitoring of mental state during this period and consider the use of an alternative antipsychotic to control psychotic symptoms. In non-psychiatric hospital units, specialist psychiatric advice is required (for example, by consultation-liaison psychiatry services) for management following an interruption in therapy.

8.3 Discontinuing clozapine therapy

If a planned discontinuation of clozapine takes place, the dose of clozapine should be gradually reduced over one to two weeks (if inpatient) or 4-12 weeks (if outpatient), with an introduction of an alternative antipsychotic if clinically indicated.

If abrupt discontinuation is necessary, the patient's mental state and cholinergic rebound (for example; headache, nausea, vomiting and diarrhoea) should be carefully observed.

Haematological post-therapy monitoring is required by the clozapine patient monitoring systems.

For patients on weekly blood test monitoring (i.e. in the initiation phase) a WBC and ANC should be performed at least weekly for four weeks after discontinuation.

For patients on four-weekly blood test monitoring (i.e. in the continuation phase) a WBC and ANC should be performed as close as possible to the time of discontinuation and then at least two follow-up counts four weeks after discontinuation.

These post-cessation WBC and ANCs must be green (according to traffic light system) or further monitoring will be required.

9. Training and education

Hospital and Health Services are responsible for ensuring training is provided to all relevant clinicians (primary care health practitioners, general practitioners, pharmacists, nurses and clozapine coordinators) involved in the prescribing, dispensing and administration of clozapine to patients. Services should use existing protocols and online training packages available from the two clozapine monitoring systems, CPMS and Clopine Central™ in the development and roll-out of local education and training at clinical sites.

10. Related documents

10.1 Authorising policy and standards

- *Medicines and Poisons Act 2019*
- *Medicines and Poisons (Medicines) Regulation 2021*
- *Mental Health Act 2016 (Queensland)*
- *Human Rights Act 2019(Queensland)*
- National Safety and Quality Health Service Standards 2017
- Chief Psychiatrist Policy, Clinical need for medication (2020)

10.2 Procedures, Guidelines and Protocols

- Medication Management within Mental Health Alcohol and Other Drugs (MHAOD) Services (2021)

10.3 Forms and templates

- Adult Clozapine Titration Chart (Queensland Government)
- Physical Health Screen | Queensland Health
- Smoking Cessation Clinical Pathway (Queensland Government)

10.4 Additional Resources

- NIMC (clozapine titration) User Guide (2013)
- Best practice guide to clinical incident management (2014)
- Adult Clozapine Titration Chart (Queensland Government)
- Clozaril Monitoring System
- Clopine Monitoring System
- Choice and medication information for people who use services, carers and professionals
- Equally Well Improving the physical health and wellbeing of people living with mental illness in Australia
- Pregnancy and Breastfeeding Medicines Guide
- Guidance on the Use of Antipsychotics
- Professional Practice Guideline 7: Guidance for psychotropic medication use in children and adolescents
- Physical Health Screen - Comprehensive Care Documentation Guide | Clinical Excellence Queensland
- RANZCP Clinical practice guidelines for the management of schizophrenia and related disorders
- Bristol Stool Chart

11. Approval and implementation

Consultation

Queensland Psychotropic Medication Advisory Committee (QPMAC)

Approval Officer

Chief Psychiatrist, Mental Health Alcohol and Other Drugs Branch

Policy Custodian

Director, Clinical Governance, Office of the Chief Psychiatrist, Mental Health Alcohol and Other Drugs Branch

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Version control

Version	Date	Prepared by	Comments / reason for update
1	10/11/2016	Clinical Governance Team	First publication
2	13/08/2021	Clinical Governance Team	Review by the Office of the Chief Psychiatrist and key stakeholders
3	21/12/2021	Clinical Governance	Clerical amendment

		Team	

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