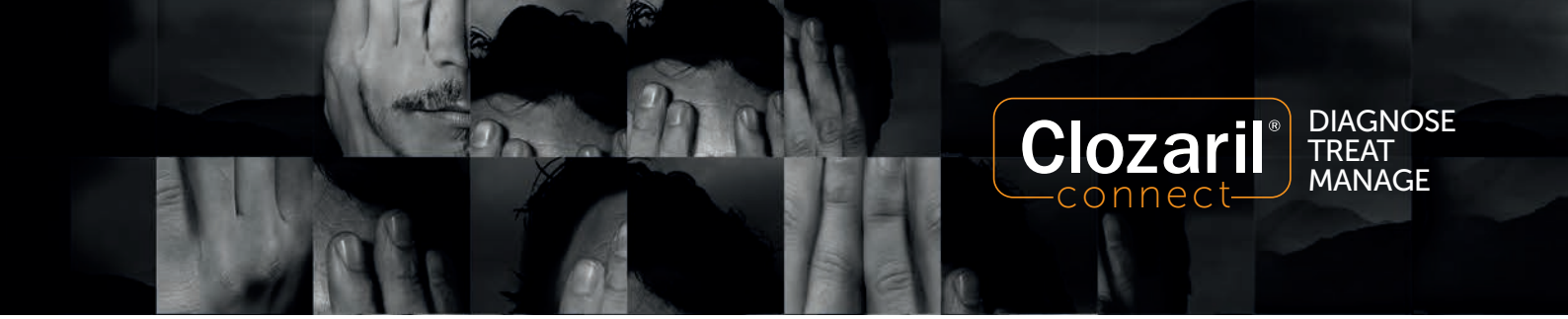


Clozapine therapy: role of therapeutic drug monitoring (TDM)

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on previous successful experience. Each case should, of course, be considered individually.

This information is provided for healthcare professionals and should not be used as a patient information leaflet.

Although antipsychotic efficacy with Clozaril® (clozapine) can be expected with doses of 200 to 450 mg/day, the approved dose range extends up to 900mg/day.[1,2] Clozapine dose is normally adjusted according to the patient's clinical response and side-effects. Therapeutic Drug Monitoring (TDM) of clozapine is not required for routine patient management, but may be helpful in certain situations:

- Dose adjustment
- Assessing non-compliance
- Monitoring the effect of changes in smoking habit
- Diagnosing dose-related adverse effects

In addition, it may be helpful to measure 'baseline' levels during successful therapy in case problems occur later in treatment.

Measurement of plasma clozapine and norclozapine, the main metabolite of clozapine, is normally only useful for patients who have been taking clozapine for at least a month although TDM earlier than this may be useful to detect patients who are poor metabolisers of the drug.[3]

To obtain an accurate level the patient should have been on a steady dose for at least 7 days and the sample taken either immediately before a normal morning dose or in the morning after an evening dose ('trough' sample). There should be a minimum of 6 hours since the last dose.[3] The sample should be collected in an EDTA tube and sent to the appropriate toxicology laboratory. It is important to note the time of sampling with respect to the time of the last dose since this may impact interpretation of the result.

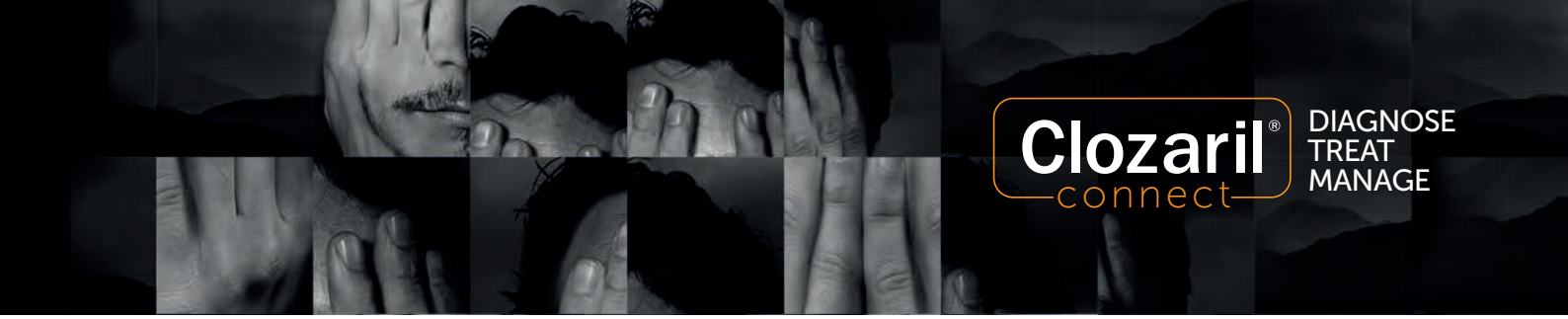
Plasma assay kits can be ordered from the Clozaril® Patient Monitoring Service (CPMS) by calling the number below and selecting Option 4:

UK: 0845 769 8269 **Ireland: 01 662 1141**

Establishment of clozapine dose and management of side-effects

There is a wide variation in clozapine dose with some patients managed at 200mg or less while others are on the maximum 900mg. Similarly, some patients will show little or no evidence of adverse effects at 900mg/day, whilst others may experience adverse effects at much lower doses.

Adverse effects that may be dose-related include seizures, drowsiness, hypersalivation, tachycardia, postural hypotension and constipation.[4] The risk of clozapine side-effects can be minimised by using a slow titration and, if side-effects occur, a dose reduction may alleviate the problem. Neutropenia/agranulocytosis is not proven to be dose-related.[5]



Several studies have suggested that efficacy in Treatment Resistant Schizophrenia may be associated with 'trough' clozapine concentrations of 0.35mg/l or above.[3,6] An upper limit for plasma clozapine has not been established clearly, although it has been suggested that trough concentrations above 0.6mg/l may indicate increased risk of adverse effect.[3]

Use of clozapine plasma levels to detect non-compliance

When checking clozapine and norclozapine plasma levels, the clozapine:norclozapine ratio may help in detecting clozapine non-compliance although it is important to remember that the plasma level reflects adherence in the last few days only.

Couchman et al reviewed the results from a clozapine TDM service between 1993-2007. They found that although clozapine and norclozapine plasma levels were generally related to dose there was a large variation. Their results are shown in Table 1.[3] Attempts to define a therapeutic range for plasma clozapine are difficult because of the increased response observed with duration of therapy in some patients and the fact that there is wide (50-fold) variation between patients in the rate at which they metabolise clozapine.[3]

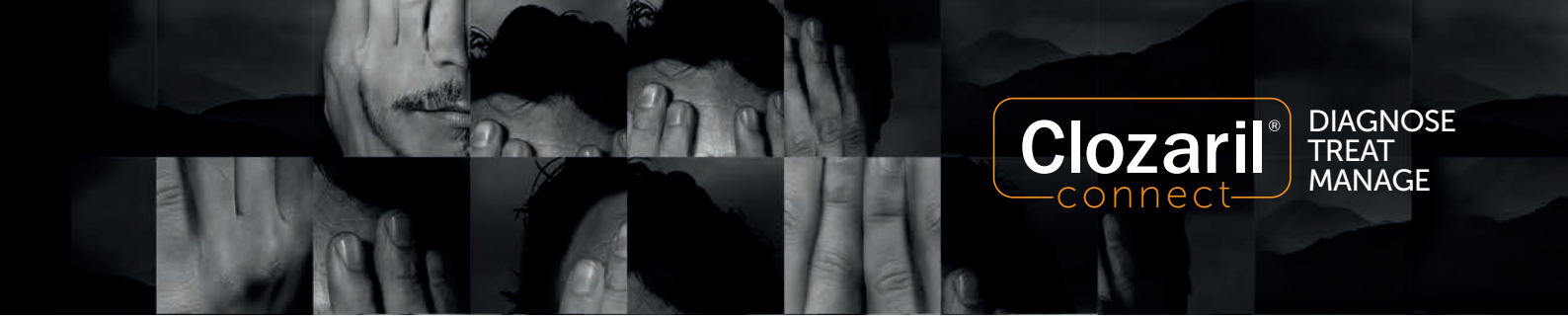
Table 1. Plasma clozapine and norclozapine concentrations (median, 10th-90th percentile) and prescribed dose in 85,958 samples in which clozapine and norclozapine were detected[3]

Clozapine dose (mg/day)	Number of samples	Clozapine (mg/l)	Norclozapine (mg/l)
50-150	2,632	0.20 (0.06-0.55)	0.13 (0.05-0.28)
151-250	8,338	0.30 (0.09-0.72)	0.19 (0.08-0.38)
251-350	18,794	0.34 (0.13-0.79)	0.23 (0.10-0.46)
351-450	20,677	0.40 (0.16-0.90)	0.27 (0.12-0.53)
451-550	14,504	0.45 (0.19-1.00)	0.31 (0.15-0.60)
551-650	10,509	0.50 (0.22-1.08)	0.35 (0.16-0.67)
651-750	5,507	0.54 (0.23-1.16)	0.37 (0.18-0.72)
751-850	3,129	0.57 (0.25-1.25)	0.39 (0.19-0.80)
851	1,868	0.55 (0.25-1.24)	0.41 (0.19-0.84)

The role of norclozapine and the clozapine:norclozapine ratio

Plasma norclozapine does not appear important when assessing clinical effect, but can be useful when assessing partial adherence. If both the plasma clozapine and norclozapine are below the bottom tenth percentile (Table 1) this suggests partial adherence, although it is possible that the patient may metabolise the drug extremely quickly (typically young male smokers).

The clozapine:norclozapine ratio has been found to average 1.3 and should normally be in the range of 0.5-2.5.[4] A ratio of >2.5 may be due to incomplete absorption of the last clozapine dose prior to collection of the sample, or indicate that metabolism of clozapine has become saturated. This may be because the prescribed dose is too high for the patient or due to inhibition of clozapine metabolism by another drug such as fluvoxamine. A clozapine:norclozapine ratio of <0.5 may indicate poor compliance within the last day or so, or that the patient may benefit from more frequent dosing.[4]



Cigarette smoking and caffeine intake

Both cigarette smoking and caffeine may affect the plasma level of clozapine.[1,2] It is important to take both smoking habits and caffeine intake into account when starting patients on clozapine and when a patient who has previously done well on clozapine starts to report side-effects.

Cigarette smoking

Tobacco smoke contains polycyclic aromatic hydrocarbons which induce CYP1A2, the enzyme responsible for clozapine metabolism.[7] As a result, smoking increases clozapine metabolism and smokers generally have a lower plasma concentration than non-smokers. Smoking cessation has been reported to increase clozapine levels considerably with figures of up to 70% reported in the literature.[8] In a study of 44 patients (10 non-smokers and 34 smokers) Seppala *et al* (1999) found that both clozapine and norclozapine levels were around 40% lower in the smokers than the non-smokers.[9]

A study by Haslemo *et al* (2006) investigated the dose-dependent effect of cigarette smoking on the plasma level of clozapine and concluded that 7-12 cigarettes per day is likely to be enough for maximum induction of clozapine metabolism.[10]

For patients who smoke and who are not responding to clozapine treatment it may be worth checking the plasma level to ensure that the clozapine dose is high enough to obtain a therapeutic effect.

Alternatively, if a patient stops smoking there may be an increase in the clozapine plasma level which can lead to an increase in adverse events, some of which may be serious. This effect can occur very quickly.[6] Case reports have described the occurrence of clozapine-induced seizures in men, who were previously heavy smokers, after they stopped smoking over a short period of time.[11,12,13] One of these men also developed stupor and went into a coma.[11]

It is important to consider the need to adjust the clozapine dose quickly in patients who stop smoking during treatment[6,14] although possible exacerbation of psychotic symptoms must also be considered. Smoking cessation may be particularly relevant when patients are admitted to hospitals which have a ban on smoking. Plasma level monitoring can be used to establish an appropriate clozapine dose.

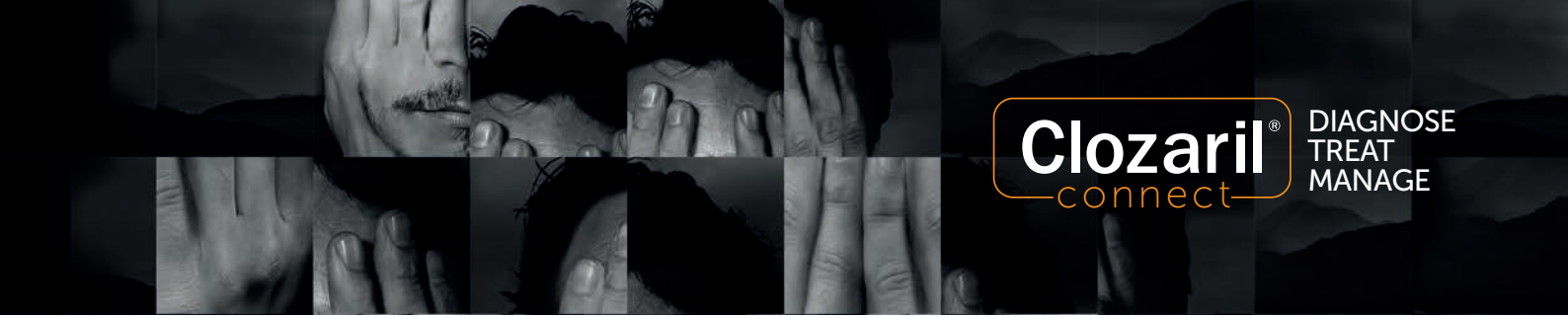
Nicotine replacement therapy (NRT) in the form of patches or chewing gum does not affect clozapine plasma levels, hence a patient who stops smoking with the aid of NRT is at the same risk of increased levels as one who stops smoking without using NRT.

Caffeine

Caffeine, which is an inhibitor of CYP1A2, may increase clozapine levels leading to an increased risk of adverse effects.[1,2] Since the plasma concentration is increased by caffeine intake and decreased by nearly 50% following a five-day caffeine-free period, dosage changes of clozapine may be necessary when there is a change in caffeine drinking habit.[1,2] Products which contain caffeine include coffee, tea, energy drinks, cola and chocolate.

Infection and inflammation

It has been suggested that infection or inflammation may inhibit cytochrome P450 1A2 leading to a reduction in clozapine metabolism and possible toxicity.[15,16] Raaska (2002) and Leung (2014) each describe cases where plasma clozapine levels have increased during infection, with patients showing signs of toxicity.[15,16]



Clozaril® connect

DIAGNOSE
TREAT
MANAGE

Interpretation of plasma level results

To understand the plasma level result for a patient, consideration should be given to the following points:

- Whether the patient has been on a steady dose for at least 7 days to allow clozapine to reach a steady state
- Check that the sample was collected at the appropriate time to give a trough level
- Is the patient responding to clozapine and are they suffering with any side-effects?
- Plasma level results may be affected by several factors including age, sex and weight
- Is the patient a smoker and has there been any change in smoking habit recently?
- Is the patient on any other drugs and have there been any changes to medication recently? For further information with respect to drugs which may affect clozapine plasma levels please consult your local clinical pharmacist or contact the CPMS
- Does the patient have any issues with liver function which may be affecting clozapine metabolism?
- Has the patient had clozapine levels checked before. If so the laboratory may have a record of previous levels for comparison
- Has the patient been unwell with inflammation or infection?

References

1. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan Products Ltd. http://www.medicines.org.uk/emc/ (Accessed on 04/07/2018).
2. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan IRE Healthcare Limited. http://www.medicines.ie/ (Accessed on 04/07/2018).
3. Couchman L, Morgan PE, Spencer EP, Flanagan RJ. Plasma clozapine, norclozapine, and the clozapine:norclozapine ratio in relation to prescribed dose and other factors: Data from a Therapeutic Drug Monitoring service, 1993-2007. *Ther Drug Monit* 2010; **32**: 438-447.
4. Flanagan RJ. Therapeutic Monitoring of Antipsychotics. *CPD Clin Biochem* 2006; **7**: 3-18.
5. Munro J *et al.* Active Monitoring of 12760 Clozapine Recipients in the UK and Ireland. *Br J Psychiatry* 1999; **175**: 576-580.
6. Rostami-Hodjegan A, Amin AM, Spencer EP *et al.* Influence of Dose, Cigarette Smoking, Age, Sex, and Metabolic Activity on Plasma Clozapine Concentrations: a Predictive Model and Nomograms to Aid Clozapine Dose Adjustment and to Assess Compliance in Individual Patients. *J Clin Psychopharmacol* 2004; **24**: 70-78.
7. Schein JR. Cigarette Smoking and Clinically Significant Drug Interactions. *Ann Pharmacother* 1995; **29**: 1139-1148.
8. Meyer JM. Individual Changes in clozapine levels after smoking cessation: results and a predictive model. *J Clin Psychopharmacol* 2001; **21**: 569-574.
9. Seppala NH, Leinonen EVJ, Lehtonen ML *et al.* Clozapine Serum Concentrations Are Lower In Smoking Than In Non-Smoking Schizophrenic Patients. *Pharmacol Toxicol* 1999; **85**: 244-246.
10. Haslemo T *et al.* The effect of variable consumption on the interaction with clozapine or olanzapine. *Eur J Clin Pharmacol* 2006; **62**: 1049-53.
11. Skogh E, Bengtsson F and Nordin C. Could Discontinuing Smoking Be Hazardous For Patients Administered Clozapine Medication? A Case Report. *Ther Drug Monit* 1999; **21**: 580-582.
12. Oyewumi LK. Smoking Cessation and Clozapine Side Effects. *Can J Psychiatry* 1998; **43**: 748.
13. McCarthy RH: Seizures Following Smoking Cessation In a Clozapine Responder. *Pharmacopsychiatry* 1994; **27**: 210-1.
14. Faber MS and Fuhr U. Time Response of Cytochrome P450 1A2 Activity on Cessation of Heavy Smoking. *Clin Pharmacol Ther* 2004; **76**: 178-184.
15. Raaska K *et al.* Bacterial pneumonia can increase serum concentration of clozapine. *Eur J Clin Pharmacol* 2002; **58**: 321-2.
16. Leung JG *et al.* Infection and inflammation leading to clozapine toxicity and intensive care: a case series. *Ann Pharmacother* 2014; **48**: 801-805.

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

UK: Reporting forms and information can be found at www.mhra.gov.uk/yellowcard

Ireland: HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Adverse events should also be reported to Mylan via cpms@mylan.co.uk

Clozaril® (clozapine)

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

CLZ-2018-0156 Date of preparation: July 2018

Mylan

Better Health for a Better World