BJPsych The British Journal of Psychiatry (2025)
227, 1, 499–500. doi: 10.1192/bjp.2025.21

Letter

# Missed clozapine doses: time to reconsider the 48 h rule

Robert James Flanagan and Susanna Every-Palmer

**Keywords**
Clozapine; hypotensive effect; tolerance; re-titration; missed doses.



A recent editorial detailed the haematological monitoring that surrounds the initiation and continued prescription of clozapine and made suggestions for change that might simplify its use.[1] There are additional considerations that affect continued use of the drug. Diagnosis of possibly impending agranulocytosis is of course important, but treatment is now vastly improved compared with 30 years ago. In addition to its use when a fall in white cell count (WCC) has necessitated stopping clozapine, granulocyte colony-stimulating factor may be used to maintain WCC in circumstances where progression to a 'red' result would otherwise lead to clozapine discontinuation. Even a simple measure such as taking a blood sample in the afternoon may be helpful.[2] Once clozapine has been stopped, a dilemma may arise as to whether it may be restarted with due caution and appropriate monitoring.

Clozapine has a marked hypotensive effect in clozapine-naive subjects; hence, cautious dose titration is mandatory when initiating and restarting the drug.[3,4] However, the time taken to lose tolerance to this hypotensive effect after stopping clozapine is unknown. A cautious (and indeed arbitrary) time to loss of tolerance of 48 h has been adopted based on estimates of the terminal clozapine plasma half-life of 12 h (range: 6 to 26 h).[3] Thus, if it is thought that clozapine has not been taken for more than 2 days, the Summary of Product Characteristics[3] specifies that patients should be re-titrated starting from 12.5 mg clozapine once or twice daily.

Such treatment breaks may occur for a variety of reasons, including precautionary withdrawal of therapy because of concerns about haematological toxicity, often but not always initiated by the regular blood monitoring specified in the product licence.[1] Other reasons include evidence or suspicion of patient non-adherence in the preceding days, transfer between care providers leading to a break in supply of the drug, and admission to an acute medical unit. In these latter circumstances, patients may take up an in-patient bed for weeks or, even worse, relapse and require compulsory treatment.[5] An extra complication is that of the UK bank holidays, when the supply chain may be effectively closed for 96 h, for example, over Easter.

If clozapine was withdrawn as a result of either suspected impending or actual agranulocytosis, restarting the drug if it is thought that clozapine may not have been the cause of the low WCC has to be undertaken with all due caution. However, in instances where it is clear that the treatment break was not due to haematological concerns, it is stated that patients may be re-titrated to their previously established dose at a faster rate than someone taking clozapine for the first time, if it is safe to do so.[3] Such patients must have had a satisfactory full blood count not more than 10 days before restarting clozapine. An electrocardiogram should be performed before resuming treatment, and blood test frequency should revert to weekly for 6 weeks if there has been a break of more than 72 h (Denzapine, Zaponex) or 96 h (Clozaril).

After 6 weeks, patients may resume their previous blood sampling schedule if authorised to do so by the relevant monitoring service, although this may be overcautious.[6] All this is stressful for patients and adds to staff workload, assuming of course that the patient is willing to undergo re-titration. The process is justified if the treatment break has been for clinical reasons, but there is much less justification if the 48 h rule has been transgressed simply because of a failure in the supply of the drug. There is also the risk of clinical disaster (https://www.bbc.co.uk/news/uk-england-somerset-32997527).

We now know from population pharmacokinetic analyses using therapeutic drug monitoring (TDM) data that the clozapine plasma half-life in a non-smoking White male of age 40 years and body weight 70 kg averages 36 h, whereas the *N*-desmethylclozapine (norclozapine) half-life averages 69 h.[7] These half-lives mean that given initial plasma clozapine and norclozapine concentrations of 0.35 and 0.25 mg/L, respectively, clozapine and norclozapine would still be detectable in plasma (limit of accurate measurement 0.01 mg/L) for 1 and 2 weeks, respectively, in the absence of further clozapine dosage.

The plasma half-life of clozapine is 30–50% shorter in smokers and also shorter in younger people and those of African–Caribbean ancestry; moreover, it is around 20% longer in women and also longer in older people and those of Asian ancestry.[7] Thus, even allowing for a half-life of 18 h in a young male smoker, and given the situation outlined above (initial plasma clozapine of 0.35 mg/L), clozapine would still be detectable in plasma 90 h after the last dose, and norclozapine would be detectable for a proportionally longer time. Given these data, and the fact that there has been little research into the events leading to loss of tolerance once clozapine has been withdrawn, we suggest that the elapsed time between the last dose of the drug and the time specified at which to initiate re-titration should be re-evaluated. The current pharmacokinetic data suggest that an elapsed time of 96 h should be considered, provided that the time and date of the last clozapine dose are known with confidence.

Finally, TDM audit data have shown that 1–2% of samples sent for analysis do not contain clozapine. Although it is possible that some non-adherent patients may collapse and perhaps die if given their normal dose of the drug, such events must be rare.[8,9] The availability of a point-of-contact test or rapid turnround (TDM) assay of appropriate selectivity and sensitivity would help to assess adherence before clozapine dosage if adherence is in doubt. A simple qualitative test using oral fluid would suffice if such a device were available. Oral fluid has several advantages over blood, even capillary blood, for qualitative work (relatively low infectivity, non-invasive collection and ease of collection).



https://doi.org/10.1192/bjp.2025.21 Published online by Cambridge University Press

## Funding

None.

## Declaration of interest

The authors declare no conflict of interest

**Robert James Flanagan**, Precision Medicine, Networked Services, Bessemer Wing, King's College Hospital NHS Foundation Trust, London, UK; **Susanna Every-Palmer**, Department of Psychological Medicine, University of Otago, Wellington, New Zealand

**Correspondence:** Robert James Flanagan. Email: robert.flanagan@nhs.net

## References

1 Fernandez-Egea E, McCutcheon RA. Clozapine monitoring requirements: is it time for an update? *Br J Psychiatry* 2025; **226**: 1–3.

2 Hathaway DB, Frankenburg F. Diurnal variability in neutrophil counts in clozapine treatment: a case report and review of the literature. *J Clin Psychopharmacol* 2019; **39**: 506–8.

3 Electronic medicines compendium (emc). *Clozaril 25 mg Tablets*. emc, 2024 (https://www.medicines.org.uk/emc/product/4411/smpc#gref [cited 14 Oct 2024]).

4 Stanworth D, Hunt NC, Flanagan RJ. Clozapine—a dangerous drug in a clozapine-naïve subject. *Forensic Sci Int* 2012; **214**: e23–5.

5 John AP, Burrows S, Stanley S, Acabo C, Shymko G, Jaworska A, et al. Demographic and clinical characteristics of patients who recommence clozapine following therapy interruptions. *Acta Psychiatr Scand* 2022; **145**: 293–300.

6 Northwood K, Myles N, Clark SR, Every-Palmer S, Myles H, Kisely S, et al. Evaluating the epidemiology of clozapine-associated neutropenia among people on clozapine across Australia and Aotearoa New Zealand: a retrospective cohort study. *Lancet Psychiatry* 2024; **11**: 27–35.

7 Reeves S, Bertrand J, Obee SJ, Hunter S, Howard R, Flanagan RJ. A population pharmacokinetic model to guide clozapine dose selection, based on age, sex, ethnicity, body weight and smoking status. *Br J Clin Pharmacol* 2024; **90**: 135–45.

8 Khan Z, Miller EA, Pervaiz AM. Clozapine intoxication in a patient on chronic use with a short-term noncompliance. *Cureus* 2021; **13**: e16578.

9 Leung JG, Rakocevic DB, Courtis SN, Leloux MR, Allen ND. Iatrogenic clozapine intoxication after hospital admission: a case-based rationale for an inpatient pharmacy clozapine monitoring service. *J Am Pharm Assoc* 2022; **62**: 1711–6.



https://doi.org/10.1192/bjp.2025.21 Published online by Cambridge University Press