BJPsych | The British Journal of Psychiatry (2025) 226, 53–54. doi: 10.1192/bjp.2024.232

Commentary

Clozapine, relapse and adverse events: 10-year electronic cohort study in Canada: commentary, Kikuchi

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Keywords
Clozapine; relapse; adverse events; cohort study; Canada.

Response

I read with great interest the paper by Balbuena et al that investigated the impact of clozapine on the risk of readmission to hospital owing to psychiatric symptoms or adverse effects, based on 10 years of electronic records in Canada.[1] The study found that, compared to other antipsychotics, clozapine was associated with a reduced risk of psychiatric readmission to hospital after the initial 21 months in the adult cohort, a higher risk of readmission to hospital owing to adverse effects in the adult cohort and a lower risk of psychiatric readmission to hospital in the child or youth cohort. However, I would like to highlight some methodological concerns that may affect the interpretation of these results.

First, the study did not consider the clinical diagnosis or indication for treatment of the patients in the cohort. The patient diagnoses included in the study were diverse, with 49% of the adult cohort and 72% of the child or youth cohort diagnosed with bipolar disorder. The number of patients treated with clozapine and their diagnoses were not clearly stated. In addition, the number of patients treated with other antipsychotics and their diagnoses were not reported. Furthermore, the study did not account for confounding by indication, which arises because of the more severe conditions of patients treated with clozapine. To address this, previous studies have conducted within-individual analyses,[2–4] focused on patients with treatment-resistant schizophrenia[5] or adjusted as much as was feasible for covariates that could reflect the disease severity.[6,7] The Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders 2018 guidelines for the management of patients with bipolar disorder support the use of clozapine in treatment-resistant bipolar disorder. Therefore, although it was not inappropriate to include patients with bipolar disorder, it is necessary to compare clozapine treatments with other antipsychotic treatments, stratified by patient diagnosis and disease severity. Given that clozapine is the most well-established treatment for treatment-resistant schizophrenia, its efficacy may have been underestimated. In the study by Balbuena et al, it would be more appropriate to compare clozapine treatments with other antipsychotic treatments among patients with schizophrenia who have used clozapine or to conduct within-individual analyses.

Second, admissions to hospital owing to adverse reactions were limited to neutropenia, cardiomyopathy, myocarditis, pneumonia and constipation. However, given that these adverse effects are relatively more common with clozapine than with other antipsychotics, the number of admissions to hospital attributed to the adverse effects of clozapine may be relatively overestimated. A previous Finnish registry study, which included all somatic and cardiovascular admissions to hospital, did not find that clozapine was associated with significantly more somatic readmissions to hospital than other antipsychotics.[4] Recent studies indicate that clozapine is associated with a higher risk of pneumonia[8,9] and ileus,[9] which may align with Balbuena et al's findings. Furthermore, the risk of several clozapine-related adverse effects, including pneumonia, increases with age;[8,9] thus, it may have been beneficial to stratify the adult cohort by age in this study.

Third, this study did not analyse the period of antipsychotic non-use. A total of 10 952 (19%) adults and 683 (32%) children and adolescents were excluded from the analysis because they experienced a relapse or admission to hospital owing to adverse events before antipsychotic medication was prescribed. In addition, readmissions to hospital that occurred after a prescription had been interrupted for >1 month were excluded based on the interpretation that it was not related to any drug. Given the notable impact of nonadherence on relapse, this exclusion was significant. There may be some debate about how to set the length of the interruption period. However, if there were more interrupted prescriptions for antipsychotics other than clozapine, the relapse of antipsychotics other than clozapine could have been underestimated. Moreover, the study does not describe how long-acting injections were administered. Categorising the duration of antipsychotic non-use medications might have allowed for a more comprehensive analysis.

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First received 24 Sep 2024, revised 9 Oct 2024, accepted 10 Oct 2024

Data availability

Data availability is not applicable to this article, as no new data were created or analysed in this study.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

None.

https://doi.org/10.1192/bjp.2024.232 Published online by Cambridge University Press

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https://doi.org/10.1192/bjp.2024.232 Published online by Cambridge University Press