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1. Clozapine Information

Clozapine is a second generation antipsychotic licensed for use in treatment resistant schizophrenia and psychosis in Parkinson's Disease (PD). For a patient to be eligible for consideration of clozapine therapy, they must have failed to respond adequately to at least two other antipsychotics (at least one of which must be a second generation). Clozapine has been shown to be one of the more effective drugs used in treatment resistant schizophrenia.

The maximum licensed dose for schizophrenia is 900mg/day which can be divided into 2 doses with the higher dose at night due to sedation. Psychosis in PD has a much lower licensed maximum dose of 100mg/day.

Patients must be made aware of the side effects and monitoring requirements of clozapine.

The mental health pharmacy team can assist with any queries relating to clozapine. Please see Appendix 5 for guidance on clozapine out with pharmacy opening hours.

2. Clinical Eligibility for Clozapine

The clinical decision to initiate clozapine must consider the views of the patient, carers and multidisciplinary team. The following considerations should be taken into account. These will be part of the clinical pharmacy team review of the patient prior to clozapine titration.

- Contraindications or allergy to clozapine
- Past medical history
- Appropriate indication
- At least two previous failed trials of antipsychotics (at least one of which must be a second generation).
- Does the patient have a full understanding of clozapine, monitoring requirements and side effects
- Does the patient consent to treatment and monitoring or is treatment available under the mental health act (is there a valid T3 and/or Section 47 of AWI)
- Interactions of clozapine with prescribed, non-prescribed and illicit medicines assessed
- Assessment of total anticholinergic burden
- Assessment of risk of QTC prolongation
- Renal and hepatic function
- Assessment of diabetic control – will the patient require further support from the diabetes specialist service to manage diabetes whilst prescribed clozapine
- Assessment of frailty
- Assessment of falls risk
- What community pharmacy do they use and are they registered with the clozapine patient monitoring system (CPMS) for repeat future dispensing
- Medicines management assessment
- Arrangements for ongoing prescribing
- Arrangement for ongoing supply
- Practicalities of ongoing blood monitoring

3. Monitoring Requirements of Clozapine

Clozapine requires regular blood monitoring as per Medicines and Healthcare Regulatory Agency (MHRA) which is a legal requirement. The monitoring system we use is called clozapine/clozaril (brand name) Patient Monitoring System (CPMS). All patients, supervising medical specialist, the dispensing pharmacy and pharmacy staff involved must be registered.

BGH Pharmacy utilises CPMS to oversee blood monitoring for all patients in the Borders on clozapine and will follow up patients whose bloods are overdue. A full blood count is required weekly for the first 18 weeks of treatment, then every 2 weeks until the patient has had a year of treatment, then monthly for as long as clozapine treatment continues.

Monitoring frequency	Sample due day	Overdue notification	Maximum cover from date of last sample	Clozaril prohibited day
Weekly	Every 7 days	Day 10	10 days	Day 11
Fortnightly	Every 14 days	Day 20	21 days	Day 22
Monthly	Every 28 days	Day 36	42 days	Day 43
Status on screen	Active	Active	Active	Clozaril Prohibited

Every Monday the pharmacy technician sends out emails to the relevant teams with patients whose bloods are overdue that week and the final date they have to get a blood done before becoming ‘prohibited.’ The teams will then get in touch with the patients to make sure they have an appointment booked before that date and if not then to make one. If a patient is unable to get an appointment at their health centre it can be facilitated on one of the mental health wards as a priority.

Patient's blood results can be classified as green, amber or red. The table below shows what this means and the action that needs to be taken. We have an agreement that if a patient's blood comes back as 'red' a member of the team must go and collect them and bring them into hospital in which a clinical decision will be made on further treatment. The pharmacy technician will contact the relevant teams if a patient's result comes back as amber or red (as a priority). See Appendix 7 for further guidance on management of red result.

Colour Alert	WBC count (x10^9/L)	Neutrophil count (x10^9/L)	Action
Green	>3.5	>2.0	Continue
Amber	3.0-3.5	1.5-2.0	Bloods twice weekly
Red	<3.0	<1.5	Stop clozapine

4. Assay Levels

Clozapine assay levels are taken to determine how much clozapine is in the patient's blood and if they are on an appropriate dose for full effect and should be taken 12 hours post clozapine dose. Consultant psychiatrists request these to be done and they get sent to Magna Labs in England. The results are then emailed to the requesting consultant and the BGH Pharmacy mental health inbox then put on to EMIS.

Assay levels tend to be requested when a patient first starts taking clozapine to establish if they are on a suitable dose, if a patient starts/stops smoking and annual reviews.

It is important to note that an assay level is different to a full blood count which is required for monitoring whilst on clozapine.

Assay kits are available from the BGH Pharmacy, or can be ordered directly from Magna Labs.

See Appendix 6 for information relating to interpretation of assay results.

5. Side Effects, Interactions and Management

- Agranulocytosis –
  This leads to a lack of white bloods cells, an inability to fight simple infections and a significant risk of neutropenic sepsis. Bloods are monitored and chased up by BGH Pharmacy if overdue
- Severe constipation –
  One of the worst and most deadly side effects of clozapine. All patients should be on regular laxatives (either Senna or Lactulose or Laxido or a combination of Senna +/- Lactulose). If a patient presents complaining of constipation let doctor/consultant know and can be reviewed. Especially important to be aware of when first starting clozapine
- Hypersalivation –
  Very common with clozapine and can be distressing/upsetting for some patients, make doctor/consultant aware as may be possible to prescribe pirenzipine or hyoscine hydrobromide to help
- Weight gain –
  Very difficult to manage with diet/exercise. Metformin can sometimes be used off label with the aim to reduce weight or prevent further weight gain
- Myocarditis –
  Inflammation of the heart. In the first 3 weeks of starting clozapine the patient requires weekly ECG and Troponin I levels to monitor for this side effect
- Postural Hypotension –
  Low BP upon standing/feeling dizzy. This is monitored closely when titrating. These side effects would be picked up in the first weeks of treatment and if a patient is experiencing these their clozapine dose may be reviewed or stopped completely
- Smoking cigarettes/cigars interaction –
  Reduces clozapine levels. If a patient suddenly stops smoking or switches to vaping/nicotine replacement therapy then there is a risk of a significant rise in clozapine blood levels, leading to an increase in side effects and potentially toxicity, may need to increase monitoring
- Drug interactions –
  Carbamazepine, certain antibiotics such as co-trimoxazole, cytotoxic medicines used in chemotherapy and medicines used to treat rheumatoid arthritis should be avoided if a patient is taking clozapine as they can increase the risk of developing agranulocytosis

6. Starting Clozapine – Community Initiation

6.1. Pre-initiation

6.1.1. Background

Historically clozapine initiation has taken place in hospital; however it may also be initiated in the community. This has been shown to be both safe and effective for eligible patients. Community initiation of clozapine can help improve access to effective treatment for patients, allowing them to be treated in an environment less disruptive to their daily lives. There are, however significant risks to both physical and mental health during initiation and these must be carefully assessed before deciding on this route.

The following local guidance has been developed between the community rehabilitation team (CRT), the crisis team (BCT) and BGH pharmacy. For eligible patients, it can be used within any community mental health team (CMHT) provided there are sufficient staff available and BCT agree to joint working.

This guidance describes the process for joint working between CMHT, BCT and BGH pharmacy to deliver the essential physical and haematological monitoring required during the titration period.

6.1.2. Eligibility for Community Initiation

Patients considered suitable for community initiation must fulfil the following eligibility criteria:

6.1.3. Eligibility Criteria

- Treatment resistant schizophrenia OR psychotic disorders occurring during the course of Parkinson's disease when standard treatment has failed
- At least two other antipsychotic drugs that have been ineffective or not tolerable, including at least one of which must be a second generation
- Capacity to give informed consent or appropriate Mental Health Act/AWI certificates in place for treatment with clozapine
- If treatment is in accordance with the MHA ensure valid T2 and T3 are available and up to date
- Be able to consent regarding the risks associated with community initiation, to regular monitoring and to the holding of health information

- The patients' mental health is likely to remain sufficiently stable during the initiation period to allow them to function at home
- Patient has access to support of a live in carer, family or friend during the first week or someone who is nearby and can be called
- Patient is aware of and agrees to the necessity for daily attendance/home visits and monitoring by the mental health team(s)
- Current symptoms, physical health and safety risk has been assessed by the responsible psychiatrist and community initiation of clozapine deemed appropriate
- Motivated patients who wish to remain at home for initiation of clozapine and agree not drive for the 2 week initiation period

In addition the relevant services must have adequate facilities and staffing available to carry out all necessary clinical monitoring over a 12-14 day period depending what is agreed.

6.1.4. Exclusion Criteria

The following patients should **not** be considered for initiation of clozapine in the community:

- Patients under 18 years old
- Elderly frail patients who are at high risk of postural hypotension and falls
- Patients who are not willing to comply with minimum monitoring requirements for community initiation
- Pregnant or breast feeding
- History of hypersensitivity to clozapine
- Patients with myeloproliferative disorders or a history of toxic or drug-induced neutropenia / agranulocytosis (with the exception of previous chemotherapy)
- Impaired bone marrow function
- Epilepsy or a history of seizures
- History of cardiac disease
- Hypotension or hypertension
- Unstable diabetes
- Circulatory collapse and/or CNS depression of any cause
- Severe renal disease
- Acute liver disease with jaundice, nausea or anorexia; progressive liver disease or hepatic failure
- History of or current paralytic ileus
- Concomitant use of other drugs with a substantial potential to cause agranulocytosis

- Continued use of illicit substances/alcohol
- Currently taking significant doses of sedatives, benzodiazepines, methadone, beta blockers or ACE inhibitors
- Complex cross titration of antipsychotic medication
- Patients with other cautions or contraindications to commencing clozapine
- Known illicit drug use

6.1.5. Eligible with Caution

- History of neuroleptic malignant syndrome
- Stable diabetes

6.1.6. Pre-initiation Preparation and Checklists

Patients considered for community initiation of clozapine are under the care of the CMHT. The CMHT will therefore be considered the 'initiating team' for the purposes of this guidance.

Since home visits and physical monitoring is required daily during the initial 12 days of titration within the community, CMHTs and BCT may jointly work with the patient during the initiation phase, thus avoiding an unnecessary hospital admission.

Joint working should be agreed by both CMHT and BCT in advance of starting clozapine and the CMHT should initiate liaison with BCT**.** A meeting should then be held with all teams involved (CMHT, BCT and BGH pharmacy) to discuss and delegate tasks to certain teams (see tasks in section 6.2.2). This must include the pharmacy technician/pharmacist and at least one doctor to agree escalation review plans should the patient experience significant side effects.

All teams should be aware of clozapine side effects and what to look out for, if not, a training session can be held or training presentation sent round the appropriate staff.

Once it has been decided to initiate a patient on clozapine in the community the following must be undertaken:

TASK	**WHO IS RESPONSIBLE**
Completion of pre-initiation checklist (Appendix 3)	CMHT medical and nursing team CMHT should identify one person within team to oversee patient through titration period
Refer patient for joint working	CMHT should initiate liaison with BCT and agree a suitable start date for both teams. CMHT should inform the patient

	and clinical pharmacist/technician of this date. Any requirement for monitoring observations beyond day 12 must be specifically agreed by both teams
Develop a care plan for joint working	Jointly between CMHT and BCT, the care plan should identify what action to be taken and who to contact in the event of an adverse reaction from clozapine both in and out of hours

- The patient must be provided with a patient information leaflet and thorough counselling before starting titration https://www.choiceandmedication.org/nhs24/printable-leaflets/patient-information-leaflets/37/ALL/
- The patient must also be informed of data transfer on to CPMS
- Pharmacy must be made aware and need to know the agreed start date (this should be on a Monday preferably or on a week day) due to having to register the patient with CPMS (this can take 24-48 hours) and the patient must have a full blood count (FBC) within 10 days of starting clozapine

6.2. Initiation

6.2.1. Prescribing Clozapine

Clozapine should be commenced at a dose of 12.5 mgs and gradually increased as per the 'Clozapine Dosage Escalation Chart' (Appendix 8) unless stated otherwise. Clozapine treatment should commence on Mondays (not public holidays) within the community setting.

Prescribers should refer to the 'Clozapine Dosage Escalation Chart' as appropriate and fill out a blue HBP prescription stating 'as per clozapine dosage escalation chart' clearly stating the commencement date and/or dates depending on the titration and if patient receives compliance support for medication. You must allow 48 hours for dispensing and delivery of clozapine.

After considering the risks of night-time postural hypotension and syncope if the patient gets up at night, the consultant psychiatrist may decide to prescribe the first dose at night-time.

Doses should not be increased over a weekend/public holiday or other times when treating medical staff are not available.

Once a patient has been maintained on a stable dose of clozapine, a 'repeat' prescription may be written, valid for 6 months. This should be sent to the relevant dispensing pharmacy to obtain further supplies.

6.2.2. Monitoring throughout Community Titration

Frequent haematological and physical monitoring is required during the initiation of clozapine and must be undertaken according to the same schedule regardless of which setting clozapine is initiated.

Patient requires observations pre and post morning dose on days when clozapine dose is increased. See Appendix 9 for Physical Monitoring Record for Initiation of Treatment with clozapine in the Community for physical observation requirements. The patient must be made aware of pre-dose checks so that they do not take their medicine before the nurse/support worker arrives.

If an evening dose of clozapine is prescribed a clinical decision may be made to omit observations around this dose. This should be clearly communicated to all parties involved.

Further information of the roles and responsibilities of each team during initiation of clozapine in the community is described below.

TASK	**WHO IS RESPONSIBLE**
Prescribing and supply of clozapine	Responsible psychiatrist or prescriber supervised by responsible psychiatrist within CMHT to write the prescription on a HBP. CMHT are responsible for prescribing the clozapine initiation schedule and sending to pharmacy for dispensing. The pharmacy are responsible for ensuring an adequate supply of clozapine is provided and made available for the patient. A copy of the clozapine escalation chart (Appendix 8) should be kept in the

	patients' home to be accessed by both teams. Prescribe laxatives to prevent the patient from getting clozapine induced constipation. Pharmacy register patient with Clozapine patient monitoring system (CPMS) and add to database. Pharmacy and CMHT to discuss if patient is independent with medication or requires a medicine management review.
Monitor mental state	Overall monitoring of mental state should be undertaken by the responsible psychiatrist who should assess patient face to face at least weekly during titration. Mental state assessment should be undertaken by nursing staff at each patient contact, this should be documented on EMIS.
Monitor physical observations and presence of side effects	CMHT/BCT staff to monitor baseline and for six hours post dose on Day 1. CMHT/BCT should monitor baseline and post-dose observations after the morning dose (30 minutes to 2 hours post dose), Mondays to Fridays from Day 2. Some flexibility is available for the initial post morning dose however sufficient time for proper absorption of clozapine should be considered. CMHT/BCT should undertake post dose observations after 6 hours on Mondays-Fridays on days where dose is increased. If clozapine is prescribed and administered twice daily on the standard

	escalation chart, then it is not necessary to check observations around the night time dose however, if specifically agreed, BCT may undertake observations before the night time dose which is included in the physical monitoring record for pre dose. **On days where the clozapine dose does not increase (normally Saturday/Sunday) observations are not required. A clinical decision to monitor observations on these days should be made on a case by case basis providing adequate staff are available.** Each team is responsible for provision of own equipment unless specifically agreed (i.e. for hygiene reasons). Observations should be recorded in the 'Community Physical Monitoring Record for Initiation of clozapine' (Appendix 9) which should be stored in patients home. Any side effects experienced by the patient should be recorded on EMIS. If these are serious they should be discussed urgently with the patient's psychiatrist.
Escalation of issues	Medical advice should be sought in the event of any abnormal readings which are stated at the bottom of each physical monitoring record. These should be referred to the responsible psychiatrist. In the 'out of hours' period urgent medical advice can be accessed by referral to A&E and/or through Crisis Team, on call doctor or on call pharmacist.
Haematological monitoring	Arrangements to undertake weekly haematological monitoring should be

	made by CMHT. This will likely be done in the patients GP practice health board treatment room. CPN to support the patient to book FBC.

On completion of clozapine titration all relevant clinical documents should be uploaded on to EMIS and all contacts with the patient should be recorded. The procedure for continuation and monitoring of clozapine after titration is weekly bloods for a total of 18 weeks then fortnightly bloods until patient has been on clozapine for a year then four weekly bloods thereafter.

7. Starting Clozapine – Hospital Initiation

If it is felt most appropriate for a patient to initiate clozapine as an inpatient they should be admitted to Huntlyburn, East Brig or Lindean ward. Pharmacy should be informed to assess eligibility and assist with pre-initiation preparation.

7.1. Pre-initiation

Similar to community initiation, eligibility must be assessed and thereafter completion of pre-initiation checklist (Appendices 2 & 3). Logistics of hospital initiation should be arranged with the agreed ward.

7.2. Initiation

The doctor should prescribe clozapine on the kardex ‘as per chart’ and attach titration chart to kardex (Appendix 8). The clozapine titration monitoring chart (Appendix 10) should also be attached to the kardex for nurses to check blood pressure etc.

BGH Pharmacy will supply 1 box of each strength for titration and send to ward labelled ‘Take as directed’ before start date and once patient is registered with CPMS.

Laxatives should be prescribed to help stop clozapine induced constipation.

In addition to weekly FBC it should be noted in the ward diary to do weekly Troponin, CRP and ECG for the first 3 weeks of titration.

Once the patient is stable on clozapine and looking at discharge planning they need to be made aware to make appointments weekly for FBC at their health centre (CPN can help with this).

A discussion will also need to happen with the patient in regards to what community pharmacy they use. If the patient’s pharmacy is not registered with CPMS, BGH Pharmacy will dispense and they will need to collect clozapine along with their other medication. If the patient struggles with medication a medicine management assessment can take place on the ward to determine if they need support for taking clozapine.

8. Ongoing Prescribing and Monitoring

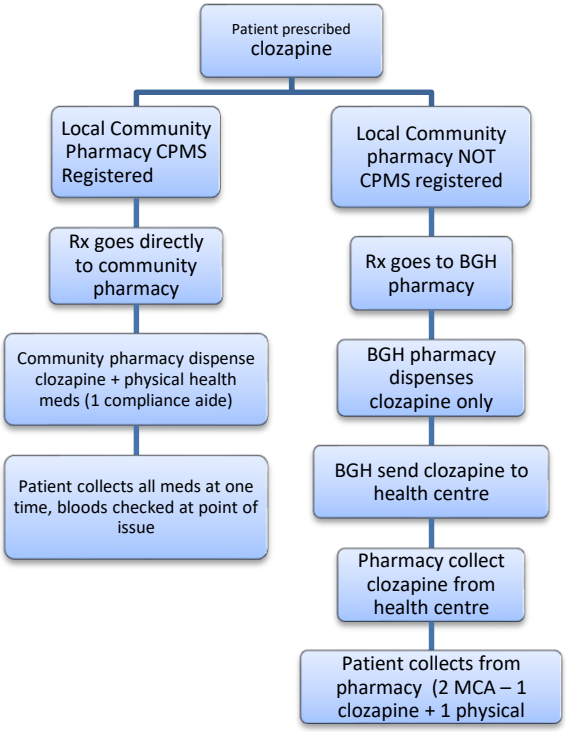
Following initiation, ongoing prescribing of clozapine will be the responsibility of the patient's psychiatrist.

The regular monitoring of physical health of patients should be undertaken as per the guidance in Appendix 1.

The ongoing haematological monitoring will continue as per arrangements agreed at pre-initiation planning.

9. Supply of Clozapine

Depending on the patient's home address will depend whether their community pharmacy will dispense clozapine or if it's BGH Pharmacy. All pharmacies that dispense clozapine must be registered. Not all Borders Pharmacies are currently registered. If a patient's community pharmacy isn't registered to dispense clozapine, BGH Pharmacy will dispense and send it out to their health centre for them to collect.



10. Treatment Breaks

In patients who have had a treatment break of >72 hours but less than 4 weeks, clozapine must be re-escalated at a dose of 12.5mg. Additional physical observations are required and FBC monitored weekly for 6 weeks in patients who are currently undergoing 4 weekly FBC monitoring. If FBC remains normal during these 6 weeks, the patient can return to 4 weekly monitoring. Suitability for community re-escalation should be assessed as per the inclusion and exclusion criteria described above.

A clinical decision may be made to increase the dose quicker than the initiation guidelines, if it is known that the patient had no problems or abnormal readings during the initiation of clozapine.

The standard physical monitoring schedule should be followed for days 1-3. If the first three days monitoring are satisfactory, once daily physical monitoring during working hours is acceptable from day 4 onwards. If patients' were previously stabilised on night time only dosing, this can be prescribed once daily at night from day 4.

11. Discontinuing Clozapine

If clozapine is to be discontinued, reducing gradually over a 1 to 2 week period is recommended. If stopped unplanned and abruptly, then the patient should be carefully observed for withdrawal side effects. It is important to let the mental health pharmacy team know if one of your patients is discontinuing treatment as they need to make CPMS aware so they can be deregistered.

Any patient stopping clozapine must have a further month of blood monitoring once stopped. For example if a patient is on weekly monitoring they require 4 blood tests and if monthly they only need to have one more blood test. This is because haematological abnormalities can still develop during this period.

If a patient has to stop clozapine due to developing abnormal leucocyte or neutrophil findings CPMS maintain a database which includes all patients who should not be re-exposed to clozapine due to this side effect.

Appendices

Appendix 1: Antipsychotic and Lithium Initiation (APLI) Monitoring Protocol

Appendix 3: Pre-Initiation Checklist

Appendix 5: Clozapine Out of Hours

Appendix 6: Clozapine Plasma/Assay Levels

Appendix 7: Guidance for a clozapine red result

Appendix 8: Clozapine dosage escalation chart

Appendix 9: Community Initiation of clozapine in adults

Appendix 10: Hospital clozapine initiation record