A Guide to the Therapeutic Drug Monitoring of Clozapine

Contents

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 treatment who have no evidence of previous levels as part of their annual physical review

Side effects that are thought to be associated with high plasma levels or toxicity 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

Variable	Effect on plasma clozapine (with constant dose)
Age	Increased in older patients. Consider more frequent monitoring in elderly patients.
Gender	Increased in females
Ethnicity	Increased in several Asian ethnicities
Liver disease	Possibly increased
Caffeine intake (e.g. coffee, tea and energy drinks)	Increased with significant caffeine intake
Infection (especially chest)	Increased, consider dose reduction of up to 50% in those with moderate to severe infection requiring hospitalisation
Cigarette smoking	Significantly decreased in smokers (see Appendix I: Managing patients on clozapine who stop smoking)

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

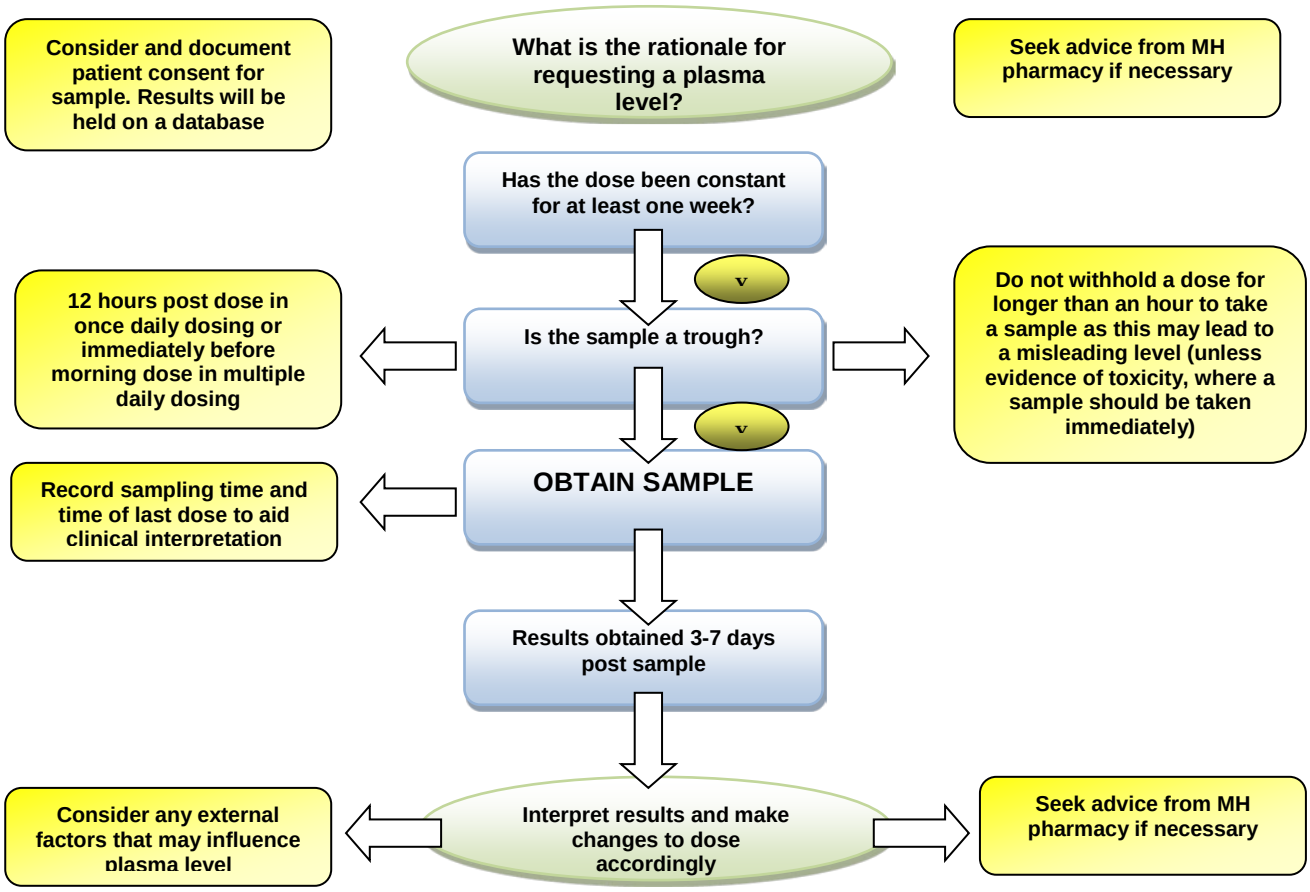
Increase plasma clozapine levels	Decrease plasma clozapine levels
High clinical significance	
Fluvoxamine (very significant)	Rifampicin
Other SSRIs (modest increases)	Phenytoin
Ciprofloxacin	Phenobarbital
Sodium valproate in non-smokers**	Primidone (metabolised to phenobarbital)
Ritonavir***	Sodium valproate in smokers**
	Carbamazepine***
Less/unknown clinical significance	
*Cimetidine**	*Omeprazole**
*Combined oral contraceptive with ethinyloestradiol**	*St John's wort**
*Erythromycin**	
*Lamotrigine**	
*Modafinil**	
*Pregabalin**	
*Risperidone**	
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



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 but there is around a 50-fold variation between individuals and the way they metabolise clozapine. In chronic dosing, the ratio of clozapine to norclozapine should remain the same for a particular individual.

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.

Trough sample	Suggested action
<0.05mg/L	Review patients' compliance with treatment as potentially no clozapine taken for up to a week before sampling
<0.35mg/L	If response **good** maintain current dose
	If response **poor** or incomplete, review and address issue of compliance. If compliance OK, consider cautious dose increase and repeat assay after 1 week.
0.35 – 0.6mg/L	If response **good** maintain current dose. If side effects present and are serious or persistent consider cautious dose reduction.
	If response **poor** and there has been an adequate trial consider cautious dose increase or augmentation
0.6 – 1.0mg/L	If response **good** review current dose and consider cautious dose reduction if mental state allows
	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.
1.1 – 1.9mg/L*	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.
	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.
2mg/L & above*	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
	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.

With levels >1mg/L, plasma clozapine may continue to rise in the short term even after dose reduction is commenced.

* Seizure risk is increased in levels >0.6mg/L and significantly increased in levels >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 and discontinued if no longer required.

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.

N.B. Sodium valproate has restriction on use in both in women of child-bearing potential and men <55years-old, further guidance can be found here. 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.

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) Is the patient on once daily dosing?

- Levels can be up to 23% higher at 12 hours compared to those on twice daily dosing
- Correcting for this may be appropriate, seek advice from pharmacy

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

5) Treat the patient NOT the level

- Clozapine TDM is an aid to clinical decision making, it should not dictate practice.

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

9. References:

1. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines. 14th edition. Wiley Blackwell

2. Bazire S. Psychotropic Drug Directory 2020/21. Lloyd-Reinhold Publications

3. Zaponex fact sheet – Clozapine metabolism and plasma level monitoring June 2021

4. Zaponex 100mg tablets Summary of Product Characteristics. Last updated 13/7/18 www.medicines.org.uk accessed online 20/12/18

5. Stockley's Drug Interactions. Last updated 13/11/18. www.medicinescomplete.com accessed online 19/12/18

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/vaping does not affect plasma clozapine at constant clozapine dose.

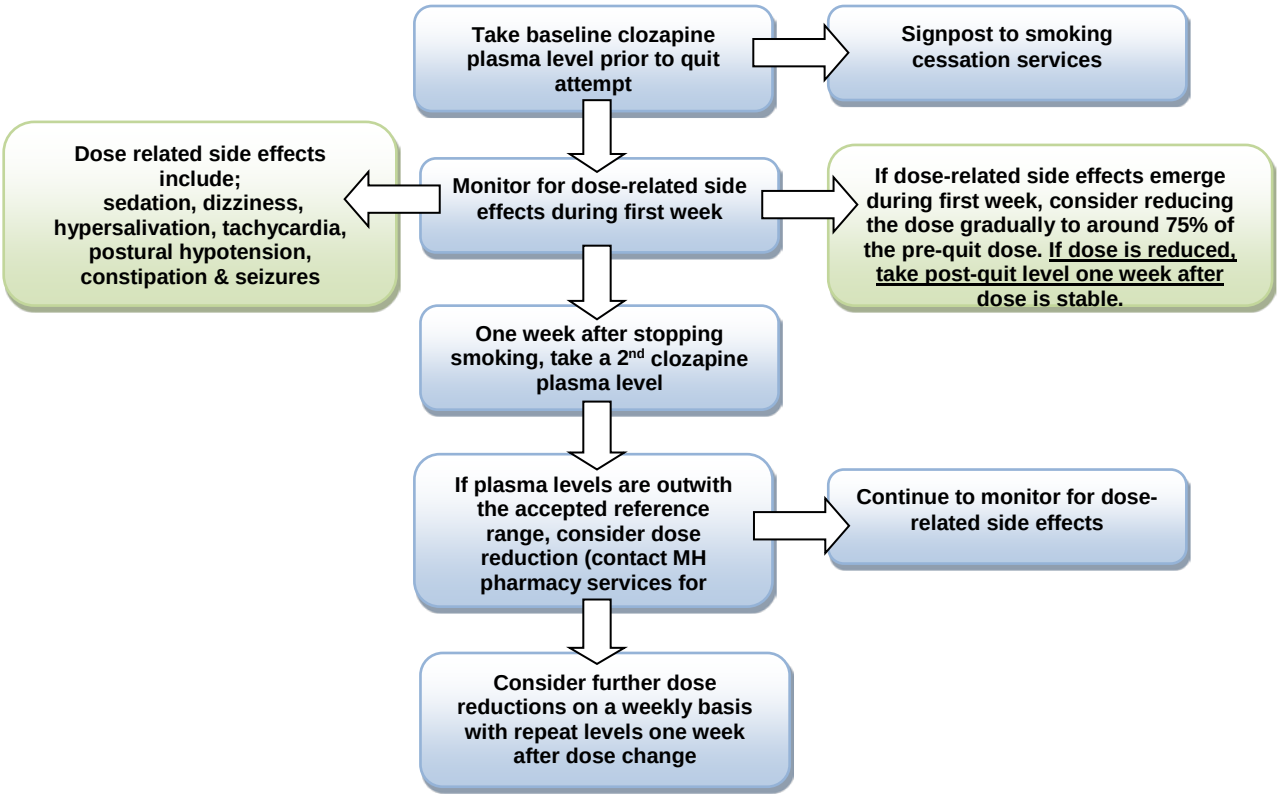
For patients on clozapine who smoke and are also prescribed valproate, the increase in clozapine plasma levels seen after stopping smoking may be greater than that seen in patients not taking valproate.

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



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