CLOZAPINE TREATMENT GUIDELINES
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<tr>
<td>Oct 2015</td>
<td>1</td>
<td>New document (3 documents merged into 1) - now incorporates policies on: Initiating patients on clozapine in the community, Clozapine Red results and Clozapine therapeutic drug monitoring</td>
</tr>
<tr>
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</tr>
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</table>

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**DO NOT AMEND THIS DOCUMENT**

Further copies of this document can be found on the Foundation Trust intranet.
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1. Introduction
The trust strives to ensure the safety of its service users by encouraging and promoting the safe and effective prescribing of medicines. This document provides guidance on clozapine treatment and ensures systems are in place to minimise the clinical risks associated with clozapine. It outlines responsibilities and the procedure to be followed when initiating, dispensing, administering and monitoring clozapine treatment.

Clozapine is more effective for treating psychosis than any other antipsychotic and increased response may still be seen 12 months after initiation of clozapine¹.

1.1. Aims and objectives
This document aims to provide staff with guidance on safely initiating Clozapine for inpatients and in the community setting. It aims to provide a step-by-step guide on the patient monitoring requirements when initiating Clozapine, continuing and discontinuing therapy.

1.2. Scope of the policy
All clinical staff involved in the prescribing, administering, monitoring and dispensing clozapine

1.3. Duties and responsibilities
All staff involved in the process are responsible and accountable for ensuring they have read, understood and follow these guidelines. It is the responsibility of all staff involved in any aspect of this guideline to inform their manager of any variation in practice or inability to follow the processes defined. Tasks should not be undertaken or delegated to a member of staff who is not legally entitled, authorised or appropriately trained.

Table 1: Roles and associated responsibilities

<table>
<thead>
<tr>
<th>Title of Health care professional</th>
<th>Key Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribers</td>
<td>Consult the most up-to-date evidence when making treatment decisions about clozapine and medications and evaluate the risks &amp; benefits of clozapine treatment on a case-by-case assessment. • Where possible, decisions about clozapine treatment should be made jointly with the patient (and advocate/carer) and with their consent. • Must ensure that baseline investigations have been completed and are satisfactory prior to initiating clozapine and ongoing follow-up investigations are completed and satisfactory when continuing clozapine. • To complete a full medical history inclusive of interactions with other medicines and contraindications prior to initiation of clozapine. • Prescribe clozapine in accordance with these guidelines. • Must monitor the patient’s physical and mental health. • To monitor the patient for side effects and ensure these are managed in accordance with these guidelines. • Ensure to inform the patient’s GP and community team on discharge from the ward when clozapine has been initiated or when an existing patient on clozapine has been admitted. To write the outpatient prescription on discharge (electronic patient records – medication tab) and when requested thereafter. • Junior doctors should also refer to senior colleagues (Specialist Registrar/Consultant) for clinical advice on clozapine treatment. • Care needs to be shared and clearly communicated to the clozapine</td>
</tr>
<tr>
<td>Clinic, pharmacy team, care co-ordinator and other healthcare professionals (e.g. GP) involved in patient care</td>
<td></td>
</tr>
<tr>
<td>• Treatment plans must be clearly documented in the patient’s clinical notes.</td>
<td></td>
</tr>
<tr>
<td>• To handover patient’s if they leave/move post.</td>
<td></td>
</tr>
<tr>
<td>• Liaise with CPMS as appropriate.</td>
<td></td>
</tr>
</tbody>
</table>

### Pharmacy Staff

**Pharmacists:**

- To clinically screen and endorse inpatient clozapine prescriptions (in accordance to the Pharmacy Endorsing Standards) and outpatient repeat clozapine prescriptions (in the electronic patient records) and check dispensed clozapine as per the clozapine standard operating procedure (SOP).
- To check clozapine blood tests as per local clozapine procedures.
- Dispense clozapine in accordance to these guidelines, the SOP and clozapine manufacturers’ licensing requirements.
- Liaise with Clozaril Patient Monitoring System (CPMS) as appropriate.
- Feedback any concerns around clozapine treatment to the prescriber, clozapine clinic, lead professional, care coordinator or any other clinical team(s) involved in the patient’s care.
- Adhere to clozapine SOP.

Provide advice to carers/patients and healthcare professionals on clozapine treatment using more up- to-date literature.
- Provide training on clozapine to healthcare professionals as appropriate.
- Liaise with acute staff pharmacy staff as appropriate.

**Technicians:**

- To dispense clozapine as per the clozapine SOP.
- To follow local procedures to ensure there is a valid outpatient repeat clozapine prescriptions (in the electronic patient records – medication tab) for dispensing.
- Refer any concerns regarding clozapine to the pharmacist/prescriber/nursing staff/clozapine clinic as appropriate.

### Nursing Staff

**Registered Nurse (A nurse who is listed on the Nursing and Midwifery Council (NMC) Register as a qualified nurse):**

- Should ensure that in conjunction with the prescriber that the baseline investigations have been completed prior to initiating clozapine.
- That vital signs and side effect monitoring are completed in accordance with the guideline.
- Any concerns with vital signs, over sedation or other intolerable associated side effects are reported back to the prescriber and documented within the clinical notes.
- Should liaise with the Care Coordinator to arrange follow up with the clozapine clinic on discharge from the ward.

**Care Co-ordinators:**

- Should ensure that the patient attends the clozapine clinic in accordance with their monitoring schedule.
- Should monitor the patient’s physical and mental health in partnership with the clozapine clinic.
- Report any concerns to both the prescriber and the clozapine clinic.
- Ensure the patient has a valid prescription for clozapine and this is reviewed as part of the CPA or Outpatient review.
- Ensure the clozapine clinics are made aware of any changes to the prescribed medication.
- Feedback any concerns around compliance with clozapine treatment to the prescriber and clozapine clinic i.e. deterioration in mental state.
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Clozapine Clinic Nurses:
- Ensure the appropriate blood monitoring is completed.
- Ensure the patient is monitored for side effects.
- Monitor the patient’s physical health when attending the clinic and document it on the EPR.
- Report any concerns back to the prescriber.
- Ensure non-attendance to the clinic is reported back to the prescribing team and pharmacy.
- Report any concerns regarding compliance with clozapine back to the prescriber and involved care team.

Clozapine Clinics-Point of Care Testing (POCT):
(In addition to the clinic nurse role)
- Ensure that they are familiar with the contents of the guideline.
- Are suitably trained and certified to use the POCT equipment.
- Adhere to local SOPs in place to support POCT.
- Advise their service lead if they are unable to adhere to, or have to deviate from the procedures outlined in their local SOPs.

Suitably trained healthcare professional
- Suitably trained healthcare professionals who have completed the clozapine competency framework can assist in monitoring clozapine titrations.
- Suitably trained healthcare professionals can observe self-administration of clozapine for patients prescribed a maintenance dose of clozapine.

Service Leads
- To ensure that the clozapine clinics are completing the monitoring as outlined in the guideline.
- To ensure that all delivering POCT within the clozapine clinic adhere to the relevant SOPs.
- Ensure staff receive the relevant training/update to operate POCT equipment.

All Staff
- Should familiarise themselves with this guideline and ensure they are competent to carry out their professional duties.
- Know how to signpost patients/carers with questions about the use of clozapine.
- If appropriate inform relevant clinical team(s) involved in patients care.

2. Clozapine treatment
Indications for clozapine:

- Treatment-resistant schizophrenia.

  Treatment resistance is defined as a lack of satisfactory clinical response despite the use of adequate doses of at least two different antipsychotic medicines, including an atypical antipsychotic medicine, prescribed for adequate duration.

- Patients who have severe, untreatable neurological adverse reactions to other antipsychotic medicines, including atypical antipsychotics.

- A diagnosis of psychosis during the course of Parkinson's disease, in cases where standard treatment has failed.

Clozapine is the only medicine with established efficacy in reducing symptoms and risk of relapse for adults with treatment resistant schizophrenia. It is the only antipsychotic with established efficacy in reducing negative symptoms.
An increased response can still be seen twelve months after initiation.

**Choice of proprietary brand**
There are 3 brands of clozapine and associated monitoring services available in the UK:
- CPMS (Clozaril Patient Monitoring Service) monitors Clozaril®.
- ZTAS (Zaponex Treatment Access System) monitors Zaponex®.
- DMS (Denzapine Monitoring System) monitors Denzapine®.

**Camden & Islington NHS Foundation Trust (C&I) patients should be started on “CLOZARIL”.** The tablets are available as 25mg and 100mg. In exceptional circumstances, the liquid formulation can be ordered (Denzapine brand) and this is subject to approval by submitting a non-formulary medicine request form. Moreover, patients must be registered with Denzapine Monitoring Service.

The UK CLOZARIL Patient Monitoring Service (CPMS) is available 24 hours a day on the following contacts:

**Tel:** 0845 769 8269  
**E-mail:** cpms@mylan.co.uk

The use of CLOZARIL is restricted to patients who are registered with CPMS. All clozapine treated patients must be under the supervision of a consultant psychiatrist. In North Central London (NCL), clozapine is on the “red list”* and therefore should only be prescribed and dispensed in secondary care.

* Red list -contains medicines that are on hospital formularies, but owing to their speciality, safety or monitoring requirements. GPs should not be asked to continue to prescribe clozapine. The responsibility for prescribing these medicines should remain with the hospital trust consultant unless shared care has been agreed or in exceptional cases where transfer of treatment for an individual patient has been agreed with both the consultant and GP.

2.1. **Contraindications to use of clozapine**
The following contraindications are taken from the Clozaril® Summary of Product Characteristics¹ (SPC):

- Hypersensitivity to the active substance or to any of the excipients.
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- History of clozapine induced agranulocytosis.
- 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).
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
- Paralytic ileus.

Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis (see Appendix 1 medicine interactions with clozapine).

Concomitant use of depot antipsychotics is not recommended.
2.2. Switching to clozapine

From oral antipsychotics

Clozapine manufacturers recommend stopping the previous antipsychotic before starting clozapine due to the increased risk of blood dyscrasias and additive side effects of combinations. In practice, this is not always possible due to the mental state of the patient. A good general rule, when switching from an oral antipsychotic to clozapine, is that the dose of the previous antipsychotic should have been reduced significantly by the time the clozapine titration is at a dose of 100mg daily. The cross titration plan must be clearly documented in the Electronic Patient Records (EPR).

From depot antipsychotics

At the earliest, clozapine can be started after the date the depot would have been due, however it is important to be aware of the increased risk of agranulocytosis and the inability to withdraw the depot should this occur.

3. Monitoring

3.1. Frequency of blood monitoring

In the UK, a white cell count with a differential count must be monitored:

- **0 – 18 weeks** of treatment: weekly monitoring
- **19 – 52 weeks** of treatment: fortnightly monitoring
- **After 1 year of treatment** with stable neutrophil counts: 4 weekly monitoring

CPMS reports blood results in three colour bands that apply to both initial and on treatment samples as follows:

<table>
<thead>
<tr>
<th>Result</th>
<th>Reference range</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GREEN</strong></td>
<td>WBC &gt; 3.5 x 10^9/L and/or neutrophils &gt; 2.0 x 10^9/L</td>
<td>A satisfactory result that is within acceptable ranges, valid to initiate/continue clozapine treatment. For the initiation of clozapine treatment, a green result is required.</td>
</tr>
<tr>
<td><strong>AMBER</strong></td>
<td>WBC 3.0 – 3.5 x 10^9/L and/or neutrophils 1.5 – 2.0 x 10^9/L</td>
<td>A result that indicates that although the patient may continue clozapine treatment, extra caution must be exercised and additional bloods tests will be required. Clozapine cannot be initiated until a satisfactory green result is received. Results may show as amber if patient has benign ethnic neutropenia*</td>
</tr>
<tr>
<td><strong>RED</strong></td>
<td>WBC &lt; 3.0 x 10^9/L and/or neutrophils &lt; 1.5 x 10^9/L</td>
<td>Result is not satisfactory, not valid to initiate or to continue clozapine treatment. Please refer to Appendix 2 Red Results Policy for information.</td>
</tr>
</tbody>
</table>

The following actions will be taken with respect to these results:

<table>
<thead>
<tr>
<th>Table 3: Results and actions</th>
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<tbody>
<tr>
<td><strong>Pre-treatment</strong></td>
</tr>
<tr>
<td>Green</td>
</tr>
<tr>
<td>Amber</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Red</strong></td>
</tr>
</tbody>
</table>

3.2. **Management of Red Results**

On receiving a red result, stop clozapine treatment immediately and follow the red results policy (see appendix 2 and figure 1).

The first of these two results must have been provided to the monitoring service within 24 hours from the red result notification. Follow up blood tests must be at least 24 hours apart and samples should be sent to the local pathology laboratories.

Local laboratories:
- Whittington Hospital
- University College London Hospital
- Royal Free Hospital

If the initial red result is confirmed with a second red result, the patient will then be classified as “non-rechallengable”. The patient’s details are added to the Central Non-Rechallengable Database (CNRD) which is accessible by all three clozapine monitoring services.

Refer to Section 3.6 and 3.8 for information on recommencing clozapine following a treatment break (i.e. >48 hours).
3.3. **Benign Ethnic Neutropenia (BEN)**
BEN is a condition characterised by the adherence of neutrophils to blood vessel walls. These neutrophils are still available to fight infection. However, the neutrophil count may be below normal ranges. Afro-Caribbean or African populations experience BEN more commonly than other ethnic groups.

To allow for this variation, the clozapine monitoring services will adjust the neutrophil reference ranges for green, amber and red results for patients with a confirmed BEN diagnosis, meaning that a lower neutrophil count can still constitute a green result. A BEN diagnosis requires confirmation by a haematologist.

3.4. **Platelets and eosinophils**
A low platelet count does not constitute a ‘Red’ result, but will be highlighted on the monitoring service database.

Eosinophil counts are monitored. Abnormally high results will also be highlighted on the monitoring service database. Eosinophilia is co-reported in 14% of patients with myocarditis and may therefore be significant, although its reliability as a predictor is unknown.
Eosinophil count > 3.0 x 10⁹/L or
Platelet count < 50 x 10⁹/L
Discontinuation of clozapine is recommended.

Clozapine therapy should be restarted only after the eosinophil count has fallen below 1.0 x 10⁹/L or the platelet count is above 50 x 10⁹/L. The monitoring service will notify clinicians and recommend twice weekly monitoring. The prescriber should review the patient and assess whether to continue clozapine treatment. See the CPMS fact sheet which can be accessed via the website⁵.

3.5. Treatment Break and monitoring frequency
If clozapine has not been taken for more than 48 hours patients must have their clozapine re-titrated.

This is due to the increased risks of cardiac complications when restarting clozapine (e.g. postural hypotension, tachycardia or bradycardia). Once the medicine has been discontinued the clozapine plasma level drops quickly. Based on an average half-life of between 7 and 14 hours, after 35 - 70 hours (5 times the half-life) there will be no detectable clozapine remaining. Large increases in doses following treatment breaks have caused death in patients that had already been taking clozapine. The re-titration must commence at a dose of no more than 12.5mg - 25mg. The dose can then be increased according to patient tolerability. A more rapid titration e.g. increasing by 50mg-100mg per day may be appropriate if the patient has previously tolerated initiation of clozapine, there are no significant co-morbidities and they're physically fit and well (see Appendices 3 and 4 clozapine titration).

3.6. Frequency of blood monitoring following a treatment break

<table>
<thead>
<tr>
<th>Monitoring Frequency</th>
<th>Time Off Clozapine ≤ 48 hours</th>
<th>Time Off clozapine &gt; 48 hours BUT &lt; 7 days</th>
<th>Time Off clozapine &gt;7 days</th>
<th>Time off clozapine &gt;28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td>No change to frequency continue at normal dose</td>
<td>No change to monitoring frequency. Re-titrate clozapine dose</td>
<td>Restart at 18 weeks of weekly monitoring. Re-titrate clozapine dose</td>
<td>Restart 18 weeks of weekly monitoring Re-titrate dose as per initial titration PATIENT REGISTRATION FORM REQUIRED</td>
</tr>
</tbody>
</table>

Contact CPMS
### Table 5: Protocol for treatment breaks - Fortnightly and monthly monitoring patients

<table>
<thead>
<tr>
<th>Monitoring Frequency</th>
<th>Time Off Clozapine ≤ 48 hours</th>
<th>Time Off clozapine &gt; 48 hours BUT &lt; 4 days</th>
<th>Time off clozapine &gt; 4 days BUT &lt; 28 days</th>
<th>Time off clozapine &gt; 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortnightly &amp; Monthly</td>
<td>No change to frequency continue at normal dose</td>
<td>No change to monitoring frequency. Re-titrate clozapine dose</td>
<td>'Treatment break' Weekly blood tests for 6 weeks and then return to previous monitoring frequency. Re-titrate clozapine dose Contact CPMS</td>
<td>Restart 18 weeks of weekly monitoring. Re-titrate as per initial titration. PATIENT REGISTRATION FORM REQUIRED Contact CPMS</td>
</tr>
</tbody>
</table>

#### 3.7. Monitoring requirements following Treatment Discontinuation

Following discontinuation of clozapine for non-haematological reasons, 4 additional weeks of haematological monitoring after the last dose are required at the frequency in use at the time of treatment cessation.

- Weekly - 4 additional blood results at weekly intervals
- Fortnightly - 2 additional blood results within 4 weeks after discontinuation
- 4-weekly -1 additional blood result 4 weeks after discontinuation

If clozapine treatment is discontinued, ward staff / clinic nurse must notify CPMS of this and the reason for discontinuation within 24 hours.

For monitoring requirements following a 'Red' result, refer to Appendix 2.

If clozapine therapy has been discontinued for any reason, all stock held by the patient should be removed in order to prevent any unauthorised re-initiation to the patient.

Removal should be undertaken, even if the intention is to re-titrate in the near future.

#### 3.8. Rechallenging a Non-Rechallengeable Patient

Clozapine is unlicensed in patients who are classified as non-rechallengeable.

The mechanism for clozapine-induced neutropenia or agranulocytosis is unknown and extreme caution must be exercised if re-exposing someone to clozapine after a dyscrasia. Each clozapine monitoring service has their own protocol for re-challenging non-rechallengeable patients. Please contact your ward/lead pharmacist for information relating to these protocols.

If the prescriber does wish to re-challenge a patient who has been classified as non-rechallengeable, they must:

- **Contact CPMS for advice**
- Liaise with the clozapine clinic nurse, the care co-ordinator and the pharmacist about their decisions.
- Discuss the decision with the patient and carers and get informed consent from the patient, including the risks (1 in 3 chance of a repeat dyscrasia) and benefits. The
patient’s capacity to consent should be considered and documented. If lacking capacity, the principles of the Mental Capacity Act (2005) should apply.

- The decision and plan should be clearly recorded in the EPR.
- Consider need for crisis team or inpatient admission during the high risk re challenge period.
- The patients and carers should be informed to report any physical concerns, particularly fever, sore throat or any signs of infection urgently.

4. **Initiation of clozapine**

The use of clozapine is restricted to patients who are registered with CPMS. Consultant psychiatrist. A nominated pharmacist must also be registered. Patients must be registered with CPMS. C&I use the CLOZARIL brand. Registration forms for the patient/consultant/pharmacist can be obtained from [https://www.clozaril.co.uk/](https://www.clozaril.co.uk/).

**a. General requirements for initiating Clozapine:**

- The doctor should liaise with the pharmacist and the clozapine clinic when formulating the plan to initiate a patient on clozapine.
- Clozapine titrations in the community should be overseen by the crisis teams (and in Camden alongside the ADU). If assistant practitioners (APs) assist in overseeing the clozapine titration (in the crisis teams), the AP must have completed and passed the clozapine competency framework (appendix 5).
- It is not advisable to start clozapine at the weekends or on bank holidays.
- Attention should be paid to ensuring good communication between all teams involved during this period, and a clear management plan outlining different teams’ responsibilities should be established.

- A blood test (full blood count) must be taken as part of the CPMS registration requirements prior to starting clozapine.

- The first dose of clozapine must be given within 10 days of the baseline “Green” full blood count, a second full blood count is required within 7 days of this dose.

**b. Prescribing and the initial dose titration**

Clozapine must be started at 12.5mg and titrated slowly due to the risks of cardiovascular side effects. Dose increases should follow the Clozapine Titration shown in appendix 3. The initial target dose is usually 300mg per day. The average daily dose is approximately 200-450mg/day (maximum 900mg/day). The dosing should be based on the patient’s clinical presentation and the plasma clozapine level. Slower titrations should be considered for special populations and where clinically appropriate.

For maintenance therapy, the lowest dose of clozapine to maintain remission should be used. Once at a stable dose, treatment should be continued for at least a year before fully assessing the benefits. Studies have shown that of patients who have previously been refractory to treatment, 30% improve significantly after 6 weeks of clozapine treatment and up to 60% respond after 1 year⁹.

**c. General points**

Blood pressure (sitting and standing), pulse and temperature must be checked before each dose, and again 30 minutes after each dose. The pulse should be checked by touching the patient and not be relied upon with a machine. All results should be recorded on the NEWS chart.
d. Routine monitoring after initiating clozapine

Table 6: Monitoring for titration of clozapine in the community

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Before administering clozapine, check and record vital signs:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Blood pressure (lying and standing)</td>
</tr>
<tr>
<td></td>
<td>• Pulse</td>
</tr>
<tr>
<td></td>
<td>• Temperature</td>
</tr>
<tr>
<td></td>
<td>If within normal limits the clozapine dose can be administered.</td>
</tr>
<tr>
<td></td>
<td>Repeat BP, pulse and temperature 30 minutes after clozapine administration.</td>
</tr>
<tr>
<td></td>
<td>Any results outside normal limits should be discussed with a doctor.</td>
</tr>
<tr>
<td></td>
<td>The nurse or doctor must stay with the patient for at least half an hour after the dose, or until the patient is ready to go to bed. Confirm overnight contact number and family/carer availability.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 2 Onwards</th>
<th>Twice daily visits should be continued during the titration period and monitoring completed as for Day 1.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Check if the patient is experiencing any side effects. This should be done at weekly intervals. Continue monitoring monthly thereafter or where indicated (e.g. dose increase).</td>
</tr>
<tr>
<td></td>
<td>Monitor if patient is constipated and actively treat the constipation.</td>
</tr>
<tr>
<td></td>
<td>Patient should attend the clozapine clinic</td>
</tr>
</tbody>
</table>

| Week 2 | Following medical review and if patient is tolerating treatment, understands the regimen and physical signs are within acceptable limits, visits may be reduced to once daily. |

<table>
<thead>
<tr>
<th>Week 3</th>
<th>Following medical review:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• visits may reduce to alternate days</td>
</tr>
<tr>
<td></td>
<td>• routine blood testing should occur at the clozapine clinic (if not before)</td>
</tr>
<tr>
<td></td>
<td>• the patient may begin to collect their weekly clozapine supply from the pharmacy or clinic as per local arrangement.</td>
</tr>
</tbody>
</table>

| Side effects | Side effects should be recorded. The GASS tool (in the electronic patient record should be competed on a weekly basis. |

| Communication | Any patients undergoing clozapine titration should be discussed in the daily handover. Discussion should include report of observations, side effects and adherence. |

A doctor should be informed if:

- Temperature rises above 38°C.
- Pulse > 100bpm.
- Systolic or diastolic BP drop > 30mmHg.
- Systolic BP > 140mmHg and/or diastolic BP is > 90mmHg.
- Systolic BP: <100mmHg
- Diastolic BP: < 60mmHg
- Sore throat or fever.
- If there are other concerns e.g. constipation or over sedation.
- Red or amber results.
- Non-adherence to one dose or more and a plan made and documented.
- There is a NEWS score. If the score flags up, refer to the NEWS action protocol.

The clozapine clinics manage the mandatory blood testing and physical health monitoring for individuals already established on clozapine treatment, ensuring that patients are monitored both physically and mentally and for any adverse effects. The clinics support the care coordinators to ensure that individuals using the clinic have an annual physical health
assessment before their CPA review. They also provide health promotion and advice on issues such as smoking and weight management.

The clozapine clinics are located in:-

- The Daffodil Unit, Highgate Mental Health Centre
- The Hoo Clozapine Clinic, Daleham House
- The Clozapine Clinic, Jules Thorne Recovery Centre

On-going review of mental state and side effects should take place in the clozapine clinics and by the care teams. Any concerns should be escalated to the consultant psychiatrist.

All patients prescribed clozapine in the trust should be under a named consultant. As a minimum, patients should have an annual psychiatric review by a psychiatrist.

The NICE Clinical Guidelines for Psychosis and Schizophrenia recommends that GPs and other healthcare workers should be involved with the monitoring of the physical health of people with schizophrenia and that the results of physical health checks should be clearly documented by the primary care clinician. These results should be communicated to secondary care, and recorded in the patient's secondary care notes.

5. **Ongoing physical health monitoring and review**

**Monitoring at clozapine clinic**

Vital sign monitoring may be reduced after a minimum of two weeks on review by a doctor. Mandatory FBC monitoring should be continued as outlined in Section 3.

Blood pressure, pulse, temperature, weight and mental state should be assessed at each visit to the Clozapine Clinic.

**Annual monitoring for patients prescribed an antipsychotic**

**What should be monitored?**

- Weight
- Waist circumference
- Pulse
- Blood Pressure
- Fasting Blood Glucose
- HbA1C*
- Lipids**
- (Assessment of any movement disorders)
- (Assessment of nutritional status, diet and level of physical activity)**

**Who should monitor?**

"GPs and other primary healthcare professionals should monitor the physical health of people with psychosis or schizophrenia when responsibility for monitoring is transferred from secondary care, and then at least annually. The health check should be comprehensive, focusing on physical health problems that are common in people with psychosis and schizophrenia. Refer to relevant NICE guidance on monitoring for cardiovascular disease, diabetes, obesity and respiratory disease. A copy of the results should be sent to the care coordinator and psychiatrist and put in the secondary care notes."

Clozapine is included in the ‘red list’ of North Central London Formulary. A medicine included on the ‘red list’ is prescribed by a specialist and is not considered a shared care medicine. Trust consultants continue to prescribe clozapine and are registered with CPMS.
The patients will need to be reviewed by the psychiatrists usually every 6 to 12 months depending on the individual. Clozapine is dispensed via the Hospital Pharmacy Department.

6. Dispensing of clozapine
Clozapine can only be dispensed to a patient when there is a valid prescription and a valid blood result is present. ‘Green’ blood result is considered to be a valid result.

<table>
<thead>
<tr>
<th>Table 7: Validity of blood results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MONITORING FREQUENCY</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>WEEKLY</td>
</tr>
<tr>
<td>2 WEEKLY</td>
</tr>
<tr>
<td>4 WEEKLY</td>
</tr>
<tr>
<td>STATUS ON CPMS WEBSITE</td>
</tr>
</tbody>
</table>

Pharmacy Department provides clozapine for all inpatients, community units and all three clozapine outpatient clinics. The amount of clozapine dispensed depends on the monitoring frequency and valid green blood test results. See table below:

<table>
<thead>
<tr>
<th>Table 8: Amount of clozapine that can be supplied for each monitoring frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring Frequency</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Weekly</td>
</tr>
<tr>
<td>Fortnightly</td>
</tr>
<tr>
<td>4 weekly</td>
</tr>
</tbody>
</table>

*If result is AMBER and the patient is clinically well, continue clozapine but repeat blood test twice weekly until GREEN again. Pharmacy will supply medication for 3-5 days until the result is GREEN.

For red results, patient must stop treatment and no clozapine will be dispensed. See Appendix 2.

See the clozapine standard operating procedure for the dispensing procedure.

6.1. Out of hours supplies
Highgate Pharmacy is open from 9 – 5.15pm Monday – Friday and Saturday 10.00 – 1.00pm.

It is responsibility of the ward pharmacist/medicines management technician to check inpatient supplies on Friday to ensure that there is adequate supply to cover the weekend.

If clozapine is required outside of normal working hours for existing inpatients or new admissions, the site manager needs to contact the on - call pharmacist via the Camden and Islington NHS Foundation Trust Switchboard. The Trust phone number: 020 3317 3500.
Medicines should only be given to the patient for whom they were prescribed/dispensed according to C&I Medicines Management policy and the clozapine standard operating procedure.

7. Discharge and outpatient clozapine clinics

7.1. Discharging after the initial titration

Ensure also, that:

- A clozapine outpatient prescription has been completed (by the inpatient consultant) in the electronic patient record (medication tab) and the pharmacy department notified for continuation of supply. The community consultant will prescriber thereafter.
- The amount of clozapine supplied on a discharge TTA must correspond to the patient's blood test monitoring frequency. Pharmacy can only supply medication for the duration of the current valid blood test result.
- Details of the clozapine clinic where the patient is to attend for subsequent weekly blood tests.
- CPMS have been informed of the new responsible clinician (RC) and treatment location.
- The Clozapine Clinic has been informed.
- See the clozapine standard operating procedure for the supply procedure.

7.2. Non-collection of Clozapine for outpatients

All attempts must be made to contact the patient/carer/care coordinator to remind them of the need for collection and/or to establish that the patient has enough clozapine to last until they are able to collect. The pharmacy team should follow the Pharmacy department Clozapine SOP for non-collection of clozapine.

7.3. Dispensing for holiday period

The Responsible Consultant and MDT should be made aware if the patient plans to go on holiday. In some cases, the patient may require more clozapine and an extra blood test to cover their holiday period. The pharmacy department should be notified of a separate outpatient prescription in the electronic patient record to cover the holiday period supply. The clinic nurse should liaise with the Responsible Consultant and pharmacy to ensure that this is available in advance.

8. Clozapine therapeutic drug monitoring

Clozapine levels should not be taken routinely. It should be carried out in the following scenarios:

- When the maintenance dose of clozapine has been achieved
- When non-compliance is suspected and patient shows poor response to treatment
- Slow metabolism suspected
- Following dose adjustments and addition/removal of interacting agents (e.g. smoking, Very large changes in caffeine intake can alter clozapine metabolism)
- At least annually to ensure correct levels are achieved and any insidious changes in levels which may present as asymptomatic.
- If toxicity is suspected (intentional or unintentional)

Please refer to appendix 6 for more information.
9. **Augmentation**

Augmentation strategies should only be considered after optimised clozapine treatment has been administered for a period of at least 3 months. An adequate trial of augmentation may need up to 8-10 weeks\(^2.6\). Below is a table of augmentation options including non-antipsychotics from the Maudsley Prescribing Guidelines\(^6\).

<table>
<thead>
<tr>
<th>Suggested options for augmenting clozapine(^7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride 400-800mg/day</td>
</tr>
<tr>
<td>Aripiprazole 15-30mg/day</td>
</tr>
<tr>
<td>Haloperidol 2mg/day</td>
</tr>
<tr>
<td>Lamotrigine 25-300mg</td>
</tr>
<tr>
<td>Risperidone 2-6mg/day</td>
</tr>
<tr>
<td>Sulpiride 400mg/day</td>
</tr>
</tbody>
</table>

Some evidence and experience suggests it may be worthwhile. Only one small RCT. May allow clozapine dose reduction.

Very limited evidence of therapeutic benefit. Improves metabolic parameters.

Modest evidence of benefit.

May be useful in partial and non-responders. Several negative reports, but meta-analysis suggests moderate effect size.

Supported by a randomised controlled trial, but there are two negative RCTs each with miniscule response rates. Small number of reports of increases in clozapine plasma levels.

May be beneficial in partial and non-responders. Supported by a randomised controlled trial (RCT).

10. **Discontinuation of clozapine**

If possible, when a patient’s clozapine is to be discontinued, the dose should be gradually tapered over 1–2 weeks\(^7\). Note if a red result obtained, clozapine must be stopped abruptly.

After stopping clozapine, particularly if stopped abruptly (e.g. because of e.g. a red result or agranulocytosis, a patient’s physical and mental state should be monitored closely for symptoms reflecting cholinergic rebound or rebound psychosis, particularly in the first week\(^6\). The need for crisis team input should be considered.

If clozapine therapy is temporarily interrupted for more than 48 hours, it must be restarted at a dose of 12.5–25 mg/day. If this dose is well tolerated, with no cardiovascular or respiratory symptoms, and previous standard dosage titration has been uneventful, then it may be reasonable to titrate the dose to the therapeutic level more rapidly than is recommended for initial treatment. As stated in the SmPC for clozapine, if a patient previously experienced respiratory or cardiac arrest with initial dosing, but titration to a therapeutic dose was subsequently successfully achieved, re-titration should be carried out with extreme caution\(^7\).

**Rapid rebound psychosis**

**Given the high risk of relapse/ rebound psychosis careful consideration should be given to alternative antipsychotics and symptomatic adjunctive treatments e.g hypnotics given the risk of insomnia if Clozapine is discontinued.**

Also see 3.7. See appendices 3 and 4.
11. **Adverse effects**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Time Course</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Usually persists – take care with additive effects of anti-muscarinic medication</td>
<td>A gastrointestinal history and/or abdominal examination should be considered prior to starting clozapine. If there is pre-existing constipation, this should be adequately treated. Advise the patient on a high fibre diet, fluid intake and exercise. Avoid concomitant medication known to cause constipation. The lowest effective dose of clozapine should be used. Screen and monitor for symptoms of constipation - <strong>abdominal pain, abdominal dilation, vomiting, overflow diarrhoea, absent or high pitched bowel sounds and signs of sepsis.</strong> Effective treatment or prevention is essential. Monitor using the Bristol Stool Chart. If constipation occurs an abdominal examination is indicated. If intestinal obstruction is excluded, the patient should be treated with laxatives. If possible other medicines which cause constipation should be stopped. Use stimulants in combination with a stool softener or osmotic laxative. Avoid bulk-forming agents for the treatment of constipation. These agents may be considered for the prevention of constipation, but only if the patients who would be able to follow the instructions to drink sufficient amounts of water. With insufficient fluid intake, bulk forming agents will contribute to constipation. Caution – constipation may be severe and lead to stasis of bowel/ ileus / obstruction. Paralytic ileus and obstruction are considered to be dose/plasma levels. In the case of serious motility impairment, the patient needs to be referred to a gastroenterologist and clozapine should be stopped. Constipation may inhibit the absorption of clozapine in the gut. Plasma clozapine levels may be reduced when a patient is constipated and increased as the constipation resolves. Also see appendices 10 and 11.</td>
</tr>
<tr>
<td>Fever</td>
<td>First 3 weeks</td>
<td>Give antipyretic but check FBC. This fever is not usually related to blood dyscrasias. Be aware of myocarditis or cardiomyopathy.</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>First few months. May persist, but sometimes wears off. Can be particularly troublesome at night.</td>
<td>Give hyoscine hydrobromide (Kwells) 300micrograms sucked or chewed up to three times a day. Alternatives: - Benzhexol (trihexyphenidyl) All treatments are unlicensed. Hypersalivation is most common in the first few months of treatment but may persist longer term in some people. First line treatment is hyoscine hydrobromide 300micrograms up to three times daily, which should be sucked or chewed. If this is not effective, other pharmacological treatments should be tried.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>First 4 weeks, sometimes longer</td>
<td>Monitor closely and increase dose as slowly as is necessary. Treatment with a cardio-selective beta blocker (e.g. atenolol, bisoprolol) may be necessary.</td>
</tr>
<tr>
<td>Hypotension</td>
<td>First 4 weeks</td>
<td>Advise patient to take their time when standing up Reduce dose or slow down titration Risk of orthostatic hypotension with or without syncope may be reduced with a slow titration during initiation. Circulatory</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Management</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Collapse</strong></td>
<td>Collapse is rare but can be profound and may be accompanied by respiratory arrest and/or cardiac arrest.</td>
<td></td>
</tr>
<tr>
<td><strong>Tachycardia</strong></td>
<td>First 4 weeks, sometimes persists</td>
<td>Very common in early stages of treatment but usually benign. Tachycardia, if persistent at rest and associated with fever, hypotension, chest pain or heart failure may indicate myocarditis or cardiomyopathy. In this situation, stop the clozapine and refer to a cardiologist immediately. Refer immediately to cardiologist. Benign tachycardia may be treated with atenolol or bisoprolol. Other causes must be excluded first. This would usually include an ECHO and a referral to a cardiologist. An ECG is not sufficient.</td>
</tr>
<tr>
<td><strong>Myocarditis, cardiomyopathy, pericarditis or pericardial effusion</strong></td>
<td>Rare. Myocarditis is more likely to occur early in treatment. Cardiomyopathy can occur at any time.</td>
<td>Observe for signs or symptoms, e.g. tachycardia, palpitations, fever, arrhythmia, symptoms mimicking myocardial infarction, chest pain, shortness of breath and other unexplained symptoms of heart failure. Refer to cardiologist for an ECHO and stop treatment if suspected. (NB – an ECHO is required because diagnosis may not be confirmed from an ECG).</td>
</tr>
<tr>
<td><strong>QTc prolongation</strong></td>
<td></td>
<td>May occur increasing the risk for the ventricular arrhythmia torsades de pointes. ECG monitoring is recommended.</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>First 6 weeks</td>
<td>May give anti-emetic such as domperidone or cyclizine.</td>
</tr>
<tr>
<td><strong>Neutropenia / agranulocytosis</strong></td>
<td>Most common during first 18 weeks (but may occur at any time)</td>
<td>Stop clozapine. Admit to hospital if confirmed. Neutropenia and agranulocytosis are not dose related effects. See the clozapine red results policy (appendix 2).</td>
</tr>
<tr>
<td><strong>Nocturnal enuresis</strong></td>
<td>May occur at any time</td>
<td>Try reducing the dose or manipulating the dose schedule. Avoid fluids before bedtime. May resolve spontaneously. In severe cases, desmopressin is usually effective but beware of hyponatraemia.</td>
</tr>
<tr>
<td><strong>Sedation</strong></td>
<td>First few months, usually wears off but may persist</td>
<td>Give smaller doses in the morning. Check clozapine level. Reduce dose if necessary.</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>May occur any time. Increased risk with clozapine plasma levels above 0.6mg/L</td>
<td>Seizures can be dose related or dose increase related. Recommend plasma level monitoring. Seizures are more common at plasma levels above 0.6mg/L. Consider prophylactic sodium valproate (1-2g daily) if clozapine level above 0.6mg/L. See MHRA advice (for valproate) if the patient is a woman of child bearing age. If seizure develops, withhold clozapine for 1 day, restart at a reduced dose and give sodium valproate. EEG abnormalities are common in those on clozapine. Myoclonic jerks are particularly common.</td>
</tr>
<tr>
<td><strong>Signs of infection e.g. sore throat</strong></td>
<td>May occur at any time</td>
<td>Request FBC to rule out development of neutropenia. Treat symptomatically e.g. paracetamol.</td>
</tr>
<tr>
<td><strong>Altered glucose tolerance</strong></td>
<td>Can rarely occur</td>
<td>Patients may require adjustment in antidiabetic medicines or insulin.</td>
</tr>
<tr>
<td><strong>Increased blood lipids</strong></td>
<td>Can rarely occur</td>
<td>Patients may require treatment with simvastatin.</td>
</tr>
<tr>
<td><strong>Weight gain</strong></td>
<td>Usually during the first year of treatment</td>
<td>Dietary advice is essential. Advice may be more effective if given before weight gain occurs. Weight gain is common and often profound (&gt;4.5kg).</td>
</tr>
</tbody>
</table>
**Agranulocytosis and Neutropenia**
The life-time incidence of agranulocytosis with clozapine is 0.78%, with 70% of incidents occurring within the first 18 weeks of treatment\(^1\). The risk of agranulocytosis decreases by approximately 17% for every 10 year increase in age at initiation. Afro-Caribbean populations are at greater risk of agranulocytosis.

Neutropenia can also occur with other antipsychotics and is not only associated with the use of clozapine. It is not a dose related side effect of clozapine, however a previous history of medicine induced neutropenia is associated with a higher risk \(^10,11\). In severe cases, lithium or GCSF may be used to boost a patient’s white cells, however this is not common practice and should only be considered if it is strongly felt that prior neutropenic episodes were unrelated to clozapine. It is recommended that patients are referred to a haematologist for a full review before prescribing in this way. Seek advice from pharmacy if needed.

**Myocarditis**
Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction. If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist.

Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

C-reactive protein can be an indicator for myocarditis. Cessation of clozapine is advised if C-reactive protein is over 100 mg/l. Combining this parameter with ECG results has an estimated sensitivity for symptomatic clozapine-induced myocarditis of 100%. The sensitivity for asymptomatic disease is unknown.

Side-effects that are thought to be dose-related include drowsiness, headache. Often these can be avoided by careful and slow dose escalation or alleviated by reducing the dose.

**12. Dissemination and implementation arrangements**
This document will be circulated to all managers who will be required to cascade the information to members of their teams. It will be available to all staff via the Foundation Trust intranet.

**13. Training requirements**
For training requirements, please refer the Core Skills Training Policy on the trust intranet.
14. Monitoring and audit arrangements

<table>
<thead>
<tr>
<th>Elements to be monitored</th>
<th>Lead</th>
<th>How trust will monitor compliance</th>
<th>Frequency</th>
<th>Reporting arrangement(s)</th>
<th>Acting on recommendations and Lead(s)</th>
<th>Change in practice and lessons to be shared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing of clozapine</td>
<td>Chief Pharmacist</td>
<td>Medication charts are clinically screened by a pharmacist.</td>
<td>Ongoing</td>
<td>Drugs and Therapeutics Committee</td>
<td>Drugs and Therapeutics Committee</td>
<td>Review of policy; implementation practices and procedures. Re-audit. Give feedback to prescribers</td>
</tr>
</tbody>
</table>

15. Review of the policy
This policy will be reviewed in 3 years or earlier should a significant change came to light.

16. Associated documents
- Antipsychotic prescribing guidelines
- Medicines management policy

17. References
3. CPMS website. [https://www.clozaril.co.uk/](https://www.clozaril.co.uk/) (accessed 8th of June 2019).
6. The Maudsley Prescribing Guidelines
Appendix 1: Medicine Interactions with Clozapine
Please refer to manufacturers’ SPCs for a full list of interactions and contact your ward pharmacist for further advice.

<table>
<thead>
<tr>
<th>Class of medicine</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Due to CYP1A2 inhibition by fluvoxamine, clozapine levels may be increased. It is recommended to avoid the use of fluvoxamine. Other SSRIs such as fluoxetine, paroxetine and sertraline do not inhibit CYP 1A2 and therefore, interactions are less likely.</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td><strong>Carbamazepine</strong> should be avoided with clozapine due to its myelosuppressive potential. Phenytoin can also reduce clozapine levels due to enzyme induction.</td>
</tr>
<tr>
<td>Anti-infectives.</td>
<td>Ciprofloxacin, norfloxacin, clarithromycin, erythromycin, rifampicin and ritonavir are known to increase clozapine levels. Avoid if possible. Doses of clozapine may need to be reduced by 50%.</td>
</tr>
<tr>
<td>Bone marrow suppressing medicines</td>
<td>Co-trimoxazole, methazolamide, nitrofurantoin, other antipsychotics, benzylpenicillin (long-term, high dose), carbimazole, dapsone, dipyrene, procainamide, propylthiouracil, rituximab, sulfasalazine, thiamazole, and ticlopidine all have myelosuppressive potential. Increased risk of agranulocytosis, avoid if possible.</td>
</tr>
<tr>
<td>Buspirone.</td>
<td>Increased risk of GI bleed and hyperglycaemia. Avoid if possible.</td>
</tr>
<tr>
<td>Caffeine.</td>
<td>The plasma concentration of clozapine can be increased by large quantities of caffeine intake and may decrease by nearly 50% following a 5-day caffeine-free period. Dose changes of clozapine may be necessary. NB: this is not usually significant as extremely large quantities of caffeine would need to be consumed to exert any clinical effect.</td>
</tr>
<tr>
<td>Lithium.</td>
<td>There is a possible increased risk of Neuroleptic Malignant Syndrome (NMS), neurotoxicity and ketoacidosis. Use this combination with caution and observe for signs and symptoms of NMS.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Decreases clozapine levels by up to 70%. Encourage smoking cessation. Observe patients for signs of decreased clozapine efficacy when nicotine is added to clozapine. Monitor clozapine levels during restarting smoking/cessation/.</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Increased risk of respiratory depression. Use with caution.</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Increased risk of excessive anticholinergic effects (sedation, constipation, dry mouth). Use this combination only when clearly indicated. Monitor for excessive anticholinergic effects.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>The plasma concentration of clozapine is possibly reduced by rifampicin. Monitor levels and adjust dose as appropriate.</td>
</tr>
</tbody>
</table>
Appendix 2: Clozapine Red Results Policy

1. Introduction

These guidelines have been produced to assist clinicians in managing a red result for an individual taking Clozapine.

Clozapine Patient Monitoring Service (CPMS) uses a system of traffic lights (Red, Amber and Green) to review blood test results.

<table>
<thead>
<tr>
<th></th>
<th>Green</th>
<th>Amber</th>
<th>Red</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count</td>
<td>( \geq 3.5 \times 10^9/L )</td>
<td>3.0 - 3.5 \times 10^9/L</td>
<td>&lt; 3.0 \times 10^9/L</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>( \geq 2.0 \times 10^9/L )</td>
<td>1.5 - 2.0 \times 10^9/L</td>
<td>&lt; 1.5 \times 10^9/L</td>
</tr>
</tbody>
</table>

The guidelines relate to a confirmed red result under CPMS guidelines.

Make arrangements to undertake confirmatory blood counts on the 2 days following the date of the red alert sample. If either of these follow up blood counts is in the red alert range, then red alert status is taken to be confirmed.

In its most severe form, it can result in agranulocytosis, when the neutrophil count is <0.5 \times 10^9/L.

### Afebrile Patients

A local agreement would be made with the consultant haematologist as to where (home, psychiatric unit or acute general hospital) each patient will be managed.

Patients with a neutrophil count of <0.5 \times 10^9/L are of particular risk

Mild neutropenia (neutrophils >1 – 1.5 \times 10^9/L):

FEBRILE patients should be admitted to an acute general hospital.

Moderate to Severe neutrophilia (neutrophil counts <1 \times 10^9/L):

FEBRILE patients should be admitted to an acute general hospital.

Patients with neutropenia and fever must be treated as a medical emergency; they must receive immediate treatment.

2. Initial notification of a Red Result

A red result status is generally communicated by telephone and fax. The person receiving a red result should take personal responsibility for ensuring that the patient is contacted as a matter of URGENCY, and that the following people are also informed.
RMO (consultant psychiatrist or nominated deputy)  
Clozapine Clinic Staff  
Pharmacy  
Duty Nurse (if inpatient & out of hours)  
Care co-ordinator or Key Worker  
Ward Manager  

(Please cascade this information to the administration support team/ secretaries to contact clinicians on receiving any communication marked urgent from the CPMS)

The Pharmacy Department will require up to date contact details for the Care Coordinator/Community staff to be provided on the clozapine outpatient prescriptions in order to undertake this role.

General management for outpatients and inpatients

Management of a red result should initially be under the clinical leadership of the patient’s Consultant Psychiatrist or the Consultant Psychiatrist on call or nominated deputy such the On-Call SpR (Specialist Trainee 4-6) until such time that a Consultant Physician or Consultant Haematologist assumes this role.

<table>
<thead>
<tr>
<th>ACTION POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. STOP CLOZAPINE IMMEDIATELY</td>
</tr>
<tr>
<td>2. Undertake confirmatory blood counts. Should the results be in the red range then the red alert status is confirmed. Should the results be in amber or green range repeat the blood tests daily for the next two days, if any of these follow up is in the red alert range, then the red alert status is taken as confirmed.</td>
</tr>
<tr>
<td>3. See monitoring criteria below</td>
</tr>
<tr>
<td>4. Review any other medication that may contribute to neutropenia e.g. carbimazole, penicillamine, and co-trimoxazole. If necessary introduce an alternative. Please note that Carbamazepine is strongly not recommended for patients on clozapine.</td>
</tr>
<tr>
<td>5. TRY NOT to give other antipsychotic medicines, but use Haloperidol (as required, provided the patient is not sensitive/ allergic to Haloperidol or contraindicated for other reasons) if absolutely necessary.</td>
</tr>
<tr>
<td>6. If the red result is confirmed, THE PATIENT SHOULD NOT RESTART CLOZAPINE</td>
</tr>
<tr>
<td>7. Every attempt should be made to try to ensure the patient understands the potential seriousness of the situation.</td>
</tr>
<tr>
<td>8. An unconfirmed ‘red result’ occurs when the follow up results in the following two days are amber and/or green. If the red result is unconfirmed, re-initiation can only occur if authorised by CMPS.</td>
</tr>
</tbody>
</table>

Afebrile Patients

A local agreement would be made with the consultant haematologist as to where (home, psychiatric unit or acute general hospital) each patient will be managed. Patients with a neutrophil count of $<0.5 \times 10^9/L$ are of particular risk.

Mild neutropenia (neutrophils $>1 – 1.5 \times 10^9/L$):  
FEBRILE patients should be admitted to an acute general hospital.

Moderate to Severe neutrophilia (neutrophil counts $<1 \times 10^9/L$):  
FEBRILE patients should be admitted to an acute general hospital.
2.1. Community (outpatient) management of mild neutropenia only (neutrophils > 1 – 1.5 x 10^9/L)

The decision to manage a patient in the Community should be made in conjunction with the consultant haematologist or consultant physician.

**a) Afebrile**

The risk of infection **may** be reduced if the patient can be managed in their home environment.

<table>
<thead>
<tr>
<th>Criteria for community or home management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily visits by an RMN from the Community Team/local Crisis Resolution Team</td>
</tr>
<tr>
<td>Immediate access to hospital admission if any deterioration in physical status</td>
</tr>
<tr>
<td>Neutrophil count &gt; 1.0 x 10^9 /L</td>
</tr>
<tr>
<td>No fever (temperature of 38°C or less)</td>
</tr>
<tr>
<td>Family or carer support available</td>
</tr>
<tr>
<td>Stable mental state</td>
</tr>
</tbody>
</table>

**The following should be monitored daily**

- Temperature
- Blood pressure
- Pulse rate
- Respiratory rate
- Clinical signs and symptoms of infection e.g. fever, sore throat and mouth ulcers
- Full blood count and C Reactive Protein (CRP). If the CRP is rising, this is an indication of developing infection. It is important to seek advice from Haematology
- Mental state

Give advice about diet – avoid salads, yoghurt, un-peeled fruit or soft cheese. Use sterilised milk, sterilised water or canned drinks.

Every attempt should be made to try to ensure the patient understands the potential seriousness of the situation.

**Where the neutrophil count continues to fall**

If the neutrophils continue to fall, continue with daily full blood counts. If the neutrophils go below a level of 1.0, admit to hospital and follow the guidelines for the management of moderate or severe neutropenia.

2.2. Inpatient management of mild or moderate neutropenia

**Mild neutropenia (neutrophils >1 – 1.5 x 10^9/L):**

**AFEBRILE** patients - the decision to manage a patient in a psychiatric unit should be made in conjunction with the consultant haematologist or consultant physician.

**FEBRILE** patients should be admitted to an acute general hospital.

**Moderate to Severe neutropenia (neutrophil counts<1 x 10^9/L):**

**IN THE MAJORITY OF CASES:**

**AFEBRILE or FEBRILE** patients should be admitted to an acute general hospital.
IN EXCEPTIONAL CIRCUMSTANCES ONLY:

AFEBRILE patients may be admitted to a psychiatric inpatient unit (e.g. under the Mental Health Act).
- The responsible consultant psychiatrist with the agreement of a consultant haematologist or consultant physician should only make such a decision.
- Management in a psychiatric inpatient unit should only proceed if the patient remains AFEBRILE and APPROPRIATELY qualified medical and nursing staff are available to prescribe and administer the recommended treatment as per guidelines below.

FEBRILE patients MUST be admitted to an acute medical unit as a matter of urgency and to be managed under the direct supervision of a Consultant Haematologist or Consultant Physician.

1) Mild neutropenia (neutrophils >1 – 1.5 $\times 10^9$/L)

a) Afebrile

<table>
<thead>
<tr>
<th>THE FOLLOWING SHOULD BE MONITORED DAILY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Pulse rate</td>
</tr>
<tr>
<td>Respiratory rate</td>
</tr>
<tr>
<td>Clinical signs and symptoms of infection e.g. fever, sore throat and mouth ulcers</td>
</tr>
<tr>
<td>Full blood count and C Reactive Protein (CRP). If the CRP is rising, this is an indication of developing infection. It is important to seek advice from Haematology</td>
</tr>
<tr>
<td>Mental state</td>
</tr>
</tbody>
</table>

Give advice about diet – avoid salads, yoghurt, un-peeled fruit or soft cheese. Use sterilised milk, sterilised water or canned drinks.

Where the neutrophil count continues to fall

If the neutrophils continue to fall, continue with daily full blood counts. If the neutrophils go below a level of 1.0 $\times 10^9$/L, discuss admission to an acute general hospital with the haematologist/physician. Follow the guidelines for the management of moderate or severe neutropenia.

b) Febrile

<table>
<thead>
<tr>
<th>OBSERVATIONS/TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Pulse rate</td>
</tr>
<tr>
<td>Respiratory rate</td>
</tr>
<tr>
<td>Oxygen saturation</td>
</tr>
<tr>
<td>Clinical signs and symptoms of infection e.g. sore throat and mouth ulcers</td>
</tr>
<tr>
<td>Full blood count and C Reactive Protein (CRP).</td>
</tr>
<tr>
<td>Clotting screen</td>
</tr>
<tr>
<td>Urea and electrolytes</td>
</tr>
<tr>
<td>Liver function tests</td>
</tr>
<tr>
<td>Blood cultures</td>
</tr>
<tr>
<td>Weight to calculate antibiotic doses</td>
</tr>
<tr>
<td>Mental state</td>
</tr>
</tbody>
</table>
If the patient develops a fever (temperature greater than 38°C maintained for more than 1 hour or >38.5°C on one occasion this is a medical emergency will require urgent transfer of the patient to an acute medical unit under the direction of a consultant haematologist or consultant physician.

**Note** there are limited Haematology beds and it may be that the patient is transferred to a general medical bed under the care of a consultant physician. It is extremely important to liaise with the hospital consultant haematologist about the overall management plan.

### 2) Moderate or severe neutropenia (neutrophils < 1.0 x 10^9/L)

**a) Afebrile**

<table>
<thead>
<tr>
<th>INITIAL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Check Urea &amp; Electrolytes, liver and renal function tests</td>
<td></td>
</tr>
<tr>
<td>Examine the patient for a focus of infection and take appropriate swabs and a midstream urine for culture</td>
<td></td>
</tr>
</tbody>
</table>

**THE FOLLOWING SHOULD BE MONITORED FOUR HOURLY**

- Temperature
- Blood pressure
- Pulse rate
- Respiratory rate

**THE FOLLOWING SHOULD BE CHECKED DAILY**

- Clinical signs and symptoms of infection e.g. fever, sore throat and mouth ulcers
- Full blood count and C Reactive Protein (CRP). If the CRP is rising, this is an indication of developing infection and it is important to seek advice from Haematology
- Mental state

**MEDICATION**

Liaise with the Consultant Haematologist or Consultant Physician at the closest acute general hospital and treatment should be according to their advice

Nurse in a single room and wash hands in alcohol based hand wash before and after contact with the patient.

Give advice about diet – avoid salads, yoghurt, un-peeled fruit or soft cheese. Use sterilised milk, sterilised water or canned drinks.

**Where the neutrophil count continues to fall**

If the neutrophils continue to fall, continue with daily full blood counts. If the neutrophils go below a level of 1.0 x 10^9/L, discuss admission to an acute general hospital with the haematologist/physician. Follow the guidelines for the management of moderate or severe neutropenia.
b) Febrile

<table>
<thead>
<tr>
<th>OBSERVATIONS/TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Pulse rate</td>
</tr>
<tr>
<td>Respiratory rate</td>
</tr>
<tr>
<td>Oxygen saturation</td>
</tr>
<tr>
<td>Clinical signs and symptoms of infection e.g. sore throat and mouth ulcers</td>
</tr>
<tr>
<td>Full blood count and C Reactive Protein (CRP).</td>
</tr>
<tr>
<td>Clotting screen</td>
</tr>
<tr>
<td>Urea and electrolytes</td>
</tr>
<tr>
<td>Liver function tests</td>
</tr>
<tr>
<td>Blood cultures</td>
</tr>
<tr>
<td>Weight to calculate antibiotic doses</td>
</tr>
<tr>
<td>Mental state</td>
</tr>
</tbody>
</table>

If the patient develops a fever (temperature greater than 38°C maintained for more than 1 hour or >38.5°C on one occasion this is a **medical emergency** will require urgent transfer of the patient to an acute medical unit under the direction of a consultant haematologist or consultant physician.

**Note** there are limited Haematology beds and it may be that the patient is transferred to a general medical bed under the care of a consultant physician. It is extremely important to liaise with the hospital consultant haematologist about the overall management plan.

3. When the Neutrophil Count increases

If the patient’s neutrophils rise over the period of monitoring, it is recommended by the Clozapine Patient Monitoring Service (CPMS):

a. that daily full blood counts should be taken until the neutrophils are > 1.5 (amber results).

b. Then continue with twice weekly full blood counts (amber results) as per CPMS guidelines until the neutrophil count returns to the normal range (green result).

**NB:** if the patient has received lenograstim or filgrastim – may get a rising neutrophil count for a period. This should gradually return to within the normal neutrophil range.

When the neutrophil count returns to within the normal range (green result), introduce an alternative antipsychotic medicine.

4. Clozapine Induced Fever

<table>
<thead>
<tr>
<th>Observations/Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
</tr>
<tr>
<td>Creatine phosphokinase</td>
</tr>
<tr>
<td>Urine and electrolytes if clinically indicated</td>
</tr>
<tr>
<td>Liver functions tests if clinically indicated</td>
</tr>
<tr>
<td>Chest X rays if clinically indicated</td>
</tr>
<tr>
<td>Blood cultures if clinically indicated</td>
</tr>
</tbody>
</table>
Fever or benign transient hyperthermia is a common side effect of clozapine therapy. It generally occurs during the first three weeks of treatment. It is generally involves an increase in temperature of 0.5 – 1°C and is of no clinical significance resolving over a few days. It is often spiking in nature.

Whenever a patient on clozapine presents with a raised temperature, a full blood count with a differential must be undertaken. If the patient is neutropenic, clozapine must be stopped immediately.

Provided the count is satisfactory and the temperature is not more than 38.5°C, treatment with clozapine may continue. If the fever is high (>38.5°C) or persistent, withholding clozapine until the fever subsides should be considered. Symptomatic treatment with antipyretics may be required. If clozapine is stopped and restarted, consideration should be given to using a slower titration schedule. If treatment is stopped for more than 48 hours, treatment should be retitrated from 12.5mg and seek advice from Pharmacy or CPMS.

Fever may be accompanied by tachycardia. If persistent, an ECG should be undertaken. The presence of any other cardiac symptoms such as chest pain, shortness of breath, oedema and any other signs of cardiac failure should be noted and the possibility of myocarditis/ cardiomyopathy should be considered. If myocarditis or cardiomyopathy is suspected, clozapine treatment should be stopped immediately and the patient referred to a cardiologist urgently.

Creatine phosphokinase should be measured to eliminate the possibility of neuroleptic malignant syndrome (NMS). If NMS is suspected, clozapine and any other antipsychotics should be immediately stopped and the patient referred for urgent hospitalisation.

https://www.clozaril.co.uk
Telephone: 0845 7698269.

5. Miscellaneous

The following blood dyscrasias do not result in a red alert. CPMS advise treatment should be stopped in the following cases. However, the decision to stop treatment is made by the medical team:

**Thrombocytopenia**
Platelets < 50 x 10⁹/L

**Eosinophilia**
Eosinophils > 3 x 10⁹/L

Eosinophilia has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis/pericardial effusion; however it is not known if eosinophilia is a reliable predictor of myocarditis. Clozapine should not be restarted until the eosinophil count has fallen below 1.0 x10⁹/L. There is a CPMS factsheet available via the CPMS website.

If myocarditis or cardiomyopathy is suspected, clozapine should be stopped immediately and the patient referred to a cardiologist urgently.

There is a CPMS factsheet available via the CPMS website.

6. Off-Label Re-challenge
There may be occasions where the Clinical Team are of the opinion a patient needs to resume treatment despite a confirmed red result.

In this case, the consultant would need to write to the Clozapine Patient Monitoring Service Medical Adviser requesting an off-label re-challenge. If approved, different red alert criteria would be set for the specific patient in question.

An off label re-challenge should be clearly be documented in the notes.

Dispensing can only occur if the request is approved.

**Summary of individual roles when a Red Result occurs:**

<table>
<thead>
<tr>
<th>Staff</th>
<th>Role</th>
</tr>
</thead>
</table>
| Medical Team (RMO, Senior Specialist (Trainee 4-6), SHO (Core Trainee)) | - Cross Off Clozapine prescription, and check arrangements for informing the patient to STOP clozapine.  
- Mark Clozapine as contraindicated on the prescription chart and the patient’s notes.  
- Carry out observations as requested in guideline.  
- If linked to a Clozapine Clinic - inform clinic staff at the earliest possible time. Staff will be able to give advice and help with the STOP procedure.  
- Liaise with General Medical Team or preferably a haematologist and any other professionals as per guideline.  
- Liaise with CPMS for advice.  
- Prescribe appropriate medication as per guideline, preferably only under direction and supervision of consultant haematologist or physician.  
- Monitor for clozapine discontinuation syndrome (an acute psychotic relapse which occur in some patients following acute withdrawal of clozapine. At times this relapse may be delayed. |
| Pharmacy                                        | - Remove patient’s clozapine from the Ward (If inpatient).  
- Support all staff via guidelines. |
| Key worker, Ward Manager, Registered Nurses     | - Contact patient, and ensure that CLOZAPINE IS STOPPED and remove clozapine. Inform RMO and medical team.  
- Carry out observations as required in guideline.  
- Administer medication as required in guideline.  
- Inform the GP if the patient is in the Community |
Appendix 3

CLOZAPINE TITRATION - Inpatient titration

If clozapine is omitted for greater than 48 hours, it is essential to restart clozapine from initial starting doses. However, faster upward titration may be required depending on the patients tolerance.

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Medicine</th>
<th>Morning dose</th>
<th>Evening dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time:</td>
<td>Time:</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>CLOZAPINE</td>
<td>12.5mg</td>
<td>12.5mg</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>CLOZAPINE</td>
<td>12.5mg</td>
<td>12.5mg</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>CLOZAPINE</td>
<td>25mg</td>
<td>25mg</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>CLOZAPINE</td>
<td>25mg</td>
<td>25mg</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>CLOZAPINE</td>
<td>25mg</td>
<td>50mg</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>CLOZAPINE</td>
<td>25mg</td>
<td>75mg</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>CLOZAPINE</td>
<td>25mg</td>
<td>75mg</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>CLOZAPINE</td>
<td>50mg</td>
<td>75mg</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>CLOZAPINE</td>
<td>50mg</td>
<td>100mg</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>CLOZAPINE</td>
<td>50mg</td>
<td>100mg</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>CLOZAPINE</td>
<td>50mg</td>
<td>125mg</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>100mg</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>125mg</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>150mg</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Generally this dose 100mg OM and 200mg ON

Target doses: female, non-smoker 250mg/day, male, non-smoker 350mg/day, Female smoker, 450mg/day, Male smoker 550mg/day. According to plasma levels.

If problematic side-effects occur, consider slower dose titration.
Appendix 4

CLOZAPINE TITRATION PRESCRIPTION CHART – Quick titration
When a patient has previously been on clozapine and they tolerated the titration. NOT for patients with other medical conditions that may result in an increase in side effects e.g. cardiac, renal impairment.

If problematic side effects occur, consider slower dose titration or decreasing dose to one previously tolerated.

If clozapine is omitted for greater than 48hrs it is essential to restart clozapine from initial starting doses. However, according to tolerance, upward dose titration may be faster than on first trial. If previously on clozapine, date stopped:

<table>
<thead>
<tr>
<th>DAY</th>
<th>DATE</th>
<th>MEDICINE</th>
<th>MORNING DOSE</th>
<th>EVENING DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time:</td>
<td>Time:</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>CLOZAPINE</td>
<td>12.5mg</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>CLOZAPINE</td>
<td>12.5mg</td>
<td>12.5mg</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>CLOZAPINE</td>
<td>25mg</td>
<td>25mg</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>CLOZAPINE</td>
<td>25mg</td>
<td>50mg</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>CLOZAPINE</td>
<td>50mg</td>
<td>50mg</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>CLOZAPINE</td>
<td>75mg</td>
<td>75mg</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>100mg</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>100mg</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>150mg</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>150mg</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>200mg</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>200mg</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>250mg</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>250mg</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>CLOZAPINE</td>
<td>100mg</td>
<td>300mg</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prescribe the dose on the regular side of the prescription chart. Consider the dose the patient was previously on.

Target doses female non-smoker = 250mg/day (day 9), Male non-smoker = 350mg/day (day 13), Female smoker = 450mg/day and Male smoker = 550mg/day. According to plasma levels.

From the Sussex Partnership NHS Foundation Trust. Procedure and Guidance for the use of clozapine. August 2015
Appendix 5

Clozapine Competency Framework for non-nursing staff

Competencies required

- FBCs – frequency of FBCs and the traffic light results.
- Monitor blood pressure via an automatic monitor.
- Monitor pulse via an automatic monitor.
- Undertake a manual BP measurement via a sphygmomanometer stethoscope.
- Undertake a manual pulse.
- Undertake a temperature via an ear thermometer.
- Monitor bowel movement via the Bristol stool chart.
- Side effect monitoring: complete a GASS tool on Carenotes (under the medication tab).

Attainment of competencies to be supervised by a CRT nurse. The assistant practitioner must attend the clozapine clinic to observe the clinic activity.

Frequency of monitoring

First Dose

- BP, pulse and temperature should be undertaken before the dose and then half an hour afterwards.
- Document on the NEWS chart.
- Monitor bowel movement via the Bristol stool chart and document in Carenotes.
- Baseline: Complete a clozapine GASS tool on Carenotes.
- Report any physical health concerns to a nurse.
- If clozapine self-administration is supervised, it must be documented on the medicine chart and Carenotes.

Day 2 onwards:-

AM and PM dose:-

- BP, pulse and temperature should be undertaken before the AM dose, then half an hour post dose.
- Record on a NEWs - 2 chart.
- Monitor for bowel movement on a weekly basis via the Bristol stool chart.
- Undertake a clozapine GASS on a weekly basis.
- If clozapine self-administration is supervised, it must be documented on the medicine chart.

Monitoring vital signs

- If the BP is abnormal, repeat the measurement. Consider a manual reading if there is a concern of faulty equipment.
- If the pulse is abnormal repeat the measurement. Consider a manual reading if there is a concern of faulty equipment.
- The assistant practitioner must be able to undertake the above with no intervention.
- Abnormal results must be reported to the nurse and documented in the NEWs - 2 chart.

Monitoring bowel movement

- The Bristol Stool Chart shows seven categories of stool. The important thing is that stools are soft and easy to pass – like types 3 and 4 below.
- Type 1–2 indicate constipation
- Type 3–4 are ideal stools as they are easier to pass, and
- Type 5–7 may indicate diarrhoea and urgency.
Blood test monitoring
- A traffic light system is used to indicate the blood test range
- Patients do not need to delay taking clozapine before the FBC
- **Red** result – stop clozapine and then daily FBCs (must be reported to nurse).
- **Amber** result – repeat FBC twice a week, but continue clozapine unless otherwise advised (must be reported to nurse).
- **Green** result – continue treatment.
- Frequency of FBCs - usually weekly during initiation. Confirm with the clozapine clinic for each individual patient.

Red Results
- If a red result is obtained, a minimum of two follow-up FBCs on the following two days should be taken.
- If one of these results is also ‘red’, the ‘red’ status is confirmed. The patient should not restart clozapine.

Non-adherence
- If the patient misses one dose, the nurse and medical team must be informed and a plan made and documented.
- A treatment break of more than 48 hours requires a re-titration.

Medical / Nursing staff must be informed if
- Temperature rises above 38°C.
- Pulse > 100bpm.
- Systolic or diastolic BP drop > 30mmHg.
- Systolic BP > 140mmHg and/or diastolic BP is > 90mmHg.
- Systolic BP: <100mmhg
- Diastolic BP: < 60mmHg
- Sore throat or fever.
- If there are other concerns e.g. constipation.
- Red or amber results.
- Non-adherence to one dose or more.
- There is a NEWS score. If the score flags up, refer to the NEWS action protocol.

(The assistant practitioner must withhold the dose until nursing or medical advice is obtained. Nursing staff must be informed before seeking advice from a doctor). The nurse must always refer the information in red to the medical team.

**Red Flags**
- Temperature rises above 38°C.
- Sore throat or fever.
- FBC - Red (stop) or amber (continue monitoring FBC twice weekly).
- NEWS Score - >3
- Nursing Staff **must** be informed immediately. Nursing staff must always refer the above information to the medical team.

---

**Talk to me in SBAR...**

Have you got the Drug Chart, NEWS2 chart and Carenotes ready? It's time to communicate more effectively! By taking an SBAR approach, it reduces repetition and helps colleagues formulate information with the right level of detail, enabling necessary progress.

- **S**ituation
  - Who are you?
  - Where are you?
  - What is going on?
  - Give the headline

- **B**ackground
  - What has led to this point?
  - Admission details
  - Complexities

- **A**ssessment
  - Use your judgement
  - What has happened?
  - Mental state
  - Use NEWS2*

- **R**ecommendation
  - What do you want to happen and when?

---

**Communication – Use SBAR At Handover**

- Situation – History of medication
- Background – Started Clozapine when? Titrated? Concordance?
- Assessment - Baseline observations & Side effects Concordance NEWS Score
- Recommendation – team decision “what do you need to do?”

---

**Clozapine Clinic Attendance**

- The assistant practitioner must spend at least half a day in the clozapine clinic to observe the clinic activity.
- Soft skills / Management
Appendix 6  
**Clozapine Therapeutic Drug Monitoring**

The measurement of clozapine and norclozapine levels may be helpful in optimising treatment in certain situations. Clozapine levels should not be taken routinely.

**When to consider an assay**

- When the maintenance dose of clozapine has been achieved.
- When non-adherence is suspected and patient shows poor response to treatment.
- Slow metabolism suspected.
- Following dose adjustments and addition/removal of interacting agents (e.g. smoking, very large changes in caffeine intake can alter clozapine metabolism).
- At least annually to ensure correct levels are achieved and any insidious changes in levels which may present as asymptomatic.
- If toxicity is suspected (intentional or unintentional).

### Approach to abnormal assay levels:

**Unexpected high/low result**

- Has steady state been reached (low assay levels)
- Adherence to medication (not taking/taking too much)
- Change to smoking status including cannabis (see smoking and clozapine levels)
- Drug interactions (any medications recently started/stopped?)
- Correct timing of assay (for example was morning dose omitted before sampling)
- Any change to physical status of the patient e.g. liver impairment
- Are patients experiencing increase in dose related side effects or signs of toxicity (constipation, seizures, confusion)

### Advice for healthcare professionals:

- monitoring blood clozapine levels for toxicity is now advised in certain clinical situations such as when:
  - a patient stops smoking, switches to an e-cigarette or NRT products
  - concomitant medicines may interact to increase blood clozapine levels
  - a patient has pneumonia or other serious infection
  - poor (reduced) clozapine metabolism is suspected
  - toxicity is suspected
- if blood clozapine level monitoring is carried out, this should be in addition to the required blood tests to manage the risk of agranulocytosis
- refer to the full Summaries of Product Characteristics for other important warnings, interactions, and recommendations for clozapine
Timing of the assay
The assay should be a trough level and therefore taken 12 hours after the last dose and just before the next dose if it is twice daily dosing (i.e. just before their morning dose). Steady state is achieved after approximately 5 – 7 days of taking a stable dose. Therefore, if the dose has been changed, ensure that steady state has been achieved before taking a sample.

How to determine clozapine levels
- The trust clozapine assay results are sent to ASI.
- The clozapine assay request form and associated sample packaging (for ASI) can be obtained from CPMS (Tel: 0845 769 8269). This includes a plastic addressed envelope.
- Blood (at least 2.0ml in the EDTA tube) is best taken immediately before the normal morning dose or if dose is once daily, 10-12 hours post-dose (“trough” sample). It is important to record the time of sampling with respect to dosage since this may influence interpretation of the result.
- The sample should be sent in the addressed envelope to ASI. There is a charge of £15 for each assay. DO NOT send to local blood laboratory as it cannot be processed.
- Clinicians can register for ASI clozapine assay results online (asilab.co.uk).

An entry must be made in the patient’s case notes recording the reason why the test was requested. On receipt of the results, these should be clearly documented in Carenotes and communicated to the prescriber. The consultant / pharmacist should comment on the significance of the result and propose action points.

The usual target range for plasma clozapine levels is 0.35-0.60mg/L, however plasma clozapine levels should always be interpreted in the context of the patient's clinical presentation. Please see below for interpretation for results.

Interpretation of results

<table>
<thead>
<tr>
<th>'Trough' clozapine (mg/L)</th>
<th>Clinical Response to Clozapine</th>
<th>Suggested action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.01</td>
<td>Any</td>
<td>Review patient – if dose &gt; 50 mg/d result suggests no clozapine taken for up to a week</td>
</tr>
<tr>
<td>&lt; 0.35</td>
<td>1. Good</td>
<td>Repeat assay at 6 months, then annually unless response deteriorates or side effects become apparent</td>
</tr>
<tr>
<td>2. Poor/ incomplete</td>
<td>1. If poor/non-compliance suspected, consider supervised administration and/or crushing clozapine (preferably via a crushing syringe). Notes re-titration should be undertaken while crushing tablets. Consider psycho-education. Review patient and repeat assay after at least 1 week supervision. 2. Consider cautious dose increase (special caution if dose already 450 mg/d or above). Monitor mental state and side effects. Review patient and repeat assay after at least 1 week on new dose.</td>
<td></td>
</tr>
<tr>
<td>0.35 - 0.60</td>
<td>1. Good</td>
<td>1. Repeat assay at 6 months, then annually unless response deteriorates or side effects appear. 2. If side effects are present and are persistent/serious consider cautious dose reduction (e.g. 25 mg/d in week 1, further 25 mg/d in week 2 etc.), but bear in mind possible effect on response to clozapine.</td>
</tr>
<tr>
<td></td>
<td>2. Poor / incomplete</td>
<td>If clozapine treatment at current dose at least 3-6 months, consider psychosocial intervention and/or augmentation</td>
</tr>
<tr>
<td>Range</td>
<td>Result</td>
<td>Interpretation</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>0.61 – 1.00</td>
<td>1. Good – no clinical features of toxicity</td>
<td>Review. Consider cautious dose reduction, but balance against risk of diminishing response to clozapine. Consider sodium valproate as prophylaxis against seizures if dose reduction thought inadvisable. See MHRA advice (for valproate) if the patient is a woman of child bearing age&lt;sup&gt;9&lt;/sup&gt;. Monitor mental state. Repeat assay after at least 1 week on a new dose, otherwise 3-monthly.</td>
</tr>
<tr>
<td></td>
<td>2. Poor/ incomplete / reduced and/or clinical features of toxicity</td>
<td>Cautious dose reduction (see above) to bring plasma clozapine below 0.6 mg/L. Monitor mental state. Repeat assay after at least 1 week on a new dose.</td>
</tr>
<tr>
<td>1.01 – 1.99</td>
<td>1. Good – no clinical features of toxicity</td>
<td>Review. Consider cautious dose reduction to bring plasma clozapine below 1 and possibly below 0.6 mg/L, but balance against risk of diminishing response to clozapine. Consider sodium valproate for prophylaxis against seizures. See MHRA advice (for valproate) if the patient is a woman of child bearing age&lt;sup&gt;9&lt;/sup&gt;. Monitor mental state. Repeat assay after at least 1 week on a new dose. Plasma clozapine may continue to rise in the short term even after dose reduction commenced.</td>
</tr>
<tr>
<td></td>
<td>2. Poor/ incomplete / reduced and/or clinical features of toxicity</td>
<td>Cautious dose reduction to bring plasma clozapine below 1 and possibly below 0.6 mg/L. Consider sodium valproate for prophylaxis against seizures. See MHRA advice (for valproate) if the patient is a woman of child bearing age&lt;sup&gt;9&lt;/sup&gt;. Monitor mental state. Repeat assay after at least 1 week on a new dose. Plasma clozapine may continue to rise in the short term even after dose reduction commenced.</td>
</tr>
<tr>
<td>2 &amp; above</td>
<td>1. Good – no clinical features of toxicity</td>
<td>Urgent review. Consider cautious dose reduction to bring plasma clozapine below 1 and possibly below 0.6 mg/L. Consider sodium valproate for prophylaxis against seizures. See MHRA advice (for valproate) if the patient is a woman of child bearing age&lt;sup&gt;9&lt;/sup&gt;. Repeat assay after at least 1 week on a new dose. Plasma clozapine may continue to rise in the short term even after dose reduction commenced.</td>
</tr>
<tr>
<td></td>
<td>2. Poor/ incomplete / reduced and/or clinical features of toxicity</td>
<td>Urgent review and dose reduction. If patient is in the community, consider admitting for observation. Stop clozapine for 24-h and re-start at 75% of last dose, thereafter reduce slowly to bring plasma clozapine below 1 and possibly below 0.6 mg/L. Consider sodium valproate for prophylaxis against seizures. See MHRA advice (for valproate) if the patient is a woman of child bearing age&lt;sup&gt;9&lt;/sup&gt;. Monitor mental state. Repeat assay after at least 1 week on a new dose. Plasma clozapine may continue to rise in the short term even after dose reduction commenced.</td>
</tr>
</tbody>
</table>

**Interpretation of norclozapine levels**

<table>
<thead>
<tr>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norclozapine equates to 2/3 of the clozapine level</td>
<td><strong>No action required</strong> – Unless the dose of clozapine has been changed, the patient stops smoking or any undesirable effects are noted</td>
</tr>
<tr>
<td>Norclozapine&gt;2/3 of the clozapine level</td>
<td>Repeat the level, if found to be similar this may indicate that: The patient has been only partially compliant in the preceding days. The patient is on a medication that increases liver enzymes and increases metabolism of Clozapine. The patient is a fast metaboliser.</td>
</tr>
<tr>
<td>Norclozapine&lt;2/3 of the clozapine level</td>
<td>Repeat the level, if found to be similar this may indicate that: The patient has been only partially compliant in the preceding days. The sample was not a trough i.e. the Clozapine dose had been...</td>
</tr>
</tbody>
</table>
Clozapine treatment guidelines

Smoking and Clozapine Levels
The hydrocarbons in cigarette smoke (including cannabis) induce the liver enzyme CYP1A2 and therefore can reduce clozapine levels by up to 70% by increasing the metabolism of clozapine. On starting, stopping, increasing or reducing smoking, check the clozapine level and adjust the dose accordingly. If a patient has stopped smoking, or reduced to less than 7-10 cigarettes per day, check their clozapine levels and consider a 50% dose reduction one week later. Changes in plasma levels usually occur within 1-4 weeks of changes in smoking habit.

During periods of initiation and cessation of smoking, increased monitoring of Clozapine levels and subsequent dose changes should be carried out. The effect of smoking can be related to the number of cigarettes smoked in a day. Changes in liver enzymes can take three to six months to stabilise.

Clozapine levels may fall within 3-5 days of starting smoking and rise equally quickly when stopping.

Note if a patient prescribed clozapine is admitted due to relapse, it is likely the patient has been non-adherent. Inpatient wards are non-smoking. If a re-titration is undertaken in a patient who smokes in the community, the previous maintenance dose may result in elevated levels as the patient may not be given leave. Serum levels should be undertaken when a maintenance dose is reached and the dose adjusted if necessary. On discharge the serum level should be rechecked in the Community.
Appendix 7: Flow Chart for Managing Clozapine Assay

Results in Islington

ASSAY REQUEST FROM CLINICIAN VIA Clozapine.HMHC@candi.nhs.uk

- DATE FOR ASSAY NOTED IN DIARY

- ASSAY DONE

- KING'S PATH-LAB EMAIL RESULT TO Clozapine.HMHC@candi.nhs.uk

ABNORMAL RESULT

- RESULT IS <0.1 OR >1
  - URGENT- ACTIONED DAILY (WITHIN WORKING HRS)
    - ATTEMPT URGENT PHONE CONTACT WITH RC URGENT STANDARDIZED EMAIL TO RC (COPYING TO CC/ OTHER NAMED CLINICIAN AS DOCUMENTED IN CARE NOTES) REQUESTING ACKNOWLEDGEMENT AND ACTION PLAN WITHIN 12 HOURS IN ABSENCE OF RC, CONTACT COVERING CONSULTANT AS ABOVE, OR ESCALATE TO CRISIS TEAM/ DUTY DOCTOR IF NO RESPONSE DOCUMENT RESULT IN PROGRESS NOTES

- RESULT IS 0.1-0.35 OR 0.5-1
  - ROUTINE- INTAKE DAY (FRIDAY)
    - COMMUNICATED TO CONSULTANT IN WEEKLY EMAIL UPDATE FROM CLINIC (COPYING TO CC/ OTHER NAMED CLINICIAN AS DOCUMENTED IN CARENOTES) DOCUMENT RESULT IN PROGRESS NOTES

NORMAL RESULT (RANGE 0.35-0.5)

- ROUTINE- INTAKE DAY (FRIDAY)
  - COMMUNICATED TO CONSULTANT IN WEEKLY EMAIL UPDATE FROM CLINIC (COPYING TO CC/ OTHER NAMED CLINICIAN AS DOCUMENTED IN CARENOTES) DOCUMENT RESULT IN PROGRESS NOTES

- DATE FOR REPEAT ASSAY PUT IN DIARY, AS AGREED WITH RC IN PLAN

- DATE FOR REPEAT ROUTINE ANNUAL ASSAY ADDED TO DATABASE

ROUTINE ANNUAL ASSAY DUE AS PER DATABASE

DATE FOR REPORT UPDATE IN DATABASE

DATE FOR REPEAT ROUTINE ANNUAL ASSAY ADDED TO DATABASE
Appendix 8: Standardised Email For Abnormal Clozapine Assay Results

Subject: Significantly Abnormal Clozapine Assay - Urgent Response Required Please

RE: Patient Name, DOB, NHS no

Dear Dr…(name of consultant)

The clozapine clinic has just been notified of the following clozapine assay result for the above named patient:

- Result copied and pasted from Viapath email
- From a sample taken on... (date of sample)

As this result is significantly abnormal, please could you kindly acknowledge receipt of this result and advise on action to be taken by replying to this email within the next 24 hours. This is to ensure that this result is not missed.

Please could you specifically advise if and when a repeat assay sample should be taken.

Many thanks,

Clozapine Clinic

Please note: This is a standardized email to urgently highlight all clozapine assay results of 0 or greater than 1.
Appendix 9: Special populations and precautions for use

<table>
<thead>
<tr>
<th>Special population</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly(^{16})</td>
<td>Elderly patients may be more susceptible to side-effects and should be started on lower doses e.g. 6.25mg at night, with much slower titration regimens increasing at no more than 25mg increments. Average doses tend to be lower than the general adult population (137mg/day on average).</td>
</tr>
<tr>
<td>Patients with HIV(^{17,18})</td>
<td>Clozapine is not routinely recommended in those with HIV due to the risk of reduction in white cell counts. Check medicine-medicine interactions if clozapine is concomitantly prescribed with antiretroviral treatment.</td>
</tr>
<tr>
<td>Liver/hepatic disease</td>
<td>Increases in liver enzymes up to twice the upper limit are seen in up to 61% of patients. Clozapine should be stopped in elevations in liver function tests more than three times the upper normal limit, jaundice, cholestasis, hepatitis, hepatic necrosis or any severe liver disease.</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Clozapine is contraindicated in severe renal disease. In mild to moderate renal failure, initiate clozapine more slowly than normal and monitor serum levels. Rare reports of interstitial nephritis and acute renal failure occur, however, nocturnal enuresis and urinary retention are common. Anticholinergic, sedative and hypotensive side-effects occur more frequently in patients with renal disease.</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Clozapine is contraindicated in uncontrolled epilepsy. Use cautiously.</td>
</tr>
</tbody>
</table>
Appendix 10: Management of Constipation: Guide to commencing clozapine

**Counselling**
- Counsel patient / carer:-
- Gastrointestinal side effects & risks of clozapine.

**Lifestyle Advice**
- Dietary intake
- Fluid intake
- Regular exercise

**Medication review**
- Review concomitant medication which can cause constipation if appropriate
- Consider addition of osmotic laxatives. Eg: Macrogol or Lactulose
- Adequate fluid intake (2-3 litres/day) is essential
- Avoid caffeine containing drinks

**Monitor**
- Actively screen and monitor for symptoms & complications of constipation

Also see section 11
Appendix 11: Clozapine-induced constipation identified

Recommend changes in lifestyle, diet & fluid intake

Consider reducing clozapine dose

Stop or decrease medication that can cause constipation.

If intestinal obstruction is excluded

Consider the addition of an osmotic laxative, e.g. Macrogol (1-3 sachets daily) or Lactulose (15ml Twice daily)
2-3 l of fluid intake is essential. Avoid caffeine containing drinks

Add a stimulant laxative
If ineffective, add Senna 2-4 tabs at night (Short term only)

Consider tolerability & preference

Docusate or softening and stimulating enemas would be an alternative

Stop Clozapine & other anti-muscarinic agents. Refer for emergency medical treatment

Prolonged use of stimulant laxatives may lead to degenerative changes in colonic muscles and nerves

Also see section 11
Appendix 12: Clozapine Treatment in Child and Adolescent Mental Health (CAMH) Patients

The safety and efficacy of Clozapine in children and adolescents under the age of 16 years have not yet been established.1

- There is evidence that clozapine is effective in treatment-resistant psychosis in adolescents, although this population may be more prone to neutropenia and seizures than adults. Olanzapine should probably be tried before moving to clozapine.5

- Five studies (n=176) examining the efficacy of clozapine for up to 12 weeks suggested that clozapine has superior efficacy compared to other antipsychotic medicines when used in the treatment of refractory childhood onset schizophrenia (COS).12

- Three randomised controlled trials have demonstrated greater improvements in symptoms with clozapine than with both olanzapine and haloperidol, but clozapine is associated with a greater burden of adverse events, most notably seizures and neutropenia.13,14,15

- Five long-term studies (12 weeks to 9 years) have suggested that clozapine is associated with sustained clinical improvement and a reduction in the number and duration of hospitalization. However, they collectively included a relatively small sample (n=110)12.

**Patient eligibility**

- Offer clozapine to children and young people who have not responded adequately to pharmacological treatment despite the sequential use of adequate doses of at least 2 different antipsychotic medicines each used for 6-8 weeks.16

- Questions to bear in mind:
  - Is the diagnosis correct? NICE recommend reviewing the diagnosis in non-responders.
  - Is the current dose of antipsychotic adequate for the patient?
  - Has the patient had an adequate trial of antipsychotic? (at least 6-8 weeks)
  - Are side effects masking the response e.g. akathisia?
  - Are there any other causes of non-response e.g. comorbid substance abuse, concurrent medication or physical illness?

- If the patient is eligible, offer comprehensive information on the risk/benefits of clozapine and ensure to gain informed consent from the child (over 16 years old) or parent/guardian. Patient and family education is essential, and the child’s first experience is crucial to the long-term outcomes and adherence.

Consider initiating in an inpatient setting as easier for monitoring. Alternatively, arrangements must be made for pre and post dose monitoring twice a day if the titration takes place in the Community (see appendix 5).

**Patient Registration**

Requests for all patients from CAMH Early Intervention Service (EIS) should be undertaken via the non-formulary process. The non-formulary form is located in the medication tab in Carenotes. Once completed, it should be brought to the attention of a Lead Pharmacist for review and will be approved by the Chief Pharmacist/Medical Director.

For all patients, a CPMS registration form must be completed and sent to CPMS.
Clozaril is licensed for patients between 16 – 17 years old. Clozapine is not licensed for patients under the age of 16 years old. If the patient is less than 16 years old, an off-label agreement letter will be sent by CPMS to the consultant.

Clozapine Clinic Referral

The Trust has three clozapine clinics – the Daffodil Unit at Highgate Mental Health Centre, the Clozapine Clinics at Peckwater and Daleham House (Camden).

The patient must be referred to the clozapine clinic linked to their borough. The patient must be accepted by the clinic before initiation of clozapine.

Blood tests can be undertaken in the Clozapine Clinics.

Baseline screen

- Ethnicity
- Smoking status
- Medical history
- Neurological and physical examination (weight, BMI, BP)
- FBC, LFTs, U&Es, lipids, glucose/HbA1C. Consider troponin, CRP and ESR. B-type natriuretic peptide can be requested if possible. B-type natriuretic peptide is a hormone secreted by cardiomyocytes in the heart ventricles in response to stretching caused by increased ventricular blood volume.
- ECG
- EEG (in adults is only if clinically indicated. In children, seizures and EEG changes appear more frequent so is recommended)
- Registration with CPMS. An off-label agreement may be required if the child is less than 16 years.
- Baseline blood tests (WBC and differential count)

Clozapine initiation titration

- Start 12.5mg/day, increasing every 2-3 days in 12.5-25mg increments according to response.
- Aim for 75-100mg/day in 2-3 weeks depending on tolerability. A clozapine level may be done when the dose has reached 75mg daily.
- Adjust the dose for optimal efficacy and tolerability.
- Response to clozapine has been seen in doses as low as 150mg/day
- The average maintenance dose is between 250-350mg/day, although studies do go up to 900mg/day. In the two RCTs the overall mean final dose of clozapine was 327mg/day (SD, 113mg; range 150-500mg) and 149mg/day (range 25-525mg/day)\textsuperscript{13, 14}.
- Some patients show a positive clinical response even with relatively low-dose clozapine, and this possibility should be explored during the next 2 or 3 weeks before titrating to higher dosages. When psychotic symptoms persist, a further increase to 150–200mg/day is recommended, and then, possibly, to 300mg/day. Further increases can be evaluated cautiously, given the dose-related risk of seizures (5% when dosage is higher than 400mg/day). The patient should be maintained at the target dose, as the full effect is evident in the following 4–6 weeks, although further improvements occur during the following 6–8 months. Common adverse effects inducing a slower titration are sedation, drooling, hypotension and mild fever\textsuperscript{18}.
• If the patient is experiencing excessive sedation with the maintenance dose, consider dividing the dose and perhaps giving the larger dose at night.

**Monitoring**

• Monitor the following parameters closely during titration
  - FBC weekly for 18 weeks, then 2 weekly up to 52 weeks then 4-weekly thereafter
  - BP, pulse, temperature
  - Weight and metabolic profile
  - ECG at the end of the titration
  - EEG to be repeated six weeks into clozapine treatment

• Monitor for adverse effects such as hypersalivation, constipation, weight gain, sedation and tachycardia.

• Note that neutropenia with clozapine is more common in children and adolescents compared with adults. Younger age, Afro-caribbean ethnicity and male gender are significant risk factors.

• The monitoring and guidance outlined in the trust clozapine treatment guidelines should be followed.

**Plasma monitoring**

• Plasma clozapine levels appear to be related linearly to clinical improvement. Similarly to adults, plasma clozapine levels are broadly related to prescribed dose, however studies have indicated considerable variation\textsuperscript{12,16}.

• Plasma levels are generally lower in younger patients, males and smokers. Aim for a plasma level between 0.35mg/L to 0.5mg/L.

**Trial Period**

Allow time for an adequate trial of treatment as children will often require longer periods of treatment before responding.

**Clozapine Augmentation**

For children and young people whose illness has not responded adequately to clozapine at an optimised dose, consider a multidisciplinary review, (including measuring therapeutic clozapine levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. A medicine that does not compound the common side effects of clozapine should be considered\textsuperscript{16}.

**Prescribing**

Titration prescriptions can be written on a crisis team prescription chart and dispensed at the Trust Pharmacy. Maintenance prescriptions can be written on the Clozapine Outpatient Prescription Chart on Carenotes and dispensed at the Trust Pharmacy.

Acknowledgements: The Medicines Information Department. The Maudsley Hospital. 23.6.2021