Management of Clozapine Discontinuation Factsheet

**ACTIONS TO TAKE PRECEDING OR FOLLOWING CLOZAPINE DISCONTINUATION**

- **Patient has stopped or has had to stop abruptly or unplanned**
  - Inform consultant psychiatrist
  - Liaise with community team, CPFS, the clozapine counsellor and the physical health team

- **Patient requesting to stop or needs to stop for health reasons**
  - Consider:
    - Urgent Medical Review and/or NCP Psychosocial

**Consider Reason**

- **Physical Health Concern**

- **Patient Choice or Suspected Non-Adherence**

**RED RESULT**

**IS CLOZAPINE GOING TO BE RESTARTED**

1. **Discuss with a consultant or a senior pharmacist**
2. **Consider the following**:
   - Is the physical health concern? Does this require cessation or is there an alternative option e.g. dose reduction, omitting a dose etc.
   - If dose is reduced or stopped:
     - Consider a hypothesis for symptoms if present
   - Consider an alternative antipsychotic if clozapine is stopped e.g. haloperidol (Consider an ECG)
   - **GO TO ADVICE FOR INSOMNIA/ALTERNATIVE ANTIPSYCHOTIC (Page 2)**
   - If clozapine has stopped and needs to be restarted see box

**GO TO ADVICE FOR INSOMNIA/ALTERNATIVE ANTIPSYCHOTIC (Page 2) - C&I: The Management of Symptoms of Clozapine Discontinuation Factsheet**

**GO TO RE-INITIATION GUIDANCE (Page 21 & 22) - C&I: Clozapine Treatment Guidelines**

1. **Clotico in be stopped**
2. **Follow RED RESULTS GUIDANCE (Page 23)**

**Considerations**

- **Only 1 red result:** Consider restarting clozapine. If within the 48-hour window, restart at the same daily dose, otherwise re-trial.
- **2 red results:** Within these days, then clozapine is contraindicated in future

- After a red result, consider an alternative antipsychotic e.g. haloperidol (Consider an ECG)
  - **GO TO ADVICE FOR INSOMNIA/ALTERNATIVE ANTIPSYCHOTIC (Page 2)**
This factsheet focuses on the management of patients who have discontinued clozapine including the risk of relapse and rebound psychosis. Abrupt cessation of clozapine can lead to a relapse within a week.

All discontinuations should be discussed with a consultant. The consultant should decide the appropriate action.

The patient should be referred to the crisis team or for an inpatient admission unless there is clear evidence why this should not happen. Re-titrations must be referred to the crisis teams.

**Rapid rebound psychosis**

Acute withdrawal reactions have been reported following abrupt cessation of clozapine treatment. These reactions include recurrence of psychotic symptoms and symptoms due to cholinergic rebound (e.g. profuse sweating, headache, nausea and vomiting and diarrhoea) and severe movement disorders e.g. dystonias and dyskinesia. Be aware of the risk of insomnia and high risk of relapse/rebound psychosis. **Careful consideration should be given to cross-tapering to another antipsychotic (preferably a sedative type) and symptomatic adjunctive treatments e.g. a hypnotic for the management of insomnia.**

<table>
<thead>
<tr>
<th>Table 1: Symptomatic adjunctive treatments³</th>
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<tbody>
<tr>
<td><strong>Discontinuation symptom</strong></td>
</tr>
<tr>
<td>Rebound psychosis and insomnia</td>
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</table>
Clozapine retitration is not planned:
A short-term benzodiazepine should be considered for agitation/aggression.
An alternative antipsychotic should be considered.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Consider simple analgesia.</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>An antiemetic can be considered. Prochlorperazine and metoclopramide – avoid if previous EPSEs. Domperidone – avoid if underlying cardiac risk or QT prolongation. Ondansetron may be a good choice, but it may cause constipation.</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Encourage the patient to remain hydrated.</td>
</tr>
</tbody>
</table>

If clozapine treatment is discontinued, ward staff / clinic nurse must notify CPMS of this and the reason for discontinuation within 72 hours.

**Planned discontinuation for therapeutic reasons**

If possible, when a patient’s clozapine is to be discontinued, the dose should be gradually tapered by steps of 12.5mg\(^1\) (or 25mg every two days\(^4\)) over 1–2 weeks\(^1,5\).

**Discontinuation following a red result**

<table>
<thead>
<tr>
<th>Table 2: A red result is defined as</th>
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<tbody>
<tr>
<td>RED</td>
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<table>
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<tr>
<th>Table 3: Patients prescribed benign ethnic diagnosis. A red result is defined as</th>
</tr>
</thead>
<tbody>
<tr>
<td>RED</td>
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</tbody>
</table>

Note if a red result obtained, clozapine must be stopped immediately\(^1\).
After clozapine discontinuation, particularly if stopped abruptly (e.g. because of a red result or agranulocytosis), a patient’s physical and mental state should be monitored closely for symptoms reflecting cholinergic rebound e.g. profuse sweating, headache, nausea, vomiting and diarrhoea or rebound psychosis, particularly in the first week.

Arrangements should be made 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.

If the patient had a confirmed red result, then consideration should be given to starting an alternative antipsychotic (preferably a sedative type). Ideally the blood results should be ‘green’ before an alternative antipsychotic is initiated.

**Red results inpatients suspected or confirmed to be Covid-19 positive**

A Covid-19 test should be considered for all patients with red results, particularly if there is no previous history. The CPMS red results guidance must be followed. Following a red result, if the two subsequently blood results are amber or green, CPMS usually authorise clozapine to be restarted. If either follow up result is red, the first red result is considered a confirmed red result. Clozapine in this case can only be recommenced if an off-label agreement is signed with CPMS by the consultant.

**Discontinuation due to non-adherence for 48 hours or less**

If clozapine therapy is stopped for 48 hours or less, clozapine can be restarted at the patient’s therapeutic dose.

**Discontinuation due to non-adherence for more than 48 hours**

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 (see appendix 4 of the Clozapine Treatment Guidelines or the table 4 below). 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.

<table>
<thead>
<tr>
<th>Table 4: Re-starting clozapine</th>
<th>Action to restart</th>
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</thead>
<tbody>
<tr>
<td>Up to 48 hours</td>
<td>Restart at previous dose – no retitration required.</td>
</tr>
<tr>
<td>48 – 72 hours</td>
<td>Begin retitration as soon as possible. One day 1, restart with half the previously prescribed daily dose given in divided doses 12 hours apart. Then give 75% of the previous daily dose on day 2. If prior doses have been tolerated, the whole of the previous daily dose in the normal dosing schedule can be administered on day 3.</td>
</tr>
<tr>
<td>72 hours to 1 week</td>
<td>Begin re-titration with 12.5mg or 25 mg clozapine.</td>
</tr>
</tbody>
</table>
Try a second dose 12 hours later if the first is well tolerated. Increase to ‘normal dose according to the patient’s tolerability over at least 3 days.

More than 1 week
Re-titrate as if new patient.
Aim to reach the previously prescribed dose within 2-4 weeks. Increase according to tolerability.

Frequency of blood monitoring following a treatment break

| **Table 5: Protocol for treatment breaks - weekly monitoring patients** |
|--------------------------------------------------|--|----------------------------------|---------------|------------------|
| **Monitoring Frequency** | **Time Off Clozapine ≤ 48 hours** | **Time Off clozapine > 48 hours < 7 days** | **Time Off clozapine >7 days** | **Time off clozapine >28 days** |
| Weekly | No change to frequency continue at normal dose | No change to monitoring frequency. Re-titrate clozapine dose | Restart at 18 weeks of weekly monitoring. Re-titrate clozapine | Restart 18 weeks of weekly monitoring  
Re-titrate dose as per initial titration  
PATIENT REGISTRATION FORM REQUIRED  
Contact CPMS |

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| **Table 6: Protocol for treatment breaks - Fortnightly and monthly monitoring patients** |
|--------------------------------------------------|--|----------------------------------|---------------|
| **Monitoring Frequency** | **Time Off Clozapine ≤ 48 hours** | **Time Off clozapine > 48 hours BUT < 4 days** | **Time off clozapine > 28 days** |
| Fortnightly & Monthly | No change to frequency continue at normal dose | No change to monitoring frequency. Re-titrate clozapine dose | ‘Treatment break’ weekly blood tests for 6 weeks and then return to previous monitoring frequency.  
Re-titrate clozapine dose  
Contact CPMS | Restart 18 weeks of weekly monitoring.  
Re-titrate as per initial titration.  
PATIENT REGISTRATION FORM REQUIRED  
Contact CPMS |
**Clozapine assay results: Very low levels (0.01mg/l) or very high levels (>1.0mg/l)**

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. Refer to the Clozapine Treatment Guidelines (appendix 6) for guidance on the management of assay levels.

<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. Very low levels must be referred to the prescriber as soon as possible.</td>
</tr>
</tbody>
</table>

**Consider the following:**

- Has steady state been reached (low assay levels). Steady state assay levels are achieved after 5 - 7 days at the same dose.
- Adherence to medication (not taking/ taking too much)
- Change to smoking status including cigarettes and cannabis (see smoking and clozapine levels). If the patient stopped or reduced smoking, levels should be rechecked a week after the change in the smoking habit\(^4\). Refer to the prescriber urgently.
- Medicine interactions (any medications recently started/ stopped?)
- Correct timing of assay (for example was the morning dose omitted before sampling)
- Any change to physical status of the patient e.g. liver impairment
- Are patients experiencing an increase in dose related side effects or signs of toxicity (constipation, seizures, confusion)

**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\(^1\).

For monitoring requirements following a **‘Red’ result**, refer to Appendix 2 of the Clozapine Treatment Guidelines.

**Supplies of clozapine**

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. Community patients who have stopped clozapine or their carers should be advised to return any remaining clozapine supplies.

**Management of side effects**

Refer to section 11 in the Trust Clozapine Treatment Guidelines.
References


Useful contact numbers:
Crisis Resolution Team telephone number: 020 3317 6333
The Pharmacy Department telephone number: 020 7561 4103 or 4104
The on-call pharmacist: Contact the Whittington Hospital switchboard: 020 7272 3070
Kaylene Oliver, The North Camden Clozapine Clinic: -020 7685 4600/4608
Kaylene Oliver, Peckwater Centre: 020 3317 6712
Prithviraj Gungabissoon, Janice Dunn, The Islington Clozapine Clinic (Daffodil Unit): 020 7561 4127/4559
CPMS telephone number: 08457698269