North Central London
Medicines Optimisation Committee

Guidance for Pharmacy Staff Managing Clozapine For Patients Admitted to Acute Hospitals

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Document control

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June 2017	1.0	New document
December 2018	1.1	Section 1.7 - Parenteral Administration Policy changed to Enteral Feeding Policy

Document management

Groups / Individuals who have overseen the development of this guidance:	Barnet, Enfield and Haringey Mental Health Trust (Adapted from CNWL Guideline January 2018)
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Contents

Overview

a) Clozapine needs to be considered as a "Red Listed" critical medicine and is therefore not prescribed by GPs or other primary care prescribers (except by shared care agreement with the clozapine monitoring service).
b) All clozapine patients, their Supervising Specialists and their dispensing pharmacies must be registered with a clozapine monitoring service.
c) The clozapine monitoring service maintains a patient profile and must be informed of the admission. During the admission the clozapine monitoring service may need to be updated on significant clinical changes or discontinuation of treatment on medical grounds.
d) Clozapine dispensing is brand specific and is restricted to registered active patients who have not had a break in treatment and who have a valid blood result.
e) As a critical medicine, supplies to patients admitted to an acute hospital, and who do not have their own supply, should be provided in a timely manner. Delays in doses mean the patient is liable to acute psychotic relapse which may complicate their physical healthcare and require clozapine dose re-titration.
f) The patient's Mental Health Trust dispensing pharmacy should be notified of the admission.
g) Prescribing of clozapine needs to be under the supervision of a Supervising Specialist and in accordance with the clozapine monitoring for the specific patient.
h) The management of individual cases is best discussed with the Liaison Psychiatry team (or equivalent) and it is advised that they are informed of the patient on admission.
i) All sections of this guideline are intended to be read in conjunction with the Summary of Product Characteristics (SmPC) and recognised reference sources including the BNF and the Maudsley Prescribing Guidelines

1. Introduction

Clozapine is an antipsychotic licenced for the treatment of schizophrenia resistant to other treatments i.e. non-responsive to or intolerant of other antipsychotic medications. It is also licensed for use (at lower doses) for the treatment of psychosis in Parkinson's disease when other treatment strategies have failed.

1.1. Full blood count monitoring and role of clozapine monitoring services

Patients prescribed clozapine must have regular full blood count (FBC) monitoring due to the risk of a non-dose related clozapine-induced neutropenia and agranulocytosis. A clozapine monitoring service provides for the centralised monitoring of leucocyte and neutrophil counts which is a mandatory requirement for all patients in the UK who are treated with clozapine.

The validity of a blood test under usual clozapine treatment conditions is defined for the specific date of blood sampling and is classified by a traffic light system combined with a monitoring frequency e.g. ***Green 04.06.18 for one month*** and the next blood test due date is calculated from the last sampling date. Review of monitoring is supervised by the monitoring service.

Monitoring Frequency; a white cell count with a differential count must be monitored:

- At least weekly for the first 18 weeks of treatment
- At least at 2 week intervals between weeks 18 and 52
- After 1 year of treatment with stable neutrophil counts, patients may be monitored at least at 4 week intervals
- Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation

Blood test validity is graded by a traffic light system as below:

Monitoring Service Blood Alert Level	White Blood Count(WBC)/mm3 (/l)	Absolute Neutrophil Count(ANC)/mm3 (/l)	Action required
Green	≥ 3500 (≥ 3.5x109)	≥ 2000 (≥ 2.0x109)	Continue clozapine treatment
Amber	Between ≥ 3000 and < 3500 (≥ 3.0x109 and < 3.5x109)	Between ≥ 1500 and < 2000 (≥ 1.5x109 and < 2.0x109)	Continue clozapine treatment, sample blood twice weekly until counts stabilise or increase
Red	< 3000 (< 3.0x109)	< 1500 (< 1.5x109)	Immediately stop clozapine treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

It is a license requirement that for all patients prescribed clozapine the patient, their consultant psychiatrist and the nominated pharmacist are registered with the clozapine monitoring service.

There are three UK brands of clozapine - Clozaril, Denzapine and Zaponex - each with their own associated monitoring services Clozaril Patient Monitoring Service (CPMS), Denzapine Monitoring Service (DMS) and Zaponex Treatment Access System (ZTAS) respectively. As a consequence of a recent European regulatory initiative, the Summary of Product Characteristics (SmPC) for each clozapine manufacturer has been harmonised across Europe.

- Supply of clozapine for each brand is direct from the manufacturer and restricted to hospital and community pharmacies registered with the associated clozapine monitoring service. Clozapine is not sold to, or distributed through wholesalers.

- Patients must only be prescribed one brand of clozapine and only registered with the monitoring service connected to that brand in order to prevent the disruption to effective monitoring that may be caused if patients switch brands.
- Acute Trusts, and their nominated pharmacist, may need to register with more than one clozapine monitoring service in order to obtain the specific clozapine brand that the patient has been maintained on prior to admission.

See Sections 7 and 8 for contact details of each clozapine monitoring service, and for contact details and brands of clozapine used by each NCL Mental Health Trust.

Each clozapine monitoring services maintains a 24 hour telephone service for information and to allow for checking of specific details for their registered patients e.g. registration, blood test validity and blood monitoring frequency.

Each monitoring service also maintains a database for their registered patients and a secure website. This is accessible only to nominated staff to view profiles of patients registered to their dispensary or service. The registered lead pharmacist/supervising specialist/clinic will also receive email alerts and notifications associated with their registered patients**.**

It is important to keep the clozapine monitoring service updated with relevant clinical information, details of the patient's supervising clinical team and their contact details.

1.2. Side effects

Side effects of clozapine include, but are not limited to (see SmPC for full information):

- Common or very common: Drowsiness, sedation, hypersalivation, postural hypotension, dizziness, tachycardia, constipation, altered glucose control, diabetes, dyslipidaemia, myoclonus and reduced seizure threshold, elevated liver enzymes, urinary retention, blurred vision, nausea.
- Less common: Neuroleptic Malignant Syndrome, severe constipation leading to impaction or obstruction (and rarely paralytic ileus)) - please note symptoms of faecal impaction/ intestinal obstruction may have fast onset and could potentially be fatal so patients must be treated immediately and there should be a low threshold for referral to gastroenterology.
- Rare and serious adverse reactions include agranulocytosis, fever, seizures, cardiomyopathy and cardiovascular effects – cardiac arrhythmias, pericarditis/pericardial effusion and myocarditis; also rarely circulatory collapse, thrombocytopenia, thromboembolism, delirium, dysphagia.

1.3. Significant drug interactions

Significant drug reactions include, but are not limited to (see SmPC for full information):

- Contra-indicated; concomitant administration of clozapine with other drugs known to have a substantial potential for causing agranulocytosis e.g. carbamazepine, carbimazole, cytotoxic medicines.
- Caution; Benzodiazepines, anticholinergics, antihypertensives, alcohol, MAOIs, CNS depressants including narcotics, highly protein bound substances, phenytoin, lithium, CYP1AS inducing substances (e.g. omeprazole) , CYP1A2 inhibiting substances (including caffeine, ciprofloxacin and hormonal contraceptives)

1.4. Contraindications

Contraindications to conditions that arise during the course of treatment will need to be discussed with the clozapine monitoring service ; agranulocytosis, impaired bone marrow function, uncontrolled epilepsy, alcoholic and other toxic psychoses, drug intoxication, comatose conditions, circulatory collapse, severe renal or cardiac disorders, active or progressive liver disease, paralytic ileus. See SmPC for full information.

1.5. Monitoring of compliance:

Omission of clozapine for more than 48 hours necessitates re-titration of the dose starting at 12.5 mg given once or twice on the first day; and during which frequent monitoring of physical parameters is mandatory. Whenever possible, such a treatment break should be **avoided**.

Sudden discontinuation of clozapine may result in an abrupt and severe relapse of psychotic symptoms and symptoms related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhoea.

The clozapine monitoring service **must be informed of any treatment breaks longer than 48 hours** and if treatment is stopped for clinical reasons. Depending on the duration of the treatment break, the monitoring service may reset the blood monitoring frequency for an individual to a more frequent monitoring schedule for a period of time.

In some medical scenarios e.g. acute infection (usually a chest infection), certain cardiac symptoms; or following a sudden cessation or decrease in smoking, patients may need a lower dose of clozapine than usual. The management of individual cases is best discussed with the Liaison Psychiatry team.

Raised clozapine levels may cause drowsiness, ataxia, confusion, seizures or constipation.

Clozapine serum levels may be:

- Markedly raised by cessation/reduction of cigarette-smoking – be aware of this if smoking is stopped/prevented during admission.
- Nicotine replacement therapy **DOES NOT** prevent the rise in serum levels.
- Raised or lowered by interaction with other medicines.

1.6. Clozapine serum level monitoring

Monitoring of clozapine serum levels is distinct from the routine monitoring of the full blood count. It is used to monitor compliance and in the optimising of treatment. Allowing for individual variation the therapeutic range is 0.35mg/l to 0.42mg/l and levels above 1.0mg/l are associated with an increase of side effects.

Serum level monitoring is not advocated as routine requirement during an acute admission.

Concerns about emergent side effects, or drug interactions affecting clozapine levels, should be discussed with the medical and Liaison Psychiatry teams. If an elevated level is suspected consideration should be made to adjust the patient's dose (or initiate treatment to control the side effect) rather than to monitor the clozapine level. A clozapine assay will take up to one week to be processed and reported.

If a clozapine plasma level is required a separate sample is taken and sent to Kings College Hospital Pathology. Contact KingsPath (020 3299 5881) for further advice.

1.7. Changing clozapine dose form

The only licensed clozapine liquid formulation is Denzapine.

For patients registered with DMS a change in dose form does not affect the patient's registration. For patients registered to CPMS or ZTAS changing to Denzapine liquid will require the patient's registration to be moved to DMS. Seek advice from the patient's clozapine monitoring service and Liaison Psychiatry.

Outside of the manufacture's licence clozapine tablets may be crushed and dispersed in water. Clozapine is highly insoluble and care must be taken to administer the full dose if given orally or to flush enteral lines after doses. Acute Trusts will need to take into account their own Unlicensed Medication Policy, Enteral Feeding Policy and the NEWT Guideline.

2. General Advice to Acute Trusts

- Register with all three clozapine monitoring bodies; CPMS, ZTAS, DMS.
- Maintain supplies of the clozapine brands used by the local Mental Health Trust
- Keep contact details for Mental Health Trusts in the locality (MI services and on call details)
- Clozapine is advised to be listed on critical/high risk medicines lists to reduce the chance of dose omissions (with the clear guidance that advice should be sought if the patient has had a treatment break for >48 hours).

2.1. Out of hours advice

- Each clozapine monitoring services provides a 24 hour on call service (see Section 7)
- CNWL, C&I and BEH also provide an advisory on call service (see Section 8)
- Clozapine should be supplied out of hours (weekends and bank holidays) if clinically appropriate (depending on blood results and clinical support advice from monitoring service).
- Ensure there has not been a treatment break of >48 hours.

3. What to do when a clozapine patient is admitted

3.1. Compliance

Establish if the patient has missed any doses. If the patient has missed any doses seek advice from the Liaison Psychiatry team and the patient's clozapine monitoring service on both dose and FBC monitoring.

Note: for treatment gaps of 48 hours or more the patient MUST NOT be continued on their usual dose of clozapine as they will need dose re-titration and may also need blood monitoring frequency re-assessment by the monitoring service.

3.2. Clozapine Dose

Contact the dispensing pharmacy within the Mental Health Trust to notify them of admission and establish the patient's currently prescribed clozapine dose and any other related info. The GP Summary Care Records may not include current information as clozapine a 'red' listed medicine.

Consider the role of clozapine and its side-effects in the context of:

- The current presentation, including cardiomyopathy/myocarditis, constipation and problems related to raised serum levels
- Recent, current and intended co-prescribed medicines
- Changes in smoking status

3.3. Blood Test Validity

The clozapine monitoring service will advise on the current blood test validity and on any further monitoring requirements. On contacting the monitoring service the Acute Trust may need to provide an up to date FBC result for assessment of whether the blood monitoring needs to be reviewed. Also relay information on the patient's reason for admission and anticipated duration of stay.

If the duration of admission is anticipated to be more than 48 hours or clozapine needs to be dispensed by the Acute Trust the monitoring service is to be contacted to transfer the patient's registration to the Acute Trust, e.g. UCLH if patient is admitted to UCLH. This ensures the monitoring service's alerts and notifications information for the patient is up to date.

3.4. Supplying Clozapine

Clozapine treatment needs to be continued on admission and dispensed by the Acute Trust if the patient has not brought in their own supply of clozapine or if their own clozapine is not suitable for use. The relevant monitoring service is to be notified of the need to dispense for the patient and may require the allocated dispensing pharmacy to be changed from the Mental Health Trust to the Acute Trust.

See Algorithm (Section 6) at end of this guideline on how to maintain the supply of clozapine to a patient.

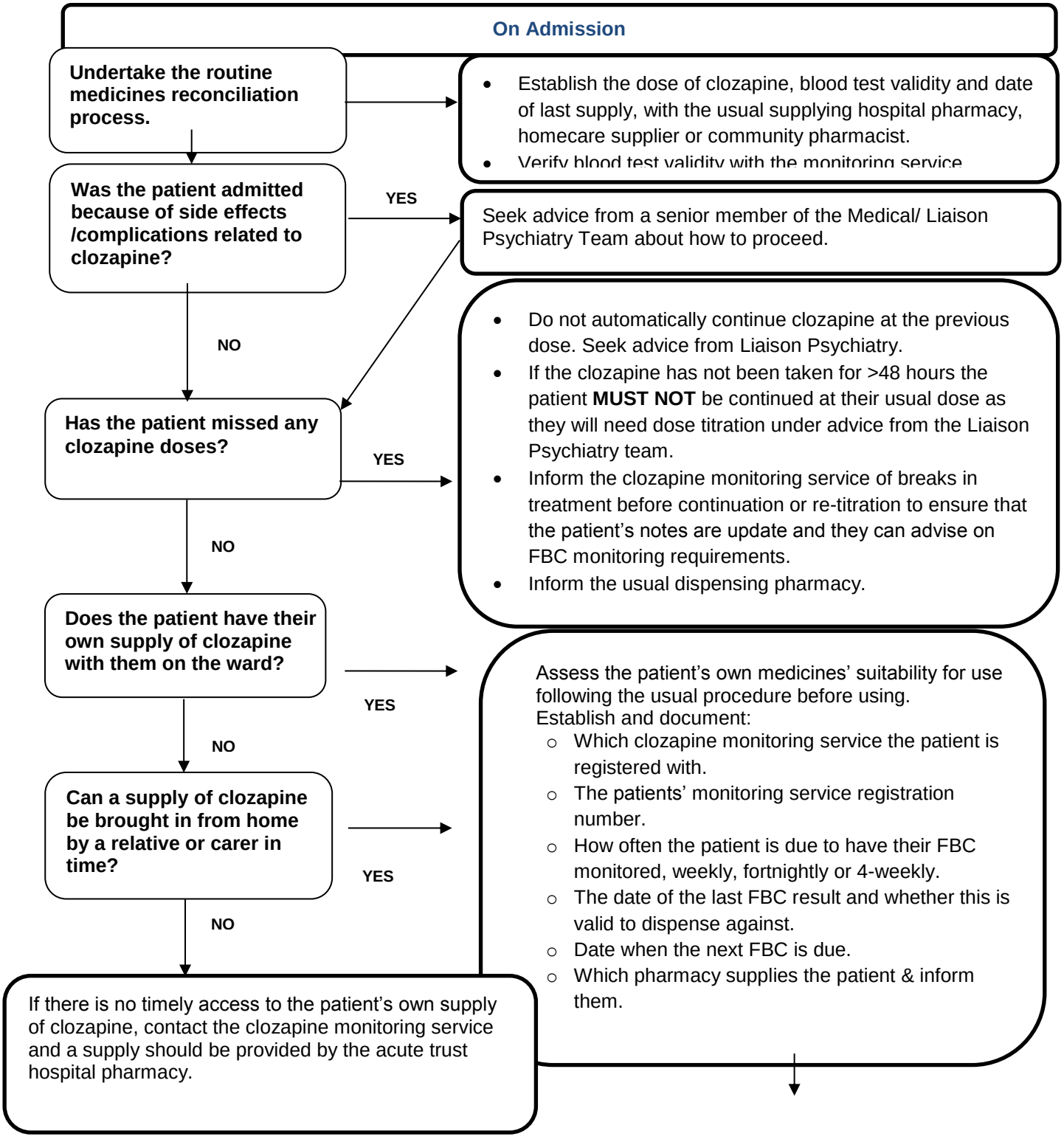
4. During Admission

- Confirm if the patient is a smoker. For patients who are smokers manage the potential impact of enforced smoking cessation on their clozapine levels to avoid toxicity, check levels and amend the dose as needed.
- Continue to monitor the FBC results at the interval recommended by the patient's registered clozapine monitoring service.
- Report values of FBC to the relevant clozapine monitoring agency.
- The acute trust hospital should continue to provide supplies of clozapine for the duration of the patient's admission (e.g. if the Patients Own supplies are used up) and update the monitoring service of the change of dispensing pharmacy.
- Inform the usual supplying pharmacy of the patient's admission and therefore no need to supply.

5. On Discharge

- Provide a sufficient supply of clozapine based on the patient's clozapine monitoring service blood validity result and the blood monitoring schedule.
- Inform the relevant Mental Health Trust pharmacy department (and agree who will notify the responsible outpatient team e.g. CMHT and/or Clozapine clinic or mental health inpatient team) of the patient's discharge and the details including the amount of clozapine supplied, any dose adjustment and the reason for the dose adjustment to ensure follow up e.g. a copy of the discharge summary.
- Note: if the patient was a smoker has not smoked during admission this will need to be highlighted at handover and on the discharge letter to as recommencing smoking will reduce clozapine plasma levels.
- Discharge summary to patient's GP should also include details of clozapine for reference on the Summary Care Record.
- Contact the monitoring service to transfer the dispensing pharmacy back to the Mental Health Trust if the patient's registered pharmacy was changed during admission.

6. How to maintain supplies of clozapine for patients



Clozapine should be considered a "critical medicine" and supplies should be provided in a timely manner. Delays in doses mean the patient is liable to acute psychotic relapse, which may complicate their physical healthcare. Re-titrating clozapine to the previous maintenance dose may take 2-3 weeks.

7. Clozapine Monitoring Services.

Brand	Medicinal Forms	Monitoring Service (24 hours)	Contact
Clozaril	Tablets: 25mg, 100mg	Clozaril Patient Monitoring Service (CPMS)	0845 769 8269
Denzapine	Tablets: 25mg, 50mg, 100mg, 200mg Liquid: 50mg/ml (expiry: 1 year unopened reduced to 90 day expiry on opening)	Denzapine Monitoring Service (DMS)	0333 200 4141
Zaponex	Tablets: 25mg, 100mg	Zaponex Treatment Access System (ZTAS)	0207 365 5842

8. Hospital contacts and brand of clozapine used

NHS Trust	Pharmacy (dispensing and clinical advice)	Out of Hours Contact	Brand Supplied
Barnet, Enfield & Haringey Mental Health Trust	St Ann's Hospital 0208 702 5435	On-call pharmacist via switchboard 0208 702 3000	Clozaril
Camden and Islington NHS Foundation Trust	Pharmacy Department 0207 561 4103/4104 Mon – Fri 9-5.15pm Sat (& Bank Hols) 10am - 1pm	On-call pharmacist via Whittington Health switchboard 020 7272 3070 Note: WH oncall pharmacist has access to C&I CPMS records but not EPR. (All C&I Liaison teams have access to C&I EPR)	Clozaril (Denzapine for liquid)
Central and North West London NHS Foundation Trust	St Charles Hospital Pharmacy 0208 206 8618 Medicines Information 0208 206 7271	CNWL On-call pharmacist 07970 753751	(London Services) Zaponex
Central and North West London NHS Foundation Trust	MK Acute Trust 01908 995 701 MK Clinical Pharmacy Team 01902 243 894 ext. 5261	CNWL On-call pharmacist 07970 753751	(MK Services) Clozaril

If the patient was transferred from another Mental Health Trust, the pharmacy service for that Trust must be contacted.