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

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

August 2017

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: http://www.safetyandquality.health.wa.gov.au/home/index.cfm

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- WA Therapeutic Advisory Group (WATAG)
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Summary of the WA Clozapine Initiation, Titration and Maintenance Care Pathway[1,2,3]

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).

↓

Medical history and pre-commencement screen

Check medical and psychiatric history for 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 7).

↓

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 patients carer or Guardian must be consulted.

↓

Conduct pre-treatment tests and baseline monitoring requirements.

Complete all pre-clozapine baseline tests within 10 days prior to clozapine commencement (Appendix 1).

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).

Green WBC (white blood cell) and neutrophil results = clozapine is appropriate to be commenced.

Review current medications to check interactions. Treat constipation if pre-existing. Record smoking status.

Send results to Acute Mental Health Team (MHT), if applicable, with referral.

↓

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

The prescriber must register the patient with ClopineCentral™ (or *Clozapine Patient Monitoring Service (CPMS)*.

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 S100 requirements are met.

↓

Clozapine Initiation (Inpatients and Community Patients)

Do not initiate clozapine until approved by ClopineCentral™ or CPMS and patient clozapine number is allocated

Prescribe morning dose of 12.5mg daily for inpatients, and then follow the titration chart[3].

For community patients, a lower dose of 6.25mg may be appropriate with slower titration.

Obtain supply of clozapine from the pharmacy. Inform the nursing team of the titration schedule using the WA clozapine initiation and titration chart.

↓

Day 1

Initial dose administration:

Monitor vital signs (Temperature, respirations, pulse and lying down and standing BP) *hourly for six hours (inpatients and community patients), then every 6 hours for the first 24 hours (inpatients)*

Day 2-14 (Weeks 1 and 2)

Monitor vital signs *twice daily or more frequently if clinically required (inpatients); once daily for community patients.*

↓

Weeks 3 and 4

Monitor vital signs *daily if inpatient, weekly if community based/outpatient.*

Use the *WA Clozapine Initiation and Titration Chart to guide blood monitoring and physical health monitoring for week 1-4.*

Week 5 to 18			
Inpatient setting Monitor vital signs: Temperature, respirations, pulse and lying down and standing BP ***conducted daily*** Include Trop T or I and C-reactive protein **weekly** for the first month. (see Appendix 2)		**Community setting** Monitor vital signs: Temperature, respirations, pulse and lying down and standing BP ***conducted daily if possible*** Include Trop T or I and C-reactive protein **weekly** for the first month. (see Appendix 2)	
Use *Clozapine Monitoring Form (Appendix 5) to guide physical health monitoring protocols*			
Continue haematological monitoring weekly (FBC). ↓			
Green result	←	**Amber result**	→ **Red result**
WBC greater than 3.5 x 10^9/L AND Neutrophils greater than 2.0 x 10^9 /L		WBC 3.0 - 3.5 x 10^9/L AND/OR Neutrophils 1.5 - 2.0 x 10^9 /L	WBC less than < 3.0 x 10^9/L AND/OR Neutrophils less than < 1.5 x 10^9 /L
Continue clozapine		Continue clozapine therapy with twice-weekly blood tests until return to green range	**STOP** immediately. Sample blood daily until a green result is achieved. Monitor for signs of infection.
↓			
Ongoing monitoring from 18 weeks Inform clozapine clinic, community team and ClopineCentral™ or CPMS if changing teams or consultant. Provide a GP letter to ensure GP is aware of ongoing clozapine prescription and FBC 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 Form (Appendix 5) to guide physical health monitoring protocols*** Ensure GP is aware of ongoing clozapine prescription and FBC requirements. Update care plan 3 monthly.			

NOTE: Recommencing clozapine therapy after interruption

Dosing recommendations if clozapine dose is missed for > 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)*
- This is a guide only – for further dosing options refer to treating psychiatrist.

↓

FBC monitoring after interruption of therapy (For other protocols see Appendix 6)

Clozapine missed for less than 72 hours	**Clozapine missed for greater than 72 hours but less than 4 weeks**	**Clozapine missed Greater than 4 weeks**
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 in cases where patients are non-responsive, or suffer intolerable side effects, to at least two neuroleptic agents other than clozapine.

Because of the risk of neutropenia and agranulocytosis, all patients taking clozapine are enrolled in a registry and monitored regularly.

Protocols for monitoring the haematological and physical health of people prescribed clozapine are outlined in these guidelines[2,3,4].

These guidelines align with the WA Department of Health *High Risk Medication Policy* OD0561/14, as a supporting document in section *7.1 Clozapine*, to guide monitoring protocols and practices.

Health Services should monitor compliance of the physical health monitoring protocols for people taking clozapine. Dosing and monitoring do not replace clinical judgement.

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

- All patients treated with clozapine
  a. have an identified case manager / care 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 should be involved in care of all patients taking clozapine, including ongoing physical monitoring.
- Centres coordinating physical and mental health should define communication processes to ensure appropriate sharing of clinical information (across professions, services and carers where appropriate).

1. Introduction

"Clozapine has made a huge difference to my daughter's life. She has been on this drug for 18 years. Whilst the monitoring is intensive and the side effects like weight gain and constipation are ongoing, she has a better quality of life. She feels her mind is much clearer". Parent and Carer, Carers WA

1.1 Purpose

These guidelines provide recommendations regarding best practice for safe, 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 4: Medication Safety.

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 (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' drug for use in the management of treatment resistant schizophrenia in cases where patients are non-responsive to, or intolerant of, at least two neuroleptic agents other than clozapine. Despite its proven and widely accepted clinical benefits clozapine can cause potentially life threatening side effects due, in particular, to metabolic and cardiac effects.

Vigilant haematological and physical health monitoring is required for patients on clozapine.

Attention must be paid to interruption of clozapine therapy and the initiation and titration protocols that 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 side effects. The occurrence of agranulocytosis is a substantial hazard, particularly in the first 18 weeks of the administration of clozapine, but this hazard can be reduced by monitoring the white cell count.[5]

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 a number of 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

2.2 Registration: Clozapine Patient Monitoring Services

There are two brands of clozapine available in Australia - Clopine® from Hospira and Clozaril® from Novartis.

Currently (March 2017), only Clopine® is supplied by WA Department of Health, however the tender for medications is reviewed periodically which may affect future prescribing requirements.

Each of these brands of clozapine has an associated clozapine patient monitoring system – ClopineCentral™ for Clopine® and Clozaril Patient Monitoring System (CPMS) for Clozaril®. It is important that once a patient is commenced on a specific brand of clozapine, they continue on this brand as each has a separate monitoring service and information is not transferrable across systems.

The two clozapine patient monitoring systems or services require:

- All patients, prescribing doctors, dispensing pharmacists, pharmacies, centre coordinators and centres using clozapine to be registered. Pharmacies are registered as a Clopine Clinic under Clopine Central and are attached to the appropriate Clopine Centre to which the patient belongs.
- Clozapine will only be dispensed for patients that are registered in accordance with the relevant clozapine patient monitoring system protocols.
- All health care professionals involved in the supply of clozapine must be registered with the relevant monitoring system database. It is recommended that every centre nominates a centre coordinator who will oversee and facilitate successful adherence to the clozapine monitoring protocols.
- Medical Officers must also be registered with the monitoring system before prescribing. Under Clopine Central, prescribers are registered as belonging to centres. If they move to a different centre, they must notify Clopine Central that they are practicing at the new centre. Medical Officers can belong to multiple centres.
- Patients are listed as 'belonging' to a specific centre through their registration at the centre.

- Pharmacists may only dispense prescriptions for clozapine written by a registered prescriber.

The two monitoring systems can be accessed at https:/www.clopine.com.au/ for Clopine®[6] or http:/www.ecpms.com.au/ for Clozaril®[7]

3. Assessment of Patient Suitability for Clozapine Therapy

3.1 Contraindications to the Use of Clozapine

The following are contraindications to commencing clozapine[2]

- 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 (e.g. myocarditis, cardiomyopathy).
- Severe hepatic disease including active hepatic disease associated with nausea, anorexia or jaundice; progressive hepatic disease; hepatic failure
- Uncontrolled epilepsy.
- Paralytic ileus.

Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis. Concomitant use of depot antipsychotics is to be discouraged.

3.2 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 neuroleptic agents; AND
- The patient must be treated by a psychiatrist or in consultation with a psychiatrist affiliated with a hospital or specialised unit managing the patient.
- Prior to the commencement of clozapine therapy, agreement must be reached with the patient to comply with the treatment and a regular blood monitoring regime.
- The name of the consulting psychiatrist must be included in the patient's medical records.

3.3 Patient Consent and Consent for Inclusion on CPMS Database

> ***"Due to the erratic lifestyles that many people with serious mental health experience, and their inability to actually express what is happening to them (because they are continually living in a fog), coupled with cognitive deterioration, depression, flatness of mood, paranoia and high insomnia, monitoring of this treatment is just not possible, without family input".***
>
> Family Member; Mental Health Matters 2 (MHM2).

Clozapine treatment is given after informed consent has been obtained (with the exception of patients who do not demonstrate capacity or who are unable to give informed consent for treatment under S25 (1) and S22 (1) of the WA Mental Health Act 2014).

Please refer to the *WA Health Consent to Treatment Policy 2016*

Patient consent for inclusion on the clozapine database should be obtained using the relevant site based adapted form. (Appendix 7.1)

3.4 Patients Being Treated under the Mental Health Act 2014

Forensic patients and patients under involuntary treatment orders must continue to be treated within an authorised mental health service (AMHS). While the majority of these AMHS are in the public sector there are a small number of involuntary patients in the private sector attached to treatment in private hospital settings by private psychiatrists.

The requirements for involuntary patients and their treatment and care within AMHS, are stated in the Mental Health Act 2014. These requirements include the allocation of case managers, clear articulation of a treating psychiatrist and compliance with certain frequencies of review (medical and other). Involuntary patients receiving clozapine could receive their clozapine under any of the outlined models of care, including a shared care model of care, if all legislative, clinical and other eligibility requirements are adequately met.

3.5 Clinical Assessment Prior to the Commencement of Clozapine

> ***"Clinicians should ensure cultural and gender sensitivity to issues which might impact on the consumer / family sharing accurate information with them at initial assessment or review times".*** *Carer, Mental Health Matters 2*

A comprehensive physical and psychiatric assessment of the patient must be undertaken if prescribing clozapine is being considered [8,9], 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 of Afro-Caribbean or African ancestry, that infers a risk of benign ethnic neutropenia with naturally low neutrophil counts
- history or family history of cardiac related disorders
- history or family history of diabetes mellitus, dyslipidemia 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 status (female)
- breast feeding status (female) as clozapine is excreted in breast milk

Baseline measurements:

- full blood count (FBC)
- blood group
- urea / electrolytes
- fasting glucose and lipids
- liver function tests
- C-reactive protein (CRP)
- troponin
- echocardiogram (Echo)
- electrocardiogram (ECG).
- weight
- waist circumference

Pre-treatment/baseline white blood cell and neutrophil counts and blood group must be reviewed and provided in accordance with ClopineCentral™ or CPMS.

Regular Monitoring

The risk of cardiovascular toxicity is highest in, but not limited to, the first 6 weeks of therapy[4]. The characteristic clinical findings of myocarditis include electrocardiogram (ECG) abnormalities, increased CRP, increased Troponin levels and Eosinophilia. Any patient who exhibits signs or symptoms of myocarditis (fatigue, dyspnoea, chest discomfort, palpitations, fever or flu-like illness, peripheral oedema) while receiving clozapine should undergo an immediate cardiac assessment[10].

Echocardiogram

ClopineCentral™ recommends, but does not make mandatory, an Echocardiogram at baseline and then at 3 months and years 1, 2, 5 and 10 from the commencement of clozapine. Clinical judgement coupled with the practicalities of the treatment setting (including equipment availability), frequency of contact with patients, any emerging signs and symptoms of myocarditis, cardiomyopathy or congestive heart failure will determine appropriate intervals for Echocardiogram monitoring. These guidelines recommend an Echocardiogram at baseline, at 3-6 months from the commencement of clozapine and then as clinically indicated. Patients on high doses of clozapine may require more frequent monitoring.

The possibility of cardiomyopathy must always be considered if there is clinical evidence of heart failure including resting tachycardia, tachypnoea, shortness of breath or hypotension. Routine echocardiograms at 3 months, 1 year, 2 years, 5 years and 10 years of treatment may assist with detection but does not replace monitoring for clinical signs and symptoms.

4. The Initiation of Treatment with Clozapine

4.1 WA Clozapine Initiation and Titration Chart

The WA Clozapine Initiation and Titration Chart[3] (Appendix 1.1) launched in 2015, facilitates clinical handover and prescription for the safe management of patients initiated or re-titrated on clozapine. Decision support is also 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 or outpatient settings.

Clozapine can cause agranulocytosis, which is a potentially fatal side effect. Therefore, as part of the monitoring process, all patients on clozapine **must** have regular full blood counts. The chart below provides a traffic light system for monitoring blood results and the recommended action.

Table 1: Clozapine Blood Results Monitoring System

Clozapine Blood Results Monitoring System		**Recommended Actions**	
		Prior to Initiation	**Ongoing monitoring**
Green Range	WBC greater than 3.5×10^9/L and NC greater than 2.0×10^9/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 3.5×10^9/L and/or NC 1.5 to 2.0×10^9/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.

Clozapine Blood Results Monitoring System		Recommended Actions	
		Prior to Initiation	**Ongoing monitoring**
Red Range	WBC less than 3.0×10^9/L and/or NC less than 1.5×10^9/L	**DO NOT START THERAPY**. Seek haematologist advice	**STOP CLOZAPINE THERAPY IMMEDIATELY** Consult treating psychiatrist and contact haematologist and Clozapine Patient Monitoring System (e.g. ClopineCentralTM)

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

A usual commencement dose of 12.5 mg is administered once daily on the first day, preferably in the morning. Further dosing titration can be guided by the *WA clozapine initiation and titration chart.* More rapid titration may sometimes be used under close psychiatric supervision.

In older or underweight patients or those suffering from renal, hepatic or cardiovascular disorders, cerebrovascular insufficiency or cerebral sclerosis, any dose increase should be slow and gradual.

All patients should be kept under close supervision for approximately six hours, ideally in an environment with appropriate resuscitation facilities. Monitoring of vital signs must take place hourly for six hours, and then 6 hourly for the first 24 hours after the first dose is administered for hospitalised patients. For subsequent doses, observations of patients should be taken at least twice daily for the first week of titration, second daily for the first month and then weekly until completion of 18 weeks for outpatients (more frequently if clinically required). Patients initiated on clozapine in the community should be monitored for the first 6 hours.

4.2 Dosing

Finding the best clozapine dosage can be challenging because any given dose of the drug yields highly variable clozapine serum levels.

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 such as caffeine and other prescribed medications.

As outlined in the Clopine® Product Information[2]:

Therapeutic dose range

In most patients, antipsychotic efficiency can be expected with 200 to 450 mg/day in divided doses. The total daily dose may be divided unevenly, with the larger portion or entire dose at bedtime. The average dose at which optimal plasma

levels are reached varies according to gender and hepatic metabolic pathways which are greatly affected by smoking status.

The primary criteria for determination of the therapeutic dose should be clinical signs and symptoms shown by the patient. The therapeutic dose of clozapine should not be solely determined by plasma concentration, but when a patient appears to not be responding adequately to treatment, it is worth ensuring that the achieved plasma concentration is at least 350 micrograms/L with a range up to 1000 micrograms /L as tolerated.

It is worth noting that a potential cause of non-response to clozapine is through inadequate plasma concentrations. Assessing plasma concentration can be also very helpful when determining a patient's adherence to treatment.

Maximum dose

For most patients the recommended maximum dose is 600 mg/day. However, a few patients may require larger doses to obtain maximum therapeutic benefit, in which case judicious increments (i.e. not exceeding 25mg – 50mg per increase per week or fortnight) are permissible up to a maximum of 900 mg/day. The possibility of increased side effects occurs with doses over 450mg/day. Careful plasma monitoring along with serum clozapine levels should occur.

In patients who are not responding to clozapine it is also important to reach a plasma concentration of at least 350 micrograms /L, with a range up to 1000 micrograms /L, as tolerated. In these patients it is also important to determine if any pharmacotherapeutic issues exist (e.g. smoking; excess caffeine intake; poor adherence; drug interactions etc) that may affect the ability to achieve a therapeutic level and to address these factors to the greatest extent possible.

Maintenance dose

After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration can occur if appropriate clinically to the level of 150-300 mg/day given in divided doses. If the daily dose does not exceed 200 mg, a single administration in the evening may be appropriate, especially for those experiencing day time sedation side effects.

Clozapine augmentation

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.

The addition of another antipsychotic 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 drug is given as a depot injection. The following tables (see link below) summarise the available evidence found in various psychotropic texts, journal articles and review articles relating to clozapine augmentation efficacy and safety.
Clozapine Augmentation – Graylands Hospital Drug Bulletin 2004;12(1).

4.3 Clozapine Serum Levels: Therapeutic Drug Monitoring

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

Monitoring of plasma levels is encouraged and may be useful:

- to monitor adherence especially if non-adherence is suspected
- when response to an adequate dose seems poor

- if increasing clozapine dose from an already high dose (after previous levels)
- if side effects suggest a high serum level i.e. myoclonus as a warning sign of seizure
- if chronic adverse effects persist and clozapine dose is lowered
- if there are other signs of toxicity
- if changes need to be made to other concurrent medications
- if augmentation of clozapine is being considered
- if a patient is making a change to caffeine or smoking habits
- in the presence of liver disease.

Obtaining clozapine serum levels

Clozapine reference ranges are standardized to 12 hour trough levels. Thus clozapine levels are usually drawn 12 hours after the last dose (such as in the morning after the nightly dose) and several days after treatment begins. When a clozapine level is ordered, most laboratories report: clozapine and norclozapine levels as micrograms/L.

Interpreting clozapine serum levels

Although there is no simple relationship between clozapine levels, therapeutic efficacy and toxicity the following ranges are described as follows[8]

- **Low range:** (50 to 150 micrograms /L) may not be as effective as medium to high levels
- **Medium range:** (200 to 300 micrograms /L) is usually the initial target
- **Therapeutic range:** (350 to 450 micrograms /L) can be achieved if clinical response is insufficient at lower levels
- **High range:** (450 micrograms /L to 1000 micrograms /L)
- **Very high levels:** (i.e. >1000 micrograms /L levels) have no proven benefit and increase seizure risk.

The clozapine level guides are based on dosage two times a day 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.

4.4 Community Dispensing and Community Titration

The monitored initiation of clozapine therapy in an outpatient or community setting can be a practical and safe option for a small subgroup of eligible patients. Commencing clozapine in the outpatient or community setting would usually require a lower starting dose (which may be as little as 6.25 mg) and much slower upward titration[4].

Monitoring for side effects must still take place after the first dose for the usual six hour duration. Daily observations should then be taken with vital signs (temperature, heart rate, blood pressure standing and lying and respiratory rate)

observed half an hour after the daily dose is administered. Daily monitoring should continue for at least two weeks to determine tolerability to side-effects and ensure there are no unacceptable side effects. After that, alternate day monitoring may be undertaken until a stable dose is reached, and further monitoring should take place at the time of blood testing.

Community pharmacies can now 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 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.

4.5 Restarting Clozapine following an Unplanned Discontinuation

Clozapine discontinuation causes a rapid decline in plasma levels. Based on an average half-life between 7 to 14 hours after 35-70 hours (5 times the half-life) there will be no detectable clozapine. The speed of the titration depends on the original acceptance and tolerability of clozapine and can often be more rapid than the original titration. Hypotension, tachycardia and seizures are particular risks when re-starting clozapine but so is relapse, so re-titration regimens must balance these risks. Depending on how long clozapine is missed, the frequency of FBC monitoring may need adjusting (see below table 2).

Table 2: Blood test monitoring after interruption of therapy[3]

Period of interruption **(time since last dose taken)**	**Dosage**	**Monitoring requirements**
Less than or equal to 48 hours	No change to dosage	No change to monitoring
Greater than 48 hours and less than or equal to 72 hours	Start on 12.5mg once or twice a 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.	No additional monitoring requirements.
Greater than 72 hours and less than or equal to 28 days	Start on 12.5mg once daily and rapidly titrate up as per new patient.	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	Restart patient with a new Patient registration form. Start at 12.5mg once daily and titrate up as per new patient.	Commence as a new patient. New pre-treatment result and baseline monitoring. Weekly monitoring for 18 weeks.

Discontinuation of clozapine therapy:

In the event that a planned discontinuation of clozapine takes place, the dose of clozapine should be gradually reduced over two weeks.

If abrupt discontinuation is necessary, the patient's mental state and cholinergic rebound should be carefully observed.

Haematological post-therapy monitoring is required by ClopineCentral™ and the CPMS. For patients on weekly blood test monitoring (i.e. in the initiation phase) a WBC and NC 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 NC should be performed as close as possible to the time of discontinuation and then follow-up counts four weeks later.

These post-cessation WBC and NCs must be green (according to traffic light system) or further monitoring will be required. A 'Therapy Event / Termination of Treatment Form' must be submitted to ClopineCentral™ or CPMS by the treating team.

5. Side Effects Associated with Clozapine Therapy

> ***If side effects are discussed with clinicians, it is important to give advice on what to do. Family members should also get this advice. Otherwise everyone just worries more".*** Consumer, HelpingMinds

The table below outlines the more common side effects related to clozapine and signs and symptoms should be carefully monitored[4,17]. For a list of pharmacological options and actions, the treating team should contact the clinical pharmacist.

Table 3: Side-effects associated with clozapine therapy

Side-effect / Signs and symptoms	Rate	Recommended Action
Haematological effects		
Neutropenia WBC <3.0 x 109/L or Neutrophils < 1.5 x 109/L. Flu-like symptoms such as sore throat & fever. (This is relatively common within the first 18 weeks – but may uncommonly occur after this maximal risk period)	3.2%	**Contact Doctor. Stop clozapine.** Contact haematologist at ClopineCentral™ or clozapine patient monitoring centre if further advice required. Re-introduction of clozapine should only occur with haematologist support
Agranulocytosis WBC <3.0 x 109/L or Neutrophils < 1.5 x 109/L. Flu-like symptoms such as sore throat & fever. (First 18 weeks – but may occur at any time)	0.8%	**Contact Doctor. Stop clozapine.** Contact haematologist at ClopineCentral™ or clozapine patient monitoring centre if further advice required. Re-introduction of clozapine should only occur with haematologist support.
Benign ethnic neutropenia	Rare	The presence of benign ethnic neutropenia should not prevent treatment with clozapine however a haematologist review prior to commencing clozapine is of benefit which may lead to an adjustment of the white blood cell count green, yellow and red ranges.

Cardiac effects		
Myocarditis Tachycardia at rest with rapid breathing, dyspnoea, hypotension, raised jugular venous pressure, fatigue, flu-like symptoms, chest pain or fever. (If myocarditis occurs, it is usually within 1 - 4 to 6 weeks of starting clozapine).	0.7-1.2%	**Contact Doctor and team. Refer to cardiologist.** Check Troponin and C-reactive protein (CRP) levels. Withhold clozapine. Repeat ECG and Echocardiogram. If confirmed contact cardiologist at clozapine monitoring centre. Submit the 'Therapy Event' form and 'TGA Adverse Event' form. Re-introduction of clozapine should only occur with cardiologist support. Australia has a significantly higher incidence of myocarditis than the rest of the world.[18, 19]
Cardiomyopathy Cardiomyopathy may occur at any time. The possibility of cardiomyopathy must always be considered there is clinical evidence of heart failure including resting tachycardia, tachypnea, shortness of breath or hypotension.	0.1%	**Contact Doctor and team. Refer to cardiologist.** Check Troponin and C-reactive protein (CRP) levels. Withhold clozapine. Repeat ECG and Echocardiogram. If confirmed contact cardiologist at clozapine monitoring centre. Submit the 'Therapy Event' form and 'TGA Adverse Event' form. Re-introduction of clozapine should only occur with cardiologist support.
Tachycardia	25%	**Contact Doctor.** Check FBC, WBC, ECG, ECHO. Note that a benign tachycardia can occur in up to 25% of patients which is often self-limiting.
Orthostatic hypotension May be problematic for patients on clozapine therapy; it often improves as tolerance develops.	9%	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. Treatments to address the hypotension are available (including anti-hypotensives) but must only be used under specialist support. Note that some patients may develop hypertension on clozapine.
Venous thromboembolism	Rare 0.02%	Avoid Immobilization; early detection important as potentially life threatening event.
Central nervous system effects		
Sedation First 4 weeks. This may persist but generally improves. This is the most common side effect of clozapine.	50%	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 This dose dependent risk increases with higher plasma levels (especially dosages greater than 600 mg/day), rapid dose titration, concurrent use of drugs that lower seizure threshold and pre-existing seizure disorders and illness. (Seizures may occur at any time).	up to 5%	**Contact Doctor.** Consider reduction in dose. Clozapine need not be discontinued. Check with Clinical Pharmacist for pharmacological anticonvulsant options. Valproic Acid is commonly used and can be rapidly titrated Monitor serum clozapine levels regularly.
Myoclonus	2%	Uncommon side effect. May be a precursor to seizures and may require an anticonvulsant.
Gastrointestinal effects		
Hypersalivation Excessive drooling – very troublesome at night. (First few months especially but can be ongoing). This is the second most common side effect.	50% (up to 85%)	Give hyoscine hydrobromide 300 micrograms sucked and swallowed at night. Hyoscine patches may be considered as an alternative. Atropine-related oral anticholinergics or sublingual ipratropium may also be considered. Wrapping a towel around a pillow at night and frequent swallowing during the day can assist.
Side-effect / Signs and symptoms	**Rate**	**Recommended Action**
Constipation Less frequent bowel motions, hard stools, abdominal bloating, cramping or pain, decrease appetite or fatigue. (Usually persists).	14 – 25%	Recommend high-fibre diet and increased fluid intake; osmotic and stimulant laxatives are first line if required. Review other medications that may cause constipation ***Constipation should be considered a serious adverse effect, as it can have potentially fatal complications.***

Nausea Can develop early or later in the course of treatment.	11%	May give antiemetic. Avoid prochlorperazine and metoclopramide if previously experienced Extra Pyramidal Side Effects (EPSE).
Parotid swelling Painful swelling of the parotid glands associated with hypersalivation. In some instances this spontaneously resolves but may persist.	Rare	Cessation of clozapine; or use of minimal effective dose. A combination of benztropine and terazosin may be considered.
Weight gain and metabolic effects		
Weight gain This may occur early in treatment and be can be significant.	50%	Dietary and lifestyle counselling before weight gain occurs. Ongoing monitoring and support.
Hyperglycaemia This may occur at any time in treatment and may progress to diabetes type II.	10%	Regularly screen for evidence of diabetes. Use oral hypoglycaemics e.g. metformin or insulin as per guidelines for managing diabetes. Consider specialist referral
Hyperlipidaemia	Up to 50%	Regularly screen for evidence of elevated triglycerides and lipids. Use lipid lowering agents (as per guidelines for managing hyperlipidaemia) especially the addition of a statin.
Other		
Benign Fever (Temperature $\geq 38^0$ C within first 3 weeks * Note: a benign fever can occur in up to 20% of patients initiated on clozapine which is generally self-limiting within 3 days of onset.	Up to 20%	Contact Doctor. Reduce rate of dose titration of clozapine. Check FBC, WBC, troponin and CRP. Physical examination for signs of infection. Consider ECG, Echo. Do not give paracetamol until doctor notified and agranulocytosis / myocarditis excluded.
Nocturnal enuresis Loss of bladder control, especially at night (bed wetting). (May occur at any time).	23-30%	Avoid high intake of fluids in the evening and ensure adequate voiding at bedtime; plan middle-of-the-night awakenings to empty bladder Consider the careful addition of an α adrenergic agonist / anticholinergic medication such as a tricyclic antidepressant. Desmopressin may be an effective symptomatic treatment (in nasal or oral form). Consider a continence referral.
Obsessive Compulsive Behaviour Symptoms may be transient but can follow a more persistent and chronic course and can be disabling	10-40%	Dose reduction may lead to symptom improvement. Cognitive behavioural therapy or pharmacological agents such as serotonin-specific reuptake inhibitors (antidepressants). Caution must be applied as many antidepressants can have an effect on clozapine serum levels.
This is not an exhaustive list of side-effects. Please see Clozapine Product Information for further advice.		

"To read these side effects is extremely alarming for both consumers and families. Many families have some knowledge of the side effects that consumers experience, when treated with clozapine. But quite frankly many do not".
Carer, Mental Health Matters 2

Clozapine and smoking

Baseline smoking habits and regular updates must be documented at each visit. Smoking can cause a reduction in the plasma concentration of clozapine through the induction of the P450 CYP1A2 metabolic hepatic pathway.

Any change in the patient's smoking status should be documented and clearly communicated to the treating team. Abrupt cessation of smoking 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 a review of the clozapine dose.

Prescribers must be aware of a possible similar effect on clozapine levels with a 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[8]. Note: It is the polyaromatic-hydrocarbons within the tar of cigarettes which affects clozapine metabolism and levels, not the nicotine. Nicotine replacement therapy (NRT) does not affect clozapine levels[4].

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[7].

Important drug interactions with clozapine

There are a number of important potential interactions to consider with clozapine as per the following table[10,17].

Of note is that some antidepressants may increase clozapine levels through the inhibition of the P450 CYP1A2 (Fluvoxamine) or CYP2D6 (Fluoxetine) pathways. Although these interactions should be approached with caution it is also possible to prescribe these antidepressants with clozapine to cautiously increase serum plasma levels in patients who are not responding to clozapine and have sub-therapeutic plasma levels (i.e. below 350 microg/L). This undertaking may lead to a clinical improvement and should occur with a gradual increase in antidepressant dose and careful monitoring of serum levels.

Table 4: Important Drug Interactions with clozapine

Drug	Interactions	Comments
CYP1A2 inhibiting substances (e.g. fluvoxamine, caffeine, ciprofloxacin)	Concomitant use may increase clozapine levels	Potential for 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.
CYP2D6 inhibiting substances (e.g. fluoxetine, paroxetine)	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.
Bone marrow suppressants • carbamazepine, chloramphenicol • sulphonamides (e.g. co-trimoxazole), • pyrazolone analgesics (e.g. phenylbutazone), • penicillamine, • cytotoxic agents and • long-acting depot injections of some antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	Clozapine use is not recommended concomitantly with other agents having a well-known potential to suppress bone marrow function. Depots have been used clinically in some cases.
Anticholinergics	Clozapine potentiates action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.
Antihypertensives	Clozapine can potentiate the hypotensive effects of these drugs due to its sympathomimetic antagonistic 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 with these substances.	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.
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 toxicity.	Observe for signs and symptoms of toxicity.
Drug	**Interactions**	**Comments**
Antibiotics and Erythromycin	Use of antibiotics may produce a rogue low neutrophil count on blood	Use of antibiotics due to clinical need should be reported to the local Clozapine Clinic. Observe for increase side effects

	sampling. Erythromycin may exacerbate the side effects of clozapine due to increasing plasma levels	with erythromycin.
CYP1A2 inducing substances (e.g. carbamazepine)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.

6. Physical Health Monitoring of Patients on Clozapine Therapy

"Patients and carers need accurate information about the process involved in weekly/ monthly reviews. A couple of years ago, from personal experience, this involved spending practically the whole day hanging around in the city; between having the initial blood test in the morning; waiting for the results to be sent and then screened; being seen by a doctor there for a new script and then waiting for the medication to be ready for pick-up at the pharmacy outlet. It was unlikely that the individual would have waited around for all of this to happen over a period of 6-7 hours. It also presumes that they and their accompanying friend / family member does not have work or child-care responsibilities and are in sufficiently good health to spend this time just waiting around. It was this lengthy process, rather than the medication itself, which contributed to the individual I supported coming off it. Neither he nor I were informed that the process would be so lengthy". *Carer, Mental Health Matters 2*

Patients on clozapine require regular clinical assessments, to review side effects across the systems and to review blood tests[11,12,13].

At each review patients must be reminded of the signs and symptoms of infection and other high risk adverse effects and should be instructed to notify treating clinicians should symptoms emerge between clinical reviews.

To aid the monitoring of the physical health of patients on clozapine, a table of best practice physical health monitoring protocols is located in Appendix 2.

A prompt checklist (Appendix 3) can be used by clinicians to assess potential side effects related to clozapine.

A clozapine side effect rating scale (GASS-C) (Appendix 4) is a simple tool which patients can use prior to each clinical review.

The *My Medicines and Me Questionnaire (M3Q)* for mental health medications (Appendix 7.1) was developed to enhance effective communication and capture patients' perceptions on possible side effects, open the door for a dialogue around medication issues and improve premature discontinuation of medications and is particularly useful at an annual review.

6.1 Health Care Professional Responsibilities

Psychiatrists and Eligible Prescribers are now able to prescribe clozapine without the need to demonstrate an association with a hospital.

Treatment centres, individual patients, prescribers and pharmacists must also be registered with the appropriate clozapine patient monitoring system relevant to the brand of clozapine prescribed.

When prescribing clozapine, prescribers are reminded that patients need to be monitored according to the clozapine monitoring system for the development of side effects.

All prescribers are required to use the authority approval process when prescribing PBS subsidised clozapine. The authority prescription can be any type of PBS authority prescription. Clozapine does have a streamlined authority. More detailed information on this authority approval process is on the Australian Government Department of Human Services website.

Consumers should be provided with consumer medication information leaflets (Appendix 7) and information regarding their treatment including the weekly blood tests for the first 18 weeks of treatment, followed by 4 weekly blood tests, and other ongoing physical health monitoring.

Medical Officers are also responsible for ensuring each consumer commenced on clozapine is known to the clozapine clinic that will manage their care. They must ensure that the consumer meets the criteria prior to prescribing, that the required tests are ordered at appropriate intervals, and that prescriptions meet Therapeutic Goods Administration (TGA) and S100 regulations. They must be aware of monitoring requirements and treatment options for likely effects of clozapine.

A medical practitioner should request a quantity sufficient until next blood test. Up to five repeats can now be authorised with a phone authority (under the new arrangements that came into effect in July 2015) when clozapine is prescribed in a shared care arrangement in the community.

Nursing staff who administer clozapine are responsible for ensuring they are aware of the TGA requirements, the patient monitoring service data entry requirements, monitoring for likely side effects and treatment options, and all other care requirements of a consumer on clozapine.

Clozapine Clinic Coordinators are responsible for updating the patient monitoring service database, for assessing the consumer as per protocol, notifying medical staff if complications are observed, and reporting on a regular basis against blood monitoring protocols. Inform case managers when blood tests are overdue.

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. Even prior to the recent legislative changes, different services have constructed the coordinators' roles differently – at times the job has been fulfilled by a clinician who has personally case managed each clozapine patient in the service, in other services a clinical pharmacist might have taken on this responsibility. It is likely that the recent legislative changes and likely expansion of clozapine service delivery with new shared care models will have some impact on the role of clozapine coordinators.

Pharmacists are permitted to source, supply and make claims under the PBS for clozapine supplied to eligible patients. All pharmacies (hospital based or community) must meet all relevant PBS, state and clozapine monitoring system requirements in order to be reimbursed. Community pharmacies will need to be registered under a clozapine monitoring system.

Pharmacists will need to confirm prescriptions are accompanied by appropriate haematological test results and are available within the monitoring system prior to dispensing. Continuation of supply is extremely important.

Case Managers work closely with people taking clozapine and clozapine coordinators and are *responsible for following up on adherence to monitoring protocols, particularly blood tests.*

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.

> ***"There is a clear need to have carers supporting someone on this medication included as partners in care as distinct from 'medication compliance police' which just puts further strain on often already-stretched family relationships. Sensitivity is required to ensure that family members have the necessary information to help work with the individual"***
>
> Carer, Mental Health Matters 2

6.2 Managing Complications

Analysing adverse incidents and critical events informs process improvements to enhance the safe and quality use of medications. Patient safety incident monitoring is a mandatory requirement of National Safety and Quality Health Service Standards. 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 (using relevant form) and the Clozapine Patient Monitoring System within 24 hours of the event taking place or being first noted.

Management of benign ethnic neutropenia

The presence of benign ethnic neutropenia should not prevent treatment with clozapine. Patients with benign ethnic neutropenia who develop a clozapine-induced decrease in the neutrophil count, but have no evidence of infection or impaired phagocytosis, may resume clozapine as soon as they have > 1,000 neutrophils/mm[3,14]. Haematologist consultation prior to initiating clozapine in this group is recommended as this may lead to an adjustment of the white blood cell count and green, yellow and red ranges.

7. 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. Recent legislative changes 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, *the Clozapine Monitoring Form* (see Appendix 5) is used to record physical monitoring protocols and can be used weekly to 18 weeks or as an ongoing monthly clinical review form.

7.1 Models of Clozapine Management for Maintenance Patients

A number of potential service models providing improved integration of mental and physical health care have been explored in other jurisdictions[8]. The importance of the general practitioner in all aspects of care, and their potential for providing leadership is emphasized.

A **Clozapine Clinic** is an outpatient treatment program that provides comprehensive mental health services for adults that are currently being prescribed clozapine or would like to start 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.

Potential models of maintenance care include:

- Supported self-management for physical and mental health.
- Enhanced support in primary care.
- Colocation of primary and mental health services
- Consultation and liaison services
- Integrated multidisciplinary teams.

Supported self-management for physical and mental health often involves group work but requires high levels of motivation from patients in order to maintain group attendance and active participation.

Enhanced support in primary care typically involves case managers working with general practitioners or specialist medical teams and mental health teams, using standardised protocols to proactively manage problems. This type of program has been best evaluated for patients with depression and comorbid diabetes[13].

Colocation of primary care and mental health services facilitates a 'liaison-physician' role in mental health services. As many patients on clozapine do not have a consistent relationship or strong attachment to a general practitioner despite the range of health problems they experience, this model is attractive to ensure regular monitoring and patient support. The application of this model can range from a comprehensive primary care service to interventions targeted at specific issues, and will be influenced by geographic location and proximity to other services, workload and funding models.

Consultation and liaison services may be reactive and less specialised than some of the other options. This model can work in general hospital settings but can be difficult to achieve in more isolated specialised and community settings. This model may not be well suited to providing continuity of care.

Integrated multidisciplinary teams may work within the community or within hospitals. These teams involve dedicated multidisciplinary staff and involve dedicated physical medicine expertise working within mental health teams to provide specialised care and create opportunities for proactive, integrated care. Integrated care does not necessarily mean co-located care, but requires special attention to collaboration and communication and typically an investment in electronic data accumulation and communication. This approach may be relatively costly compared with other models of care[15].

The particular approach selected will be determined largely by patient characteristics, modified by resource availability, and more than one model may be used within a service. Individuals with strong initiative and community support

can self-manage, there are some who can be effectively managed in primary care settings, still others who can achieve this with the facilitation of a case manager and finally a group who because of their level of risk of non-adherence to therapeutic plans will be heavily reliant upon the sustained input of mental health services to maintain the possibility of positive outcomes.

7.2 Considerations for Clozapine Shared Care

Strong links must be established between all parties in clozapine shared care models. It is important to highlight that all models of shared care for the management of clozapine 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 of 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. 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 community based care include the following:

- a patient's compliance history with clozapine and other medication
- their ability to independently attend appointments, blood tests and other investigations
- long-term sustainable support (family, partner, carer)
- their ability to access a suitable pharmacy
- their satisfaction with the transition to community care and
- their practical ability to access the community scheme.

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. All services must have a full understanding of legislative or other requirements before implementing new models of care for clozapine. Where public mental health services retain involvement in the care of a patient on clozapine under any model of care, the service must continue oversight of any shared care models.

8. 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.

9. Special Precautions for the Use of Clozapine

Pregnancy[16,17]

Clozapine is only recommended for use during pregnancy when the benefit of treatment outweighs the risk that inadequately controlled psychiatric illness might pose to both mother and child[16,17]. There is insufficient data to identify risks related specifically to clozapine use during pregnancy. The rare but severe adverse effects associated with clozapine (including agranulocytosis and severe constipation) in other patient populations could be devastating in a pregnant patient and might preclude its use for many pregnant patients.

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 must therefore be advised.

Breastfeeding

Since clozapine is excreted in breast milk, mothers receiving clozapine should be informed of the possible risks whilst considering the benefits of breastfeeding**.**

Additional guidance can be sourced from The Pregnancy and Breastfeeding Medicines Guide (Royal Women's Hospital Victoria 2016)[16], Guidance on the use of Antipsychotics Version 3[17]; and the Royal Australian and New Zealand College of Psychiatrists Professional Practice Guideline 7: Guidance for psychotropic medication use in children and adolescents (2016) [20].

Older People

Use in the older people requires a lower dose at initiation of treatment, and the dose titrated up more slowly as older people are more susceptible to side effects[4, 11].

Seizures / Renal / Liver Impairment

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[11].

10. Related Documents

10.1 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

10.2 Authorising policy and standards

- National Safety and Quality Health Service Standards 2012, standards 4 and 9
- National Standards for Mental Health Services 2010
- National safety priorities in mental health: a national plan for reducing harm 2005
- National Medicines Policy 2000
- Poisons Standard 2015 (SUSMP No. 16 February 2017)

10.3 Procedures, guidelines and protocols

- Guidelines for the use of the WA Clozapine Initiation and Titration Chart
- WA Department of Health Incident Management Tool Kit 2015
- National Adult Clozapine Titration Chart User Guide, Australian Commission on Safety and Quality in Health Care 2012
- Clozapine patient monitoring protocols and services published and operated by ClopineCentral™ from Hospira https://www.ecpms.com.au/
- Mistura Enterprise Limited Choice and Medication http://misturainformatics.org/cms/category/mistura-enterprise-ltd/

11. ClopineCentral™ Contact Information

Currently (April 2017), only Clopine® is prescribed by WA DOH, 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 and cardiac advice for patients on clozapine.

ClopineCentral™

- Phone: 1800 656 403
- Fax: 1800657454
- Email**:** Clopinecentral@pfizer.com

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

- Phone: 03 9387 1000

Consultant Cardiologist

The Cardiologist is only available via formal cover letter query, sent in to ClopineCentral (via fax number 1800 657 454 or email - clopinecentral@pfizer.com) with a detailed account of the query, relevant medical background/history and relevant test results (such as echocardiogram, full blood analysis and ECG). The Cardiologist will respond within 5 to 10 business days and thus this is intended for **non-urgent queries only**.

12. Acronyms, initials and definitions

ADR	Adverse drug reaction
AMHS	Authorised Mental Health Service
ANC	Absolute neutrophil count
bid	2 times a day
BMI	Body mass index: weight (kilograms) divided by height (metres) squared
Centre	A 'centre' is defined as a hospital, clinic or other facility that is involved with the use of clozapine.
ClopineCentral™	WA Department of Health uses the ClopineCentral™ monitoring system in accordance with the current contract for purchase of pharmaceuticals.
CMI	Consumer Medicine Information
CNS	Central Nervous System
CPMS	Clozapine Patient Monitoring System
CRP	C-reactive protein
CVD	Cardiovascular disease
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.
ECG	Electrocardiogram
Echo	Echocardiogram
eGFR	Glomerular Filtration Rate
EMHS	East Metropolitan Health Service
EPSEs	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. 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
MHM2	Mental Health Matters 2
M3Q	*My Medicines and Me* side effect questionnaire for mental

	health patients
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
SMHS	South Metropolitan Health Service
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
THC	THC, or tetrahydrocannabinol, is the chemical responsible for most of marijuana's psychological effects
tid	3 times a day
TRS	Treatment resistant schizophrenia
ULN	Upper Limit of Normal
UWA	University of Western Australia
WACHS	WA Country Health Service
WADOH	WA Department of Health
WAPDC	WA Psychotropic Drugs Committee
WATAG	WA Therapeutics Advisory Group
WBC count	White Blood Cell count

13. Appendices of Useful Resources

Appendix 1: WA Clozapine Initiation and Titration Chart

1.1 WA Clozapine Initiation and Titration Chart

http://ww2.health.wa.gov.au/Articles/U_Z/WA-Clozapine-initiation-and-titration-chart

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

http://ww2.health.wa.gov.au/Articles/U_Z/WA-Clozapine-initiation-and-titration-chart

Appendix 2: Ongoing Physical Health Monitoring Parameters.

Individual Health Service Providers will determine how best to undertake the physical health monitoring of patients on clozapine. The table below outlines recommended physical health monitoring for people on clozapine[10,11,12]. WA Department of Health has done everything practicable to make this document accurate, up-to-date and in accordance with accepted legislation and standards at the date of publication. If this document is printed, it is only valid to the date of printing.

<table>
<tr><th></th><th>Baseline</th><th colspan="5">Initiation</th><th colspan="2">Maintenance (Stable dose)</th></tr>
<tr><th>Parameter</th><th>Baseline
(10 days prior to initiation)</th><th>Initiation
Day 1</th><th>Initiation
Day 2-7</th><th>Initiation
Week 2-4
1st Month only</th><th>Initiation
Week 5-18</th><th>At 3 months</th><th>At 6 months</th><th>6 monthly and Annually</th></tr>
<tr><td>Monitor side effects during initiation, regularly thereafter, and at least at any point of blood sampling, with specific reference to gastrointestinal, cardiac and haematological side effects.</td><td>Establish if constipation pre-exists</td><td colspan="7">Assess at every review</td></tr>
<tr><td>Record current smoking status, caffeine intake, lifestyle and diet</td><td>√</td><td colspan="7">Assess at every review</td></tr>
<tr><td>Investigate potential problems with prescribed, purchased or herbal medication, illicit drugs and alcohol</td><td>√</td><td colspan="7">Discuss at every review</td></tr>
<tr><td>Weight: BMI & abdominal circumference</td><td>√</td><td colspan="7">Weekly for 18 weeks then Monthly</td></tr>
<tr><td>Monitoring of vital signs: <u>Inpatient setting</u>
Blood Pressure (lying down and standing); Pulse; Temperature, Respiratory Rate</td><td>√</td><td>Hourly for first six hours, then every 6 hours for the first 24 hours</td><td>Twice daily</td><td>Daily in the first month.
Then weekly</td><td>Weekly when patient moves to a community setting</td><td colspan="3">Monthly from 18 weeks onwards</td></tr>
<tr><td>Monitoring of vital signs: <u>Community setting</u>
Blood Pressure (lying down and standing); Pulse; Temperature, Respiratory Rate</td><td>√</td><td>Hourly for first six hours,</td><td>Daily</td><td colspan="2">Weekly</td><td colspan="3">Monthly from 18 weeks onwards</td></tr>
</table>

Urea and electrolytes (including eGFR)	√					√	√	√
	Baseline	**Initiation**					**Maintenance (Stable dose)**	
		Initiation Day 1	Initiation Day 2-7	Initiation Week 2-4 1st Month only	Initiation Week 5-18	At 3 months	At 6 months	6 monthly and Annually
Full Blood Count (WBCs, Neutrophils, Eosinophils) or WBC and differentials	√	FBC weekly for 18 weeks, then monthly. (May be required more frequently if amber or red results on haematological monitoring).						
Troponin T or I (depending on local availability)	√	Weekly in the first month (to 6 weeks if indicated)				√	√	√
C-reactive protein	√	Weekly in the first month (to 6 weeks if indicated)				√	√	√
ECG	√	After any significant dose changes, if cardiac risk factors present or clinically indicated. Ideally first 6 weeks, at 3 months, 6 months and then at least annually.						
Blood lipids (full lipid profile including triglycerides), Fasting sample ideally.	√					√	√	√
Weight: BMI & abdominal circumference	√	Weekly for 18 weeks then Monthly						
Plasma glucose (fasting sample ideally)	√					√	√	√
Liver Function Tests (ALT, AST, bilirubin, albumin, prothrombin). Fasting sample ideally	√					√	√	√
Echocardiogram (Echo)	√	Performed at baseline, and at 3-6 months. ***Repeat echocardiogram as clinically indicated.**				√ at 3- 6 months		As clinically indicated

- During the first 4-6 weeks, vital signs and direct enquiry regarding side effects ought to be assessed according to the WA clozapine initiation and titration chart. Any patient who exhibits signs or symptoms of myocarditis (fatigue, dyspnoea, chest discomfort, palpitations, fever or flu-like illness, peripheral oedema) while receiving clozapine should undergo an immediate cardiac assessment[10]
- If the patient develops signs or symptoms of unidentified illness OR a HR $\geq$ 120 bpm OR CRP 50-100 mg/L OR mild elevation in troponin ($\leq$ 2ULN), it is recommended that troponin and CRP be measured daily and the patient monitored for developing illness until features normalise.
- If Troponin levels are only mildly raised ($\leq$ 2 ULN) and CRP remains less than 100 mg/L, clozapine may be continued with increased monitoring (Check Troponin and CRP daily)
- Discontinuation of clozapine and investigation by echocardiography is advised if Troponin I or T >2ULN or CRP is more than 100mg/L in the absence of a clearly identified cause for elevated CRP unrelated to clozapine.
- The possibility of cardiomyopathy must always be considered if there is clinical evidence of heart failure including resting tachycardia, tachypnea, shortness of breath or hypotension. Routine echocardiograms at 3 months, 1 year, 2 years, 5 years and 10 years from the commencement of clozapine may assist with detection but does not replace monitoring for clinical signs and symptoms.

Appendix 3: Clinician prompt checklist to assess clozapine side effects

This assessment checklist supports the assessment of potential side effects related to clozapine therapy[21]. 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: [21] 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 4: 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 5: Clozapine Monitoring Form

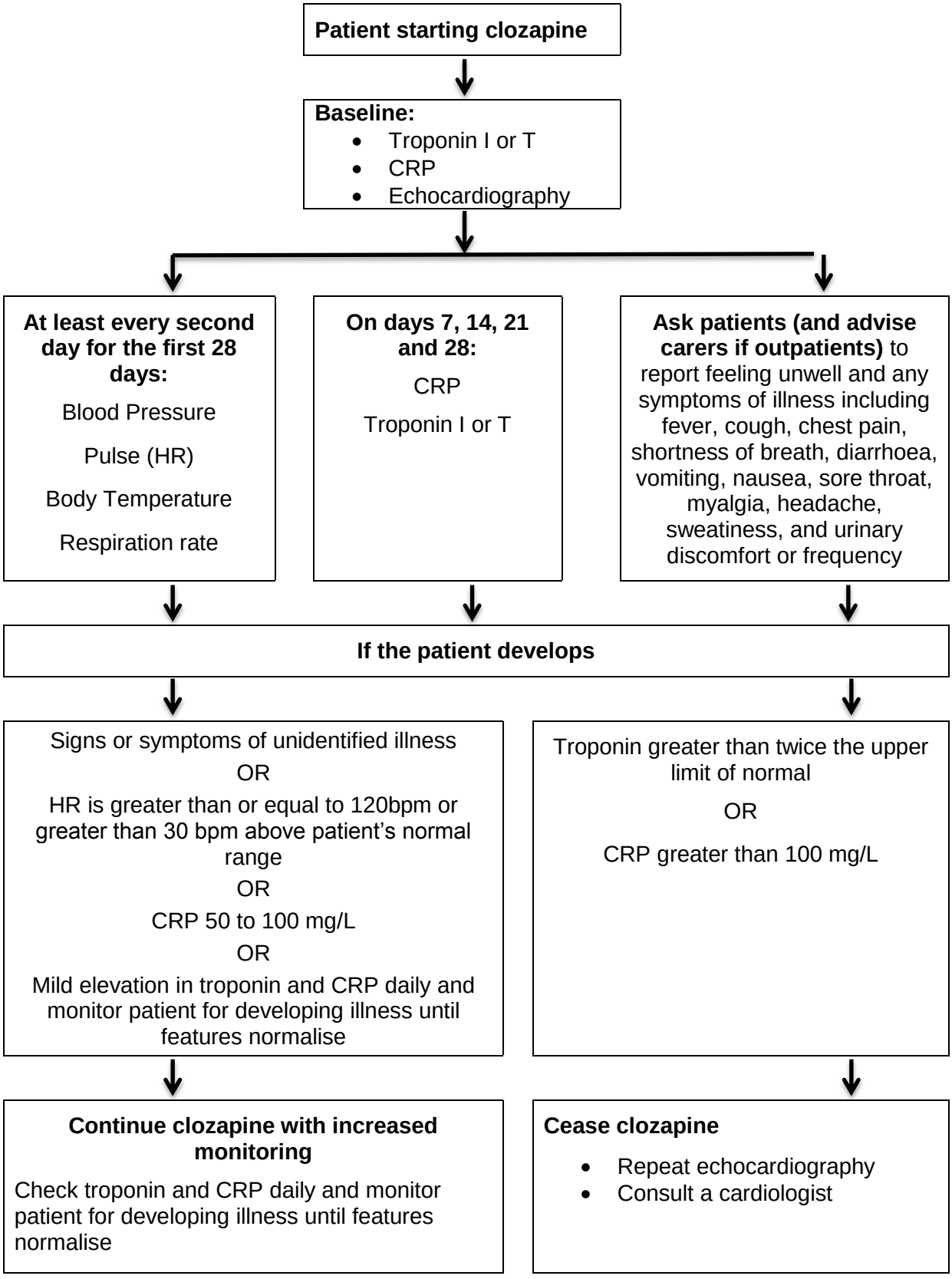
5.1 Clozapine monitoring form

Available:http://ww2.health.wa.gov.au/Articles/U_Z/WA-Clozapine-initiation-and-titration-chart

5.2 Guidelines for completion of the clozapine monitoring form

Available: http://ww2.health.wa.gov.au/Articles/U_Z/WA-Clozapine-initiation-and-titration-chart

Appendix 6: 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 7: Patient Resources

7.1 CLOPINE® (clozapine) Monitoring System Privacy Statement

Patient Privacy Statement - 2015.pdf

7.2 My Medicines and Me Questionnaire

Available at: http://ww2.health.wa.gov.au/Articles/U_Z/WA-Clozapine-initiation-and-titration-chart

7.3 Clopine® Consumer Medication Information

Clopine Medicine Information.pdf

7.4 Clozapine Patient Information Leaflet (PILL)

http://www.choiceandmedication.org/wadoh/pages/wadoh_leaflets/#IL

pillclozapineau.pdf

7.5 Clozapine Brief Information leaflet (BILL)

http://www.choiceandmedication.org/wadoh/pages/wadoh_leaflets/#IL

billclozapineau.pdf

7.6 Clozapine Quick Information Leaflet (QuILL)

http://www.choiceandmedication.org/wadoh/pages/wadoh_leaflets/#IL

quillclozapineau.pdf

7.7 Handy Facts on clozapine and constipation

handyfactsheetclozapineandconstipationa

7.8 Handy facts of clozapine and smoking

handyfactsheetsmoki
ngandclozapineau.pd

7.9 Taking Care of Your Physical Health: Consumer Diary Guide

http://www.psychiatry.uwa.edu.au/__data/assets/pdf_file/0011/1848647/Consumer-Diary-Brochure.pdf

Consumer-Diary-Broc
hure.pdf

7.10 Taking Care of Your Physical Health: Consumer Diary

http://www.psychiatry.uwa.edu.au/__data/assets/pdf_file/0005/1848632/Consumer-Diary.pdf

Consumer-Diary.pdf

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This document can be made available in alternative formats on request for a person with a disability.

Guidelines for the safe and quality use of clozapine therapy in WA
Department of Health