Cambridgeshire and Peterborough NHS Foundation Trust

Clozapine – Prescribing and Monitoring Guideline

Author:	Advanced Clinical Pharmacist
Sponsor/Executive:	Medical Director
Responsible committee:	Patient Safety Executive
Ratified by:	People Safety and Quality Committee
Approved by:	Medicines Governance Group 03/07/2023
This document replaces:	3.0
Date ratified:	28 July 2023
Date issued:	7 August 2023
Review date:	28 July 2026
Version:	4.0
Policy Number:	MM04
Purpose of the Policy:	To provide guidance for CPFT staff on the safe prescribing and monitoring of clozapine
If developed in partnership with another agency, ratification details of the relevant agency	N/A
Policy in-line with national guidelines:	Yes

Signed on behalf of the Trust: ……..

Anna Hills, Chief Executive

Elizabeth House, Fulbourn Hospital, Fulbourn, Cambs, CB21 5EF Phone: 01223 219400

Version Control Page

Version	Date	Author	Comments
1.0	August 2009	Anwen Williams	Policy developed
2.0	October 2011	Chris Jenkins, Pharmacist	Policy reviewed in line with timescales Updated to include information about actions to be taken if service user misses doses, or runs out of medication, and the use of clozapine in Parkinson's disease.
2.1	October 2012	Chris Jenkins, Pharmacist	Strengthened warning about risk of gastrointestinal obstruction with clozapine. Minor amendment to appendix 3 – monitoring tables for days 10 and 11.
2.2	July 2016	Sara Williamson, Chief Pharmacist	Reviewed in line with timescales. Minor amendments.
3.0	Sept 2019	Sara Williamson, Clinical Pharmacist	Reviewed in line with timescale. Expanded content. Removed licensed/duplicated information. Added/amended info. on tachycardia, plasma levels, and communication with GPs. Minor outpatient titration adjustment. Addition of information for community inpatient wards (non-mental health).
4.0	May 2023	Chris Jenkins Clinical Pharmacist	Review in line with timescales. Minor additions relating to ethnicity/dose considerations, dose splitting and executive summary stated for highlighting key points.

Policy Circulation Information

Key words to be used in DtGP search.	Clozapine, medicine, prescribing

Summary

Clozapine is an antipsychotic prescribed in cases where psychosis fails to respond to other medication. It is considered to be a high-risk medicine and so is subject to a number of restrictions and checks before and during use; because of this the responsibility for prescribing, dispensing and monitoring remains within secondary care.

This document provides guidance on appropriate patient selection, the monitoring required to ensure the safe use of clozapine (i.e. the testing needed before, during and after treatment has been started), practical considerations of how initiation takes place, and what to do if a patient misses doses, or runs out of clozapine.

Advice on clozapine prescribing, blood tests, supplies and monitoring can be obtained from CPFT's pharmacy departments (contact details in Appendix 4). Outside opening hours, the on-call pharmacist should be contacted.

WARNING: Missed dose are particularly significant in someone taking clozapine. The period of time that they have been without medication could cause their symptoms to return, or mean that they need to have altered doses in the short term, and/or more frequent blood tests. If a patient has missed doses of clozapine, or is at risk of running out of clozapine, the pharmacy department should be contacted promptly (including the on-call pharmacist if pharmacy is closed).

The key features of treatment that you should be aware of are:

- Patients taking clozapine must comply with regular blood tests to be allowed to continue treatment.
- Patients and their blood test results must be maintained on a manufacturer's database. Only their system authorises patients to start/continue on treatment.
- Initiation needs to be done slowly due to many off-putting side-effects that occur early in treatment. Some of these side-effects can be severe and dangerous.
- Missing treatment for 48 hours or more is very serious. It can lead to difficulties when restarting treatment and may require the patient to need more frequent blood tests.
- Clozapine can only be prescribed in secondary care by CPFT. Patients transitioning in to, or out from the Trust must be managed carefully to ensure no break in treatment.
- Cardiomyopathy, though rare, can be caused by clozapine at any point in treatment.
- Myocarditis is most likely to occur early in treatment – though can occur at any point in treatment. It is potentially life-threatening. Symptoms suggestive of myocarditis must be investigated thoroughly.
- Constipation is a common adverse effect of treatment. Clozapine can cause severely reduced gut motility and can be fatal. Patients should be offered prompt treatment.

Contents

1 Introduction
2 Purpose
3 Scope
4 Duties and responsibilities
5 Indications
6 Contraindications
7 Information and consent
8 Before starting clozapine
9 Supply of clozapine
10 Starting clozapine
11 Required monitoring when starting clozapine
12 Adverse effects when starting clozapine
13 Ongoing monitoring while on clozapine
    13.1 Full Blood Count monitoring
    13.2 Physical health monitoring
    13.3 Severe adverse effects
    13.4 Clozapine plasma level monitoring
14 Missed doses and treatment breaks
15 Restarting clozapine after a break
16 What to do if a patient is running out of clozapine
17 Inpatient admission of a patient taking clozapine
18 Arrangements for discharge/transfer
19 Stopping clozapine
20 Communication with GPs
21 Education and training
22 Monitoring compliance
23 Links to other documents
24 References

Appendix 1 – Inpatient initiation of clozapine
Appendix 2 – Outpatient initiation of clozapine
Appendix 3 – Monitoring/observation forms for starting clozapine
Appendix 4 – Pharmacy contacts
Appendix 5 – Clozapine information for CPFT community inpatient wards (not mental health)

1 Introduction

Clozapine is an antipsychotic agent licensed for the treatment of patients with treatment-resistant schizophrenia or those who have had severe, untreatable neurological adverse reactions to other antipsychotic agents. It is also licensed for the treatment of psychotic disorders in patients with Parkinson's disease.

Some adverse effects of clozapine can be very serious. Particularly significant is the risk of neutropenia/agranulocytosis; because of this the supply of clozapine is restricted to specialist prescribing and supply, and patients are subject to regular monitoring for blood dyscrasias. Only one brand of clozapine is used within CPFT: Denzapine®. All patients must be registered with the Denzapine Monitoring Service (DMS).

Careful consideration should be given to the decision to start a patient on clozapine, and whether it is more appropriate to do this in an inpatient or outpatient setting.

Patients who are started on clozapine in the community are subject to the same requirements and monitoring as inpatients. As would be expected for an inpatient, they should have a full medical history and clinical examination.

This document gives guidance on appropriate patient selection for clozapine treatment, the monitoring required to ensure the safe use of this agent, and other practical guidance around the initiation, ongoing prescribing, and discontinuation of clozapine.

It is important to be aware that if a patient misses doses of clozapine, or runs out of medication during treatment, that the appropriate personnel are informed so that the action can be taken.

2 Purpose

The aim of these guidelines is to set standards for Cambridgeshire and Peterborough NHS Foundation Trust (hereafter referred to as 'the Trust' or 'CPFT') to follow when a patient is prescribed clozapine in the inpatient or outpatient setting. These guidelines will assist staff in managing patient's needs and in complying with legal requirements and standards laid down by their professional bodies.

3 Scope

These guidelines are for all medical, nursing and support staff involved in the initiation, prescribing and monitoring of clozapine. They apply to all patients within the Trust who are currently prescribed clozapine or are being considered for treatment with clozapine.

The current prescriber of the medication is responsible (in conjunction with the care coordinator) for ensuring that the guidance is followed.

4 Duties and Responsibilities

4.1 Medical Director

The Medical Director has delegated responsibility to ensure that appropriate medicines management arrangements and guidelines are in place within the Trust.

4.2 Chief Pharmacist

The Chief Pharmacist has primary responsibility for the development, implementation, monitoring, and review of this guidance document.

4.3 Medicines Governance Group

The Medicines Governance Group has responsibility for ensuring safe and effective medicines management within the organisation and has overarching responsibility for the development, implementation, monitoring, and review of this guidance document. MGG reports to the Quality Compliance Executive for formal approval.

4.4 All staff

Consultant psychiatrists, team managers and the Chief Pharmacist are responsible for ensuring that the requirements of the policy are met by themselves and their teams.

All staff that are in contact with patients may be approached for advice about clozapine and should be aware of the appropriate people to contact if necessary.

5 Indications

Clozapine is indicated for patients with schizophrenia who are also:

- Treatment resistant – defined as a lack of satisfactory clinical improvement despite the use of optimum doses of a least two different antipsychotic agents, including at least one second-generation antipsychotic agent, prescribed for an adequate duration. ‘Adequate duration’ may be defined as a six- to eight-week trial of an oral antipsychotic or five depot intervals of a depot antipsychotic (minimum three months).

OR

- Treatment intolerant – defined as having severe, untreatable adverse reactions to other antipsychotic agents, including second-generation antipsychotics. Severe adverse reactions include neuroleptic malignant syndrome (NMS), severe extrapyramidal side effects (parkinsonism, dystonia, akathisia or tardive dyskinesia) or other severe adverse effects (such as intolerable effects of hyperprolactinaemia).

Clozapine is also indicated for the treatment of psychotic disorders occurring during the course of Parkinson’s disease where standard treatment has failed.

There is evidence to support the use of clozapine outside of its licensed indications – i.e. ‘off-label’ prescribing (for example in treatment-refractory mania or in schizoaffective disorder). The decision to use clozapine for an unlicensed indication is the responsibility of the prescriber in conjunction with the monitoring service. Peer review or a second opinion would be recommended when making this decision.

6 Contraindications

- Hypersensitivity to clozapine or to any of the excipients in the medicine.
- Unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (except for granulocytopenia/agranulocytosis from previous chemotherapy).
- History of clozapine-induced agranulocytosis (but may be used in exceptional circumstances within clinician taking full responsibility)
- Impaired bone marrow function
- Uncontrolled epilepsy
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions
- Circulatory collapse and/or CNS depression of any cause
- Severe renal or cardiac disorders (e.g. myocarditis)
- Paralytic ileus
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease; hepatic failure.
- Clozapine treatment must not be started concurrently with drugs known to have a substantial potential for causing agranulocytosis. In particular **carbamazepine** should not be prescribed concurrently with clozapine. Concomitant use of **depot antipsychotics** should be avoided owing to the inability of these medicines to be rapidly removed from the body in situations of agranulocytosis.

The pharmacy department can be contacted for advice regarding the use of clozapine with other medications or switching from other antipsychotics (including depots) to clozapine.

7 Information and consent

Prior to commencing treatment with clozapine, the patient must be provided with information on its indications, adverse effects, monitoring requirements and alternative treatment options. These should be discussed with the patient, and written information (such as a Choice and Medication leaflet or the manufacturer's patient information leaflet) provided to supplement this discussion. The discussion should be clearly documented in the patient's notes.

Consent to clozapine treatment should be obtained (or Mental Health Act processes followed if appropriate). Careful consideration should be given to the likelihood of compliance with clozapine and the required monitoring in the longer term.

8 Before starting clozapine

Before starting clozapine, the following investigations should be carried out to ensure it is safe for the patient to take clozapine and to provide baseline measures for comparison if adverse events occur.

- Review of medical history including history of seizures, cardiovascular disease and any haematological disorders.

- Physical examination including weight and height, waist circumference, blood pressure, pulse rate and temperature.
- Full blood count (less than 10 days before intended start of clozapine).
- Other blood tests including lipids (ideally fasting), glucose (ideally fasting), Hb1A1c, liver function tests, and urea and electrolytes.
- ECG.
- EEG if there is a history of seizures.

The patient must be registered with the Denzapine Monitoring System (DMS) prior to starting clozapine; this can take up to three days. A registration form may be obtained from the local pharmacy department and must be completed by a consultant psychiatrist registered with the DMS.

9 Supply of clozapine

Clozapine is only available from hospital pharmacies and the local pharmacy department should be contacted for specific advice regarding the use of appropriate prescriptions and the supply of clozapine. The brand of clozapine used within CPFT is Denzapine®.

It should be ensured that a valid prescription is available for each supply of clozapine. The pharmacy department should be notified of any alteration in dosage. A verbal message can be taken provided this is supported by a written request (e.g. entry in electronic notes, email, or letter).

The quantity of clozapine that can be dispensed is linked to the required FBC testing. The local pharmacy department should be informed in advance when planning anything in which the supply of clozapine may be important (such as leave, going on holiday, or moving out of area). It is particularly important to contact pharmacy when planning discharge from hospital to ensure that the patient's supply of clozapine is continued in the community.

10 Starting clozapine

10.1 Starting clozapine for treatment-resistant schizophrenia or where alternative antipsychotics have not been tolerated

The following should be considered when deciding whether treatment should be initiated in an inpatient or an outpatient setting.

More suitable for **inpatient initiation** of treatment:
- Significant medical problems.
- Potential for significant adverse effects (e.g. seizures, hypotension).
- Little or no support available in the home setting.
- Particularly unwell at time treatment commences.
- CPFT community teams not able to support physical health monitoring (incl. weekends)

More suitable for **outpatient initiation** of treatment:
- No significant medical problems.

- Supportive family or caregivers.
- Ability of community teams to supervise and monitor treatment.
- Good compliance and insight.
- Accepting of treatment with clozapine.

If starting clozapine in the outpatient setting the patient should have a carer available to stay with them overnight on at least the first day of treatment (ideally for the first week). Support from the local Crisis Resolution Home Treatment Team will be necessary to facilitate the frequent monitoring required. The patient should be advised not to drive during the initial titration period.

Clozapine should be started at a low dose and titrated up slowly over several weeks. The rate at which the clozapine dose is increased during the initial titration period will depend on the place of treatment (i.e. inpatient vs. community). Initiation in the outpatient setting will require more cautious dose titration. Sample initiation regimes for both venues are given (see Appendix 1 and 2).

When planning a titration regime, the following doses may be considered as the initial maxima for specific adult patient populations:

- Female non-smoker: 250 mg/day
- Male non-smoker: 350 mg/day
- Female smoker: 450 mg/day
- Male smoker: 550 mg/day

(Based on Rostami-Hodjegan A *et al.* Influence of dose, cigarette smoking, age, sex and metabolic activity on plasma clozapine concentrations. *J Clin Psychopharmacol* 2004; **24**:70-8)

Although specific target dose recommendations are not established for ethnicity differences, studies suggest that clozapine metabolism rates may differ significantly in some ethnic groups. People with east Asian or southwest Asian ancestry may metabolise clozapine more slowly and therefore may need significantly lower doses. People with sub-Saharan African ancestry on average are more likely to be faster metabolises, and therefore are more likely to need higher than average doses.

(Based on de Leon J et al. Guideline for Making Clozapine Titration Safer. Pharmacopsychiatry 2022; 55: 73–86

Further dose increases may be made according to clinical response. Patients can continue to show improvement over six months after starting clozapine.

While the manufacturer suggests that a daily dose over 200mg should be considered for dividing into multiple administration times, in practice the decision to split the dose can be taken at any time to suit the patient response. Split doses can be considered for asymmetric dosing – with higher dose weigh given at night to account for sedative properties.

The possibility of increased adverse reactions (in particular seizures) at doses above 450 mg/day should be borne in mind. The maximum licensed dose is 900 mg/day; however, this is rarely required.

When starting clozapine, the possibility of additive adverse effects from other medications prescribed should be considered; in particular, sedation, postural hypotension, anticholinergic effects, and lowering of the seizure threshold. All antipsychotics pose some risk of agranulocytosis so should only be used concurrently with clozapine for as short a period as possible. No further depot antipsychotics should be given after starting clozapine.

10.2 Starting clozapine for psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed

The starting dose is 12.5 mg/day, taken in the evening. Dose increases should be in 12.5 mg increments, with a maximum of two increments in one week.

Normally doses of 25-37.5 mg/day are effective. If treatment for one week with a dose of 50 mg/day fails to provide a satisfactory response, the dose may be cautiously increased by 12.5 mg/day per week. The dose of 50 mg/day should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day must never be exceeded.
Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.

When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If increasing anti-parkinsonian medication results in the recurrence of psychotic symptoms, clozapine dosage may be increased by increments of 12.5 mg/day per week up to a maximum of 100 mg/day, taken in one or two divided doses.

11 Required monitoring when starting clozapine

A nurse must available to the patient for 6 hours post-dose on day 1 of treatment if clozapine is started in the outpatient setting. This also applies during inpatient stays but is obviously easier to achieve. During the initial titration of clozapine, blood pressure (lying and standing), pulse rate and temperature must be measured regularly: pre-dose then hourly for 6 hours post-dose on day 1; pre-dose then 2, 4 and 6 hours post-dose on day 2. Further monitoring is required for two to three weeks during the initiation of clozapine; Appendix 3 should be consulted for further details.

If any of the following parameters are outside the limits specified they should be brought to the attention of medical staff as soon as possible:

- Systolic blood pressure <110mgHg or postural drop >30 mmHg,
- Pulse rate >120 bpm (common but may be linked to myocarditis),
- Temperature >38°C (common but need to check FBC and may also be linked to myocarditis).

Consider using a NEWS chart to record physical observations and calculate NEWS score if there are any concerns about the patient’s physical condition.

12 Adverse effects when starting clozapine

During initiation, the patient should be asked if they are experiencing any adverse effects, and whether they have any flu-like symptoms such as fever or a sore throat. Below is a list of common side-effects with clozapine; this is not a comprehensive list and the Summary of Product Characteristics for Denzapine should be consulted for more information (available at www.medicines.org.uk). Most side-effects are dose-dependent and associated with the speed of titration. They also tend to be more common at the beginning of treatment.

Judicious use of plasma assays and dose/time adjustments may be able to reduce adverse effect burden without the need to discontinue treatment or treat an adverse effect with other agents.

Some of these adverse effects may just require reassurance that they should wear off within a few weeks; other adverse effects may require additional medication, a slower dose titration or medical review. For this reason, any adverse effects reported should be brought to the attention of medical staff as soon as possible.

Adverse effect	Management
Raised temperature, sore throat or other symptom of infection – may be a sign of a low white cell count caused by clozapine	Doctor should be informed. A blood test should be taken immediately and analysed locally. If the blood result is satisfactory and the temperature is under 38.5°C, clozapine can be continued. If the temperature is over 38.5°C, consider withholding clozapine until the fever subsides. Paracetamol may be prescribed to treat the fever. **Fever may also be linked to development of myocarditis (see section 13.3)**
Hypotension – especially postural	Blood pressure both lying and standing should be monitored. Patient should be advised to stand up slowly to avoid associated dizziness. Consider reducing the dose or use slower dose titration.
Constipation	High-fibre diet. Adequate fluid intake. Bowel movements should be monitored and laxatives prescribed if necessary. **Clozapine has been associated with gastrointestinal hypomotility, which can progress to bowel obstruction (see section 13.3).** Any abdominal pain should be investigated promptly.
Sedation – the patient must be advised not to drive if affected (and not at all during initial titration)	Consider adjusting the dose so that a higher proportion of the dose is taken at bedtime. Reduce the dose if necessary.
Hypersalivation	Hyoscine hydrobromide at a dose of 150-300 micrograms up to three times daily (as Kwells®) can help (unlicensed use). This may cause drowsiness and constipation. Other options are available; contact pharmacy for further information.
Weight gain	Counselling on diet and exercise on initiation. Regular weight checks.

Dry mouth	Sugar-free chewing gum, or citrus fruit or low calorie drinks may help. An artificial saliva mouth spray is available.
Tachycardia (fast heart rate)	If pulse is >110bpm, check whether patient has taken recent exercise or is feeling anxious (try to calm them by talking or distraction). Repeat pulse check after 10-15 minutes; if it has fallen to below 110bpm, no further action is necessary. If pulse is >120bpm, doctor must be informed. Consider reducing the dose or use slower dose titration. **Tachycardia may also be linked to the development of myocarditis (see section 13.3)** If tachycardia >120bpm persists in the longer term, and there are no concerns about cardiac health or other contraindications, consider treatment with a beta-blocker e.g. bisoprolol (starting at 1.25 mg/day) or atenolol (starting at 25 mg/day)
Headache	Paracetamol can be prescribed
Neuroleptic Malignant Syndrome Symptoms include hyperthermia or fever, severe muscle rigidity, with two or more of: diaphoresis, dysphagia, tremor, incontinence, tachycardia, altered BP, altered consciousness, raised creatine kinase level.	**Doctor called to review patient and perform bloods including creatine kinase levels immediately.** This is a RARE but important side-effect, hence has been included in this list to ensure its awareness and monitoring
Metabolic Syndrome Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus. On very rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma.	Please refer to the Trust's Medication Monitoring Guidelines for further information about the physical monitoring of patients for these side-effects

13 Ongoing monitoring while on clozapine

13.1 Full Blood Count monitoring

*Details of the exact ranges used by DMS can be found in the Summary of Product Characteristics for Denzapine® (available on www.medicines.org).

<u>White cells and neutrophils</u>

Because of the risk of neutropenia/agranulocytosis, a patient's FBC must be monitored regularly throughout treatment with clozapine.

Before starting clozapine, the patient's FBC (taken within the previous 10 days) must be in the range:

- White blood cell (WBC) count above 3.5 x 109/L
- Absolute neutrophil count (ANC) above 2.0 x 109/L

Please note that patients with benign ethnic neutropenia may be considered for different monitoring ranges* than those listed here with the agreement of a haematologist.

During treatment with clozapine, FBCs must be taken:

- Weekly (every 7 days) for the first 18 weeks; then
- Fortnightly (every 14 days) for the remainder of the first year of clozapine treatment; then
- Monthly (every 28 days) for as long as the patient remains on clozapine.

The frequency of monitoring may change if a patient has had a break in clozapine treatment. See section 14 (Missed doses) for further information.

FBC results must be entered into the Denzapine Monitoring Service system (usually by pharmacy staff). This specifies whether – and how much – clozapine can be supplied, and when the next blood test is due. The results are classified as:

- GREEN – clozapine may be dispensed and blood testing continues on usual schedule
- AMBER (i.e. WBC/ANC has dropped to borderline range*) – clozapine may be continued, but FBC must be repeated at least twice weekly until the result returns to the GREEN range
- RED (i.e. WBC/ANC has dropped below threshold*) – **clozapine must be stopped immediately** and FBC repeated daily until it returns to normal. The patient must be monitored for signs of infection. If the WBC/ANC is very low*, or continues to fall after discontinuation of clozapine, further advice on management should be sought from a haematologist.

If clozapine has been discontinued because of WBC/ANC deficiency (i.e. a RED result), it should never normally be restarted. In certain circumstances a clozapine ‘re-challenge’ may be attempted by agreement with the DMS haematologist; pharmacy can advise on the process for this.

An FBC should also be performed promptly if a patient develops any kind of infection, fever, sore throat or other flu-like symptoms (to check for neutropenia).

<u>Other blood components</u>

It is recommended that treatment with clozapine is discontinued if:

- Eosinophil count rises above 3.0 x 109/L; clozapine should be restarted only once the count falls below 1.0 x 109/L.
- Platelet count falls below 50 x 109/L.

13.2 Physical health monitoring

Guidance regarding physical health monitoring for patients on clozapine is given in the Trust’s Medication Monitoring Guidelines. In summary it advises what should be monitored, how frequently, and in what circumstance. Routine monitoring includes:

- Weight and height (to calculate BMI), waist circumference

- Blood pressure and pulse rate
- Blood glucose and HbA1c
- Lipids
- Urea and electrolytes
- Liver function tests

There is a template on Rio to record physical health monitoring

13.3 Severe adverse effects

Myocarditis/cardiomyopathy and constipation are adverse effects of clozapine that can have potentially severe consequences and these should be actively monitored for.

Myocarditis/cardiomyopathy

Tachycardia is a common side-effect of clozapine, particularly during the initial dose titration, but usually settles with time. Slowing the rate of dose titration may help. However, tachycardia may also be a symptom of myocarditis or cardiomyopathy, rare but serious conditions that have been associated with clozapine.

Myocarditis (inflammation of the heart muscle) has been reported in less than 1% of patients starting clozapine, mostly during the first month of treatment. Signs and symptoms include:

- Tachycardia
- Fever
- Chest pain
- Shortness of breath
- Reduced exercise capacity
- Peripheral oedema
- Hypotension
- Fatigue
- Arrhythmia

None of these are specific to myocarditis, but if several occur together (and especially if the patient appears unwell or breathless) it is advisable to consider urgent medical action including immediate discussion with a cardiologist or on-call physician, explaining the possibility of myocarditis owing to clozapine. Investigation by ECG, measurement of eosinophils and CRP and troponin levels may be useful, but specialist referral should not be delayed while waiting for these to be done.

Clozapine should be stopped until myocarditis has been ruled out; if it is confirmed, clozapine must be stopped permanently.

Cardiomyopathy (weakness of the heart muscle) has been reported in about 0.1% of patients on clozapine, and tends to occur later in treatment, usually after the first year. The main features are those of gradual heart failure – shortness of breath, reduced exercise capacity, and fluid retention/peripheral oedema. Referral to a cardiologist should be considered if these signs develop.

Constipation and gastrointestinal hypomotility

Constipation is a common side-effect of clozapine, but may progress to a more generalised gastrointestinal hypomotility, with severe and potentially fatal results (including bowel obstruction and toxic megacolon).

Risk factors for developing constipation include:

- Higher plasma levels of clozapine
- Prescription of other anticholinergic medications (such as procyclidine or tricyclic antidepressants) or opioids
- Lifestyle factors – low-fibre diet, obesity, lack of exercise
- Dehydration

Constipation should be assessed on an ongoing basis and should be actively treated to ensure it has resolved adequately.

13.4 Clozapine plasma level monitoring

Clozapine plasma levels do not need to be measured routinely every week/fortnight/month – but may be useful in particular situations, e.g.:

- Following establishment on a new dose, as clinically indicated
- Incomplete response at standard doses
- Severe or unexpected adverse effects
- Suspected toxicity
- Suspected non-adherence
- Change in medications (e.g. fluoxetine) or substances (e.g. cigarette
- smoking, caffeine intake) that may affect the metabolism of clozapine. See below for more information about smoking and clozapine
- Other disorders that may affect the metabolism of clozapine (e.g. liver disease)

If not done otherwise, a clozapine plasma level should be taken once a year for ongoing monitoring.

Clozapine plasma levels should be taken approximately 12 hours after the last dose. This will usually mean taking the level in the morning; if the patient normally takes a morning dose of clozapine this should be withheld until the level has been taken.

Following a change in clozapine dose it is recommended that a plasma level should not be measured until 7 days after the change to ensure steady state has been reached.

The sample must be sent in the correct plasma level pack to Analytical Services International. The pack contains a collection tube, request form and postage envelope and is available from the local CPFT pharmacy department. NB. The sample should not be sent to the local hospital laboratory as it cannot be processed there and is likely to be discarded.

In patients who have not responded to clozapine, consideration should be given to adjusting the dose to give a plasma level above 0.35 mg/L, as

response is more likely above this level. At levels above 0.6 mg/L adverse effects are more likely: in particular, the seizure threshold is lowered as the plasma level increases. Ideally the clozapine plasma level should be maintained below 0.6 mg/L; if higher levels are to be maintained (and are clinically appropriate) seizure prophylaxis with sodium valproate should be considered.

Results of clozapine plasma levels may take 3-7 days to become available. If a level has been taken because of suspected toxicity it may be appropriate to reduce the clozapine dose before the result is available.

Smoking and clozapine plasma levels

The metabolism of clozapine is increased by components of tobacco smoke. If a patient stops smoking, reduces significantly, or switches to e-cigarettes or nicotine replacement therapy, this enzyme induction is gradually lost – typically over 7-10 days – leading to increased plasma levels of clozapine (an increase of 50% is not unusual). A dose reduction may be needed (e.g. by 25%). The plasma level should be re-measured once the patient's smoking status is established.

14 Missed doses and treatment breaks

WARNING: Missed dose are particularly significant in someone taking clozapine. The period of time that they have been without medication could cause their symptoms to return, or mean that they need to have altered doses in the short term, and/or more frequent blood tests.

If a patient has missed doses of clozapine, or is at risk of running out of clozapine, the pharmacy department should be contacted promptly (including the on-call pharmacist if pharmacy is closed).

If a patient goes without taking clozapine for less than 48 hours, the normal dose can be continued when it is next due. If it is more than 48 hours since clozapine was last taken, the dose should be reduced and re-titrated (see below). If the patient has stopped clozapine for less than two weeks, it may be possible to increase the dose more rapidly than the initial titration.

If more than 72 hours have passed since the last dose of clozapine, an FBC must be taken before the patient is restarted, and FBC monitoring will need to be done weekly for 6 weeks. If a treatment break is more than four weeks, any re-start will be treated in the same way as a new clozapine initiation (dose titration, frequency of FBC monitoring).

15 Restarting clozapine after a break

If a patient goes without clozapine for more than 48 hours, treatment should be restarted from a low dose, and built up gradually to the previous dose to minimise dose-related side-effects. It is often possible that this process can be done slightly faster than the initial starting schedule, particularly if the

treatment break is less than 2 weeks. CPFT pharmacy department can advise on this, and on the frequency of FBC monitoring that will be required.

Care should be taken if clozapine re-titration is to be done under supervision (using crushed tablets or clozapine suspension), and there is any suggestion of previous non-compliance. In this case lower starting doses should be used.

The restart of clozapine requires physical monitoring of the patient for their safety, and consideration should be given to the practicality of doing this in the community.

If a patient has been off clozapine for more than 4 weeks, they will need to be re-registered with DMS and treated as if starting as a new patient.

16 What to do if a patient is running out of clozapine

WARNING: Missed dose are particularly significant in someone taking clozapine. If a patient has missed doses, or is at risk of running out of clozapine, the pharmacy department should be contacted promptly (including the on-call pharmacist if pharmacy is closed).

The supply of clozapine is restricted to secondary care only. Owing to the restrictions imposed by the manufacturer to prevent serious adverse drug reactions, the amount that is supplied is based on the result of a valid FBC. Patients are not able to keep a reserve of clozapine, and so in exceptional circumstances a patient may run out of tablets before they are next able to obtain a supply (e.g. postal delays, late blood test results, or dose adjustments where the dispensing pharmacy has not been informed).

It is important that patients are able to get supplies of clozapine without a treatment break. The pharmacy should ALWAYS be contacted if advice or further supplies are required. Treatment should not be delayed because the pharmacy is closed; there is always an on-call pharmacist available. The pharmacy department should also be informed at the earliest opportunity if an incident has occurred at any time concerning the supply or monitoring of clozapine for a patient. Contact details for CPFT pharmacy departments are listed in Appendix 4 of this guideline.

17 Inpatient admission of a patient taking clozapine

<u>Mental health wards</u>

If a patient already using clozapine has been admitted to an inpatient ward it is important to establish their recent compliance, and whether there has been any break in treatment, which will influence the appropriateness of continuing treatment as described previously.

The pharmacy department (including on-call pharmacist out of hours) should be informed promptly of any patient admitted to inpatient care taking clozapine. They will assist with ensuring that appropriate supplies and monitoring are conducted.

Occasionally a patient is admitted who is taking clozapine prescribed by another Trust (which may be another brand). Again the CPFT pharmacy department should be contacted promptly, as they can assist in liaison with the current supplier and prescriber.

Non-mental health wards

Occasionally a patient taking clozapine is admitted to a CPFT community inpatient ward. It is important to get specialist mental health input on managing clozapine as soon as the patient is admitted. This is best done by contacting the local mental health pharmacy: details are given in Appendix 5. This should not be delayed: out-of-hours there is always a mental health pharmacist on call.

18 Arrangements for discharge or transfer

It is important to consider the long-term continuity of care for patients taking clozapine. Before discharge from inpatient care it should be established:

- Where FBC tests will be taken (preferably at the local clozapine clinic, or otherwise at the local GP surgery)
- Date of next FBC (with assistance to make appointment if necessary)
- How clozapine will be supplied (at clinic, collected from CPFT pharmacy, post, etc)
- Where routine physical health checks will take place

The pharmacy department should be notified of any patient taking clozapine that is being discharged, so that appropriate supplies can be dispensed. Ward supplies of clozapine MUST NOT be given to the patient for discharge under any circumstances.

If a patient is being transferred to another ward within CPFT it should be made clear when the next blood test is due, and supplies of clozapine should be transferred with the patient.

19 Stopping clozapine

Ideally if clozapine is to be stopped the dose should be reduced gradually to avoid any rebound exacerbation of psychotic symptoms or cholinergic rebound.

For planned discontinuation, the dose should be slowly reduced over a period of at least 1-2 weeks. For unplanned or urgent discontinuation, the patient should be monitored carefully for signs of rebound psychosis and symptoms such as profuse sweating, headache, nausea, vomiting and diarrhoea, which may indicate cholinergic rebound, and need to be treated symptomatically.

For psychosis associated with Parkinson’s disease, a gradual reduction in steps of 12.5 mg over a period of at least one week (preferably two) is recommended.

Full blood count monitoring should be continued for one month following discontinuation of clozapine. The number of FBCs required will depend on the

frequency of FBC monitoring at the time of stopping, when the previous FBC was taken, and the reason for stopping. The local CPFT pharmacy department can advise. If the patient does not agree to further FBC monitoring their physical condition should be monitored for one month after discontinuation.

20 Communication with GPs

Although GPs are not responsible for prescribing, it is important that they are informed that their patient is taking clozapine: so that they can be aware of possible side-effects, the risk of neutropenia, and potential interactions with other medicines they may prescribe.

21 Education and training

There are no specific education and training requirements with this guideline.

22 Monitoring compliance

The contents of this guideline will be reviewed in connection with any alteration in the manufacturer' licensing agreement, or with changes in local arrangements.

Compliance with this guideline will be monitored by the Chief Pharmacist using a risk-based approach and as agreed by the Medicines Governance Group. Exceptions will be reported through the MGG to the Quality Compliance Executive as required.

23 Links to other documents

- Medicines Policy
- Medicines Monitoring Guidelines

24 References

Summary of Product Characteristics for Denzapine® tablets – www.medicines.org.uk/emc. Accessed online 19/09/2019

Bleakley S, Taylor D *Clozapine Handbook* (2013) Lloyd-Reinhold, Dorsington. ISBN 13-978-0-959156-1-0

NHS
Cambridgeshire and Peterborough
NHS Foundation Trust

Appendix 1:
<u>Inpatient</u> initiation of clozapine (adult)

Suggested titration regimen:

Day	Morning Dose	Evening Dose	Suggested maximum for initial target dose*
1	12.5mg		
2	12.5mg	12.5mg	
3	12.5mg	25mg	
4	25mg	25mg	
5	25mg	50mg	
6	25mg	75mg	
7	50mg	75mg	
8	50mg	100mg	
9	75mg	100mg	
10	75mg	125mg	
11	100mg	125mg	
12	100mg	150mg	Female non-smokers
13	100mg	175mg	
14	100mg	200mg	
15	100mg	225mg	
16	100mg	250mg	Male non-smokers
17	100mg	275mg	
18	100mg	300mg	
19	100mg	300mg	
20	100mg	325mg	
21	100mg	325mg	
22	100mg	350mg	Female smokers
23	100mg	350mg	
24	100mg	375mg	
25	100mg	375mg	
26	100mg	400mg	
27	100mg	400mg	
28	100mg	425mg	

*Target dose recommendations are based on population averages. Titration should stop once the target dose is reached (or before if experiencing significant adverse effects). Further dose adjustment may be made according to clinical response. The suggested maximum target dose for a male smoker is 550 mg/day.

Please note that this regimen is provided for guidance only. Actual speed of titration will depend on individual tolerability. A lower starting dose and slower titration should be used for patients who are elderly, medically compromised or more sensitive to the adverse effects of medication.

Appendix 2:
<u>Outpatient</u> initiation of clozapine (adult)

Cambridgeshire and Peterborough NHS Foundation Trust

Example regimen for titration starting on a Tuesday

(No dose increases over a weekend)

Day	Day	Morning Dose	Evening Dose	Suggested maximum for initial target dose*
1	Tuesday	6.25mg		
2	Wednesday	12.5mg		
3	Thursday	25mg		
4	Friday	37.5mg		
5	Saturday	37.5mg		
6	Sunday	37.5mg		
7	Monday	50mg		
8	Tuesday	50mg	12.5mg	
9	Wednesday	50mg	25mg	
10	Thursday	50mg	37.5mg	
11	Friday	50mg	50mg	
12	Saturday	50mg	50mg	
13	Sunday	50mg	50mg	
14	Monday	50mg	75mg	
15	Tuesday	75mg	75mg	
16	Wednesday	75mg	100mg	
17	Thursday	75mg	125mg	
18	Friday	100mg	125mg	
19	Saturday	100mg	125mg	
20	Sunday	100mg	125mg	
21	Monday	100mg	150mg	Female non-smoker
22	Tuesday	100mg	175mg	
23	Wednesday	100mg	200mg	
24	Thursday	100mg	225mg	
25	Friday	100mg	250mg	Male non-smokers
26	Saturday	100mg	250mg	
27	Sunday	100mg	250mg	
28	Monday	100mg	275mg	

*Target dose recommendations are based on population averages. Titration should stop once the target dose is reached (or before if experiencing significant adverse effects). Further dose adjustment may be made according to clinical response. The suggested maximum target dose for a female smoker is 450mg/day, and for a male smoker 550 mg/day.

Please note that this regimen is provided for guidance only. Actual speed of titration will depend on individual tolerability. A lower starting dose and slower titration should be used for patients who are elderly, medically compromised or more sensitive to the adverse effects of medication.

Appendix 3:
Monitoring/observations forms for starting clozapine (also as a template on Rio)

Patient Name:		**Hosp. Number:**		
Date of Birth:		**Consultant:**		
Day 1				
	Pre-dose	**1 hour post dose**	**2 hours post dose**	**3 hours post dose**
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				
Day 1 (cont)				
	4 hours post dose	**5 hours post dose**	**6 hours post dose**	
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				
Day 2				
	Pre-dose	**2 hours post dose**	**4 hours post dose**	**6 hours post dose**
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				

Patient Name:	**Hosp. Number:**
Date of Birth:	**Consultant:**

Day 3

	Pre-dose	2 hours post dose	6 hours post dose	
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				

Day 4

	Pre-dose	2 hours post dose	6 hours post dose	
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				

Day 5

	Pre-dose	2 hours post dose	6 hours post dose	
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				

Patient Name:		Hosp. Number:	
Date of Birth:		Consultant:	
	Day 6		**Day 7**
	Pre-dose	**6 hours post dose**	**Pre-dose**	**6 hours post dose**
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				
	Day 8		**Day 9**
	Pre-dose	**6 hours post dose**	**Pre-dose**	**6 hours post dose**
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				
	Day 10		**Day 11**
	Pre-dose	**6 hours post dose**	**Pre-dose**	**6 hours post dose**
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				

Patient Name:		**Hosp. Number:**	
Date of Birth:		**Consultant:**	
	Day 12	**Day 13**	**Day 14**
	Pre-dose / **6 hours post dose**	**Once daily pre-dose**	**Once daily pre-dose**
BP lying (mmHg)			
BP standing (mmHg)			
Pulse (bpm)			
Temperature (oC)			
Dizziness			
Sedation			
Constipation			
Hypersalivation			
Nausea			
Urinary problems			
	Day 15	**Day 16**	**Day 17**	**Day 18**
	Once daily pre-dose	**Once daily pre-dose**	**Once daily pre-dose**	**Once daily pre-dose**
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				
	Day	**Day**	**Day**	**Day**
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				

NHS
Cambridgeshire and Peterborough
NHS Foundation Trust

Patient Name: Date of Birth:		Hosp. Number: Consultant:		
	Day	Day	Day	Day
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				
	Day	Day	Day	Day
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				
	Day	Day	Day	Day
BP lying (mmHg)				
BP standing (mmHg)				
Pulse (bpm)				
Temperature (oC)				
Dizziness				
Sedation				
Constipation				
Hypersalivation				
Nausea				
Urinary problems				

Appendix 4: Pharmacy contacts

Cambridge Locality:
Pharmacy Department – Patient Resource Centre
Fulbourn Hospital
Cambridge
CB21 5EF
(01223) 219523

Opening hours for questions/queries – 0830 to 1700hrs
Opening hours for dispensing – 0900 to 1700hrs
Out of hours contact – on-call pharmacist (call duty practitioner for number)

Huntingdon Locality:
C/o Pharmacy Department – Patient Resource Centre
Fulbourn Hospital
Cambridge
CB21 5EF
(01223) 219523

Opening hours for questions/queries – 0830 to 1700hrs
Opening hours for dispensing – 0900 to 1700hrs
Out of hours contact – on-call pharmacist (call duty practitioner for number)

Peterborough Locality:
Pharmacy Department - Cavell Centre
Edith Cavell Campus
Bretton Gate
Peterborough
PE3 6GZ
(01733 776006)

Opening hours for questions/queries – 0830 to 1700hrs
Opening hours for dispensing – 0900 to 1700hrs
Out of hours contact – on-call pharmacist (call duty practitioner for number)

Appendix 5. Clozapine information for CPFT community inpatient wards (not mental health)

If a patient is admitted who is taking CLOZAPINE, it is important to contact the nearest CPFT pharmacy department **immediately** for advice. Out-of-hours, this should not be delayed – there is always a specialist mental health pharmacist on call.

Cambridge (Fulbourn Hospital Pharmacy) – 01223 219523
Peterborough (Cavell Centre Pharmacy) – 01733 776006
Out-of-hours – call the CPFT Cambridge Duty Practitioner 07983 338673 and ask for the number of the on-call pharmacist

Pharmacy can advise on prescribing/dosing, and any other actions needed urgently (e.g. blood tests), and can arrange for a supply of clozapine if needed. They can also help with contacting the mental health team who are usually responsible for prescribing and monitoring clozapine.