

## BRIEF COMMUNICATION

# Clozapine prescription trends in Brazil in the last decade

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**Objective:** Clozapine is a second-generation antipsychotic indicated for treatment-resistant schizophrenia. Studies in several countries have shown a low rate of clozapine use despite the fact that approximately 30% of schizophrenia cases are treatment-resistant. In Brazil, few studies have addressed the frequency and variety of antipsychotic use in individuals diagnosed with schizophrenia (ICD F20). The objective of this study was to measure the rates of clozapine use in this population in the last decade using Brazilian Ministry of Health data.

**Methods:** Prescriptions made between 2010 and 2020 in all 26 states and the Federal District registered at the Outpatient Information System Database from the Brazilian Health System (SIASUS) were evaluated.

**Results:** A total of 25,143,524 prescriptions were recorded in this period, with clozapine representing 8.86% of all antipsychotics. The most frequently prescribed antipsychotic for patients with schizophrenia was olanzapine (35.8%), followed by quetiapine (27.5%). From 2010 to 2020, the rate of clozapine prescriptions in Brazil increased from 7.2% to 10.9%.

**Conclusions:** Despite a slight increase in prescriptions in the last decade, clozapine is still underutilized in Brazil.

**Keywords:** Clozapine; schizophrenia, treatment-resistant; antipsychotics

## Introduction

Clozapine is a second-generation antipsychotic specifically indicated for treatment-resistant schizophrenia (TRS), a condition that affects approximately 30% of patients with schizophrenia, defined as insufficient response after two adequate trials with non-clozapine antipsychotics.<sup>1</sup> Compared to other drugs, the remission and response for clozapine are superior in patients who fail to respond to regular antipsychotics, and it is associated with lower risk of suicidal behavior and aggression. Correct identification of TRS and prescription of clozapine is a key strategy for improving schizophrenia outcomes.

Recent data from cohort studies have shown that clozapine is associated with reduced hospitalizations, lower medication discontinuation, and decreased risk of suicide.<sup>2,3</sup> However, despite its superior profile, clozapine has been largely underutilized, and its prescription largely delayed, usually 5 to 9 years. Postponing clozapine leads to worse outcomes, higher treatment costs, and a lower chance of recovery.<sup>4</sup>

In the latest version of the Brazilian Clinical Protocols and Therapeutic Guidelines for Schizophrenia (Protocolos Clínicos e Diretrizes de Tratamento para Esquizofrenia), published by the Ministry of Health in 2013, prescription of risperidone, olanzapine, quetiapine, or ziprasidone requires an ICD-10 diagnosis of schizophrenia (F20), while clozapine should be considered for “refractoriness to at least 2 drugs, used for at least 6 weeks in adequate doses, or when at least 30% improvement on the BPRS scale does not occur.”<sup>5</sup>

These antipsychotics are provided free of charge in Brazil through the National Public Health System (Sistema Único de Saúde [SUS]) and distributed through state and municipal agencies. It is estimated that 70% of the population receives treatment exclusively through SUS.<sup>6</sup>

Since no studies have investigated clozapine prescription in the public health system, the aim of this study was to identify the frequency of clozapine prescription from 2010 to 2020 for SUS patients diagnosed with schizophrenia. As a secondary outcome, we examined clozapine use in each of the 26 states plus the Federal District.

## Methods

All prescription data in the Brazilian Unified Health System Outpatient Information System Database (Sistema de Informações Ambulatoriais/Departamento de Informática do SUS) are anonymous and available to the public (<http://datasus.saude.gov.br/>). Using the microdatas package 0.3.0 in R,<sup>7</sup> data were extracted from the system on all antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, and clozapine) prescribed to patients classified as ICD F20 (F20.0 to F20.9) in all states between 2010 and 2020, including the year and state of each prescription.

## Results

Between 2010 and 2020, 25,143,524 antipsychotic prescriptions were made for patients diagnosed with schizophrenia (Table 1). The most prescribed medication was olanzapine (35.77%), followed by quetiapine (27.5%). Ziprasidone was the least prescribed (4.9%), with clozapine representing only 8.86% of all antipsychotic prescriptions. Clozapine prescription increased from 7.21% in 2010 to 10.91% in 2020, an annual growth rate of approximately 0.37% (Figure 1).

Clozapine prescription varied widely by state, with the highest rate found in Rio Grande do Sul (32%), the only state in which clozapine was the most prescribed antipsychotic, followed by the Federal District (23%) and Tocantins (21%). The lowest rates were in Amapá (2%) and Paraíba (3.7%). In the state of São Paulo, which has the largest population in the country and is responsible for 36% of all antipsychotic prescriptions, clozapine was only 5.3% of the total. Excluding data from São Paulo increased the national mean to 13% (online-only supplementary material).

## Discussion

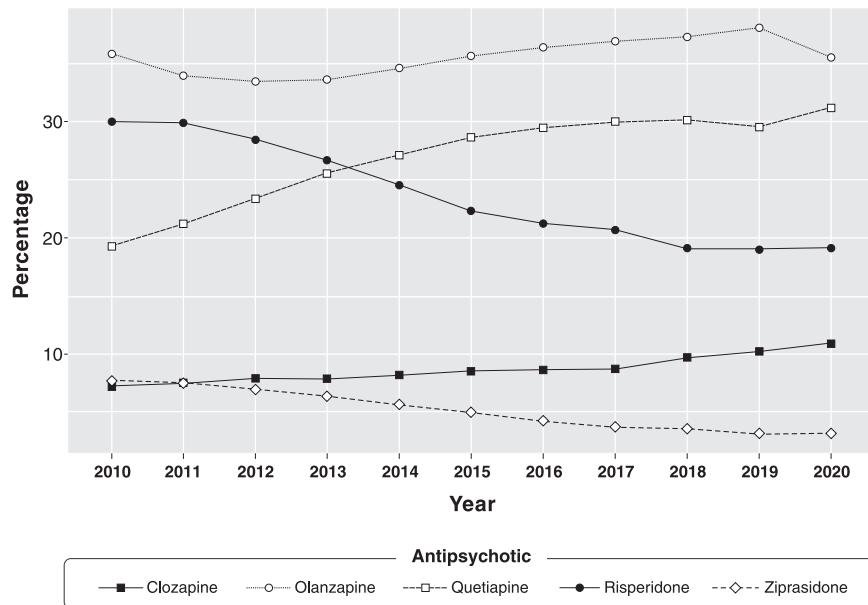
In the Brazilian National Health System, approximately 9% of all antipsychotic prescriptions made between 2010 and 2020 were for clozapine, with the rate increasing slightly during this period. Despite this increase, the gap is still large, considering the accepted prevalence of 30% treatment-resistance in schizophrenia.<sup>1</sup>

However, it should be considered that we found a large difference in prescription patterns between states, which ranged from 2.2 to 34%. This probably reflects even higher discrepancies among individual providers, e.g., small health services vs well-organized centers in large cities. In fact, a previous study showed that clozapine use among TRS SUS patients in São Paulo ranged from 10 to 50%.<sup>8</sup>

Two major issues are raised by our results: 1) the need to increase correct diagnosis and treatment of TRS in Brazil and 2) the development of a reliable TRS protocol to better standardize clozapine prescription patterns in the public health system. This study is limited by the fact that our analysis was based on national prescription data for high-cost medications. We did not include antipsychotics not covered in the Ministry of Health's clinical

**Table 1** Frequency and percentage of antipsychotic prescriptions in the Brazilian National Health System (DATASUS) for special medications for ICD F20 in the last decade

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total decade prescription
Clozapine	110,905 (7.21)	133,030 (7.45)	150,972 (7.91)	154,539 (7.82)	180,037 (8.18)	203,281 (8.46)	218,325 (8.64)	232,967 (8.72)	270,382 (9.72)	289,864 (10.23)	313,768 (10.91)	2,258,070 (8.86)
Olanzapine	550,551 (35.81)	606,230 (33.94)	637,473 (33.41)	663,141 (33.57)	760,677 (34.56)	854,466 (35.56)	920,121 (36.39)	985,617 (36.91)	1,037,068 (37.30)	1,077,495 (38.04)	1,020,130 (35.49)	9,112,969 (35.77)
Quetiapine	295,934 (19.25)	378,026 (21.16)	443,358 (23.24)	503,699 (25.50)	594,024 (26.99)	687,315 (28.61)	744,639 (29.45)	799,808 (29.95)	838,443 (30.16)	835,805 (29.51)	898,464 (31.25)	7,019,515 (27.55)
Risperidone	460,337 (29.94)	535,106 (29.96)	543,370 (28.48)	526,431 (26.65)	539,675 (24.52)	536,541 (22.33)	536,663 (21.23)	551,966 (20.67)	532,962 (19.17)	537,654 (18.98)	549,115 (19.10)	5,849,820 (22.96)
Ziprasidone	117,890 (7.67)	133,807 (7.49)	132,932 (6.97)	125,816 (6.37)	124,494 (5.66)	119,094 (4.96)	106,595 (4.22)	98,029 (3.67)	99,547 (3.58)	89,471 (3.16)	91,167 (3.17)	1,238,842 (4.86)
Total	1,537,627	1,786,199	1,908,105	1,975,639	2,200,921	2,402,712	2,528,359	2,670,404	2,780,420	2,832,308	2,874,664	25,143,524



**Figure 1** Antipsychotic prescriptions for patients clinically diagnosed with ICD F20. Data from DATASUS, Brazil.

protocols or those provided by state/municipal systems or other sources.

The underutilization of clozapine represents a serious burden for the public health systems of Brazil and other countries,<sup>2</sup> contributing to relapse and greater hospitalization rates and lengths, thus exposing patients and their families to avoidable burden and disease progression. The findings of this study call for urgent action. Clozapine is an effective and safe drug that is associated with reduced mortality,<sup>9</sup> despite the need of hematological control (traditionally considered a major barrier) and some evidence that it increases the risk of neutropenia in patients with severe medical conditions.<sup>10</sup>

Like other antipsychotics, clozapine is freely available nationwide, and its underutilization contributes to a greater burden on patients and families, as well as the public health system. This could be overcome to a great extent by correctly identifying patients with TRS and adequately prescribing clozapine for this large population.

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### Disclosure

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The other authors report no conflicts of interest.

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