Trends
in Psychiatry and Psychotherapy

JOURNAL ARTICLE PRE-PROOF
(as accepted)

Brief Communication

Hematological Changes in Clozapine Users: A Study in a Brazilian Community Sample

Natalia Daher, Mateus Diniz, Renan Biokino, Pedro Lorencetti, Carolina Ziebold, Raffael Massuda, Ary Gadelha

http://doi.org/10.47626/2237-6089-2024-0967

Original submitted Date: 01-Oct-2024

Accepted Date: 10-Dec-2024

Hematological Changes in Clozapine Users: A Study in a Brazilian Community Sample

Running title: Hematological Changes in Clozapine Users in Brazil

Natalia Daher[1,3], Mateus Diniz[4], Renan Biokino[1,3], Pedro Lorencetti[1,3], Carolina Ziebold[1,3], Raffael Massuda[2], Ary Gadelha[1,3]

[1]Departamento de Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM/UNIFESP), São Paulo, SP, Brazil.
[2]Universidade Federal do Paraná (UFPR), PR, Brazil.
[3]Programa de Esquizofrenia, Escola Paulista de Medicina, Universidade Federal de São Paulo (PROESQ-EPM/UNIFESP), São Paulo, SP, Brazil.
[4]Pax Clínica Instituto de Psiquiatria, Brazil.

Corresponding Author: Dra Natália Daher
natalia.daher@unifesp.br
Rua Botucatu, 740 - São Paulo 04021-001

ABSTRACT

Introduction: Clozapine is the only antipsychotic with proven superior efficacy for treatment-resistant schizophrenia. However, global utilization rates remain suboptimal due to concerns about hematological side effects. This study aimed to investigate hematological abnormalities among clozapine users at a large community center in the Brazilian countryside.

Methods: This study adopts a real-world approach and was conducted based on a retrospectively analyzed complete blood counts from clozapine users in Goiás, Brazil. We describe the total number and percentage of participants presenting blood dyscrasias. Logistic regression models, using Stata v.18, were employed to evaluate whether sex or age were associated with the presentation of neutropenia.

Results: Data from 6,160 complete blood counts from 486 patients taken between

2011 and 2018 were analyzed. Blood dyscrasias were observed in 37.4% of patients, with anemia being the most common (23.6%), followed by thrombocytopenia (9.46%) and eosinophilia (13.7%). Neutropenia occurred in 4.52% of patients, primarily mild (3.9%) and moderate (0.62%), with no cases of agranulocytosis identified.

Discussion: Clozapine users showed a higher prevalence of blood dyscrasias compared to the overall Brazilian population. Most cases of neutropenia were mild and transient. Our results suggest a lower risk of severe neutropenia and emphasize the need to investigate other blood dyscrasias.

Keywords: Clozapine; neutropenia; hematological monitoring; blood dyscrasias; agranulocytosis;

INTRODUCTION

Treatment resistance affects approximately 36.7% of patients with schizophrenia.[1] Clozapine is the only superior antipsychotic for treatment-resistant patients, but its use remains suboptimal across numerous countries globally.[2] A prevailing factor contributing to this underutilization, as frequently cited by both patients and healthcare professionals, pertains to concerns regarding the risk of agranulocytosis and the requirement for regular blood testing.[3]

Clozapine use has been associated with heightened risk for blood dyscrasias.[4] Despite such concerns, severe adverse hematological effects are relatively rare.[5] Moreover, most available data come from high-income countries. Even in Brazil, findings are restricted to few centers that do not reflect outpatient, community services.[6]

The present study seeks to verify the frequency of hematological changes in a large sample of patients prescribed clozapine at a public health service in the State of Goiás.

METHODS

This study adopts a real-world approach and was conducted based on a retrospectively analyzed complete blood counts (CBCs) from clozapine users in Goiás, Brazil, who were monitored at the High-Cost Drug Center (CEMAC) Juarez Barbosa, the state's reference center for clozapine dispensation. Data were collected from 2011 to 2018, focusing on patients diagnosed with chronic psychotic disorders.

The study included all patients who received clozapine from the distribution center during the study period and had at least one CBC available. Incomplete data or lack of CBC tests during the follow-up period led to exclusion from the study. The data collected included anonymized patient identification, sex, and ethnicity. CBCs were conducted at various laboratories in Goiânia, chosen by the patients, although the test's automated and standardized nature minimized variability between labs.

The analysis identified hematological abnormalities such as leucopenia (white blood cell count <4,000 cells/µL), mild neutropenia (neutrophil count <1,500 cells/µL), moderate neutropenia (1,000-500/ L), agranulocytosis (neutrophil count <500 cells/µL). Blood dyscrasias were described by total number and percentage of affected participants.[7]

Data analysis

We describe the total number and percentage of participants presenting blood dyscrasias (neutropenia, eosinophilia, anemia, and thrombocytopenia). Logistic regression models, using Stata v.18, were employed to evaluate whether sex (female vs. male) or age (in years) were associated with the presentation of neutropenia (dichotomous outcome). A p-value <0.05 was considered as statistically significant.

RESULTS

The study sample comprised 486 patients, monitored between 2011 and 2018, who underwent a total of 6,160 complete blood counts (CBCs). The mean age was 44 (SD=12.9), ranging from 16 to 73 years, and approximately 60% were male. The number of blood counts per patient varies, with some having only one and others having up to 24.

Concerning patients, 37.4% showed blood dyscrasias in at least one blood count, of which 23.6% had anemia, and 9.46% had thrombocytopenia. Eosinophilia was seen in 13.7% of cases. Neutropenia rates were 4.52%, with mild neutropenia being observed in 3.9%, moderate neutropenia in 0.62%, and no cases of severe neutropenia or agranulocytosis were found.

Out of the 486 patients, 22 developed neutropenia. Among these, 9 (40.9%) experienced recurrent mild neutropenia in more than one blood test. Only 2 patients (9%) had recurrent episodes of moderate neutropenia, while none experienced severe

neutropenia at any point. In most cases, neutropenia occurred during the first year of clozapine treatment.

The dependent variable was the occurrence of neutropenia, categorized as "yes" when present and "no" when absent. The independent variables included patient age and biological sex, all of which were collected as categorical or ordinal measures. A logistic regression analysis was performed to investigate the factors associated with neutropenia in patients using clozapine. The independent variables were introduced into the logistic regression model non-simultaneously. No significant difference was seen for neutropenia between male and female patients (OR: 1.33, 95% CI = 0.53-3.33, p = 0.538). Furthermore, no statistically significant differences were observed across patients' age in relation to the occurrence of neutropenia (OR: 0.98, 95% CI = 0.95-1.01, p = 0.204).

DISCUSSION

We found a higher rate of blood dyscrasias in patients receiving clozapine compared to the overall population.[7] Dyscrasias affected all hematopoietic lines, most commonly affecting red blood cells and platelets. The neutropenia rate in our sample was like estimates for the Brazilian population[6], but no cases of severe neutropenia were identified.

The prevalence of anemia varies greatly depending on the patient's age and gender, being more common in women of childbearing age and children. It is also influenced by nutritional issues and social vulnerability. In our study, in relation to the total number of patients, we found an anemia rate of 23.6%. As 60% of patients were male and the average age was 44 years, we would expect a prevalence of anemia of around 10%.[8] It is likely that such rate is related to the low socioeconomic level and nutritional deficiency, commonly seen in patients with schizophrenia.[9] In this sense, anemia may not be caused by clozapine, but its detection should lead to a more complete investigation and, if necessary, nutritional supplementation.

The incidence of eosinophilia in clozapine-treated patients reported in the literature varies greatly from 0.2% up to as much as 62%.[10] In our sample, the rate was similar to that in literature reports.[11] Eosinophilia was usually mild and transient, occurring only once in most patients. It is important to keep in mind that eosinophilia can occur due to other factors as well, such as parasites and allergic reactions. The incidence of eosinophilia may also be of concern, as eosinophilia is believed to be an

important marker of potentially serious inflammatory conditions in patients on clozapine.[12] In some cases, it can predict subsequent neutropenia, myocarditis, eosinophilic colitis, pancreatitis, and toxic hepatitis, and is therefore not without risk.[12]

Neutropenia is a known adverse effect of clozapine therapy, often requiring close monitoring and treatment discontinuation.[2] The overall neutropenia rate found in our study was similar to that reported in literature.[13] Most neutropenia cases were mild and transient, with no cases of severe neutropenia or agranulocytosis identified in our sample. The incidence of clozapine-associated neutropenia ranges from 2.7% to 5.2% and the rates of agranulocytosis range from 0.7% to 1.1%, depending on factors such as the studied population, medication dosage, and treatment duration.[13] As most of our patients are older, our lower severe neutropenia may reflect a smaller proportion of patients with recent usage of clozapine, thus reducing the proportion of more severe cases. From another perspective, for some patients, we had very long tracks of blood tests, which suggests long-time safety under community settings. These findings are consistent with previous literature, suggesting that severe neutropenia and agranulocytosis, while potentially serious adverse effects of clozapine, are relatively rare occurrences.[5]

Other South American countries (e.g., Chile, Argentina) have reported neutropenia prevalence and incidence in their national registries of clozapine use.[14,15] Nevertheless, in the last 5 years, only one study reported the prevalence of neutropenia in clozapine users in Brazil, comprising 1,038 patients on clozapine, finding a rate of 5.3% neutropenia and 0.77% severe neutropenia.[6] The overall neutropenia rate was similar to that of our study, but no cases of severe neutropenia were found in our sample. One reason may be the lower number of subjects, which can justify random differences considering the rarity of the event. Another possible explanation is ethnic differences. Goiás encompasses a highly admixed population with a larger proportion of Native Americans than Porto Alegre, a city of relevant European immigration and a small non-admixed African ancestry subgroup. The third possible explanation concerns the setting, in Goiás, all subjects were outpatients, whereas in Porto Alegre patients were from a university center, usually receiving more complex patients.

In conclusion, our study provides valuable insights into the frequency and clinical implications of hematological abnormalities among patients on clozapine therapy. The extended follow-up period and the low rate of moderate recurrent

neutropenia observed in our study underscore the safety and tolerability of clozapine as a treatment option for patients with treatment-resistant schizophrenia. These findings contribute to a better understanding of the hematological risks associated with clozapine use and inform clinical decision-making regarding the management of patients receiving this drug. Further research is warranted to elucidate the underlying mechanisms and risk factors associated with hematological adverse effects in clozapine-treated individuals.

Limitations

Our results must be considered under some limitations. As we used data available from a clinical setting, we do not have a probabilistic sample. Moreover, not all patients had their blood tests available, for administrative reasons. We have no indication of a systematic pattern to justify the blood tests made available, but we cannot rule out this possibility either. However, the long track of tests, the sample size considering previous Brazilian and Low- or Middle-Income Country studies and the community setting, reinforce the strength of our report. The lack of additional clinical information about the patients, such as age of onset, socio-economic variables, prior medication use, prevented us from looking for a more detailed risk profile to blood dyscrasias in Brazil. Even though we were able to identify differences across gender and age, this needs to be further explored in the future.

Acknowledgments

This study was not supported by any funding. The authors would like to thank CEMAC - Centro de Medicamentos de Alto Custo (High-Cost Drug Center) Juarez Barbosa for providing the data used in the study.

Disclosure

RM has been a consultant/advisor and/or has received honoraria from Daiichi-Sankyo, Janssen, and Boehringer Ingelheim. AG has been a consultant/advisor and/or has received honoraria from Aché, Daiichi-Sankyo, Cristália, Janssen, and Lundbeck. The other authors report no conflicts of interest.

Author contributions

AG designed the study. MD collected the data. ND analyzed the data. ND, AG and RB were responsible for writing the original draft and for review and editing. RM, PL and MD contributed to the literature search, writing, interpretation, and conceptualization. CZ contributed to statistical analysis and writing. All authors contributed to the article, read and approved the final version submitted, and take public responsibility for all aspects of the work.

Handling Editor: Dr. Ives Passos

REFERENCES

1. Diniz E, Fonseca L, Rocha D, Trevizol A, Cerqueira R, Ortiz B, et al. Treatment resistance in schizophrenia: a meta-analysis of prevalence and correlates. Braz J Psychiatry. 2023;45:448-58. doi: 10.47626/1516-4446-2023-3126.
2. de Leon J, Schoretsanitis G, Smith RL, Molden E, Solismaa A, Seppälä N, et al. An International Adult Guideline for Making Clozapine Titration Safer by Using Six Ancestry-Based Personalized Dosing Titrations, CRP, and Clozapine Levels. Pharmacopsychiatry. 2022;55(2):73-86. doi: 10.1055/a-1625-6388.
3. Verdoux H, Quiles C, Bachmann CJ, Siskind D. Prescriber and institutional barriers and facilitators of clozapine use: A systematic review. Schizophr Res. 2018;201:10-9. doi: 10.1016/j.schres.2018.05.046.
4. Silva E, Legge S, Casetta C, Whiskey E, Oloyede E, Gee S. Understanding clozapine-related blood dyscrasias. Developments, genetics, ethnicity and disparity: it's a CIN. BJPsych Bull. 2024;1-6. doi: 10.1192/bjb.2024.38.
5. Magistri C, Mellini C. Clozapine-Associated Agranulocytosis. J Clin Psychopharmacol. 2023;43(6):527-33. doi: 10.1097/JCP.0000000000001765.
6. Goldani AAS, Rabelo-da-Ponte FD, Feiten JG, Lobato MIR, Belmonte-de-Abreu PS, Gama CS. Risk of neutropenia among clozapine users and non-users: results from 5,847 patients. Braz J Psychiatry. 2022;44(1):21-5. doi: 10.1590/1516-4446-2021-1765.
7. Dacie and Lewis – Practical Haematology. 12th ed. 2017.
8. Machado ÍE, Malta DC, Bacal NS, Rosenfeld LGM. Prevalência de anemia em adultos e idosos brasileiros. Rev bras epidemiol [Internet]. 2019;22 .SUPL.2. Available from: https://doi.org/10.1590/1980-549720190008.supl.2.

9. Siafis S, Brandt L, McCutcheon RA, Gutwinski S, Schneider-Thoma J, Bighelli I, Kane JM, Arango C, Kahn RS, Fleischhacker WW, McGorry P, Carpenter WT, Falkai P, Hasan A, Marder SR, Schooler N, Engel RR, Honer WG, Buchanan RW, Davidson M, Weiser M, Priller J, Davis JM, Howes OD, Correll CU, Leucht S. Relapse in clinically stable adult patients with schizophrenia or schizoaffective disorder: evidence-based criteria derived by equipercentile linking and diagnostic test accuracy meta-analysis. Lancet Psychiatry. 2024;11(1):36-46. doi:10.1016/S2215-0366(23)00364-4.
10. Silva E, Higgins M, Hammer B, et al. Clozapine rechallenge and initiation despite neutropenia: a practical, step-by-step guide. BMC Psychiatry. 2020;20(1):1-9.
11. Chatterton R. Eosinophilia after commencement of clozapine treatment. Aust N Z J Psychiatry. 1997;31:874-6.
12. Das S, Itrat A, Hernandez MET, et al. Clozapine-induced eosinophilia: A case report. SAGE Open Med Case Rep. 2023;11:2050313X231195961. doi: 10.1177/2050313X231195961.
13. Myles N, Myles H, Xia S, Large M, Kisely S, Galletly C, et al. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. Acta Psychiatr Scand. 2018;138:101-9.
14. Mena CI, Nachar RA, Crossley NA, González-Valderrama AA. Clozapine-associated neutropenia in Latin America: incidence report of 5380 Chilean users. Int Clin Psychopharmacol. 2019;34:257-63.
15. Balda MV, Garay OU, Papale RM, Bignone I, Bologna VG, Brandolini A, et al. Clozapine-associated neutropenia and agranulocytosis in Argentina (2007-2012). Int Clin Psychopharmacol. 2015;30:109-14.