Safe and quality use of clozapine therapy in mental health services

Developed by the Queensland Psychotropic Medication Advisory Committee

2016

Document number # QH-GDL-437:2016

Queensland Government

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Published by the State of Queensland (Queensland Health), November 2016
IBNN or ISBN if needed

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

Contents

Tables

1. Purpose

This Guideline provides recommendations regarding best practice for the safe and effective use of clozapine therapy to:

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

This Guideline supports the National Safety and Quality in Health Service Standards, Standard 4: Medication Safety; medication management processes.

2. Scope

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

3. Background

Clozapine is indicated 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 there are significant safety concerns regarding its use. Clozapine can cause potentially life threatening side effects due, in particular, to haematological and cardiac effects.

National and local legislation, regulation and policies apply to ensure this highly specialised drug is prescribed, supplied, administered and monitored safely.

Clozapine treatment is usually initiated during a hospital admission and, once stabilised, the patient is discharged to community care. On occasions community based initiation can take place. Traditionally community clozapine therapy has occurred in a public community mental health service under the care of a psychiatrist and case manager, but it has been increasingly recognised that some patients have been retained within the public mental health system merely due to their clozapine monitoring requirements, and beyond their rehabilitative or other clinical needs.

In recent times legislative reform and new models of clozapine community care have become available and whilst some patients receiving clozapine will continue to require the more traditional hospital or public community clinic care for their long-term clozapine management; others can now receive maintenance clozapine therapy in a less intensive and restrictive manner that aims to increase a patient's independence and quality of life whilst maintaining the safe use of clozapine.

4. Legislation and regulations

4.1 Health (Drugs and Poisons) Regulation 1996

In Queensland clozapine is classed as a Schedule 4, regulated restricted medicine under the Health (Drugs and Poisons) Regulation 1996 due to its potential toxicity. Specialist health practitioners in the speciality of psychiatry and registrars (in psychiatry) working directly under the supervision of a specialist health practitioner in the speciality of psychiatry have the authority to prescribe clozapine.

Other prospective prescribers must apply for an approval from the Chief Executive Queensland Health. The Medicines Regulation and Quality Unit, Queensland Health, has produced a fact sheet titled, Regulated restricted (Schedule 4) medicines that can be accessed through the link https://www.health.qld.gov.au/system-governance/licences/medicines-poisons/approvals-authorities/default.asp. As part of the application a potential prescriber must provide the details of the psychiatrist who is providing the necessary supervision or professional oversight to enable them to prescribe clozapine. The relevant clozapine patient monitoring service and details of the clozapine coordinator for the clinical setting must also be stipulated.

Pharmacists do not require a separate approval to dispense prescriptions written by approved prescribers. They must, however, be registered with the same clozapine monitoring service as the approved prescriber and should be part of the shared care arrangement for the patient.

The Medicines Regulation and Quality Unit, Queensland Health, has produced a fact sheet for community prescribers and community pharmacists titled prescribing clozapine in the community that can be accessed through the link https://www.health.qld.gov.au/system-governance/licences/medicines-poisons/approvals-authorities/default.asp

4.2 Clozapine patient monitoring services

There are two brands of clozapine available in Australia - Clozaril® from Novartis and Clopine® from Hospira. Each of these brands of clozapine has an associated clozapine patient monitoring service – the Clozaril Patient Monitoring System (CPMS) for Clozaril® and Clopine Central™ for Clopine®.

The two clozapine patient monitoring systems or services require all patients, prescribing doctors, dispensing pharmacists, centre coordinators and centres using clozapine to be registered. A centre is defined as a hospital, clinic or other facility that is involved with the use of clozapine. Clozapine will only be provided to centres that are registered in accordance with the relevant clozapine patient monitoring system protocols. All health care professionals involved in the supply of clozapine at particular centres must be registered with the relevant monitoring system database. Every centre must nominate a centre coordinator who will oversee and facilitate successful adherence to the clozapine protocols. Medical Officers who hold an approval to prescribe from the Chief Executive Queensland Health must also be registered with the monitoring system before prescribing. Patients are listed as ‘belonging’ to a specific centre through their registration at the centre. Pharmacists may only dispense

prescriptions for clozapine written by an approved prescriber. It is the responsibility of the prescriber to ensure that he/she is operating within their legislative boundaries.

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

4.3 Pharmaceutical Benefits Scheme

For the purposes of initiation of treatment, clozapine 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 clozapine to patients.

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

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

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

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

Prior to 1 July 2015 medical practitioners prescribing clozapine for 'maintenance therapy' or 'continuation treatment' were, similarly, required to be affiliated with specialist hospital units and clozapine was generally available from hospital pharmacies only. Shared care arrangements existed under this scheme (where a general practitioner worked in collaboration with a local mental health service to provide care for the clozapine patient in a community setting) but the clozapine was generally available from hospital pharmacies only. General practitioners were not able to prescribe and oversight still sat largely with hospital clinics.

The Australian Government introduced changes to the PBS in July 2015 to improve community access to clozapine in the treatment of schizophrenia for maintenance therapy.

The legislative change allows clozapine to be prescribed and/or dispensed in community settings once therapy has been initiated and stabilised in a specialist setting and a patient has progressed from 'initiation therapy' to 'maintenance therapy'. While this transition to maintenance therapy can be reached at highly variable stages in treatment between different patients, it usually occurs 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.

Under the new arrangements clozapine may be prescribed by approved/registered general practitioners or other authorised community prescribers and can be dispensed by community pharmacists. Clozapine can continue to be prescribed and dispensed under the existing and longstanding hospital arrangements with hospital based psychiatrists.

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

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

Eligible prescribers will now be able to prescribe clozapine without the need to demonstrate an association with a hospital. All prescribers are required to use the streamlined authority approval process when prescribing clozapine. More detailed information on this authority approval process is at the Australian Government Department of Human Services website at: http:/www.humanservices.gov.au/health-professionals/services/pbs-for-prescribers/streamlined-authority-process.

A medical practitioner should request a quantity sufficient for up to one month's supply. Up to five repeats will now be authorised (under the new arrangements that came into effect in July 2015) when clozapine is prescribed in a shared care arrangement in the community.

Treatment centres and individual patients, prescribers and pharmacists must be registered with the appropriate patient monitoring system before the prescribing or dispensing of clozapine can occur. Prescribers must also order a blood test and review the results before each occasion of prescribing clozapine. 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 participate i.e. pharmacies will need to be registered under a clozapine monitoring system and a specific clozapine coordinator. Pharmacists will need to confirm prescriptions are accompanied by appropriate contemporary haematological test results and are available within the monitoring system prior to dispensing.

4.4 Therapeutic Goods Administration

Currently the Therapeutic Goods Administration (TGA) has implemented mandatory haematological monitoring standards in Australia to minimise the risk of clozapine side effects.

All authorised clozapine prescribers must comply with the following:

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

5. The administration, monitoring and prescribing of clozapine therapy

5.1 Prior to the commencement of clozapine

If prescribing clozapine is being considered, a comprehensive physical and psychiatric assessment of the patient must be undertaken, including:

- history of medication and other past treatments
- height, weight and waist measurements
- any possible history of drug-induced neutropenia or bone marrow disorders, or any other factors that might increase the risk of neutropenia or agranulocytosis 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
- any history or family history of cardiac related disorders that could increase the risk of cardiac related side effects while on clozapine e.g. hypertension
- any history or family history of diabetes mellitus, dyslipidemia or other metabolic disorders
- any history or family history of epileptic activity
- any history or family history of thromboembolism
- current smoking status
- pregnancy status
- current bowel habits
- allergies and adverse drug reactions
- breast feeding status—the benefits of clozapine therapy must be carefully considered as clozapine is excreted in breast milk.

Baseline measurements will include:

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

Attention must be paid to the necessary registration requirements of the patient, the centre, the clozapine coordinator and the nominated pharmacy and pharmacist; and to the necessary authority and registration of the intended clozapine prescriber. Consent

must be obtained and the relevant patient profile / registration forms must be completed.

Pre-treatment/baseline white blood cell and neutrophil counts must be reviewed and provided in accordance with the relevant clozapine patient monitoring system.

5.2 The initiation of treatment with clozapine

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

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

Table 1 Guidelines for evaluating the WBC and NC results

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

The Queensland Health Clozapine Titration Chart (CTC), along with its decision support tools and education materials, was launched in 2011. This chart was modified and adopted by the Australian Commission on Safety and Quality in Health Care (ACSQHC) as the National Adult Clozapine Titration Chart in 2013 and meets the minimum standards for clozapine titration required under National Safety and Quality Health Service Standards: Standard 4 - Medication safety.

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

When clozapine is used for maintenance treatment in the inpatient setting, the National Inpatient Medication Chart (NIMC) is to be used.

The CTC can be accessed at: http://qheps.health.qld.gov.au/dcho/contacts/health-protect/mrq-forms-charts.htm.

The CTC schedule provides an example of a regimen to commence and titrate clozapine. A usual commencement dose of 12.5 mg is administered once or twice daily

on the first day. Further dosing can be guided by the CTS. In the elderly or underweight patients or those suffering from renal, hepatic or cardiovascular disorders, cerebrovascular insufficiency or cerebral sclerosis, any dose increase should be gradual. More rapid titration may sometimes be used under close psychiatric supervision.

The Clozapine Quick Reference Guide (Ally, BAS. 2016) also provides a recommended clozapine initiation dosing schedule for reference.

It is recommended that clozapine not be used in combination with other antipsychotics unless approved by a specialist psychiatrist with appropriate consent and adequate clinical justification. Cross tapering is sometimes necessary when initiating clozapine therapy (when discontinuing the preceding antipsychotic preparation is not realistic) but this must be done with caution. Appropriate monitoring of over-sedation, blood pressure changes and the possibility of aspiration due to hypersalivation should be put in place, especially during the titration phase.

A clozapine medical alert must be made in the patient's medical record (both paper and electronic) by the clozapine coordinator to alert other clinicians who may provide treatment later.

As outlined in the CTC, the patient's temperature, pulse, respiration rate, and lying and standing blood pressure should be taken prior to the administration of clozapine.

To monitor for any adverse effects after the first clozapine dose, all patients should be kept under close supervision for approximately six hours in an environment with appropriate resuscitation facilities. Monitoring of vital and neurological signs must take place half hourly for two hours, and then hourly for four hours after the first dose is administered. This occurs regardless of the setting in which the medication is commenced. For subsequent doses, observations of patients should be taken at least twice daily.

5.3 Consideration for 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.

Guidelines for the initiation of clozapine for community based consumers are published by Maudsley (Taylor 2015).

Monitoring for adverse effects must still take place after the first dose for the usual six hour duration. Daily observations should then be taken with vital signs observed half an hour after the daily dose is administered. Daily monitoring should continue for at least two weeks or until there are no unacceptable adverse 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.

5.4 Management and monitoring of clozapine therapy

Dosing

For most patients the usual recommended maximum dose is 600 mg per day. A few patients may require larger doses to obtain the maximum therapeutic benefit. In most patients antipsychotic efficacy can be expected with 200 to 450 mg per day in divided doses. The total daily dose may be divided unevenly with the larger portion at bedtime.

After the maximum therapeutic benefit has been achieved, the minimum effective dosage should be used to maintain clinical remission.

Clinical assessments

Patients on clozapine require regular clinical assessments that involve taking a patient history and a physical examination to identify signs and symptoms of infection, to review side effects across the systems and to review blood tests.

At each review patients must be reminded of the signs and symptoms of infection and other high risk adverse effects and provided with instructions in relation to notifying treating clinicians should symptoms emerge between consultations.

The Clozapine Decision Support Tool (Ally, BAS. 2016) has been developed as a reference guide for clinicians who prescribe, dispense and administer clozapine. It supplements the CTC and incorporates current best practice and approved guidelines.

Haematological monitoring and management

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

- White cell and neutrophil counts must be performed for all patients on clozapine therapy at least weekly for the first 18 weeks of therapy and then at least every four weeks after the first 18 weeks of therapy. In some cases more frequent monitoring is required.

A traffic light system is used, again, for this blood count monitoring and must be adhered to at all times during clozapine therapy (refer to Table 2).

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

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

Table 2 Clozapine blood count monitoring protocol

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

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

Clinicians should be aware that clozapine induced neutropenia is more common in younger patients and all clinicians should be familiar with the identification of all other high risk variables for the development of neutropenia and agranulocytosis in patients receiving clozapine treatment.

In the event that a patient on clozapine develops neutropenia consideration must be given to switching to an alternate antipsychotic and reducing or ceasing other medications that decrease white cells (e.g. sodium valproate). Lithium has been used to increase baseline white cells in patients with benign ethnic neutropenia who develop neutropenia whilst on clozapine but not when the neutropenia is thought to have been related to the clozapine. Specialist haematology advice should be sought if this is considered a management option. In some cases of neutropenia, granulocyte colony stimulating factor (GCSF) has been used to stimulate the bone marrow and increase neutrophil counts. GCSF is not thought to protect against agranulocytosis and carries with it significant treatment risks of its own and should only be considered in specialist settings with haematology specialist input.

It may be possible to rechallenge with clozapine in some patients who have previously experienced a neutropenic episode if the potential benefits of the clozapine treatment outweigh any risks associated with the rechallenge. Rechallenge can only take place when the neutropenia is judged not to have been clozapine induced. Haematology advice must be sought if this is to be considered and increased blood monitoring will be required. Clinicians must be aware that neutropenia on rechallenge with clozapine usually occurs sooner (typically within 10 weeks) and is frequently more severe than the first episode (Dunk 2006).

Cardiac monitoring and management

Attention must be paid to the risk for cardiac complications with clozapine therapy. Myocarditis, cardiomyopathy, hypertension, hypotension, tachycardia and venous thromboembolism are recognised cardiovascular complications.

Tachycardia is a common side effect of clozapine in the initial period of treatment and will often settle and resolve within the first two months, or as tolerance develops. It is important, however, not to dismiss it as an expected and unimportant side effect, as it can also be an important sign of more serious cardiac complications such as myocarditis. If a patient presents with tachycardia along with other symptoms such as chest pain or heart failure, close attention must be paid to the possibility of additional pathology. A full history must be taken, a clinical examination conducted, vital signs reviewed and an ECG performed. Consideration should be given to the cessation of the clozapine until the exclusion of other more serious cardiac complications. Clozapine related tachycardia, in the absence of additional cardiovascular complications, is sometimes treated with beta blockers but only once the patient has been on clozapine treatment for a sufficient period (to allow for tolerance to have developed) and once additional pathology has been excluded. Cardiology advice is often helpful in this event.

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

Clozapine induced hypotension may also be problematic for patients on clozapine therapy but, like clozapine induced hypertension, it usually passes as tolerance develops. Patients must be provided with advice on managing postural dizziness and the modification of dietary salt and fluid intake. Specialist support may be needed if the symptom persists. Treatments to address the hypotension are available but must only be used under specialist support.

Cardiac monitoring through clozapine therapy includes the following:

- An ECG (that was obtained prior to starting therapy as a baseline reading against which future events may be measured) must be repeated at weeks one, two, three and four and every six months thereafter or sooner if clinically indicated.
- An echocardiogram (that was obtained prior to starting therapy as a baseline reading against which future events may be measured) should be repeated at six months and thereafter as clinically indicated or in line with local protocols (often annually).
- CRP, troponin – weekly for the first month, monthly to six months and then six monthly unless clinically indicated. CRP, generally a nonspecific marker of inflammation, is an early diagnostic indicator of the presence of myocarditis where other cardiac biomarkers are elevated.
- Regular monitoring of vital signs throughout therapy – blood pressure, pulse rate, temperature and respiratory rate – at least second daily for the first month of therapy, weekly for the first 18 weeks of therapy and then monthly.

Clozapine induced myocarditis usually occurs within the first month of commencing clozapine treatment but the risk persists throughout the period of treatment. It carries with it a high morbidity and must be identified and treated early. The symptoms are generally non-specific and may present mildly so clinicians must maintain a high clinical suspicion for an early diagnosis of cardiac involvement. Routine active monitoring for myocarditis for the first month of treatment is recommended.

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

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

Appendix 1 provides a protocol for monitoring patients commenced on clozapine for clozapine-induced myocarditis. Where myocarditis is suspected, investigation for clozapine induced cardiac impairment should be conducted promptly following the withdrawal of clozapine. If no specific impairment of cardiac function is measured, no specific therapy apart from cessation of clozapine is required. If the echocardiography reveals moderate or severe cardiac impairment specialist advice will guide drug or mechanical intervention.

Given the potential success of clozapine, every opportunity for the continuation of clozapine should be taken provided it can occur safely. Its continuation may be contemplated in the presence of mild cardiac disease, but only under specialist monitoring and support and if there is a certainty that cardiac function is not at risk. Slow titration of clozapine in that event is essential.

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

Several cases of venous thromboembolism have been reported with clozapine therapy. Clinicians must be aware of any past history of venous thromboembolism or risk factors for this when commencing clozapine therapy. Preventative measures such as compression stockings or anticoagulation may be needed for patients at high risk of clotting (Manu 2012).

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

Metabolic monitoring and management

Weight gain is common in patients on clozapine therapy. It is most rapid in the first six months of treatment but may continue through the long term. Patients must be informed of, and supported in, lifestyle and dietary improvements particularly targeting exercise and a balanced diet. Referral to a dietician may be considered. There is also

increasing evidence for the use of pharmacological strategies for clozapine associated weight gain. Metformin has been used with some positive results.

- Weight, body mass index (BMI), and waist measurements must be taken (in addition to baseline readings) at monthly intervals.

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

- It is recommended that fasting glucose (that was performed pre-treatment) be tested at one month, six months and then six monthly unless otherwise clinically indicated.
- Lipids (performed pre-treatment) should be tested six monthly unless otherwise clinically indicated.

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

- Liver function tests (that were performed pre-treatment) should be re-tested six monthly unless otherwise clinically indicated.

Gastrointestinal monitoring and management

Clozapine induced hypersalivation is a common side effect. It can be embarrassing for patients and can impact significantly on quality of life. It is often worse on initiation of treatment, may improve over several months and is likely to be dose related. It may be worse for patients at night time. It may lead to aspiration pneumonia and must not be dismissed. In milder cases non-pharmacological strategies are usually of benefit. Clinicians should ensure that the minimal effective clozapine dose is used and that dose splitting is considered. Pharmacological strategies might be needed and include hyoscine hydrobromide and pirenzepine – despite a lack of research evidence for their efficacy. Such medications might potentially exacerbate other side effects of clozapine and so caution must be used in their use. Other treatments that are used and have some research support include amisulpiride, sulpiride, glycopyrrolate and propantheline.

Nausea is common with clozapine therapy. It is caused, in part, by clozapine's anticholinergic effects and may be compounded by hypersalivation, increased appetite and specific hypothalamic effects. It is usually worst on initiation of treatment and patients may develop tolerance for it. Patients may require specific treatment such as antiemetics if it is intolerable. Hyoscine hydrobromide has also been helpful.

Clozapine related constipation is very common and can have a significant impact on a patient's compliance in addition to the serious complications of bowel obstruction, paralytic ileus and toxic megacolon. Unlike many other side effects of clozapine it tends to persist and patients do not develop a tolerance for it. Clinicians must pay attention to patients' bowel habits and initiate monitoring using a stool chart or similar process. Patients must be educated about the need for adequate hydration, dietary fibre and exercise. Laxatives or other bowel agents might be required.

Central Nervous System monitoring and management

Sedation is common with many antipsychotic preparations but can be particularly pronounced with clozapine. It is usually more severe early in treatment and most patients will develop tolerance for it over a few months. It can impact on a patient's quality of life and contribute to poor compliance. It is best managed through slow dose titration, minimising the use of other sedating medications, attention to the use of the minimal effective dose and the use of asymmetric dose splitting (with the largest dose in the evening). Plasma levels should be reviewed if oversedation is persistent and troubling. Aripiprazole in low doses is sometimes used to address clozapine related sedation.

Clozapine is epileptogenic. The risk of seizures increases with doses of clozapine greater than 600 mg or blood levels above 1000 microgram/L. Clozapine related seizures occur more frequently in those with a prior head injury, a history of seizure activity or a lowered seizure threshold (which may be contributed to by other medications such as antidepressants, anticholinergics, lithium and other antipsychotics, electrolyte imbalances). Clozapine patient electroencephalograms (EEGs) are frequently abnormal even in the absence of seizures. Clinicians must ensure the minimum effective clozapine dose is used at all times and that blood levels are monitored. Patients can also experience myoclonic jerks which may indicate an increased seizure risk. The management of both myoclonus and seizures is similar, although lamotrigine can exacerbate the former. Sodium Valproate is useful, particularly if a mood stabilising effect is also desirable. Carbamazepine and Phenytoin should be avoided due to their impact on clozapine metabolism (increased clearance and reduced levels) and increased risk of agranulocytosis (Pisani 2002).

Other general monitoring and management

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

Clozapine is frequently associated with urinary symptoms of nocturnal enuresis, urinary incontinence, urgency and frequency. These symptoms are often under-reported and must be asked about specifically in all clinical reviews to ensure their timely identification. Urinary symptoms usually persist and patients do not develop tolerance to them. Strategies to address enuresis include attention to limiting evening fluid intake, bedtime voiding, limiting the use of diuretic substances, attention to the minimal effective dose and minimising night time dosing. Pharmacological intervention includes desmopressin, amitriptyline, alpha-1 agonists, anticholinergic agents.

Clozapine can be associated with an increase in obsessive compulsive symptoms, greater than that in schizophrenia generally. These symptoms may be transient but can also follow a more persistent and chronic course and can be disabling and impact on quality of life. These symptoms are often under reported and attention must be paid in all clinical assessments to their emergence. Dose reductions may lead to symptom improvement and so attention must be paid to ensuring the lowest effective dose is used at all times. If symptoms persist treatment options include cognitive behavioural therapy or pharmacological agents such as selective serotonin reuptake inhibitors.

Caution must be applied as many antidepressants can have an effect on clozapine levels.

Clozapine and smoking

Baseline smoking habits and regular recordings must be documented at each visit. The Queensland Health smoking cessation pathway should be applied. For consumers who smoke, the amount of inhaled smoke and serum clozapine levels should be monitored to assist with dose adjustments. 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. Any cessation of smoking should be done under supervision and in a tapered manner, and be accompanied by an immediate reduction in the clozapine dose. Prescribers must be aware of a similar effect on clozapine levels with a cessation of cannabis smoking. Regular assessment of cannabis use should be undertaken and use monitored. Consumers should be offered support to decrease and manage cannabis use. Nicotine Replacement Therapy (NRT) or Champix (varenicline) does not impact on serum clozapine levels. The clinical team should provide ongoing support and advice to the patient and care giver, regarding the possible impacts that may emerge with smoking cessation or reduction.

Clozapine and caffeine

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

Clozapine levels – therapeutic drug monitoring

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

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

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

Levels are particularly helpful in the following circumstances:

- if there has been a poor clinical response
- if poor adherence is suspected
- if there are side effects that are likely to be related to the serum clozapine level i.e. seizures
- 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 nicotine intake
- in the presence of liver disease.

There is no role for routine testing in every day practice in circumstances outside of these indications.

5.5 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 and may often be beyond 18 weeks post-commencement). This phase can be reached at highly variable stages in treatment between different patients. Definitions of maintenance therapy 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. 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.

Models of clozapine management for maintenance patients

Community care for the patient receiving maintenance therapy with clozapine can occur through different arrangements:

1. Public mental health services only: A patient's clinical needs might require clozapine prescribing and monitoring to occur through a specialist hospital setting. These patients may require ongoing public mental health service intervention to meet their rehabilitation needs and/or to satisfy legislative requirements under the *Mental Health Act*; or they are not deemed suitable for any transition of care from the public system because of unstable mental health, clozapine dosing or clozapine side effect profile. In this model clozapine is prescribed by psychiatrists, registrars or other medical staff working within the Hospital and Health Service, but can be obtained either at the hospital pharmacy or from a community pharmacy. The frequency of reviews will be determined by the patient's clinical need and the routine 91 day review cycle but may also be impacted on by legislative requirements. Patients under this model of care might be under the direct clinical care of a public health system psychiatrist or might be under a registrar or other medical officer who is working under the supervision of a psychiatrist. These patients will frequently have case management within the public health system and will be well known to the public health system's clozapine coordinator.
2. General Practitioner (GP) prescribing shared care: In this model of care a GP assumes primary responsibility for prescribing and monitoring clozapine for the patient (including all necessary physical health reviews, mental state reviews and all cardiac, haematological and other monitoring required). The GP must personally review the blood tests before prescribing the clozapine. The GP must work under the supervision and professional oversight of a psychiatrist in either the public or the private health system. The frequency of psychiatric reviews and the nature of these reviews is at the discretion of the individual psychiatrist according to the shared care arrangements in place locally and the needs of the individual patient. This model of

care allows patients whose needs can be met outside of the public mental health system the flexibility and independence to move almost entirely to a community based primary care service. In this instance patients may or may not remain open to community mental health services such as case management. In this model the clozapine community prescriber must be designated and eligible in accordance with the Health (Drugs and Poisons) Regulation 1996 and all other legislation, regulation and guidelines and the patient can have the clozapine dispensed either from the hospital or community-based pharmacy.

3. General Practitioner (GP) monitoring shared care: In this model community patients are reviewed regularly by both the public and primary health care systems. A patient may be seen monthly by their GP for mental state monitoring, a review of all necessary physical health care needs (along with all of the other general health needs of patients with chronic mental illness) and other specific monitoring required in accordance with the relevant clozapine monitoring system. In this model the GP does not, however, prescribe the clozapine. The patient will also see a psychiatrist, registrar or other medical officer in the public health service at regular intervals who will prescribe the clozapine. These medical reviews within the public health service will be determined according to clinical and/or legislative need but might entail two, three or six monthly reviews with the nominated treating doctor at the public health service. Under this model the psychiatrist or registrar who prescribes the clozapine for the patient is allowed to prescribe five repeats that can be available at the nominated pharmacy (either public hospital or community based) for dispensing when the community general practitioner is satisfied that the patient is stable, has ordered and reviewed the standard haematological and other monitoring results and has determined that a continuation of therapy is appropriate. A psychiatrist must continue to provide supervision and professional oversight for the patient's care. Under this model the patient will often retain contact with the public health system for additional services such as case management. Locally developed shared care models must be in place to support this model of care.
4. Private psychiatrist only care: In this model a private psychiatrist assumes responsibility for the patient's full care including the monitoring and prescribing of clozapine, all necessary physical health reviews, mental state reviews and all cardiac, haematological and other monitoring as required. The patient will usually not have additional legislative requirements, may or may not have case management (either in the public or private health system), will need to link in with a clozapine coordinator that may be based with the private psychiatrist or a private psychiatric hospital setting, and will usually receive their clozapine through a community pharmacy.

Community dispensing

Community pharmacies can now dispense and supply 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 (i.e. brands and pharmacies) 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.

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 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 if it is to be considered.

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

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

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 mental health services retain involvement in the care of a patient on clozapine under any model of care, the service will retain responsibility for all mandatory clinical reviews.

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 senior 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. Expanded tasks will arise in the establishment of relationships with general practitioners, private psychiatrists and community pharmacists. Clozapine coordinators may be required to take the lead role in identifying, preparing and initiating the transition of patients into community care arrangements, may be the first line response for consultation and advice for community prescribers and dispensers, may take a lead role in education and training of these health professionals, will retain some shared understanding of the patients with the

community clinicians and will provide a rapid response and facilitate re-entry to the public health system if required.

Patients being treated under the Mental Health Act 2000

Forensic patients and patients under involuntary treatment orders must continue to be treated within authorised mental health services (AMHSs). While the majority of these AMHSs are in the public sector there are a small number of involuntary patients in the private sector attached to treatment with private hospital settings and private psychiatrists. The requirements for involuntary patients and their treatment and care within AMHSs is clearly articulated in the Mental Health Act Resource Guide and is being incorporated into policies and guidelines for revised mental health legislation. These requirements include the allocation of case managers, clear articulation of a treating authorised 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, so long as all legislative and clinical and other eligibility requirements are adequately met.

5.6 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 local clinical incident management system, with the relevant clozapine patient monitoring system and with the Therapeutic Goods Administration adverse event monitoring within 24 hours of the event taking place or being first noted.

5.7 Restarting therapy after interruption

Any interruption to clozapine therapy (for whatever reason) must initiate a review of the circumstances of the dose interruption and an assessment of the patient. Subsequent action is guided by the period of interruption i.e. the time since last dose was taken.

Table 3 Restarting therapy after interruption

Period of interruption (time since last dose taken)	Dosage and monitoring requirements
Less than or equal to 48 hours	No change to dosage or monitoring.
Greater than 48 hours and less than or equal to 72 hours	Start on 12.5mg and rapidly titrate up. No additional monitoring requirements.
Greater than 72 hours and less than or equal to 28 days	Start on 12.5mg and rapidly titrate up. The six week rule applies. For weekly 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 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. New pre-treatment result and baseline monitoring. Start at 12.5mg and titrate up as per new patient. Weekly monitoring for 18 weeks. No initial six hour vital sign monitoring required.

5.8 Discontinuing 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 the clozapine patient monitoring systems.

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 a 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.

6. Training and education

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

7. Special circumstances

Additional information specific to the use of clozapine in particular patient groups is also available within dedicated resources that are freely available online. When using references published outside Australia, clinicians must be aware that drug doses, licensed indications, and arrangements for government subsidy may vary between countries. The Australian Medicines Handbook and PBS listings will clarify Australian arrangements.

Pharmacists with specialist mental health knowledge and experience are also a significant source of information and advice.

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. 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.

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

8. Related documents

8.1 Authorising policy and standards

- Health (Drugs and Poisons) Regulation 1996
- *Mental Health Act 2000*
- 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
- Patient Safety Health Service Directive 2014

- Business rules for the operation of the Pharmaceutical Benefits Scheme and Efficient Funding of Chemotherapy, in Queensland Health public hospitals 2013
- Queensland Health List of Approved Medicines for Queensland Hospitals 2016

8.2 Procedures, guidelines and protocols

- Australian Commission on Safety and Quality in Health Care NIMC (clozapine titration) 2012
- Queensland Health Best Practice Guide to Clinical Incident Management 2014
- 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 the corresponding pharmaceutical manufacturers – CPMS (Clozaril Patient Monitoring System) from Novartis and Clopine Central™ from Hospira
- Mistura Enterprise Limited Choice and Medication [website]

8.3 Forms and templates

- Queensland Health Clozapine Titration Chart (CTC)
- Queensland Health Metabolic Monitoring Form (MMF)
- Queensland Health Smoking Cessation Clinical Pathway
- A number of registration and monitoring forms are incorporated within the individual clozapine monitoring systems in the state with CPMS and Clopine Central™.

9. Approval and implementation

Consultation:

- Queensland Psychotropic Medication Advisory Committee (QPMAC)
- Queensland Health Mental Health Alcohol and Other Drugs Clinical Clusters
- Medicines, Regulations and Quality, Chief Medical Officer and Healthcare Regulation Branch, Prevention Division, Department of Health

Approval

- Chief Psychiatrist, Mental Health Alcohol and Other Drugs Branch (MHAODB)

Next Review due: November 2018

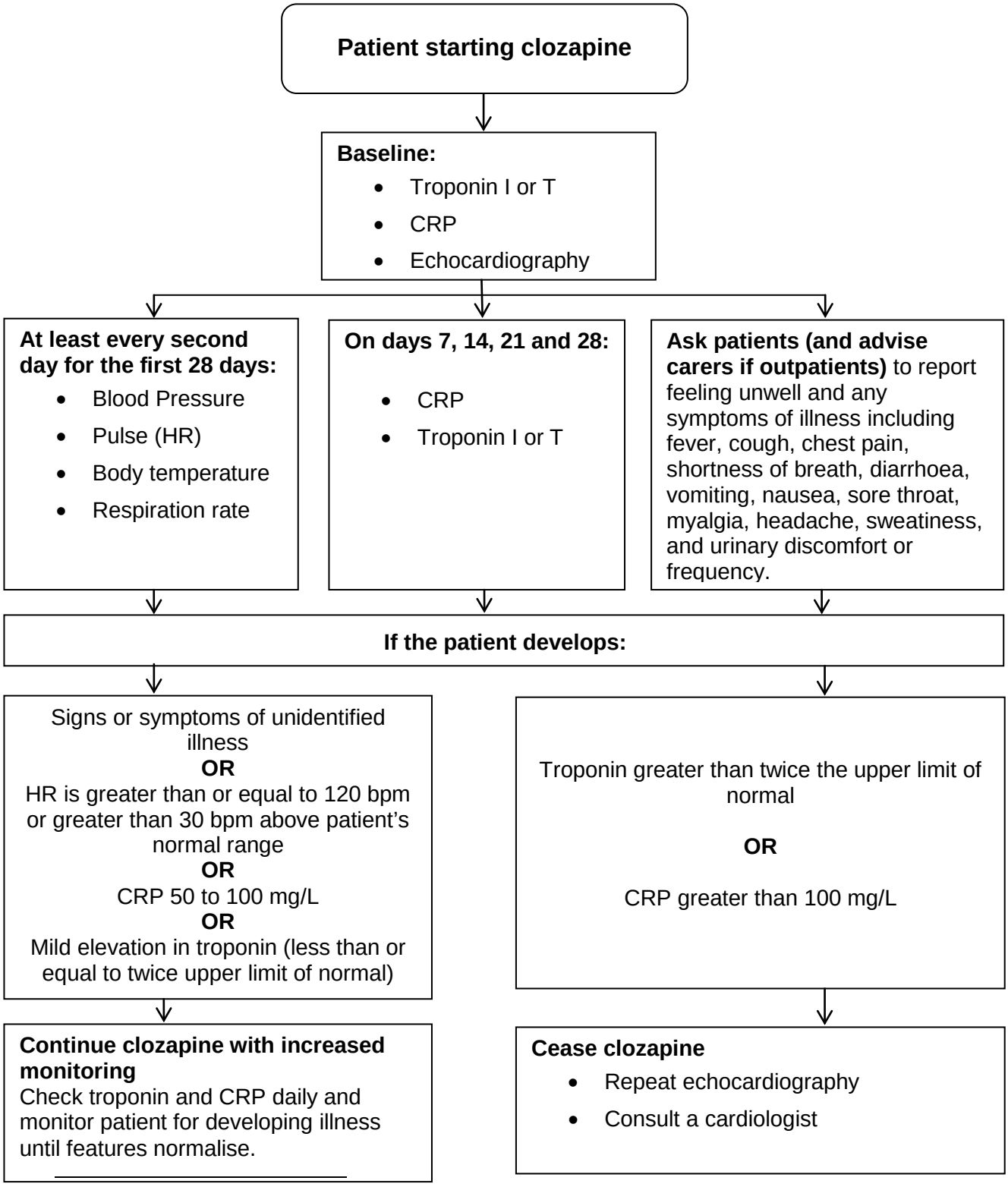
Effective from: November 2016

Version control

Version	Date	Prepared by	Comments / reason for update
1	10/11/2016	Clinical Governance Team	First publication

Appendix 1

Protocol for monitoring patients commenced on clozapine for clozapine-induced myocarditis[1]



[1] Adapted from: 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.

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