

# 18 - References

## References

882 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 11 References

1. Varma S, et al. Clozapine-related EEG changes and seizures: dose and plasma-level relationships. *Ther Adv Psychopharmacol* 2011; 1:47-66.
2. Northwood K, et al. Optimising plasma clozapine levels to improve treatment response: an individual patient data meta-analysis and receiver operating characteristic curve analysis. *Br J Psychiatry* 2023; 222:241-245.
3. Tralongo F, et al. Association between clozapine plasma concentrations and treatment response: a systematic review, meta-analysis and individual participant data meta-analysis. *Clin Pharmacokinet* 2023; 62:807-818.
4. Bogers J, et al. Feasibility and effect of increasing clozapine plasma levels in long-stay patients with treatment-resistant schizophrenia. *J Clin Psychopharmacol* 2023; 43:97-105.
5. Yusufi B, et al. Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. *Int Clin Psychopharmacol* 2007; 22:238-243.
6. Malik S, et al. Sodium valproate and clozapine induced neutropenia: a case control study using register data. *Schizophr Res* 2018; 195:267-273. Table 11.4 (Continued ) Plasma concentration Response status Tolerability status Suggested action

“ 1000mcg/L Poor Poor Add antiseizure drug. Attempt augmentation. Reduce dose to give level of <1000mcg/L. Consider abandoning clozapine treatment. Poor Good Add antiseizure drug. Attempt augmentation. If augmentation successful, reduce dose to give level <1000mcg/L. If unsuccessful, consider abandoning clozapine treatment. Good Poor Add antiseizure drug. Attempt slow dose reduction to give plasma level <1000mcg/L. Good Good Add antiseizure drug. Monitor closely; attempt dose reduction only if tolerability declines. Notes Poor response No response or unsatisfactory response to clozapine. For example, not sufficiently well to be discharged. Good response Obvious positive changes related to use of clozapine. Patient likely to be suitable for discharge to either supported or unsupported care in the community. Poor tolerability Dose constrained by adverse effects such as tachycardia, sedation, hypersalivation, hypotension, etc. (see Chapter 1 for suggestions of treatment for adverse effects). Good tolerability Patient tolerates treatment well and there are no signs

of serious toxicity. Augmentation Adding another antipsychotic or mood stabiliser (see Chapter 1). In all situations, ensure adequate treatment for clozapine-induced constipation. Constipation is dose-related. Ensure regular bowel movements and record bowel function. Stimulant laxatives such as senna are required (see Chapter 1). Seizures are dose- and plasma level-dependent. Suitable antiseizure agents are valproate, lamotrigine and, rarely, topiramate. Use lamotrigine if response is poor; valproate if affective symptoms are present (see Chapter 2). Note that use of valproate increases risk of neutropenia with clozapine.<sup>6</sup> Both valproate and topiramate are contraindicated in women of child-bearing age. \*This table applies to results for patients on a stable clozapine dose with confirmed good adherence. †Antiseizure drugs should usually be used in patients whose plasma level exceeds 600mcg/L, unless EEG is normal, and in those with lower plasma levels who experience clozapine-induced seizures.

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Revision #1

Created 2026-01-04 20:18:10 UTC by Omar Ayman

Updated 2026-01-04 20:18:10 UTC by Omar Ayman