DEVELOPING TREATMENT PLANS FOR MANAGEMENT OF THE OFF-LABEL USE OF CLOZAPINE

TARGET AUDIENCE	Nursing, medical and pharmacy staff working within Mental Health & Learning Disability Services
PATIENT GROUP	Eligible patients on clozapine treatment

Clinical Guidelines Summary

- Clozapine is the gold standard treatment for treatment-resistant schizophrenia (TRS).
- Clozapine is contraindicated in patients with a history of clozapine-induced neutropenia or with concomitant use of medicines with potential myelosuppressive effects.
- There is a process that allows exposure to clozapine following an episode of clozapine-induced neutropenia or concurrent use of medicines with potential myelosuppressive effects under certain conditions and involves the consultant psychiatrist signing an off-licence agreement.
- The benefit of clozapine and chance of neutropenia should be risk assessed before using clozapine via an off-licence agreement. This involves understanding the risk of occurrence or re-occurrence of neutropenia in such cases.
- Where a red result has not been confirmed and medicines with potential myelosuppressive effects are not being used, clozapine can be started or re-started within the product licence.
- This guideline provides instruction on how to develop a treatment plan for re-challenge in patients with a previous episode of neutropenia or with concomitant use of medicines with potential myelosuppressive effects (contraindicated treatment).

Aim:

The aim of this guideline is to provide support for developing treatment plans for managing the off-label use of clozapine. This includes scenarios of: 1. Re-challenge after an episode of clozapine-induced neutropenia; 2. Initiation of clozapine in patients already receiving medicines with potential myelosuppressive effects; 3. Continuation of clozapine for patients commencing other treatments with potential myelosuppressive effects (eg, chemotherapy)

Introduction:

Clozapine is the gold standard treatment for treatment-resistant schizophrenia (TRS). TRS will affect about one in three patients with schizophrenia[1]. Clozapine-naïve patients have an approximately 30-40% chance of significant improvement when compared to other antipsychotic treatment. Approximately 2.7 % of patients treated with clozapine develop neutropenia; half of those within the first 18 weeks of treatment and three quarters by the end of the first year[2]. This reaction is unpredictable and does not appear to be dose-related[2]. As such, blood results are closely monitored, using a traffic light system, to ensure that any blood dyscrasias are noted early and receive appropriate intervention.

In accordance with the manufacturer summary of product characteristics (SPC), clozapine is contraindicated in patients with a history of clozapine induced neutropenia. The use of clozapine after a confirmed “red” result (WBC < 3.0 x 10^9/L and/or neutrophil <1.5 x 10^9/L[3]) is therefore out with the marketing authorisation (or product licence). This use is referred to as “off-label” or “off-licence”.
The SPC also states that clozapine must not be started concurrently with “substances known to have a substantial potential for causing agranulocytosis”.[3] Therefore, the use of clozapine with medications known to have a myelosuppressive effect is also off-label.

The clozapine manufacturers have a process that allows exposure to clozapine following an episode of clozapine-induced neutropenia or concurrent use with potentially myelosuppressive medications under certain conditions and involves the consultant psychiatrist signing an off-licence agreement.

Re-challenge in Previous clozapine-induced neutropenia:

When Considering Clozapine Re-challenge After Neutropenia
Consider a second opinion from a different consultant psychiatrist
Gain specialist pharmacist advice including medication history to support re-challenge.
Gain advice from a haematologist to support the re-challenge and minimise risk factors
Consider a case discussion to establish clear lines of responsibility and practical issues regarding monitoring
Have a risk: benefit discussion with patient and/or carer
Ensure statutory treatment plan includes off-label prescribing of clozapine if under the Mental Health (Care and Treatment) Act 2003

Risk assessing blood dyscrasias:

Is clozapine prohibited?:

In some cases, clozapine will have been withdrawn after one red result. *(After a single red result, daily full blood count testing should commence. Confirmation of a 'true' red result is made after two blood counts on two consecutive days, although clozapine should be discontinued on receipt of the first red result. The red alert is confirmed if one of the follow-up blood counts is in the red range and the non-re-challengeable procedure is initiated).* Where one red result is followed by an amber or green result, clozapine can be re-started within the product licence.

Was another cause for the original neutropenic episode implicated?:

- Does patient have BEN (benign ethnic neutropenia)? – haematology should be contacted to confirm a diagnosis as altered blood count parameters may be suitable for such patients. The clozapine monitoring service should be made aware so clozapine can be used within the product licence subject to BEN criteria.
- Was a viral illness implicated? – Common adverse effects of clozapine include fatigue, fever and headache. If it is possible to demonstrate a relationship between low neutrophil counts and viral illness, clozapine could be recommenced within the product licence.
- Could other drugs be implicated in the original neutropenia? – Other implicated drugs may be the cause of neutropenia, particularly in the first 18 weeks or possibly one year of taking clozapine. [4] Illicit substances should also be considered. [7]

Previous Clozapine-induced neutropenia:

Consider the speed of onset, how low blood counts fell, duration and presence of infection. The risk of a subsequent episode of neutropenia is higher than the original risk associated with starting clozapine and carries significantly more risk of life-threatening complications. [4]

A review looking at a cohort of 53 patients who had been re-challenged with clozapine following a confirmed blood dyscrasia showed that around 38% of individuals (n= 20) experienced a second blood dyscrasia. In the majority of these

patients, the second dyscrasia was more severe, lasted longer and occurred more quickly than the first dyscrasia. 55% of the 53 (n=29) were, however, re-challenged successfully and remained in treatment.[5] The exact cause of clozapine-induced blood dyscrasias is unknown. However, it has been suggested that there are distinct mechanisms that underlie the development of the more severe, potentially lethal agranulocytosis. [6] The success rate of re-challenge after agranulocytosis is reportedly much lower than after neutropenia. [7] There are significant risks associated with a clozapine re-challenge after a blood dyscrasia and the response to a re-challenge is unpredictable. [7]

Establishing risk versus benefit of a re-challenge:
Patients with previous good response to clozapine or dramatic deteriorations on its withdrawal are most likely to benefit.

Developing a treatment plan in previous neutropenia: [7]

1. Involve mental health pharmacy services at the earliest opportunity with regards to developing a treatment plan (see appendix 2).
2. Consider whether there is a need for altered monitoring parameters for WCC/ neutrophils (e.g. reducing monitoring thresholds by 0.5 to match those of BEN parameters). Doing so will require the completion of the CPMS “Alternative Blood Monitoring Parameters Form”. This is available at request from CPMS email or via mental health pharmacy services.
3. Consider the potential benefits of using Granulocyte-Colony Stimulating Factor (G-CSF) to support continued use of clozapine. This should be discussed and agreed with haematology colleagues.
4. Consider increased monitoring in early stages (e.g. twice weekly for 18 weeks).

   The peak risk for neutropenia and agranulocytosis is between 6-18 weeks and the risk decreases after the first year of treatment. Approximately 70% of agranulocytosis cases occur within the first 18 weeks of treatment. [8]

   *Clozapine monitoring systems are unable to manually change the frequency of monitoring from their standard frequencies. (i.e. They cannot set blood count frequency as twice weekly and highlight when this is late). Therefore, if monitoring frequency is increased, bloods should be checked in accordance with the treatment plan and not solely rely on the clozapine monitoring system. Blood counts will be automatically uploaded to CPMS using the local Lanarkshire auto-upload system.

5. Avoid concurrent use of medication with a potential impact on FBC. Input from specialist mental health clinical pharmacists is key in this regard.

6. Consider sample timing. Diurnal variation in circulating neutrophils can result in lower counts early in the morning. Consider taking samples in the late morning/ early afternoon. [9]

7. Include a clear action plan in the event of an amber or red result:

    - Actions to be taken
    - Thresholds for Granulocyte-stimulating factor (G-CSF) (agreed with haematology), if included in treatment plan
    - Advice for managing potential neutropenic sepsis Neutropenic Sepsis or Immunocompromised | Right Decisions
    - Consider management options during a neutropenic episode (NB all antipsychotics have the potential for causing/ delaying recovery and should ideally be avoided until two green results have been obtained. Antipsychotics with the lowest potential for blood dyscrasias are amisulpride, aripiprazole and haloperidol as per their respective SPCs.

8. Roles and responsibilities of all disciplines involved in ongoing management.

9. Names and contact numbers for key personnel; e.g. CPMS, haematology/ oncology on call, consultant psychiatrist, CPN, pharmacist, etc.

10. Patient/ carer education. Discuss the relevance of fever, sore throat, signs of infection etc, and whom these must be reported/ actions to be taken.

11. The treatment plan and any altered monitoring parameter forms (where applicable) need to be submitted to CPMS along with written confirmation from the patient's consultant psychiatrist to support off-label prescribing and accept responsibility for the prescribing decision. (see appendix 3).

12. Where patients are not being treated under the mental health act, and where possible, patient consent should be obtained and recorded using the board approved patient consent form [11].

    Patient-consent-to-unlicensed-medicine-use.pdf

Clozapine with concomitant contraindicated treatments:

Clozapine is contraindicated with concomitant use of medications known to have a myelosuppressive effect e.g. chemotherapy. Such medications may cause reductions in WCC/neutrophils that would cause red results, ultimately leading to the discontinuation of clozapine. The off-label use of clozapine in such scenarios requires thorough treatment planning in order to mitigate risk to both physical and mental health. This situation may arise where patients established on clozapine begin to receive treatment known to have a myelosuppressive effect or where patients established on myelosuppressive treatment are to be established on clozapine

Developing a treatment plan with concomitant contraindicated treatments: [10]

1. Involve mental health pharmacy services at the earliest opportunity with regards to developing a treatment plan (see appendix 2).

2. Outline concomitant contraindicated treatment:

    - Indication and rationale
    - Name of treatment
    - Predicted course of treatment and provisional end date
    - Potential impact on haematological factors
    - Name and designation of physician responsible for relevant treatment (e.g. haematologist, oncologist, etc)

3. Altered monitoring parameters for WCC/ neutrophils/ platelets (if these are to differ from standard clozapine monitoring parameters) including:

    - Threshold for stopping/ making alterations to concomitant treatment
    - Threshold (if any) for stopping clozapine
    - Where management plans include use of G-CSF, the treatment plans should clearly state the thresholds for initiating this.

    Where altered parameters are required, this will require the completion of the CPMS “Alternative Blood Monitoring Parameters Form”. This is available at request from CPMS email or via mental health pharmacy services

4. Altered frequency for FBCs while on treatment plan (if different to standard monitoring). Frequency of monitoring often increases in line with the concomitant treatment regime (e.g. before chemotherapy cycles)

5. Any other additional monitoring e.g. closer monitoring of standard observations.

6. Roles and responsibilities of all disciplines involved in ongoing management.

7. Names and contact numbers for key personnel; e.g. CPMS, haematology/ oncology on call, consultant psychiatrist, CPN, pharmacist, etc.

8. Patient/ carer education. Discuss the relevance of fever, sore throat, signs of infection etc, and whom these must be reported/ action to be taken.

9. The treatment plan and any altered monitoring parameter forms (where applicable) need to be submitted to CPMS along with written confirmation from consultant psychiatrist to support off-label prescribing and accept responsibility for prescribing decisions (see appendix 3).

10. When the concomitant treatment is no longer prescribed (e.g. at the end of the chemotherapy regime) the clozapine monitoring service must be updated and informed that the patient is no longer subject to an off-label agreement, and standard clozapine monitoring should recommence.

11. Where patients are not being treated under the mental health act, and where possible, patient consent should be obtained and recorded using the board approved patient consent form [11].

    appendix-6-patient-consent-to-unlicensed-medicine-use.pdf

Acknowledgements:

Thank you to Greater Glasgow and Clyde mental health services for permission to adapt their guidelines “Protocol for Clozapine Rechallenge Following a Neutropenic Episode (Red result) “and “Developing a treatment plan for managing the off-licence use of clozapine with a contraindicated treatment.”

References/Evidence

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Appendices

1. **Governance information for Guidance document**

Lead Author(s):	Mogese Abbas
Endorsing Body:	Mental Health and Learning Disability (MHLD) Drug and Therapeutics Committee Area Drug and Therapeutics Committee (ADTC)
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CONSULTATION AND DISTRIBUTION RECORD	
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CHANGE RECORD			
Date	**Lead Author**	**Change**	**Version**
24/01/25	Mogese Abbas	*New guidance*	1

2. Blank Off-label Clozapine Treatment Care Plan:

Background:

Concomitant contraindicated treatment regime (if applicable):

Altered monitoring parameters and associated actions (if applicable):

Include CPMS alternative blood monitoring parameters form where applicable.

Table 1: FBC results and actions

Classification of FBC	Neutrophil / WBC results (x 10^9/l)	Action
Standard Green	Neu ≥ 2.0 **and** WBC ≥ 3.5	
BEN Green	Neu < 2.0 but ≥ 1.5 **and/or** WBC < 3.5 but ≥ 3.0	
BEN Amber	Neu ≥ 1.0 and < 1.5 **and/or** WBC ≥ 2.5 and < 3.0	
BEN red	Neu < 1.0 **and/or** WBC < 2.5	

Change in clozapine monitoring frequency (if applicable):

Table 2: Clozapine monitoring frequency

Baseline at registration	
Weekly	
Fortnightly	
Every 4 weeks	

Haematology responsibilities:

Psychiatry responsibilities:

Pharmacy Responsibilities:

Nursing responsibilities:

Key contacts:

Any other relevant information:

3. Suggested wording for correspondence from Consultant Psychiatrist to CPMS RE: Off-label Use of Clozapine

Dear CPMS

Please find attached a copy of the treatment plan and alternative blood monitoring parameters form (delete as appropriate) for "*Initials, CPMS#, DOB, CHI#*". The patient is to undergo re-challenge after an episode of neutropenia / treatment of clozapine with a concomitant contraindicated treatment (*delete as appropriate*).

I, as consultant psychiatrist, acknowledge the use of clozapine in this circumstance is outside the terms of the summary of product characteristics and accept full clinical responsibility for this off-label use of clozapine in this patient.

Kind Regards

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