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REFRESHMENT

Management of sedation due to clozapine

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SUMMARY

Sedation is one of the most common adverse effects of clozapine. Although tolerance develops to some extent, a significant proportion of patients continue to experience sedation and associated negative consequences on their quality of life. Sedation is also one of the most common reasons for the discontinuation of clozapine and it is therefore important to proactively manage it. This article provides brief guidance for clinicians.

KEYWORDS

Clozapine; adverse effects; sedation; drug interactions and side-effects; antipsychotics.

Clozapine is the only evidence-based option for people with treatment-resistant schizophrenia. However, clozapine is associated with a wide array of adverse effects, ranging from infrequent but potentially serious threats such as myocarditis and agranulocytosis to common and distressing ones such as sedation and hypersalivation.

Prevalence and impact

The most common side-effect of clozapine is sedation. A wide range of prevalence is reported in the literature (16–67%). The reason for such a wide range reflects the differing terminology used in clinical trials to identify adverse effects, such as somnolence, fatigue, dizziness and drowsiness. Sedation may be a desirable effect for managing the acute phase, but over the longer term it can be detrimental to quality of life. Sedation might also contribute to other negative outcomes, such as aspiration pneumonia and venous thromboembolism.

Individuals on long-term clozapine report sedation as the one of the most disturbing adverse effects, apart from hypersalivation and constipation (Gurcan 2021). It is also one of the most common reasons patients give for discontinuation of clozapine (Legge 2016). For these reasons, sedation must be proactively managed.

Pathophysiology

The sedative effect of clozapine appears soon after administration. It is primarily mediated through a dose-dependent antagonistic effect on histamine 1 receptors and its anticholinergic effect. However, significant interindividual variability is seen in sedation severity, owing to histamine 1 receptor polymorphism or varying bioavailability. There is also significant interindividual variability in degree of tolerance (Meyer 2020).

The sedative effect of clozapine is also influenced by factors such as age, exercise, smoking, caffeine, concomitant sedative drugs, illicit drug use and negative symptoms of schizophrenia.

Clinical assessment

Patients on clozapine should be regularly counselled about sedation and other clinically significant adverse effects. Prolonged sleep at night (>9 h) is a good proxy measure. Validated adverse effects scales such as the Glasgow Antipsychotic Side-effects Scale for Clozapine (GASS-C) should be used to improve the recognition.

Management

First, do a thorough assessment of psychiatric and physical health and lifestyle factors. Specifically, consider stopping other sedative drugs, if possible (benzodiazepines, hypnotics, opioid analgesics, sedative antidepressants and anticholinergic drugs). Sedation during the initial titration of clozapine should prompt slowing down the titration. Clinicians should endeavour to treat patients with the minimum effective dose. The summary of product characteristics (SmPC) for clozapine gives the recommended dose range for acute treatment as 200–450 mg/day (maximum: 900 mg/day) (electronic medicines compendium 2020). However, owing to varying bioavailability and adverse effects, there is increasing consensus to use therapeutic drug monitoring to decide the target dose (Meyer 2020; Chakrabarti 2021).

For sedation occurring during the maintenance phase, consider giving clozapine only at night. Owing to its half-life (mean terminal half-life: 12 h), ideally, it should be administered twice daily. However, a single dose of up to 500 mg can be given at night (Meyer 2020). If an individual is on a higher dose, then consider giving a larger part of the dose at night. In North America, most patients

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BOX 1 Handy hints to manage sedation due to clozapine

- Try to treat with the minimum effective dose, supported by therapeutic drug monitoring (0.35–0.50 mg/L)
- Consider stopping other sedative and anticholinergic medications
- Consider giving a higher dose of clozapine at night or as a single night-time dose (up to 500 mg/day).
- During the maintenance phase: if asymptomatic then consider careful dose reduction; if symptomatic then consider adding aripiprazole

are given clozapine as a single night-time dose with no suggestion of reduction in effectiveness (Takeuchi 2016).

Another option is to reduce the clozapine dose. The SmPC does not specify the maintenance dose. However, it recommends that, once the maximum therapeutic benefit has been achieved, most people can be maintained effectively on lower doses with careful downward titration.

If dose reduction is not possible, other options include augmenting with aripiprazole, methylphenidate, modafinil or fluvoxamine. However, evidence for these, except aripiprazole, is extremely limited. A few trials were conducted to test the addition of aripiprazole to clozapine. No significant improvement in psychotic symptoms occurred but improvement in the management of sedation and other metabolic parameters was observed (Meyer 2020; Chakrabarti 2021). The addition of fluvoxamine has also been tried as a method to reduce the metabolism of clozapine and thus decrease the oral dose. However, the evidence is restricted to case reports. This is also the case with the addition of stimulant drugs such as methylphenidate and modafinil. Methylphenidate might worsen psychosis, so one must be careful.

Box 1 summarises key points on management.

Author contributions

S.G. conceived the idea. S.G. and S.M.P. co-wrote the manuscript.

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