Government of **Western Australia**
Department of **Health**

Guidelines for the Safe and Quality Use of Clozapine Therapy in the WA health system

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The *Guidelines for the Safe and Quality Use of Clozapine Therapy in the WA health system* may be updated at regular intervals. For the latest version of this document, please visit the Office of Patient Safety and Clinical Quality website at: Mental Health Charts and Clozapine Resources

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Version Control

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Consultation

- North Metropolitan Mental Health Service
- WA Psychotropic Medicine Group (WAPMG)
- WA Medication Safety Collaborative
- Clinical Pharmacists working within Mental Health across Health Service Providers

Approval and implementation

Name	Position	Approval date
Audrey Koay	Executive Director Patient Safety and Clinical Quality Clinical Excellence Division	9th July 2024

Effective from: July 2024

Next Review due: 3 years from Effective Date

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Summary of the WA Clozapine Initiation, Titration and Maintenance Care Pathway

Clozapine selection

Patient has a diagnosis of treatment resistant schizophrenia, and/or suffers intolerable side effects to at least two other antipsychotics. Treating psychiatrist decides that clozapine is appropriate and in the best interest of the patient and discusses with the multidisciplinary team (MDT).

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Medical history and pre-commencement screen

Check medical and psychiatric history for precautions and contraindications to clozapine use.

Discuss indications, possible side effects, other treatment options, monitoring procedures, side effects and mitigations with the patient (and carer, close family member, guardian or personal support person (PSP)).

Provide appropriate written information and clozapine consumer medication information leaflet (Appendix 1.5).

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Informed consent

Obtain consent from the patient (particularly noting possible side effects and blood/physical monitoring requirements)

(For involuntary patients who do not demonstrate capacity or who are unable to give informed consent for treatment S25 (1) and S22 (1) WA Mental Health Act 2014 may apply). Where the patient cannot give informed consent the designated person authorised by law to make treatment decisions on the patient's behalf must be consulted.

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Conduct pre-treatment tests and baseline monitoring requirements.

Complete all required pre-clozapine baseline tests prior to clozapine commencement.

Use the WA clozapine initiation and titration chart (Appendix 1.1) to guide baseline testing and monitor patients on clozapine (first 28 days of treatment).

White blood count (WBC) and neutrophil count (NC) results in the Green results range = clozapine is appropriate to be commenced.

Review current medications to check interactions. Check allergy status/adverse drug reaction (ADR) history. Screen for and treat pre-existing constipation Record smoking status.

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Clozapine Patient Monitoring System (and consent for inclusion on clozapine database)

Register the patient with the relevant clozapine patient monitoring system.

Inform clozapine clinic / Coordinator and relevant staff as appropriate (e.g. Pharmacy department, GP, Acute Mental Health Team (MHT) and the ward team) and ensure PBS S100 requirements are met.

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Clozapine Initiation (Inpatients and Community Patients)

Do not initiate clozapine until approved by the clozapine patient monitoring system and patient clozapine number is allocated.

Prescribe morning dose of 12.5 mg daily for inpatients, use the titration chart as a guide for dosing.

(Appendix 1.1)

For community patients, a lower commencement dose of 6.25 mg and slower titration is recommended (Appendix 5)

Obtain supply of clozapine from the relevant pharmacy.

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Day 1

Monitor vital signs (Temperature, respirations, pulse and lying and standing BP) prior to the first dose of clozapine (all patients).

Inpatients: monitor vital signs hourly for six hours then every six hours whilst awake for the first 24 hours.

Community patients: monitor hourly for at least 3 hours at the mental health clinic

Days 2 – 7 (Week 1)

Inpatient: monitor vital signs twice daily

Community patient: monitor vital signs once daily during clinic days (clinic business hours)

Week 2

Inpatient: monitor vital signs daily

Community patient: monitor once daily during clinic days

Week 3

Inpatient: monitor vital signs daily

Community patient: monitor vital signs three times a week

Week 4

Inpatient: monitor vital signs daily

Community patient: monitor vital signs three times a week

All monitoring recommendations are required as a minimum - increase as clinically indicated

Use the *WA Clozapine Initiation and Titration Chart (Appendix 1.1) to guide additional physical health monitoring for weeks 1 – 4*

Week 5 to 18

Inpatient setting	**Community setting**
Monitor vital signs: Temperature, respirations, pulse and lying and standing BP ***conducted daily***	Monitor vital signs: Temperature, respirations, pulse and lying and standing BP ***conducted at each review***

Use *Clozapine Monitoring Forms A & B (Appendices 1.3 and 1.4) to guide physical health monitoring protocols*

Continue haematological monitoring weekly (FBC).

Green result	**Amber result**	**Red result**
WBC greater than or equal to 3.5 x 10^9/L AND NC greater than or equal to 2.0 x 10^9 /L	WBC greater than or equal to 3.0 and less than 3.5 x 10^9/L AND/OR NC greater than or equal to 1.5 and less than 2.0 x 10^9 /L	WBC less than 3.0 x 10^9/L AND/OR NC less than 1.5 x 10^9 /L
Continue clozapine	Continue clozapine therapy with twice-weekly blood tests until return to green range	Withold medication. Confirm red result with a repeat laboratory tested FBC. Sample blood daily until a green result is achieved. Monitor for signs of infection. Contact haematologist and clozapine monitoring service for advice

Ongoing monitoring from 18 weeks

Inform clozapine clinic, community team and clozapine monitoring service if changing teams or consultant or supplying pharmacy. Provide a GP letter to ensure GP is aware of ongoing clozapine prescription and monitoring requirements. Update care plan. Enter all results and communications in the patient health record.

Check for side effects of clozapine use at every review (Appendix 3 and 4)

Use *Clozapine Monitoring Forms A & B (Appendices 1.3 and 1.4) to guide physical health monitoring protocols*

Ensure GP is aware of ongoing clozapine prescription and monitoring requirements.

Update care plan 3 monthly.

NOTE: Recommencing clozapine therapy after interruption

Dosing recommendations if clozapine dose is missed for more than 48 hours

- Obtain psychiatric review prior to recommencing clozapine.
- Recommence at 12.5mg once or twice daily on the first day. Refer to what side effects the patient had last time when starting clozapine. The rate of titration can be adjusted to take into account emergent side effects and period of interruption *(see WA Clozapine Initiation and Titration Chart* **(Appendix 1.1)**
- This is a guide only – for further dosing options refer to specialist advice.

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FBC monitoring after interruption of therapy (For other protocols see Appendix 5)

Clozapine missed for less than 72 hours	**Clozapine missed for more than 72 hours but not more than 28 days**	**Clozapine missed for more than 28 days**
No change in monitoring	For weekly monitored patients: Monitor weekly for at least 6 weeks or for as long as necessary to achieve a total of 18 weeks of weekly monitoring (whichever is greatest). For four-weekly monitored patients: Monitor weekly for 6 weeks then continue with monthly monitoring if no problems detected	Recommence as for a new patient

Executive Summary

Clozapine is an effective antipsychotic medication for the management of treatment resistant schizophrenia. Because of risks associated with clozapine use, it is reserved for use in cases where patients have an inadequate response, or suffer intolerable side effects, to at least two antipsychotic agents other than clozapine.

Due to the risk of neutropenia and agranulocytosis, all patients taking clozapine must be enrolled in a clozapine patient monitoring system and monitored regularly.

Protocols for monitoring the haematological and physical health of people prescribed clozapine are outlined in these guidelines. Health Services should monitor compliance of the physical health monitoring protocols for people taking clozapine.

These guidelines align with the WA Department of Health High Risk Medication Policy MP 0131/20, as a supporting document to guide monitoring protocols and practices.

To support optimal care of patients on clozapine it is recommended that:

- All patients treated with clozapine
    a. have an identified case manager / clozapine coordinator
    b. have regular physical and mental health monitoring using a defined protocol
    c. are treated within a suitable model of care that facilitates adherence, support and a patient centred approach.
- General practitioners (GPs) are involved in care of all patients taking clozapine, including ongoing physical monitoring.
- Centres coordinating physical and mental health must define communication processes to ensure appropriate sharing of clinical information (across professions, services, and carers where appropriate).

1. Introduction

1.1 Purpose

These guidelines provide recommendations regarding best practice for safe and effective use and physical health monitoring for patients on clozapine therapy, including useful tools to:

- support decision making
- minimise the risk of an adverse drug event
- standardise evidence-based practice for clozapine treatment in the management of patients with schizophrenia.

The guidelines support the National Safety and Quality in Health Service Standards, *Standard 2*: Partnering with Consumers, *Standard 4*: Medication Safety, *Standard 6*: Communicating for Safety and *Standard 8*: Recognising and Responding to Acute Deterioration.

1.2 Scope

These guidelines provide information for clinicians prescribing and/or monitoring patients on clozapine and employed by WA Department of Health, and other health practitioners (e.g. private psychiatrists, general practitioners and community pharmacists), working in partnership with WA Department of Health employees.

1.3 Background

Clozapine is considered the 'gold standard' medication for use in the management of treatment resistant schizophrenia in cases where patients have inadequate response to, or are intolerant of, at least two antipsychotic agents other than clozapine. Despite clozapine's clinical benefits, this medication can cause potentially life threatening haematological, cardiac, and gastrointestinal side effects. Vigilant monitoring is required for patients on clozapine.

Attention must be paid to interruption of clozapine therapy and the initiation and titration protocols to ensure safe and quality use of clozapine.

The Therapeutic Goods Administration (TGA) has implemented mandatory haematological monitoring standards in Australia to minimise the risk of clozapine haematological side effects. The occurrence of neutropenia and agranulocytosis, particularly in the first 18 weeks of initiating clozapine treatment is a small but significant risk that can be managed by monitoring the white cell and neutrophil counts.

2. Prescribing and Supply Requirements for Clozapine

2.1 Pharmaceutical Benefits Scheme and Clozapine Prescribing

Clozapine is a Schedule 4 medicine classified under the Poisons Regulations 2016 and is classified as a 'highly specialised drug' (section 100 HSD) under the Pharmaceutical Benefits Scheme (PBS).

The PBS has several administrative requirements that must be met in relation to the prescribing and dispensing of PBS subsidised clozapine to patients.

http://www.pbs.gov.au/info/browse/section-100/s100-highly-specialised-drugs

Patients not meeting the PBS criteria for clozapine must be approved for use by the usual non-formulary processes for each Health Service Provider by raising an Individual Patient Approval through the Drug/Medicine and Therapeutics Committee or equivalent governing body by application through WAIPAS. Patients must still be registered with the relevant clozapine patient monitoring system as outlined in section 2.2 and adhere to the monitoring requirements outlined in this guideline. Consideration must also be given to the affordability of ongoing supply.

Community pharmacies can dispense and supply PBS subsidised clozapine to patients in a community setting independent of public hospitals. While patients should have as wide a choice of suppliers of clozapine as possible, they should be encouraged to nominate and remain with one pharmacy at a time. Community- based dispensers need familiarisation, training, and the necessary registration with all practical arrangements for the monitoring and supply of clozapine and a complete understanding of the pharmacology, dosage, risks and side effects of clozapine.

2.2 Registration: Clozapine Patient Monitoring Services

There are three brands of clozapine available in Australia - Clopine® (Pfizer), Clozaril® (Novartis) and Clozitor® (Pharmacor).

Each brand has an associated clozapine patient monitoring system – ClopineCENTRAL™[1] for Clopine® available at https:/www.clopine.com.au/ , Clozaril Patient Monitoring System (CPMS)[2] for Clozaril® available at http:/www.ecpms.com.au/ and Juno Connected™[3] for Clozitor® available at https://www.junoconnected.com.au.These brands are not interchangeable due to lack of connectivity between the monitoring systems.

Clopine® is the current WA Department of Health tendered brand and will be referred to as the default clozapine patient monitoring system.

The clozapine patient monitoring system requires:

- Patients, prescribing doctors, dispensing pharmacists and clozapine coordinators to be registered with the monitoring system.
- Hospitals, clinics, or any other facility managing clozapine therapy to be registered as a “Clozapine Centre”.
- Community pharmacies dispensing clozapine and GP clinics prescribing clozapine under the shared cared arrangements are to be registered as a “Clinic” under the relevant centre.

3. Assessment of Patient Suitability for Clozapine Therapy

3.1 Criteria for Commencing Treatment

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 OR intolerant of at least two other antipsychotic agents. A valid trial equates to antipsychotic treatment at an adequate dose for at least 6 weeks with good adherence.

- ☐ The patient must be treated by a psychiatrist or in consultation with a psychiatrist affiliated with a hospital or specialised mental health unit.

- ☐ Comprehensive clinical assessment and baseline measurements must be taken (section 3.2)

- ☐ All precautions and contraindications outlined in the Product Information are considered and managed (section 4).

- ☐ The patient and next of kin/carer/guardian must be provided verbal and written information regarding the treatment and monitoring system. Choice and Medication is a recommended resource for written information.

- ☐ There are adequate supports in place to enable the patient to adhere to treatment and associated monitoring ongoing.

- ☐ Registration of patient with the relevant clozapine monitoring system must occur prior to commencing clozapine therapy.

3.2 Clinical Assessment Prior to the Commencement of Clozapine

A comprehensive physical and psychiatric assessment of the patient must be undertaken if considering prescribing clozapine[4, 5], including:

- A history of medication and other past treatments
- Height, weight and waist measurements
- History of drug-induced neutropenia, bone marrow disorders, or any other factors that might increase the risk of neutropenia or agranulocytosis while on clozapine
- Relevant family history including ethnic background that may confer a risk of benign ethnic neutropenia[6] e.g. Afro-Caribbean, African or Middle Eastern ancestry
- History or family history of cardiac related disorders
- History or family history of diabetes mellitus, dyslipidaemia or metabolic disorders
- History or family history of epileptic activity
- History or family history of thromboembolism
- Current smoking status
- Current bowel habits
- Allergies and adverse drug reactions
- Pregnancy or ability to conceive status
- Breast feeding status

Baseline measurements required prior to commencing clozapine[1, 7]:

- Blood group **(required for patient registration)**
- Full blood count (FBC) **(required for patient registration - *must be taken within 10 days prior to commencing clozapine*)**
- C-reactive protein (CRP)
- Troponin (Trop)
- Electrocardiogram (ECG)
- Urea / electrolytes / creatinine (UEC)
- Liver function tests (LFT)
- Blood glucose (fasting if possible) / glycated haemoglobin (HbA1c)
- Lipid Screen (fasting if possible)
- Echocardiogram (ECHO)
    - If unable to be obtained prior to commencement, take as soon as possible after commencement.
- Weight
- Waist circumference
- Bowel function
- Quantify smoking, caffeine, and alcohol
- Pregnancy status (beta HCG) and breastfeeding status

4. Contraindications and Special Precautions for the Use of Clozapine

4.1 Contraindications to commencing clozapine therapy[4]

- Demonstrated hypersensitivity to clozapine or any other component listed in the product information
- A history of drug-induced agranulocytosis
- Bone marrow disorders
- Circulatory collapse and/or CNS depression due to any cause
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions
- Severe renal or cardiac disorders (eg. Myocarditis*, cardiomyopathy)
- Severe hepatic disease including active hepatic disease associated with nausea, anorexia or jaundice, progressive hepatic disease, hepatic failure
- Uncontrolled epilepsy
- Paralytic ileus

*Note: Rechallenge has been successfully completed and described in literature, however recurrence is also possible. Cardiologist advice must be sought on rechallenged with clozapine in patients with previous history of myocarditis.

4.2 Special Precautions[4, 7]

Fertility and Pregnancy[7-9]

Clozapine does not directly affect fertility but in women with antipsychotic-induced amenorrhea, a return to normal menstruation may occur as a result of switching from other antipsychotics to clozapine. Adequate contraceptive measures are therefore advised.

There is limited reproductive safety data available for clozapine, but existing literature indicates that there is no increased risk of foetal malformation, risk of stillbirth or delivery complications. Gestational diabetes, excessive weight gain, alterations in lipid levels and neonatal seizures may occur at a higher incidence but concerns regarding agranulocytosis in utero are still theoretical. The decision to prescribe clozapine during pregnancy must be based on a thorough risk assessment, noting that maternal mental health is an important factor influencing foetal well-being, obstetric outcome, and infant development.

Due to physiological changes that occur during pregnancy, extra monitoring (including therapeutic drug monitoring) is prudent and early management of side effects that may be exacerbated during pregnancy (e.g. constipation).

Referral to specialist perinatal psychiatric services is encouraged.

Breastfeeding[7-10]

Clozapine is transferred into breast milk, and it is considered that all clozapine related adverse effects can potentially be experienced by the nursing infant. A case report exists for one baby who developed agranulocytosis whilst being breastfed by a mother taking clozapine. This resolved spontaneously on cessation of breastfeeding.

Although there is little data on infant exposure to clozapine through breast milk, potential risks may outweigh the benefit and it is recommended that mothers refrain from breastfeeding whilst taking clozapine. Specialist perinatal psychiatric advice and close infant monitoring is recommended if the decision is taken to continue breastfeeding during concomitant maternal clozapine therapy.

Elderly[4, 7]

Use in the elderly population requires a lower dose at initiation of treatment, and the dose titrated up more slowly due to increased susceptibility to adverse effects including sedation, orthostatic hypotension, tachycardia and anticholinergic effects such as urinary retention and constipation. The presence of co-morbid physical health conditions magnifies these effects.

Constipation[4, 5, 7]

Clozapine has potent anticholinergic effects that can result in significant gastrointestinal hypomotility and associated complications if unmanaged (paralytic ileus, intestinal impaction, megacolon and intestinal ischaemia or infarction). Hospitalisation and deaths have occurred. Those patients who have a baseline reduced bowel function have an increased risk of gastrointestinal adverse event when commencing clozapine. Screening and correcting for constipation prior to treatment is essential.

Seizures / Cardiovascular / Renal / Liver Impairment[4, 5, 7, 11]

In patients with a history of seizures, or suffering from cardiovascular, renal or hepatic disorders (note that severe hepatic, renal or cardiovascular disorders including active hepatic disease associated with nausea, anorexia or jaundice, progressive hepatic disease and hepatic failure, are contraindications), the initial dose should be 12.5 mg given once on the first day, and any dose increase should be slow and in small increments.

Benign ethnic neutropenia[6]

Benign ethnic neutropenia (BEN) is a hereditary condition that is characterised by a low baseline neutrophil count, but with no reduction in ability to mount an immune response. There is a higher prevalence of BEN in individuals of African, Jewish, Middle Eastern and Afro-Caribbean descent. The presence of BEN should not prevent treatment with

clozapine. Patients with BEN who develop a clozapine-induced decrease in the neutrophil count, but have no evidence of infection or impaired phagocytosis, may usually resume clozapine as soon as the neutrophil count is greater than 1.0 x 10^9 / L. Haematologist and clozapine patient monitoring service consultation is required to approve adjustment of the neutrophil and white blood cell count reference ranges.

Use of agents (e.g. off-label lithium) to boost neutrophil counts in this population is not routine and should only be considered after a thorough risk benefit assessment.

5. The Initiation of Treatment with Clozapine

5.1 WA Clozapine Initiation and Titration Chart

The WA Clozapine Initiation and Titration Chart (Appendix 1.1) facilitates clinical handover and prescription for the safe management of patients initiated or re-titrated on clozapine. Decision support regarding titration is provided on the chart.

This chart meets the minimum standards for clozapine titration and is intended to be used as a record of the prescribing, monitoring, and administration of clozapine titration for all patients in inpatient settings.

In the outpatient setting, it is up to the individual Health Service Provider to determine the process for documenting, prescribing and ordering clozapine initiation and titration. Slower titrations and altered monitoring should be followed (see Appendix 5).

5.2 Dosing

Clozapine must be commenced at a low dose and titrated slowly to a therapeutic dose to minimise emergence of adverse effects including sedation and postural hypotension.

The usual recommended first dose is 12.5 mg administered once daily on the first day, preferably in the morning (to enable monitoring during the day). For inpatient settings, the WA Clozapine Initiation and Titration Chart outlines a suggested titration schedule, but slower titrations may be utilised. Patients commenced in the community must follow a slower titration due to reduced monitoring. Appendix 5 has a recommended community commencement titration. More gradual titrations must be considered in all settings for those with special prescribing precautions.

Maintenance therapeutic dose ranges are usually within the range 200 to 600 mg/day. A few patients may require larger doses to obtain maximum therapeutic benefit, in which case judicious increments (not exceeding 25 mg – 50 mg per increase per week) are permissible up to a licensed maximum of 900 mg/day. A combination of clinical response, presence of adverse effects and therapeutic drug monitoring should be used to determine an individualised dose. See section 5.3 for further information on therapeutic drug monitoring.

Interruptions and discontinuation to clozapine therapy[1, 12]

Discontinuation of clozapine causes a rapid decline in plasma levels and reinstating the same dose after a period of cessation carries a significant risk of physical adverse effect (e.g. postural hypotension, tachycardia, seizures, and excessive sedation).

If clozapine therapy is temporarily interrupted, the following table outlines suggested re-titration rate. If more rapid titrations are undertaken, a thorough risk assessment must weigh up risks of adverse effect versus benefit. Dose increases must not occur unless the previous dose is tolerated. Vital observation monitoring is key.

Table 1: Re-titrating clozapine after discontinuation

Period of interruption (time since last dose)	Dosage
Less than or equal to 48 hours	No change to dosage
Greater than 48 hours	Obtain psychiatric review prior to recommencing. Recommence on 12.5 mg once or twice a day on the first day. If this dose is tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. This is a guide only, for further dosing options refer to the treating psychiatrist.

If abrupt discontinuation of clozapine is necessary, the patient must be monitored for rebound psychotic symptoms and rebound cholinergic symptoms.

In the event that a planned discontinuation of clozapine takes place, the product information recommends gradually reducing over a minimum of two weeks. However, to further minimise the risk of rebound psychosis, it may be preferable to reduce more slowly (up to a few months). Tailor cessation titrations to the patient.

Notification of treatment interruption or treatment cessation must be submitted to the relevant clozapine monitoring service by the treating team.

5.3 Physical Monitoring

Physical monitoring is essential to assessing tolerability and for early identification of adverse effects. This monitoring section should be read in conjunction with section 6: Side effects associated with clozapine therapy.

All monitoring is recommended as a MINIMUM frequency. Patients may require extra monitoring as appropriate for their individual circumstance.

The WA Clozapine Initiation and Titration Chart is a mandatory chart for documenting orders and monitoring for clozapine initiation in an inpatient setting. Clozapine Monitoring Form A (Appendix 1.3) and Clozapine Monitoring Form B (Appendix 1.4) are forms that can be used after the initiation chart for maintenance therapy.

The following resources are also available to aid the monitoring of the physical health of patients on clozapine:

- A prompt checklist to assess potential side effects related to clozapine (Appendix 2)
- A clozapine side effect rating scale (GASS-C) is a simple tool which patients can use prior to each clinical review (Appendix 3)

Vital Observations - Initiation

The patient's temperature, pulse, respiration rate, and lying and standing blood pressure should be taken prior to starting clozapine.

Once clozapine is taken, monitoring of vital signs must take place hourly for six hours, and then 6-hourly for the first 24 hours (during waking hours). For subsequent doses, observations of patients should be taken at least twice daily for the first week of titration then daily for inpatients thereafter (more frequently if clinically required).

Patients initiated on clozapine in the community should be monitored for the first 3 hours, then daily during clinic business hours when patients are reviewed for the first two weeks then twice weekly for the third week, then weekly from week 4 at weekly reviews and at each monthly review once the initial 18 weeks is finished (increase monitoring if required).

Full Blood Count Monitoring

It is a mandatory requirement that WBC and NC are monitored weekly for the first 18 weeks of treatment and 4-weekly thereafter for the duration of therapy. Results must be uploaded to the relevant clozapine patient monitoring service database.

Table 2 provides a traffic light system for monitoring blood results and the recommended adjustments to FBC monitoring.

Table 2: Clozapine Full Blood Count Results Monitoring System

Clozapine Blood Results Monitoring System		**Recommended Actions**	
		Prior to Initiation	**Ongoing monitoring**
Green Range	WBC greater than or equal to 3.5 x 10^9/L and NC greater than or equal to 2.0 x 10^9/L	Clozapine therapy may be commenced subject to assessment by the treating medical officer and successful Clozapine Patient Monitoring System registration (e.g., ClopineCENTRAL™)	Continue clozapine therapy
Amber Range	WBC 3.0 to less than 3.5 x 10^9/L and/or NC 1.5 to less than 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	Continue clozapine therapy with twice-weekly blood tests until return to green range.
Red Range	WBC less than 3.0 x 10^9/L and/or NC less than 1.5 x 10^9/L	**DO NOT START THERAPY**. Seek haematologist advice	**WITHOLD CLOZAPINE THERAPY** Consult treating psychiatrist and contact haematologist and Clozapine Patient Monitoring System (e.g. ClopineCENTRAL™)

In the event there is a therapy interruption - depending on how long clozapine is missed, the frequency of FBC monitoring requires adjustment as per Table 3.

Table 3: Full Blood Count test monitoring after interruption of therapy[3]

Period of interruption (time since last dose)	Monitoring requirements
Less than or equal to 48 hours	No change to monitoring frequency
Greater than 48 hours and less than or equal to 72 hours	No change to monitoring frequency
Greater than 72 hours and less than or equal to 28 days	The six-week rule applies. **For weekly monitored patients:** Weekly monitoring for six weeks or for as long as needed to ensure a total of 18 weeks; whichever is the greatest. **For four-weekly monitored patients:** Weekly monitoring for six weeks. If no abnormality, resume four-weekly monitoring.
Greater than 28 days	Weekly monitoring for 18 weeks. The patient must be re-registered with the monitoring service if the period of cessation is *3 months or greater*

Post-therapy haematological monitoring is required by clozapine monitoring services. For patients on weekly blood test monitoring, a WBC and NC should be performed at least weekly for four weeks after discontinuation. For patients on four-weekly blood test monitoring, a WBC and NC should be performed as close as possible to the time of discontinuation and then follow-up WBC and NC four weeks later.

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

Eosinophilia

A rise in eosinophils may be associated with myocarditis. If eosinophil counts are > 3.0 x 10^9/L, it is recommended clozapine is withheld and not restarted until the count is below 1.0 x 10^9/L.

Point of Care Testing

Use Point of Care (PoC) testing for FBC monitoring is acceptable in community mental health clinics provided the relevant Health Service Providers have clear procedures to support use. Any abnormal readings (ie amber or red results) must be verified by pathology laboratory testing. Inpatient settings must use the available pathology laboratory services.

Cardiac Monitoring

Clozapine can cause tachycardia and changes in blood pressure, particularly at the commencement of therapy.[4, 13] The schedule of vital observations is largely aimed at monitoring for these side effects. Persistent blood pressure changes and tachycardia should be explored for any other pathology.

In addition, clozapine has been associated with myocarditis and cardiomyopathy.[4, 7, 11]

Myocarditis typically occurs in the first month of therapy with the median occurring at 15-20 days (although it may occur at other times).[5, 11] The characteristic clinical findings of myocarditis include increased CRP, increased Troponin levels and Eosinophilia. Abnormal ECGs may also be present. Measurement of CRP, troponin, and eosinophils (as part of FBC) and ECG are recommended to be taken at baseline, Day 7, Day 14, Day 21 and Day 28 of clozapine initiation and as clinically indicated thereafter.[14] Appendix 4 has a suggested monitoring protocol for clozapine induced myocarditis.

Any patient who exhibits non-specific signs or symptoms of myocarditis (fatigue, dyspnoea, chest discomfort, palpitations, fever or flu-like illness, peripheral oedema) at any time while receiving clozapine should undergo repeat cardiac markers and an immediate medical review.[7].

Cardiomyopathy is less common than myocarditis and has a later onset, with a median time of 9 months although it too can also occur at any time. Characteristic clinical findings in the early stages are often non-specific e.g. dyspnoea, resting tachycardia, fatigue, and reduced exercise tolerance. Cardiac assessment should be initiated in the presence of these symptoms.

Use of Electrocardiogram (ECG) and Echocardiogram (ECHO) for routine maintenance monitoring[14, 15]

After the initial titration period, an annual ECG to measure QTc is prudent for any patient taking an antipsychotic, particularly in the presence of psychotropic polypharmacy or interacting medication.[1, 5, 7]

A baseline ECHO assessment is important to provide a reference point for future imaging. Further ECHO testing is most effective when taken at the emergence of symptoms indicating cardiac abnormality. However, as some patients may not verbalise symptoms of deterioration, this guideline suggests monitoring may be considered at 1 year, 2 years, 5 years and then every 5 years routinely. Individual physical health, presence of previous abnormal ECHO and co-morbid cardiac conditions may necessitate more frequent imaging.

Clozapine Induced Gastrointestinal Hypomotility (CIGH) Monitoring[16, 17]

Clozapine induced gastrointestinal hypomotility is a very common adverse effect that can have potentially fatal outcomes. Fatality due to gastrointestinal adverse reactions occur at a rate higher than from blood dyscrasias. Contributing factors include under reporting and under investigation of bowel related adverse effects.

Risk factors may be rapid initiating titration, high clozapine dose, older age, concomitant medications that cause constipation (e.g. anticholinergics) and male sex.[12] A baseline assessment and correction of pre-existing constipation by prescription of aperients is essential. See Table 3 for options (under constipation)

CIGH may occur at any time but monitoring early in treatment is essential. A daily stool chart for 4 weeks and then aligning assessment of bowel function at each mandatory FBC (weekly until week 18 and four weekly thereafter) is recommended to help identify and prevent severe outcomes from CIGH.

Direct questioning of bowel habits is essential particularly as many patients may not report even very severe constipation. The Rome IV assessment criteria for functional constipation is a recommended tool (refer to diagnostic criteria in section C2, Functional Constipation, on the Rome Foundation website).

General, Metabolic, Renal and Hepatic Monitoring[4, 5, 7, 18]

Metabolic syndrome refers to the cluster of symptoms that act as risk factors for cardiovascular and diabetic morbidity and mortality. They include excess centripetal weight, lipid derangement, hypertension, and elevated glucose levels.

Clozapine is well known for causing weight gain which can be very rapid in the first few months and persist during therapy. Waist circumference and weight should be taken at each face-to-face visit (i.e. weekly up to 18 weeks and monthly thereafter). Vital observations (particularly blood pressure) are also recommended to be taken as directed above during initiation and then at each face-to-face visit. Questioning of smoking status should also align with these frequencies.

Lipid screen and BGLs are recommended at baseline, 3 months, 6 months and 6 - 12 monthly thereafter. Fasting tests are recommended. If non-fasting tests are taken, interpret based on fed/fasting status. HBA1c testing can be used in conjunction with BGL where practical.

Clozapine can cause transient elevation of liver enzymes and rarely causes hepatic injury. Renal insult by clozapine is very rare. LFTs and UEC should be monitored at baseline, at 6 months, then every 6-12 months. Doses should be adjusted if worsening function (independent of clozapine) or ceased in severe renal or severe hepatic disease.

A full physical exam is recommended at baseline and annually.

Clozapine Serum Levels: Therapeutic Drug Monitoring

Obtaining serum levels can help determine if a non-responsive patient remains symptomatic due to insufficient dosing or if a responsive patient can safely receive a lower dose to minimise side effects without risking psychotic relapse.

Monitoring of plasma levels is encouraged in the following situations:

- To monitor adherence especially if non-adherence is suspected.
- When response to an adequate dose seems poor.
- When prescribed high clozapine doses or targeting higher clozapine levels for therapeutic benefit.
- Presence of side effects suggestive of high serum levels e.g.myoclonus as a warning sign of seizure.

- Suspected clozapine toxicity.
- Use of concomitant interacting medications.
- If augmentation of clozapine is being considered.
- Change to caffeine or smoking habits.
- In the elderly or in the presence of renal or hepatic dysfunction.
- During systemic infection where inflammation related inhibition of CYP1A2 enzyme function can result in clozapine toxicity.

Obtaining clozapine serum levels

Clozapine levels are drawn 12 hours after the last dose (usually in the morning after the night-time dose) and 5 - 7 days after commencement or dose changes. When a clozapine level is ordered, most laboratories report clozapine and norclozapine levels (micrograms/L).

The clozapine level guides are based on dosing two or three times a day. If the patient receives clozapine only at night, take into account the higher morning level compared with the same dose administered on a split schedule.

It is acknowledged that access to clozapine levels may be variable depending on geographical location and results may be delayed due to pathology processing times.

Interpreting clozapine serum levels[7, 12, 19]

In the event that a patient is not responding to clozapine, levels should be optimised between 350 – 600 microg/L. This range is broadly accepted as the balance between therapeutic effect and minimising adverse effects. While the upper limit for plasma clozapine levels is not well established, above 600 microg/L is associated with increased risk of some dose dependant side effects (e.g. seizures, sedation, constipation). Some patients may require levels above 600 microg/L but levels approaching 1000 microg/L pose a significant risk for seizures. Patients should be reviewed for potential reasons for non-response at optimised level ranges. For patients requiring levels above the optimum range, protective measures should be considered (e.g. seizure prophylaxis).

The major metabolic pathway for clozapine is demethylation of clozapine leading to norclozapine, and this is commonly reported alongside the clozapine level. Norclozapine may be responsible for some of clozapine's therapeutic effect, with some speculation over the benefit of tweaking the clozapine/norclozapine ratios. However, the purported clinical benefit is still largely theoretical. If levels are within the usual range and patients are tolerating and responding well to treatment, there is no need for further dose adjustment.

Where the clozapine/norclozapine ratio may be helpful is as an indicator of compliance or saturated metabolism. The mean ratio is often cited as 1.3, but variability exists between individuals. In chronic dosing the ratio should remain the same for an individual. However, ratios are affected by the time of sampling so this should also be considered (high in early samples and low in later samples). After correcting for sampling times, a clozapine/norclozapine ratio of greater than 3 may indicate enzyme inhibition / metabolic saturation. A clozapine/norclozapine ratio of less than 1 may suggest poor adherence prior

to sampling or enzyme induction. Correction of the underlying cause if possible and/or cautious dose adjustment may be warranted.

Clozapine Levels During Infection[7, 12]

Systemic infection can be associated with toxic clozapine levels. This is related to inflammation inhibiting CYP1A2 enzyme activity. Concomitant use of some antibiotics and smoking reduction during illness can further contribute to the risk. Clozapine levels should be monitored during periods of systemic infection along with CRP levels. Dose reductions of 50% can be considered initially. If signs of clozapine toxicity or confirmed supratherapeutic clozapine levels, withholding doses is recommended until a normalising of infective symptoms, clozapine levels and CRP levels.

6. Side Effects Associated with Clozapine Therapy

The table below outlines the more common side effects related to clozapine and the signs and symptoms that should be carefully monitored. For further pharmacological options and actions, the treating team should seek specialist pharmacist advice.

Table 4: Side-effects associated with clozapine therapy.

Side-effect/Signs and symptoms/Onset	Rate*	Recommended Action
Haematological effects		
Neutropenia / Agranulocytosis WBC <3.0 x 10^9/L or Neutrophils < 1.5 x 10^9/L. Flu-like symptoms such as sore throat & fever. First 18 weeks highest risk – but may occur at any time	Infrequent	**Urgent medical review. Withhold clozapine. Repeat FBC.** • Investigate potential other causes (e.g. interacting medication). • Contact haematologist at clozapine patient monitoring centre for further advice. • Re-introduction of clozapine should only occur with haematologist support. This is not a dose dependant side effect – reducing the dose will not resolve the side effect.
Cardiac effects		
Myocarditis Tachycardia at rest with rapid breathing, dyspnoea, hypotension, raised jugular venous pressure, fatigue, infective or flu-like symptoms, chest pain or fever. May appear anytime but most cases occur within 4 weeks of initiation.	Infrequent (NB. Australia and NZ report higher rates than globally)	**Urgent medical review. Refer to cardiologist.** • Check Troponin and C-reactive protein (CRP) levels. • Withhold clozapine. • Repeat ECG and Echocardiogram. Re-introduction of clozapine should only occur with cardiologist support. The titration rate should be slowed.
Cardiomyopathy Consider if there is clinical evidence of heart failure including resting tachycardia, tachypnoea, shortness of breath. fatigue or hypotension.	Rare	**Urgent medical review. Refer to cardiologist.** • Check Troponin and C-reactive protein (CRP) levels. • Withhold clozapine. Repeat ECG and Echocardiogram. Re-introduction of clozapine should only occur with

May occur at any time.		cardiologist support.
Tachycardia First four weeks but can persist	Common	**Contact Doctor.** • If other symptoms present, consider other causes (e.g. myocarditis) and investigate further. • Benign tachycardia is relatively common and can often be self-limiting. • Persistent tachycardia should be addressed and may require pharmacological intervention such as a beta blocker.
Orthostatic hypotension May occur anytime, more prominent during titration/dose changes	Common	• Best managed with slow and gradual titration of clozapine. • Patients must be provided with advice on managing postural dizziness (take time standing up) and the modification of dietary salt and fluid intake. • Specialist support may be needed if the symptom persists, and pharmacological treatment is required. Note that some patients may develop hypertension on clozapine, and this should be treated accordingly.
Thromboembolism Risk highest in first 3 months but may occur any time	Rare	• Avoid immobilization. • Early detection important as potentially life-threatening event. May be dose related. • Prophylactic antithrombotic treatment usually required if clozapine is continued
Central nervous system effects		
Sedation First 4 weeks but may persist	Common	• Give smaller dose in the mornings. • Some patients can only tolerate single night-time dosing. Reduce dose if necessary. • Consider plasma level monitoring. • Avoid other sedating agents.
Seizures Myoclonus may be a precursor to subsequent seizures May occur at any time	Rare	**Medical emergency – manage seizure** • Usually dose/plasma level related. • Withhold dose for one day and restart at half the dose. • Ensure levels are maintained within normal range. • Consider anticonvulsant cover. • Sodium valproate is commonly used but other antiepileptics may also be appropriate (e.g. lamotrigine or topiramate). • Monitor serum clozapine levels regularly.
Gastrointestinal effects		
Hypersalivation Excessive drooling – very troublesome at night. Association with aspiration pneumonia which can be life-threatening First few months especially but can persist.	Common	• Hyoscine hydrobromide sucked, sublingual atropine or sublingual ipratropium may also be considered. • Caution using anticholinergics as they may worsen constipation. Atropine drops used sublingually may pose a safety risk if taken in overdose. • Wrapping a towel around a pillow at night is also recommended. Some anecdotal reports that slowing down the titration can help.

Constipation Less frequent bowel motions, hard stools, abdominal bloating, cramping or pain, decrease appetite, nausea and vomiting or fatigue. First 4 months but persists. Severe Clozapine Induced Gastrointestinal Hypomotility (CIGH) can be fatal.	Common	**Requires continuous monitoring and aggressive treatment.** All patients must be screened and treated for pre-existing constipation prior to commencing clozapine. Constipation should be considered a serious adverse effect as it can have potentially fatal complications. • Increase dietary fibre, fluid intake and exercise. • Stimulant laxatives (eg. docusate and senna) are first line, add in osmotic laxatives (eg. macrogol, lactulose) as needed. • Avoid bulk forming laxatives as the underlying cause is gastric hypomotility. • Review other medications that may cause constipation. • Consider dose reduction. • Ongoing continuous monitoring/treatment required. • Treat CIGH aggressively with laxatives. Refer to gastroenterologist and undertake risk/benefit assessment of continuing clozapine if treatment fails.
Nausea First 6 weeks	Common	• Consider antiemetic. • Avoid prochlorperazine and metoclopramide if previously experienced extra pyramidal side effects (EPSE). • Avoid domperidone if increased QTc, ondansetron may worsen constipation.
Weight gain and metabolic effects		
Weight gain Early in treatment but often persists	Common	• Dietary and lifestyle counselling before weight gain occurs. • Ongoing monitoring and support. Metformin may be considered as a first line pharmacological intervention in patients with or without glucose intolerance or diabetes.
Hyperglycaemia Any time	Common	• Regularly screen for evidence of diabetes. • Use hypoglycaemics (as per guidelines for managing hyperglycaemia)
Hyperlipidaemia Any time	Common	• Regularly screen for evidence of elevated triglycerides and lipids. • Use lipid lowering agents (as per guidelines for managing hyperlipidaemia).
Other		
Fever Temperature $\geq 38^0$ C First 4 weeks	Common	**Contact Doctor. Urgent if other symptoms present** • Reduce rate of dose titration of clozapine. Check WBC and NC, troponin, and CRP. • Physical examination for signs of infection. • Consider ECG, ECHO.
Nocturnal enuresis Loss of bladder control, especially at night. May occur at any time.	Common	• Try reducing or dividing dose to avoid excessive sedation. • Avoid fluids prior to bedtime and consider scheduled voiding during the night. • May require pharmacological intervention - consider a continence referral.
Obsessive Compulsive Behaviour Symptoms usually appear (or worsen) within the first year, may be	Rare	• Dose reduction may lead to symptom improvement. • Cognitive behavioural therapy or antidepressants noting that many antidepressants can have an effect

transient but may persist. Likely dose dependant		on clozapine serum levels.
Pneumonia May occur at any time.	Rare	**Contact Doctor, start appropriate treatment promptly.** • Dose related risk. • Hypersalivation increases risk. • May also be secondary to severe constipation.
This is not an exhaustive list of side-effects. Please see Clozapine Product Information for further advice.		

*Common >1%, Infrequent 0.1-1% and Rare <0.1%

Should an adverse event occur as a result of clozapine therapy (which could include cardiac complications, haematological or metabolic complications or any other side effects discussed above) the adverse incident must be reported in the patient medical record, the Therapeutic Goods Administration adverse event monitoring system and the Clozapine Patient Monitoring System within 24 hours of the event taking place or being first noted.

7. Important drug interactions with clozapine

There are a number of important potential interactions to consider with clozapine as per the following table.

Table 5: Important Drug Interactions with clozapine[4, 13]

Drug	Interactions	Comments
CYP1A2 inhibiting substances (e.g. fluvoxamine, caffeine, ciprofloxacin)	Concomitant use may increase clozapine levels	CYP1A2 is the major metabolic pathway for clozapine. Potential for significant increase in plasma clozapine levels and adverse effects. Care is also required upon cessation of concomitant CYP1A2 inhibiting medications as there will be a decrease in clozapine levels.
CYP1A2 inducing substances (e.g. polyaromatic hydrocarbons as found in cigarettes)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered. Care is also required upon cessation of concomitant CYP1A2 inhibiting medications as there will be an increase in clozapine levels.
CYP2D6 inhibiting substances (e.g. fluoxetine, paroxetine, duloxetine)	Concomitant use may increase clozapine levels	Potential for increase in plasma clozapine levels adverse effects. Care is also required upon cessation of concomitant CYP2D6 inhibiting medications as there will be a decrease in clozapine levels.
CYP3A4 inhibiting substances (e.g. azole antimycotics, protease inhibitors)	Concomitant use may increase clozapine levels	Potential for increase in plasma clozapine levels adverse effects. Care is also required upon cessation of concomitant CYP3A4 inhibiting medications as there will be a decrease in clozapine levels.
CYP3A4 inducing substances (e.g. carbamazepine, phenytoin, rifampicin, St John's Wort)	Concomitant use may decrease clozapine levels	Potential for decrease in plasma clozapine levels adverse effects. Care is also required upon cessation of concomitant CYP3A4 inhibiting medications as there will be an increase in clozapine levels.
Bone marrow suppressants • carbamazepine, chloramphenicol	Interact to increase the risk and/or severity of bone marrow	Increased risk of agranulocytosis or neutropenia Clozapine use is not recommended concomitantly with other agents having a well-known potential to

• sulphonamides (e.g. co-trimoxazole), penicillamine • Cytotoxic agents • Some other antipsychotic agents	suppression.	suppress bone marrow function although it is acknowledged some combinations may be unavoidable. Increased frequency of WBC and NC may be required
Anticholinergics	Clozapine potentiates action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, urinary retention especially when using to help control hypersalivation.
Antihypertensives	Clozapine can potentiate the hypotensive effects	Caution is advised due to potentiation of hypotensive effects, especially during the period of initial dose titration.
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination.	Caution is advised if clozapine is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery. Opioid based narcotics will contribute to constipation.
Highly protein bound substances (e.g. warfarin and digoxin)	Clozapine may cause increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if required.
Phenytoin	Addition of phenytoin to clozapine regimen may cause a decrease in the clozapine plasma concentrations.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.
Lithium	Concomitant use can increase the risk of development of neurotoxicity and Neuroleptic Malignant Syndrome (NMS).	Observe for signs and symptoms of neurotoxicity and NMS.
Anti-infectives	Use of anti-infectives may produce an aberrant low neutrophil count on blood sampling. Some anti-infectives increase clozapine plasma levels. Check individual agents	Monitor WBC and NC. Take plasma level if necessary. Adjusting clozapine dose temporarily may be required (eg. when concomitantly using ciprofloxacin)

Clozapine and smoking[5]

Baseline smoking habits and regular updates must be documented at each visit. Smoking can cause a reduction in the plasma concentration of clozapine through induction of the P450 CYP1A2 metabolic hepatic pathway. It is important to note that it is the polyaromatic-hydrocarbons within the tar of cigarettes which affects clozapine metabolism and levels,

not the nicotine. Nicotine replacement therapy (NRT) or e-cigarettes / vaping do not affect clozapine levels.

Any change in the patient's smoking status should be documented and clearly communicated to the treating team. Abrupt cessation of smoking or changing nicotine consumption preference to e-cigarettes may lead to clozapine toxicity through a rise in serum clozapine levels. Cessation of smoking should be done under supervision and in a tapered manner and needs to be accompanied by regular monitoring of clozapine level with appropriate dose adjustments.

Prescribers must be aware of a possible similar effect on clozapine levels with cessation of cannabis smoking. Regular assessment of cannabis use should be undertaken, use monitored, and patients should be offered support to decrease and manage cannabis use. 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 through inhibition of CYP 1A2. Changes in caffeine intake (eg. 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.

Clozapine augmentation[12]

Although clozapine is indicated for treatment resistant schizophrenia, there will still be a proportion of patients who will not respond adequately at therapeutic doses. As most patients on clozapine have no viable monotherapy options left, one strategy often explored is augmentation of clozapine treatment with another agent. Augmentation strategies are to be considered after all efforts have been made to optimise clozapine.

It should be noted that the addition of another psychotropic (particularly other antipsychotics) to an existing clozapine regimen may increase the risk of a patient developing agranulocytosis as well as increasing side effects overall. This risk is further complicated if the medicine is given as a long-acting intramuscular antipsychotic injection due to their prolonged action. Monitoring for efficacy and adverse effects is essential. If no benefit or unmanageable side effects occur, then withdrawal of the augmenting agent is recommended.

8. Health Care Professional Responsibilities

All staff involved in the management of clozapine must adhere to TGA and PBS requirements. Individual Health Service Providers are responsible for defining the roles and tasks assumed by each of the healthcare professionals and how they interact with

non-government healthcare professionals involved in clozapine management (e.g. general practitioners and community pharmacist)

Eligible Prescribers

- Be registered and familiar with the relevant clozapine patient monitoring system requirements.
- Evaluate clozapine treatment in accordance with this guideline including assessing individual suitability, eligibility, baseline characteristics, precautions and contraindications.
- Review required monitoring parameters as per this guideline.
- Prescribe clozapine in accordance with these guidelines.
- Where possible make treatment decisions jointly with the patient, carer and/or guardian. Provide adequate information both written and verbal regarding treatment.
- Monitor the patient's physical and mental health and action appropriate management if required.
- Document and communicate care plans to all relevant stakeholders including at transitions of care.
- Junior medical officers and General Practitioners involved in shared share arrangements must take direction from a psychiatrist regarding clozapine dosing.

Nursing staff

- **Inpatient Nursing Staff**
    - Ensure all relevant baseline investigations are taken as requested.
    - Administer clozapine according to the medication chart.
    - Perform observations and side effect monitoring.
    - Escalate any abnormal result(s) or any other concerns regarding mental or physical state.
    - Document and communicate handover to relevant stakeholders.

Clozapine Clinic Coordinators

- Register patients, clinics and relevant staff with the clozapine patient monitoring service.
- Ensure the required monitoring is performed as per this guideline.
- Update the monitoring service database as per business rules.
- Report and escalate identified problems to relevant stakeholders.
- Liaise with hospitals, healthcare providers and pharmacies with regards to management and medication supply.
- Support other healthcare professionals with regards to clozapine patient monitoring service requirements

It is acknowledged that individual health service providers may construct the coordinators' roles differently and consequently may be performed by a variety of healthcare professionals. Individual health service providers must outline duties to be performed by the clozapine coordinator and those undertaken by other healthcare professionals.

Case Managers

- Provide case management for people taking clozapine.
- Assist clozapine coordinators in following up on adherence to monitoring protocols, particularly blood tests.
- Assist in liaising with hospitals, healthcare providers and pharmacies with regards to management and medication supply.
- Report and escalate identified problems to relevant stakeholders.

Pharmacists

- Assess FBC test results and dispense prescriptions in accordance with PBS, state and clozapine monitoring system requirements.
- Update the monitoring service database as per business rules.
- Liaise with relevant stakeholders.
- Report and escalate identified problems to relevant stakeholders.
- Support other healthcare professionals in prescribing clozapine.
- Provide written and/or verbal information to patients, carers, and healthcare professionals regarding clozapine.

Carers

- *The Carers Recognition* Act 2004 outlines the need to include carers as partners in care. People on clozapine often need support to attend clinic reviews, have frequent blood tests and pick up medication. The views and needs of carers must be taken into account along with the view, needs and best interests of people receiving care when decisions are made that impact carers and the role of carers.

9. The Transition to Maintenance Therapy

Once treatment has been initiated and stabilised it can be described as progressing from the initiation phase or initiation therapy to the maintenance phase or maintenance therapy (at least 18 weeks). Some patients may reach a state of stabilisation before 18 weeks and some patients may take longer.

Definitions of stabilisation may differ across different jurisdictions, but generally refer to a point in clozapine therapy when the patient's mental state and functional level, clozapine dosage and any significant side effects of the medication are all considered to be at an optimal level. This can take up to two years from initial dose. The majority of patients will be receiving services in the community setting by this time. Legislative changes in 2015

support greater flexibility in prescribing and dispensing for patients at this time of transition in clozapine care.

The WA Clozapine Initiation and Titration Chart (Appendix 1.1) can be used to record treatment at initiation, recommencing after interruption of less than 28 days or continuing (up to 28 days) after which time, the Clozapine Monitoring Forms A and B (see Appendices 1.3 and 1.4) is used to record physical monitoring protocols and can be used weekly to 18 weeks or as an ongoing monthly clinical review form.

9.1 Models of Clozapine Management for Maintenance Patients

Several service models providing improved integration of mental and physical health care have been explored in other jurisdictions.

Service models fall broadly into three categories (listed below). Individual Health Service Providers may adopt variations. It is important to highlight that all models of care must ensure the safety of patients, that there is no loss of quality of service in the transition to shared care, that all clinicians involved are competent and qualified professionals, and that specialist oversight of the care remains (as is required both legislatively and clinically). All services must have a full understanding of legislative or other requirements before implementing new models of care for clozapine.

- **Public Mental Health Services**

Clozapine management is undertaken by outpatient mental health services with the involvement of WA Health Department employed prescribers and other health professionals. Clozapine patients may be managed by a case manager and/or a Clozapine Clinic service.

The Clozapine Clinic is an outpatient treatment program that provides comprehensive mental health services for adults that are currently being prescribed clozapine or about to commence clozapine. Due to the requirement of registration with a clozapine patient monitoring service, frequent blood tests and physical health monitoring, clozapine clinics specialise in the follow up and case management of people on clozapine. The role of the clozapine coordinator is essential to the overall function of the program. Review by a mental health service doctor is recommended at a minimum of 6 monthly.

- **GP Shared Care**

Generally, all mental health patients should be registered with a general practitioner for management of all aspects of their physical health care.

GP Shared Care in this context refers specifically to the role assumed by the GP in performing the clozapine monitoring schedule +/- clozapine prescribing function for suitable patients. Clozapine patients attend the nominated GP practice for routine monthly reviews, prescriptions, mental state and physical health assessments.

In no circumstance may a clozapine patient be completely discharged from a mental health service to a GP service. Oversight and regular communication must be maintained

between the GP practice and the public or private mental health service with routine review by a psychiatrist occurring every 6 - 12 months. Review can occur more frequently if clinically indicated. Additionally, a mechanism for rapid referral back to the mental health service is essential.

The division of tasks of each healthcare professional must be defined when the patient is transferred into a GP shared care model.

- **Private Psychiatrist Care**

The private psychiatrist assumes the roles and responsibilities for managing clozapine therapy and should follow the recommendations outlined in this guideline. Private psychiatrists may also participate in shared care models as outlined above.

9.2 Considerations for Clozapine Shared Care

Shared Care models may be considered for patients who are stabilised on monthly monitoring of clozapine therapy. However, not all clozapine patients on maintenance therapy are suitable for GP shared care management. It is the characteristic of the patient receiving the clozapine rather than the duration of clozapine therapy which must be the determining factor in any transition of care.

Factors that may impact on a patient's ability to move to general practice community-based care include the following:

- A patient's agreement to participate in shared care.
- a patient's adherence history with clozapine, other medication and blood tests
- their ability to independently attend appointments, blood tests and other investigations.
- long-term sustainable support (family, partner, carer)
- their ability to access the GP practice and a suitable pharmacy.

Any 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.

10. Training and Education

Health Service Providers (HSP's) are responsible for ensuring training is provided to all relevant WA health system clinicians involved in the prescribing, dispensing and administration of clozapine to patients.

11. Related Documents

11.1 Legislation

- WA Mental Health Act 2014
- Medicines and Poisons Act 2014

- Medicines and Poisons Regulations 2016.
- Pharmacy Act 2010 (WA)
- Pharmacy Regulations 2010 (WA)
- Health Practitioner Regulation National law (WA) Act 2010
- Carers Recognition Act 2004

11.2 Authorising policy and standards

- National Safety and Quality Health Service Standards 2nd Ed 2017 (updated May 2021), standards 1, 2, 4, 5, 6 and 8
- National safety priorities in mental health: a national plan for reducing harm 2005
- National Medicines Policy 2022
- Poisons Standard 2015 (SUSMP No. 16 February 2017)

11.3 Procedures, guidelines and protocols

- High Risk Medication Policy MP 0131/20
- Medication Chart Policy MP 0078/18
- WA Clozapine Initiation and Titration Chart User Guide
- WA Clozapine Initiation and Titration Chart Education Resource
- Clozapine patient monitoring protocols and services published and operated by ClopineCENTRAL™ from Pfizer Login (clopine.com.au)
- Choice and Medication Printable Leaflets Government of Western Australia Department of Health Home (choiceandmedication.org)

12. ClopineCENTRAL™ Contact Information

Clopine® is the current brand prescribed by WA Department of Health (the Department) however the tender for medications is reviewed periodically which may affect future prescribing requirements.

Clinical enquiries should initially be discussed at a local health service level however ClopineCENTRAL™ offers haematology advice for patients on clozapine.

ClopineCENTRAL™

- Phone: 1800 656 403
- Fax: 1800 657 454
- Email**:** Clopinecentral@pfizer.com

On-Call Haematologist (on call: Available 24 hours a day, 7 days a week)

- Phone: 03 9387 1000 (Pager Service)

13. Acronyms, initials and definitions

ADR	Adverse drug reaction
Centre	A 'centre' is defined as a hospital, clinic or other facility that is involved with the use of clozapine.
CIGH	Clozapine Induced Gastrointestinal Hypomotility
ClopineCENTRAL™	The Department uses the ClopineCENTRAL™ monitoring system in accordance with the current contract for purchase of pharmaceuticals.
CNS	Central Nervous System
CPMS	Clozaril™ Patient Monitoring System
CRP	C-reactive protein
Depot injection	A depot injection is an injection, usually subcutaneous, intradermal, or intramuscular, that deposits a drug in a localized mass, called a depot, from which it is gradually absorbed by surrounding tissue. Such injection allows the active compound to be released in a consistent way over a long period. All antipsychotic depot injections are delivered intramuscularly.
ECG	Electrocardiogram
ECHO	Echocardiogram
EPSE	Extrapyramidal side-effects
FBC	Full blood count
GP	General Practitioner
HbA1c	Haemoglobin A1c Test
HSD	Highly Specialised Drug
HSP	Health Service Provider
LFT	Liver Function Test
MAOIs	Monoamine oxidase inhibitors. Medications prescribed for the treatment of depression.
Maintenance Therapy at stabilisation	Definitions of stabilisation may differ across different jurisdictions, but generally refer to a point in clozapine therapy when the patient's mental state and functional level, clozapine dosage and any significant side effects of the medication are all considered to be at an optimal level
MDT	Multidisciplinary Team
NC	Neutrophil Count
NMHS	North Metropolitan Health Service
NMS	Neuroleptic Malignant Syndrome
NRT	Nicotine Replacement Therapy
OTC	Over the counter
PI	Product Information
PRN	Medicines that are taken "as needed" are known as "PRN" medicines. Some of these medicines are prescribed while others can be purchased over the counter at a pharmacy.
PSP	Personal Support Person
QUM	Quality use of medicines

SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TRS	Treatment resistant schizophrenia
ULN	Upper Limit of Normal
WAPMG	WA Psychotropic Medication Group
WATAG	WA Therapeutics Advisory Group
WBC count	White Blood Cell count

Appendix 1: Clozapine Resources

1.1 WA Clozapine Initiation and Titration Chart

https://www.health.wa.gov.au/~/media/Corp/Policy-Frameworks/Clinical-Governance-Safety-and-Quality/Medication-Chart-Policy/Supporting/WA-Clozapine-Initiation-and-Titration-Chart-Adult-Chart.pdf

1.2 Guidelines for the use of the WA Clozapine Initiation and Titration Chart

https://www.health.wa.gov.au/~/media/Files/Corporate/general-documents/Quality/PDF/WA-Clozapine-Initiation-titration-user-guide.pdf

1.3 Clozapine Monitoring Form - PART A

Clozapine-Monitoring-Form-A.PDF (health.wa.gov.au)

1.4 Clozapine Monitoring Form – PART B

Clozapine-Monitoring-Form-B.PDF (health.wa.gov.au)

1.5 Choice and Medication Consumer Information

Government of Western Australia Department of Health Home (choiceandmedication.org)

Appendix 2: Clinician prompt checklist to assess clozapine side effects

This assessment checklist supports the assessment of potential side effects related to clozapine therapy. The list is not exhaustive. Seek advice if unsure. Be cautious prescribing medicines with similar side effects to clozapine. Note any side effects in the patient's medical record. Ensure suitable intervention and follow up if side effects are raised by the patient.

1.	**General Assessment**	**Y/N**
a.	**Symptoms:** Have you noticed an increase (hallucinations, jumbled thoughts, paranoia, strange experiences) in the symptoms of your illness?	
	Have you noticed a decrease in the symptoms of your illness?	
b.	**Risk:** Have you had thoughts of harming yourself or others?	
c.	**Function:** Have you had trouble with taking care of yourself, your home or your finances?	
d.	Have you had a hospital admission since last visit?	
2.	**Assessment for drug interactions**	
a.	Review of medications at each visit	
b.	Have you ceased/ started any new medications since last visit? Include all prescribed, over the counter (OTC), complementary, topical, inhaled, oral contraceptives and PRN medications	
c.	Have you stopped/started smoking since your last visit?	
d.	Have you increased/decreased your intake or changed your drugs since your last visit? i.e. marijuana, coffee, analgesics	
3.	**Adherence status**	
a.	Have you missed, decreased or increased your dose of clozapine since your last visit?	
b.	Have you missed, decreased or increased your dose of any other medications since your last visit?	
4.	**Assessment of side effects of clozapine and general medical issues**	
a.	**Infection**	
	i. Have you noticed a fever or sweating since your last visit? (duration, timing, intensity)	
	ii. Have you felt generally well / unwell	
	iii. Do you have any specific symptoms of infection such as cough, increased mucus, nausea, vomiting, diarrhoea, pain when urinating, abdominal pain, ear or sinus pain, skin infection, muscle aches or joint pains? **Observation** – increase in vital signs	
b.	**Cardiovascular**	
	i. Since your last visit have you suffered from dizziness (particularly on standing),	

	palpitations, rapid, irregular or missed heartbeats, shortness of breath, headaches, or visual disturbances, chest pain, shortness of breath when lying down, or swelling of the ankles? **Observation** – irregular pulse on manual assessment, postural hypotension, hypertension	
c.	**Seizures/ myoclonus**	
	i. Have you suffered from involuntary muscle tics or twitches in any part of your body since your last visit?	
	ii. Have you had blackouts, seizures witnessed by others, or unexplained incontinence or injuries from biting your tongue or the inside of your mouth? **Observation** - Myoclonic jerks or witnessed seizures on observation	
d.	**Extra Pyramidal Side Effects (EPSE)**	
	i. Since your last visit have you had muscle stiffness, tremor, problems with moving your eyes, difficulty walking, or problems with performing tasks with your hands? **Observation** - Tremor, muscle rigidity or abnormal posture/gait on examination	
e.	**Sedation**	
	i. Since your last visit have you had trouble waking up, felt drowsy during the day, have had day time naps or have you spent > 8 hours per day sleeping? **Observation** - sedated on observation.	
f.	**Hypersalivation**	
	i. Since your last visit have you had excess saliva production as indicated by drooling, swallowing excess saliva, waking up with a wet pillow or waking up due to coughing from saliva? **Observation** - observed hypersalivation, drooling	
g.	**Constipation**	
	i. Since your last visit have you been using laxatives or noticed decreased frequency of stool, straining to pass stools, faecal incontinence, diarrhoea or abdominal pain, nausea or vomiting? **Observation** - Presents with faecal incontinence, abdominal distension and pain, nausea or vomiting	
h.	**Urinary Symptoms**	
	i. Since your last visit have you suffered from frequent urination (large volumes), difficulty passing urine, urinary frequency, polyuria or urinary incontinence? **Observation** - Presents with urinary incontinence or suprapubic pain/distension.	
i.	**Sexual Side Effects**	
	i. Since your last visit have you had any problems enjoying sex? ii. Men only: Have you had problems getting an erection?	
j.	**Dental**	
	i. Since your last visit have you had any problems with your teeth?	

Acknowledgement:[20] Nurse Led Clozapine Clinic assessment questions June 2013 – Scott Clark March 2011, updated June 2013.https://www.sahealth.sa.gov.au/.../nurse+led+clozapine+clinic++assessment+questions

Appendix 3: Clozapine side effect rating scale (GASS-C)

Name: _____

Date: _____

Caffeine (include energy drinks) intake: _____ **cups / day**

Smoker: Y / N _____ **cigarettes / day**

Current Medications and total daily doses:

_____

_____

_____

_____

Has there been a change in your smoking habit? Yes / No (Please circle).

If Yes, increase / decrease (please circle) by _____ **cigarettes / day.**

This questionnaire is being used to determine if you are suffering from excessive side effects from your medication. Please put a tick in the column which best indicates how often or how severely you have experienced these side effects.

Over the <u>past week</u>		Never	Once	A few times	Everyday	Severe or distressing
1	I felt sleepy during the day					
2	I felt drugged or like a zombie					
3	I felt dizzy when I stood up or have fainted					
4	I felt my heart beating irregularly or unusually fast					
5	My muscles have been tense or jerky					
6	I have been drooling					
7	My vision has been blurry					
8	My mouth has been dry					
9	I have felt like I am going to be sick or have vomited					
10	I have felt gastric reflux or heartburn					
11	I have had problems opening my bowels (constipation)					
12	I have wet the bed					
13	I have been passing urine more often					
14	I have been thirsty					
15	I have felt more hungry than usual or have gained weight					
16	I have been having problems enjoying sex Men only: I have had problems getting an erection					
I have also experienced: (please write down any other side effects, physical problems or complaints that you have experienced over the <u>past week</u>.						
17						
18						
19						
20						

Clozapine side effect rating scale (GASS-C): Staff scoring Information

1) Allow the service user to fill in the side-effects scale by themselves.
   All questions relate to the previous week.

2) Scoring

0 points	"Never"
1 point	"Once"
2 points	"A few times"
3 points	"Everyday"

3) Results

0-16	Absent/mild side effects
17-32	Moderate side effects
33-48	Severe side effects

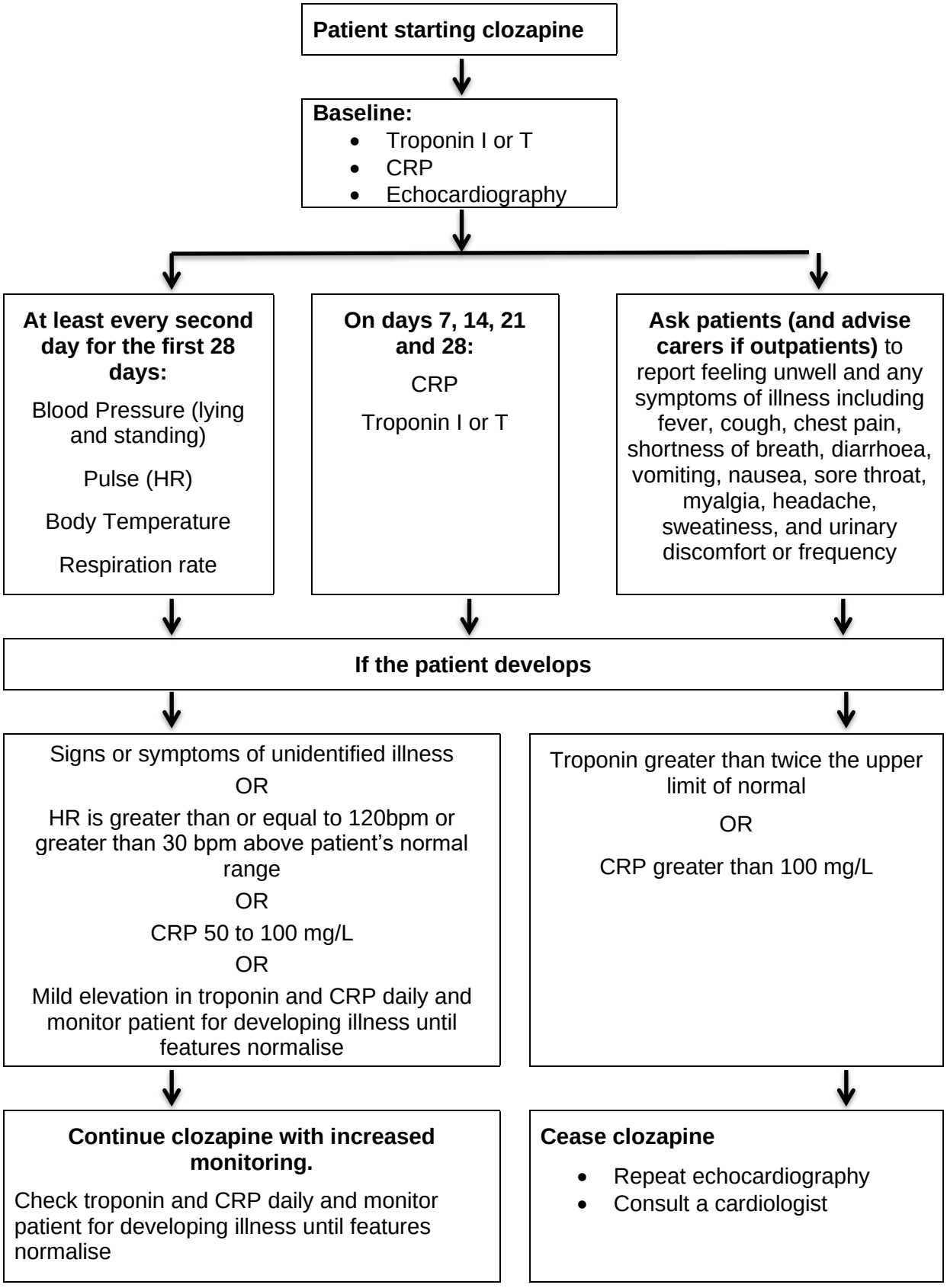
4) Side effects covered include:

1-2	Drowsiness and sedation
3	Postural hypotension
4	Tachycardia
5	Myoclonus
6	Hypersalivation
7-8	Anticholinergic side effects
9-10	Gastrointestinal side effects
11	Constipation
12	Nocturnal enuresis
13-14	Screening for diabetes mellitus
15	Weight gain
16	Sexual dysfunction

5) The column relating to the severity/distress experienced with a particular side effect is not scored, but is intended to inform the clinician of the service user's views and condition.

6) Questions 17 to 20 invite the consumer to report any other side effects or problems not already mentioned. These questions should not be scored but may instigate a discussion with the consumer if clinically appropriate.

Appendix 4: Commencement phase protocol for monitoring patients commenced on clozapine in the community for clozapine-induced myocarditis



Adapted from: [23]Ronaldson, K.J., Fitzgerald, P.B., Taylor, A.J., Topliss, D.J. and McNeil, J.J., 2011. A new monitoring protocol for clozapine induced myocarditis based on an analysis of 75 cases and 94 controls. Australian and New Zealand Journal of Psychiatry; Early Online, pp.1-8. DOI: 10.3109/00048674.2011.572852.

Appendix 5: Suggested titration regime for initiation of clozapine in the community*

DAY	AM Dose (mg)	PM Dose (mg)	Monitoring
1	6.25	6.25	A
2	6.25	6.25	A
3	6.25	6.25	A
4	6.25	12.5	A, B, FBC
5	12.5	12.5	A Check results from day 4. Remind patient of out of hours arrangements and weekend.
6	12.5	12.5	No routine monitoring unless clinically indicated
7	12.5	12.5	No routine monitoring unless clinically indicated
8	12.5	25	A
9	12.5	25	A
10	25	25	A
11	25	37.5	A, B, FBC
12	25	37.5	A Check results from day 1. Remind patient of out of hours arrangements and weekend.
13	25	37.5	No routine monitoring unless clinically indicated
14	25	37.5	No routine monitoring unless clinically indicated
15	37.5	37.5	A
16	37.5	37.5	Not seen unless problems
17	37.5	50	A
18	37.5	50	Not seen unless problems
19	50	50	A, B, FBC
20	50	50	No routine monitoring unless clinically indicated
21	50	50	No routine monitoring unless clinically indicated
22	50	75	A
23	50	75	Not seen unless problems
24	75	75	A
25	75	75	Not seen unless problems
26	75	100	A, B, FBC
27	75	100	No routine monitoring unless clinically indicated
28	75	100	No routine monitoring unless clinically indicated
Ongoing	As clinically indicated		

Note:
A = Pulse, postural BP, temperature should be taken before the dose and ideally, between 30 minutes and 6 hours after the dose. Enquire about side effects.
B = Mental state, weight, review and actively manage side effects. Consider troponin, CRP, beta-natriuretic peptide.

Commencement should take place early in the week to allow for adequate staffing and monitoring. Dose increments (not exceeding 25-50mg per increase per week) until target dose is reached (use plasma level). Dose increases should only occur during the week and not at weekends.

*Adapted from The Maudsley Prescribing Guidelines in Psychiatry 14th Edition (2021)[12]

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