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Discussing clozapine adverse effects and monitoring strategies: a focus on ethnic diversity

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We read with great interest the article by Goldani et al.,[1] which found that clozapine did not increase neutropenia risk in a sample of 5,847 psychiatric patients – 1,038 on clozapine – from Hospital de Clínicas de Porto Alegre. The study design was retrospective; data were collected from electronic medical records (EMR). Cox regression analysis identified ethnicity (specifically non-Hispanic white) and absolute neutrophil count (ANC) $>$ 2,000/μL during the first year of monitoring as protective factors against neutropenia. Presence of severe medical conditions was a risk factor, while clozapine use was not. These data hold considerable significance; nonetheless, we have some concerns about the conclusions drawn therefrom.

First, we have reservations about its external validity to inform updates of nationwide monitoring strategies. Porto Alegre is the capital of Rio Grande do Sul, a southern state of Brazil, with most of its population descending from European immigrants. More than 85% of the Goldani et al. sample comprised white non-Hispanics. This is not representative of the Brazilian population – with only 43% of white ethnicity and over 50% of self-declared black or mixed ethnicity according to the last national survey, conducted in 2021[2] –, which could lead to bias, such as a different incidence of benign ethnic neutropenia (BEN). BEN is knowingly associated with African, Arabian and Mediterranean ancestry, and could potentially lead to lower ANC at baseline and/or after treatment initiation.[3]

The absolute risk of low ANC consistently showed higher numerical values in the clozapine group. Limitations related to study design – retrospective, EMR-based – and power should be taken into account when interpreting the results as a lack of association between clozapine and moderate neutropenia. We have concerns over the possible clinical translation to psychiatric practice of such statements.

Despite these issues, we agree with the article's fundamental conclusions. Agranulocytosis is indeed a relatively infrequent adverse event – with a reported incidence of 0.9%[4] – and excessive precaution should not preclude the prescription of clozapine to patients in need. In a recent review of monitoring strategies worldwide, countries with the highest rates of clozapine usage[5] were among those with the least stringent monitoring guidelines.[6] These findings reinforce the idea that modifying monitoring strategies could enhance access to clozapine treatment.

On the other extreme, there have been claims that monitoring should be restricted to the first months of clozapine administration.[4] Against this suggestion stands evidence that, though less frequent, late-onset hematological effects of clozapine should still be a concern, with little more than 10% of agranulocytosis occurring after the second year of treatment.[7]

Taking all this into account, we support evidence-based flexibilizations of the monitoring strategy to improve accessibility and prescription of clozapine to at-risk populations, while acknowledging the risk of neutropenia arising from this prescription. In this regard, we believe that additional data from a more ethnically representative sample of the diverse Brazilian population is needed to support more generalizable treatment monitoring guidelines – which should also consider specificities when defining ANC thresholds, such as for patients with BEN.

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Disclosure

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