A Guide to the Therapeutic Drug Monitoring of Clozapine

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The information in this document is not intended as a definitive treatment strategy, but as a suggested approach. It is based on previous experience from the references quoted at the end of the document. Each case should, of course, be considered individually.

Clozapine dosage should be adjusted according to clinical response and side effect profile. Therapeutic drug monitoring (TDM) of clozapine i.e. measurements of clozapine and norclozapine concentrations in plasma samples is not required for routine patient management, but may be beneficial in certain circumstances, for example:

- If the patient’s smoking status changes
- To monitor compliance
- In poor responders after an adequate trial especially prior to consideration of augmentation strategies
- If dose reduction is being contemplated
- To diagnose dose-related side effects
- If a drug interaction is suspected
- Non-urgent investigation of suspected overdose
- Measuring baseline levels during successful treatment to use as a reference point
- For patients on long term high dose who have no evidence of previous levels being assessed

Side effects that are thought to be dose-related include; sedation, dizziness, hypersalivation, tachycardia, postural hypotension, constipation and seizures. Often these can be avoided/minimised by careful and slow dose escalation or alleviated by reducing the dose.

Clozapine TDM can be useful in certain circumstances, but is not required for routine management

As a rule, treat the patient – not the level

2. Requesting a clozapine plasma level- practical information

Clozapine plasma levels are not performed by local GGC labs. All clozapine manufacturers and monitoring services have a service level agreement with an external laboratory to perform clozapine plasma levels.

Packs and forms for measuring clozapine levels are available from the respective clozapine monitoring services. An assay request form is included in each pack and should be completed in full in order to aid interpretation of the results. A minimum of 2ml of venous blood is required to perform the assay. The sample and request form should be sent directly to the correct external laboratory for analysis.

Paper copies of the results are sent to the patient’s named consultant psychiatrist, usually within a week of the sample being taken. In addition, MH pharmacy services have access to clozapine plasma level results online. The current cost for analysis of each clozapine level is approximately £16.00 plus VAT.
3. External factors that may influence clozapine plasma levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect on plasma clozapine (with constant dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Decreased in younger patients</td>
</tr>
<tr>
<td>Gender</td>
<td>Decreased in males</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Increased in several Asian ethnicities e.g. Chinese, Korean, Taiwanese</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Possibly increased</td>
</tr>
<tr>
<td>Caffeine intake</td>
<td>Increased with significant caffeine intake</td>
</tr>
<tr>
<td>Infection (especially chest)</td>
<td>Increased</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Significantly decreased in smokers (see Appendix I:Managing patients on clozapine who stop smoking)</td>
</tr>
</tbody>
</table>

4. Constipation and clozapine plasma levels

Constipation is a potentially severe dose-related side effect of clozapine. Constipated patients may not absorb clozapine as expected and as a result, interpretation of plasma clozapine and norclozapine results may be unreliable. Continued dosing of clozapine without addressing constipation can make matters worse and can have catastrophic results. **Severe constipation can lead to paralytic ileus or bowel obstruction, which is potentially fatal.**

In a patient who develops high plasma levels unrelated to other external factors or drug interactions, the possibility of constipation (even if the patient is not complaining of this) should be considered and treated. For further advice on managing constipation, see **MRG 25 Assessment & treatment of clozapine induced constipation.**

5. Drug interactions that may affect clozapine plasma levels

<table>
<thead>
<tr>
<th>Increase plasma clozapine levels</th>
<th>Decrease plasma clozapine levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine (very significant)</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Other SSRIs (modest increases)</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Cimetidine*</td>
<td>Primidone (metabolised to phenobarbital)</td>
</tr>
<tr>
<td>Combined oral contraceptive with ethinyloestradiol*</td>
<td>Omeprazole*</td>
</tr>
<tr>
<td>Erythromycin*</td>
<td>St John’s wort*</td>
</tr>
<tr>
<td>Lamotrigine*</td>
<td></td>
</tr>
<tr>
<td>Modafinil*</td>
<td></td>
</tr>
<tr>
<td>Pregabalin*</td>
<td></td>
</tr>
<tr>
<td>Risperidone*</td>
<td></td>
</tr>
<tr>
<td>Sodium valproate in non-smokers**</td>
<td>Sodium valproate in smokers**</td>
</tr>
<tr>
<td>Ritonavir***</td>
<td>Carbatamazepine***</td>
</tr>
</tbody>
</table>

This list only includes pharmacokinetic interactions and is not exhaustive, please refer to most recent Summary of Product Characteristics or Stockley’s Drug Interactions (available via www.medicinescomplete.com) for comprehensive interaction information

* These interactions have been demonstrated in a few case reports only and may be of less clinical significance.

** There are reports of sodium valproate both increasing and decreasing clozapine plasma levels which may be dependent on whether individual is a smoker or non-smoker.

*** The use of clozapine with either ritonavir or carbamazepine is contraindicated due to risk of haematological adverse effects.
6. Factors to consider when requesting clozapine plasma levels

- Consider and document patient consent for sample. Results will be held on a database.
- What is the rationale for requesting a plasma level?
  - Has the dose been constant for at least one week? YES
  - Is the sample a trough? YES
- Obtain sample
  - 12 hours post dose in once daily dosing or immediately before morning dose in multiple daily dosing
  - Record sampling time and time of last dose to aid clinical interpretation
- Results obtained 3-7 days post sample
- Interpret results and make changes to dose accordingly
  - Consider any external factors that may influence plasma level
  - Seek advice from MH pharmacy if necessary

7. Metabolism and pharmacokinetics of clozapine

Clozapine is metabolised by N-demethylation, hydroxylation and N-oxidation. The hepatic enzyme involved is primarily CYP1A2, with possible additional contributions by CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Clozapine has a mean terminal elimination half-life of about 12 hours and its N-demethylated metabolite, norclozapine, has a plasma half-life that is around twice as long.

A clozapine plasma trough concentration of greater than 0.35mg/L has been associated with efficacy in treatment resistant schizophrenia. There is no clearly established upper limit for plasma clozapine levels, although trough concentrations above 0.6mg/L have been associated with increased risk of adverse effects, including seizures. The risk of seizures is significantly increased with levels greater than 1mg/L. The reference range for clozapine is usually quoted as 0.35 – 0.6mg/L. However, it is important to note that clozapine does not have a narrow therapeutic index and some individuals will be maintained at plasma levels outwith the quoted reference range.

Norclozapine concentration is much less affected by short term changes and can give information on compliance with treatment in the run up to the sample being taken. Norclozapine is usually present at around 70% of the parent compound; therefore measurements of norclozapine can also provide information on metabolism. If the plasma clozapine is high (>1mg/L) and the norclozapine level is much less than 70% of the clozapine level, metabolism may have become saturated.

The clozapine/norclozapine ratio is often reported as a target ratio of 1.3. In chronic dosing, the ratio of clozapine to norclozapine should remain the same for a particular individual.

There appears to be a definite relationship between the dose of clozapine and plasma concentration of clozapine and norclozapine, although there is around a 50-fold variation between individuals and the way they metabolise clozapine.

March 2019 Updated by the GGC MHS Clozapine Review Group and approved by PMG(MH)
Review March 2022
8. Interpretation of clozapine plasma levels

These suggestions are not intended as a definitive treatment strategy, but as a suggested approach. Each case should be considered individually.

<table>
<thead>
<tr>
<th>Trough sample</th>
<th>Suggested action</th>
</tr>
</thead>
<tbody>
<tr>
<td>0mg/L</td>
<td>Review patient – if dose &gt;50mg/day suggest no clozapine taken for up to a week before sampling</td>
</tr>
<tr>
<td>&lt;0.35mg/L</td>
<td>If response good maintain current dose</td>
</tr>
<tr>
<td></td>
<td>If response poor or incomplete, review and address issue of compliance. If compliance OK, consider cautious dose increase and repeat assay after 1 week.</td>
</tr>
<tr>
<td>0.35 – 0.6mg/L</td>
<td>If response good maintain current dose. If side effects present and are serious or persistent consider cautious dose reduction.</td>
</tr>
<tr>
<td></td>
<td>If response poor and there has been an adequate trial consider cautious dose increase or augmentation</td>
</tr>
<tr>
<td>0.6 – 1.0mg/L</td>
<td>If response good review current dose and consider cautious dose reduction if mental state allows</td>
</tr>
<tr>
<td></td>
<td>If response poor cautiously reduce dose to bring level down below 0.6mg/L. Monitor mental state and repeat level at least 1 week after dose reduction.</td>
</tr>
<tr>
<td>1.1 – 1.9mg/L*</td>
<td>If response good with no signs of toxicity review dose and consider cautious dose reduction to bring level below 1 and possibly below 0.6mg/L.</td>
</tr>
<tr>
<td></td>
<td>If response poor cautiously reduce dose to bring level down below 1 and possibly below 0.6mg/L. Monitor mental state and repeat level at least 1 week after dose reduction.</td>
</tr>
<tr>
<td>2mg/L &amp; above*</td>
<td>If response good with no signs of toxicity URGENT REVIEW and consider cautious dose reduction to bring level below 1 and possibly below 0.6mg/L if mental state allows</td>
</tr>
<tr>
<td></td>
<td>If response poor URGENT REVIEW and dose reduction. If patient in the community consider admitting. Stop clozapine for 24 hours and re-start at 75% of last dose and reduce dose by 25mg per week to bring plasma clozapine below 1 and possibly below 0.6mg/L. Monitor mental state and repeat level at least 1 week after dose reduction.</td>
</tr>
</tbody>
</table>

* Seizure risk is increased significantly with levels greater than 1mg/L, therefore serious consideration must be given to the pros and cons of using seizure prophylaxis. As a rule, high clozapine plasma levels should be managed by careful dose reduction and when done in a timely fashion, this may be all that is required when dealing with an acute high level. For acute high levels not associated with definitive seizure activity the use of an anticonvulsant is not usually required, although each case must be managed individually based on the actual level, clinical picture and the patient’s medical history. Consideration to short term benzodiazepine use may be advisable in managing an acute high level rather than initiating anticonvulsant treatment.

There are a small subset of patients who are maintained at levels above the upper limit of the reference range. Where an individual has a chronically high plasma level it may be more appropriate to consider seizure prophylaxis to manage the ongoing risk. Sodium valproate is usually the treatment of choice when managing clozapine seizure risk with lamotrigine as an alternative.

N.B Sodium valproate is contraindicated in women of child-bearing potential unless they participate in the pregnancy prevention programme and therefore commencing in this population will take time to consider and ensure appropriate safeguards are in place. Lamotrigine requires a slow titration due to risk of serious skin reactions, therefore it takes time to titrate to a dose that would provide seizure prophylaxis.

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Where there is evidence of seizure activity, clozapine should be withheld for 24 hours, recommenced at half the original dose and an anticonvulsant commenced irrespective of the plasma level.

Interpreting clozapine plasma levels – some practical guidance

1) Consider the norclozapine level as well as the clozapine level
   - The clozapine/norclozapine ratio can be a helpful guide to indicate recent non-compliance or saturated metabolism however if the plasma levels themselves are within the recommended range and the patient is responding well with minimal side effects it should not be used as an indicator for dose adjustment.
   - Norclozapine is usually around 70% of clozapine level
   - Norclozapine can be helpful in assessing compliance
   - The median clozapine/ norclozapine ratio is around 1.3.
   - Is the clozapine level much more (>3 fold) than the norclozapine level? (ratio >3)
     - It may not be a true ‘trough’ sample. Attempt to confirm if it is a trough sample before taking any further actions
     - Clozapine N-demethylation may have become saturated. If saturation is suspected, consider cautious dose reduction, but be aware that the level may take some time to decrease
     - May suggest recent missed doses over preceding days
   - Is norclozapine level greater than clozapine level? (ratio <1)
     - May suggest poor adherence over 24 hours prior to assay (i.e. clozapine level decreases, but norclozapine with longer half-life remains high)

2) Is the result unexpected? – consider repeating before acting on result
   - Is it incompatible with the clinical picture?
   - Is it markedly different from previous result(s) at constant dose with no other external factors implicated?

3) The use of clozapine suspension may result in variable dosing (especially if not shaken before use)

4) Treat the patient NOT the level
   - Clozapine TDM is an aid to clinical decision making, it should not dictate practice.

5) Contact MH pharmacy services for advice in interpreting plasma clozapine levels

9. References:
4. Zaponex 100mg tablets Summary of Product Characteristics. Last updated 13/7/18
   www.medicines.org.uk accessed online 20/12/18
10. Appendix I: Managing patients on clozapine who stop smoking

Tobacco smoke contains polycyclic aromatic hydrocarbons that increase the activity of certain hepatic enzymes especially CYP1A2. Smoking increases the metabolism of clozapine and consequently reduces the plasma levels. This means a higher dose of clozapine may be necessary to achieve a therapeutic effect. The effect of smoking is dose related i.e. the more cigarettes smoked, the greater the enzyme induction. This also means that any reduction in the number of cigarettes smoked per day may result in increased clozapine plasma levels. This is worth bearing in mind should a patient begin to reduce their smoking in preparation for a quit attempt.

Plasma clozapine may rise substantially within 3-5 days of smoking cessation and vice-versa (i.e. starting smoking can decrease levels and cause deterioration in mental state). Careful monitoring is therefore essential if there is a change in smoking habit. When a patient stops smoking the increased enzyme activity reduces over a week, although it can take many weeks for this to return to baseline. This will result in a likely rise of clozapine plasma level with subsequent increase in plasma-related side effects e.g. sedation, dizziness, hypersalivation, tachycardia, postural hypotension, constipation and seizures. It has been suggested that the mean increase in plasma levels is 50% but as this is an average figure, the actual increase could be lower or higher than this.

The interaction between smoking and clozapine is unrelated to nicotine, and therefore the use of nicotine replacement therapy or e-cigarettes does not affect plasma clozapine at constant clozapine dose.

For patients on clozapine who smoke and are also prescribed valproate, the increase in clozapine plasma levels seen after stopping smoking may be greater than that seen in patients not taking valproate.

Whenever possible the impact of smoking on clozapine treatment should be explained to the patient. It should be stressed that whenever patients make a change to their smoking status it must be discussed with someone responsible for their care.

Smoke free wards continue to pose a problem in managing individuals prescribed clozapine where access to smoking will be limited, a quit attempt may be temporary and the individual may choose to resume smoking when on pass or at discharge. A pragmatic approach to managing smoke free environments and those prescribed clozapine is therefore required.

The following flowcharts describe scenarios encountered in MHS for managing smoking cessation in individuals prescribed clozapine. The first describes the management of patients undergoing a planned quit attempt and the second describes the management of patients who have to quit temporarily due to being admitted to hospital.
Flowchart 1
Guidance for the management of patients on a stable clozapine dose who wish to stop smoking

- Take baseline clozapine plasma level prior to quit attempt
- Signpost to smoking cessation services
- Monitor for dose-related side effects during first week
  - If dose-related side effects emerge during first week, consider reducing the dose gradually to around 75% of the pre-quit dose. If dose is reduced, take post-quit level one week after.
- One week after stopping smoking, take a 2nd clozapine plasma level
- If plasma levels are outwith the accepted reference range, consider dose reduction (contact MH pharmacy services for advice)
- Consider further dose reductions on a weekly basis with repeat levels one week after dose change
- Continue to monitor for dose-related side effects
- Advise of smoke free policy & smoking cessation support available

Dose related side effects include: sedation, dizziness, hypersalivation, tachycardia, postural hypotension, constipation & seizures

Flowchart 2
Guidance for the management of patients who abruptly stop smoking due to a hospital admission

- Identify smoking status
- SMOKER
- Take a baseline plasma level if no recent level is available
- Monitor for dose-related side effects during first week
- Review patient’s smoking status weekly at MDT meeting
- If plasma levels are within the reference range, monitor for dose-related side effects. If side effects emerge, take a level and consider dose reduction.
- If plasma levels are outwith the accepted reference range, consider dose reduction (contact MH pharmacy services for advice)