# Pharmacological Therapy Policy Practice Guidance Note

## Safe Prescribing of Clozapine – V02

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1. Introduction

1.1 For additional information, please refer to the following Northumberland, Tyne and Wear NHS Foundation Trust (the Trust/NTW) clozapine documents; click link below:

- **Clozapine Treatment Pack**

1.2 Prior to commencement on clozapine, all patients must be fully registered with a UK based clozapine monitoring service (e.g. CPMS, DMS, ZTAS), and have a valid blood test. The monitoring service must be informed of all subsequent, relevant changes relating to the patient (e.g. consultant, location, physical illness).

1.3 The clozapine monitoring service websites provide valuable resources for patients and clinicians on the use of clozapine.

1.4 Clozapine is licensed for:

- Treatment resistant schizophrenia (TRS)
- Severe untreated neurological adverse reactions to other antipsychotic drugs
- Psychotic disorders in Parkinson’s Disease

1.5 Other indications are deemed as off license, and must be discussed with the multi-disciplinary team (MDT) and the relevant clozapine monitoring service.

1.6 Clozapine is recommended by National Institute of Health and Care Excellence (NICE) as a treatment option in TRS. Specific details about treatment can be found in:

- CG178 Psychosis and schizophrenia in adults: treatment and management February 2014
- CG120 Psychosis with Co-Existing Substance Misuse March 2011

1.7 To comply with the Product Licence of clozapine in the UK, regular monitoring of white cell count (WCC) and a differential is mandatory. The frequency of this is weekly for the first 18 weeks, fortnightly until 1 year of clear results (as stated by the monitoring service), then 4-weekly thereafter for the total duration of treatment (and 4 weeks after stopping clozapine).

1.8 The essential documentation required to commence a patient on clozapine and provide the correct safety monitoring is contained within the **Clozapine Treatment Pack** and also under the Service Specific Files > Physical Treatment > Clozapine Documentation section of RiO.

1.9 Patients should be given information and education regarding:

- Mandatory monitoring (its significance and consequences)
- Onset of action and expected benefits
- Side effects and how to combat these (The side effect monitoring record in the clozapine treatment pack and on RiO can be used as an aide memoire to support this discussion)
- Missed doses
- Clinic attendance
- Timing of plasma levels
- The effect of smoking

This discussion must be clearly documented in the clinical record

1.10 Clozapine can be initiated safely as an inpatient or in a community setting. A pre-treatment checklist must be completed for all patients that are be titrated (See Clozapine Treatment Pack and clozapine RiO documents)

2. Baseline monitoring prior to commencing clozapine

2.1 All baseline information required by the relevant clozapine monitoring service must be completed and communicated to that service by the responsible clinician. It must be established with the national database that the patient can safely be commenced on clozapine. Appendix 1 details the baseline monitoring requirements for clozapine.

2.2 The following monitoring should be carried out and recorded in the Core Physical Health Monitoring Record and the clozapine initiation documentation in RiO:
- Weight/Body Mass Index/waist circumference where possible
  (An individual should be referred to a dietitian if they have co-morbidities such as diabetes, heart disease or a BMI of 35 or above)
- Temperature, pulse, blood pressure, respiratory rate
- Glucose regulation and plasma lipids
- Full blood count, urea and electrolytes and liver function tests
- Cardiovascular risk assessment
- Prolactin
- Creatine kinase (CK)
- Electrocardiogram (ECG)
- If there is any uncertainty about the possibility of pregnancy, a urine pregnancy test should be carried out
- Side effect baseline (using ‘Side Effect Monitoring Record for Clozapine’)
- Smoking status, bowel habits and lifestyle review

3. Clozapine dose titration

3.1 Clozapine should be initiated using the NTW ‘Clozapine Titration/Re-titration Prescription’ which is available from the Pharmacy Admin Team.
3.2 Only on receipt of a valid blood result should clozapine then be ordered from the relevant hospital pharmacy department, in a timely manner according to the start date. The prescription chart must be validated by a pharmacist prior to the dispensing of clozapine.

3.3 Only clozapine labelled with the relevant patient’s name can be administered to that patient.

3.4 The temperature, pulse and blood pressure monitoring should be carried out according to the frequency specified in the initiation documentation on RiO. The physical observations and side effect monitoring recommended in the clozapine treatment pack is the minimum standard that should be applied to all patients initiated/re-titrated on clozapine in NTW.

3.5 The patient should be monitored for side effects and tolerability on a daily basis during initiation. Should any dose–dependent side effects become problematic during titration, a slower dose increase should be considered by the prescriber. The NTW ‘Clozapine Titration/Re-titratioin Prescription’ can be used to facilitate an unambiguous dose modification.

3.6 Should a break in treatment of greater than 48 hours take place the dose must be re-titrated. This applies to any stage of clozapine treatment. The relevant monitoring service must be informed and if a ‘Treatment Break’ (more than 72 hours without therapy) has been enforced, this should be communicated to clinical staff involved in the patient’s care including pharmacy. The monitoring frequency will change according to the patient’s current schedule (see Appendix 7). The speed of titration is according to the previous stage and dose of clozapine prescription, and patient tolerability to its effects. Contact Pharmacy Medicines Information – 0191 245 6786 for patient specific advice.

3.7 Outpatient/community initiation of clozapine is permitted by the UK product license and NTW. All members of the team must be aware of, and agree to, their specific roles and responsibilities in order that this is achieved in a safe manner.

3.8 For community initiation, patients should ideally have someone (supportive family/carer) at home with them overnight for the first week. However, this may not always be possible and the situation should be robustly assessed on an individual basis. The outcome of this assessment should be explicitly documented in the patient’s clinical records.

3.9 In older patients, it may be advisable to prescribe lower doses of clozapine and titrate more slowly. In Parkinson’s disease psychosis there is evidence for very low clozapine doses.

3.10 It is good practice to obtain a baseline plasma level (taken at steady state, on at least 300mg clozapine daily) – See section 6

4. **Ongoing clozapine monitoring**

4.1 Appendix 1 details the monitoring requirements for clozapine.
4.2 Prior to discharge from a ward, rigorous arrangements for clozapine monitoring and supply should be made.

4.2.1 Patients on clozapine within NTW should ideally attend a clozapine clinic for ongoing mandatory blood testing, side effect monitoring, and assessment of mental state and issue of clozapine. (See Appendix 4 - Clozapine Clinic Standard Work) The frequency of clinic attendance is based on the stage of mandatory monitoring i.e. 1-4 weekly. A formal, written referral should be made to the clinic most convenient to the patient. A referral form can be found in the Clozapine Treatment Pack - The patient should have a clozapine clinic appointment (date and time) prior to discharge from the ward. Arrangements should be in place to ensure a safe and continuous supply of clozapine until the clinic appointment.

4.2.2 If a patient cannot attend a clozapine clinic the patients’ clinical team is responsible for the completion of all relevant clozapine documentation in line with the practice guidance note (PGN).

4.2.3 In some rural areas of NTW, where patients are unable to access a clozapine clinic, a GP surgery may be utilised. An individual shared care agreement must be drawn up between the prescribing clinician and the GP detailing the responsibilities for prescribing, monitoring and supply. (See Appendix 5)

4.3 In the event of a RED result, the consultant and ward/team are contacted by the clozapine monitoring service directly. Clozapine should be stopped immediately; the patient should be assessed for any signs of infection. The relevant clozapine monitoring service must be contacted for guidance on the management of red results. (See Appendix 2 for the Red Protocol

4.4 In the event of an AMBER result, arrange a retest and contact the relevant clozapine monitoring service. (See Appendix 3 for the Amber Protocol

4.5 Clozapine plasma levels may be indicated – See section 6

4.6 Patients intending to stop/start smoking, or change their smoking habit should seek advice from the clozapine clinic staff/consultant psychiatrist, who will formulate a plan, to ensure their ongoing safety. More information is available in the clozapine treatment pack.

4.7 To ensure the ongoing safety of patients taking clozapine, the clozapine clinic staff must escalate any concerns to the consultant psychiatrist.

4.7.1 In addition to the routine clozapine clinic visits, the consultant psychiatrist should review the patient a minimum of annually to review the clozapine dose, treatment response and assess side effects. As part of the annual review, the medic should pay particular attention to the more serious potential adverse effects including seizures, cardiac arrhythmias and severe constipation. The review should include a physical examination by a medic. Where a referral is made for this physical examination, the results should be followed up by the consultant psychiatrist.

4.7.2 More frequent monitoring of side effects may be indicated where the clinical significance of the side effect warrants this. A summary of the yearly review should be recorded in the patient’s clinical records and communicated to the GP.
4.7.3 Severe constipation is a potentially life threatening complication of clozapine that can lead to intestinal obstruction, faecal impaction, paralytic ileus and ultimately death. To minimise the risk of serious constipation prescribers should:

- Educate patients about the risk of constipation and provide written information on dietary management (this should be documented)

- Be particularly vigilant for constipation in patients who are prescribed concomitant medicines with anticholinergic activity (e.g. hyoscine, tricyclic antidepressants, drugs for bladder instability)

- Use lowest effective dose of clozapine

- Intervene actively when patients report constipation, ensuring that an effective laxative regimen is prescribed promptly (e.g. senna & docusate sodium or a polyethylene glycol-based osmotic laxative) and that the effectiveness of this treatment is monitored closely thereafter

- Refer urgently all patients who present with symptoms indicating a potentially life-threatening gastrointestinal complication (e.g. abdominal pain with nausea in the context of constipation), in whom clozapine should be temporarily discontinued

4.8 Clozapine should usually be prescribed and monitored for at least one year in order to establish its effectiveness as a long term treatment.

4.9 If the decision is made to discontinue clozapine for anything other than a haematological reason. The dose should be reduced as slowly as possible, taking into account any clinical risk factors, the mental state of the patient and alternative treatment plan.

5. **Recording clozapine clinic visits**

5.1 There is a section on RiO which is specifically intended for recording information at clozapine clinic visits:

- ‘Service Specific Files’ are listed on the patient front screen (in right hand list of options). From this the ‘Physical Treatment’ section can be selected

- ‘Clozapine Documentation’ is listed on the left hand list of options

- ‘Clozapine Clinic Record New’ is used to record information generated at routine clozapine clinic visits and on inpatient wards during routine monitoring
• The ‘Side Effect Monitoring Record for Clozapine’ should be completed a minimum of annually

• A record should also be made in the progress notes that a clinic attendance has occurred, and a reference made to the relevant records (above)

6. Therapeutic Drug Monitoring of Clozapine Plasma Levels

6.1 Clozapine plasma levels are useful for optimising therapy as support to the clinical monitoring (response and adverse effects) of patients prescribed clozapine. Clozapine plasma level monitoring is useful when assessing adherence, monitoring the effect of changes in smoking habit, investigating clozapine side effects and when toxicity is suspected. For NTW patients, clinicians must check and record clozapine plasma levels at the following points:

• At baseline - levels must be taken once the target dose has been reached and has been stable for at least a week. This is useful as a reference should problems arise later in treatment

• Annually

6.2 In addition, it may also be advisable to recheck the level in the following circumstances:

• When poor compliance is suspected

• If the patient is newly prescribed an interacting drug, or following a dose change of either drug

• If the patient starts or stops smoking or changes their smoking behaviour. Investigation of possible dose-related side effects

• If the patient does not respond (after 3-6 months treatment) despite being prescribed a high dose, with consistent compliance

• If toxicity is suspected (intentional and unintentional)

• If the patient is suspected to be a poor or rapid metaboliser (a consequence of individual difference in CYP enzyme activity)

6.2 Plasma Concentration Samples

6.2.1 Plasma Assay forms can be accessed from Viapath: http://www.viapath.co.uk/our-tests/clozapine-norclozapine - see under ‘Further information’ on the website. The forms may be completed by an appropriate member of the team and sent to Viapath with the blood samples, collected and packaged as detailed on the assay request form.
6.2.2 Ideally, the blood sample should be taken 10-12 hours post (the morning after an evening dose or before the morning dose) i.e. a ‘trough’ sample. In all cases a minimum of six hours should elapse post-dose before a blood sample is taken.

6.2.3 Samples should not be taken for seven days after a dosage change to allow the drug plasma level to reach steady state.

6.2.4 Trough plasma concentrations of at least 0.35mg/l are associated with therapeutic efficacy. The reference range recommended by Viapath is 0.35-0.5mg/l. Plasma concentrations above 0.60mg/l are associated with an increased risk of seizures.

6.2.5 For clinical advice or interpretation of results, contact the Toxicology Department at King’s Hospital: Tel 020 32995881 kch-tr.toxicology@nhs.net King’s College Hospital, Bessemer Wing-3rd Floor, Denmark Hill, London, SE5 9RS

6.3 Recording Request Information/Results

6.3.1 An entry must be made in the patient’s RIO ‘progress notes’ recording the reason why the test was requested. On receipt of the results, the paper copy must be scanned into RIO documents and an entry made in ‘progress notes’. The consultant or pharmacist should comment on the significance of the result and the proposed action points. For a guide to the interpretation and clinical response to clozapine plasma levels see Appendix 6.

6.3.2 There have been several reports of inter-laboratory variation in the reporting of serum clozapine levels. Where possible the same laboratory should be used and documented in the RIO progress notes with the results.