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Regional disparities in clozapine dispensing in Brazil: associations with specialized mental health care

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Regional disparities in clozapine dispensing in Brazil: associations with specialized mental health care

Running title: Clozapine dispensing disparities in Brazil

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ABSTRACT

Objective: To investigate state-level disparities in clozapine dispensing in Brazil and their relationship with specialized mental health services and human development.

Methods: We performed a nationwide ecological cross-sectional analysis using 2024 clozapine dispensing data from the Brazilian Unified Health System. The study included dispensing events for individuals aged 16 years or older with schizophrenia and schizoaffective disorder. State-level clozapine dispensing rates were compared with mental health and primary care indicators, including psychiatrist density, inpatient beds, Psychosocial Care Centers, Family Health Teams, primary care coverage, and HDI. Correlations were tested with Spearman's coefficient, followed by multivariable linear regression and mediation analysis.

Results: We identified 3,240,406 antipsychotic dispensing events. Clozapine dispensing varied substantially across states, ranging from 15.54 to 361.24 per 100,000 inhabitants. Clozapine dispensing was positively correlated with psychiatrist density, psychiatric inpatient beds, and HDI. In the multivariable model, only psychiatrist density remained independently associated with higher clozapine dispensing (B = 12.4, 95% CI 0.77-24.1; p = 0.038).

Conclusions: State-level clozapine dispensing was more strongly associated with specialized mental health care capacity than with primary care services. These findings suggest a possible association between psychiatrist availability and clozapine dispensing within SUS, which should be examined in future research.

KEYWORDS: Clozapine; schizophrenia; mental health services; psychiatrists; health services accessibility.

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Introduction

Maintenance antipsychotic treatment reduces relapse rates and improves long-term outcomes in schizophrenia.[1] Treatment-resistant schizophrenia (TRS) affects about 36.7% of patients and is diagnosed when two efficacious antipsychotic trials yield no meaningful improvements.[2] Clozapine is the only approved antipsychotic for treatment-resistant schizophrenia.[3] Each antipsychotic tried before clozapine decreases the probability of a favorable response, and delays in its

introduction are associated with persistent psychotic symptoms, more frequent hospitalization, and worse long-term outcomes.[4, 5]

Despite its established efficacy, clozapine remains markedly underutilized worldwide, with substantial international variation in prescribing rates.[6] At the health system level, this underuse also increases the burden on families and health systems.[7] Barriers to clozapine use include concerns about adverse effects and blood monitoring, limited clinician experience, difficulty in recognizing treatment resistance, and administrative and health-system constraints.[8, 9] Most studies focus on prescriber-level factors, with relatively few examining population, health system, and socioeconomic characteristics associated with clozapine prescription rates.

In Brazil, healthcare access varies substantially across states and is generally worse in lower-HDI settings.[10, 11] Although Brazil achieved a score of 0.765 in 2020, placing it in the “high human development” category, issues such as income inequality, educational quality, and limited access to healthcare services continue to hinder equitable progress.[12] Additionally, Brazil has approximately 6.69 psychiatrists per 100,000 inhabitants, with marked differences in the number of these specialists across the country's regions.[13] There is also substantial variation in clozapine prescribing across Brazilian states; the proportion of clozapine prescriptions ranged from 2% to 32%, highlighting marked regional disparities in clozapine dispensing.[14]

Regional differences in clozapine dispensing likely reflect both clinician-level barriers and service-level barriers across states.[15, 16] To our knowledge, no studies in Brazil have compared state-level antipsychotic utilization rates and examined their associations with health systems and socioeconomic characteristics. We conducted a nationwide ecological cross-sectional study to examine state-level variation in clozapine dispensing within the Brazilian Unified Health System (SUS) and its associations with specialized mental health service capacity, primary care indicators, and the Human Development Index (HDI).

Methods

Data were obtained from DATASUS, the official repository of Brazilian public health administrative data, using its TABNET interface and the *microdatasus* R package.[17]

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During 2025, we integrated three data domains from DATASUS and complementary official sources: (1) sociodemographic information and antipsychotic medication use among individuals with schizophrenia and schizoaffective disorder; (2) health system infrastructure indicators including the number of Psychosocial Care Centers (CAPS), coverage of Primary Health Care, number of Family Health Teams (FHT), psychiatric inpatient beds, and the psychiatrist workforce by state; and (3) socioeconomic contextual variables, including Human Development Index (HDI) and population characteristics. The subsequent sections describe the collection procedures and sources for each data component.

This study was based on anonymized secondary administrative data and did not require approval by an ethics committee or informed consent.

Data collection

1) The Information Technology Department of the Brazilian Unified Health System (Datasus) is the official repository of the Brazilian public health administrative database.[18] Medication dispensing data are available through the Brazilian Unified Health System (Sistema Único de Saúde, SUS) and were obtained from Datasus using the microdatasus R package.[17] We collected clinical and demographic information on individuals diagnosed with schizophrenia and schizoaffective disorder (ICD-10 F20 and F25), living in Brazil, who received atypical antipsychotics free of charge through the Specialized Component of Pharmaceutical Assistance (CEAF; clozapine, quetiapine, risperidone, olanzapine, and ziprasidone) during 2024. Only physicians with an active psychiatric registration are authorized to initiate requests for these medications at CEAF. All antipsychotic prescriptions for individuals aged 16 years and older were included. Because the dispensing records are anonymized, the unit of analysis in the dataset was the number of prescriptions rather than individual patients. Although it does not capture the entirety of clozapine use in Brazil, the Brazilian Unified Health System accounts for approximately 71.5% of healthcare provision in the country.[19]
2) Each medication dispensing event through the Brazilian Unified Health System generates an Authorization for Medication Release (Authorization for High-

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Complexity Outpatient Procedures). This authorization contains patient-related information as well as the number of tablets dispensed for one month. The mean daily dose was estimated by dividing the total number of tablets dispensed by 30.

3) Psychosocial Care Centers (CAPS) are community-based mental health services for people with severe and persistent mental disorders. Primary Health Care potential coverage reflects the capacity of Family Health Teams (FHT) to provide territory-based primary care within SUS.[20] We collected data from Datasus in July 2024 regarding the number of CAPS in Brazilian states and data in October 2024 related to other primary care indicators[21] and the total number of psychiatric inpatient beds by state in October 2024.[22]
4) The Brazilian Institute of Geography and Statistics (IBGE) is the main provider of geographic and statistical information in the country. Data on the Brazilian population and the Human Development Index (HDI) were obtained from IBGE via the Atlas Brasil platform.[12] Throughout the research, we used the most recent data available. The human development data at the municipal level are based on the 2010 census, and at the state level, they come from the 2021 National Household Sample Survey (PNAD).
5) The Federal Council of Medicine (CFM) provides data on the number of physicians registered with the Regional Medical Councils in the psychiatry specialty across Brazilian cities and states.[23] In this research, we identified the number of primary registrations of psychiatrists in the regional medical councils of Brazilian states in October 2024. Additional details on data collection and the codes used for data extraction are provided in the Supplementary Material.

Data analysis

Data analysis was carried out in the following five steps:

1) Data selection and processing: the available data were filtered to include dispensing events for individuals with schizophrenia or schizoaffective disorder (ICD-10 F20 and F25) during 2024. We restricted the analysis to individuals 16 years or older to focus on the adult population. The data were combined into a

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single database of prescriptions per year and grouped by state in Brazil. The variables available for study and their interpretation are described in the Supplementary Material.

2) Graphical analysis: to visualize geographic variation in clozapine dispensing across Brazilian states, we constructed choropleth maps showing state-level clozapine dispensing rates per 100,000 inhabitants within CEAF/SUS in 2024. The polygons representing Brazilian states in these maps were derived from shapefiles provided by the Brazilian Institute of Geography and Statistics.[24]
3) Ecological correlation analysis: variables assessed in this study were correlated at the state level using Spearman's rank correlation coefficient, with 95% confidence intervals. The primary outcome was the clozapine dispensing rate, defined as the number of clozapine dispensing events recorded in the Specialized Component of Pharmaceutical Assistance (CEAF) per 100,000 inhabitants in each Brazilian state and the Federal District in 2024. This measure reflects dispensing activity within the Brazilian Unified Health System (SUS) rather than the number of individual clozapine users.
4) Linear regression: to examine the association between specialized mental health services and clozapine dispensing, we fitted a state-level multiple linear regression model with the 2024 clozapine dispensing rate per 100,000 inhabitants as the dependent variable. The predictors were the density of psychiatrists registered in the regional medical councils (per 100,000 inhabitants), the number of psychiatric inpatient beds (per 10,000 inhabitants), and the number of CAPS (per 100,000 inhabitants). These variables were selected a priori because they represent key components of specialized mental health service capacity and showed the strongest bivariate associations with clozapine dispensing. Given the limited number of analytical units (26 states plus the Federal District), the multivariable model was restricted to three predictors to reduce the risk of model overfitting. Linear regression assumptions were assessed by visual inspection of standardized residuals versus fitted values and Q-Q plots, as well as by examination of outliers and influential observations. Collinearity among predictors was evaluated using variance inflation factors (VIFs), with values <5 considered

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indicative of no concern for multicollinearity. No meaningful violations of residual normality, homoscedasticity, or collinearity were observed. Given the small number of analytical units, regression findings should be interpreted as exploratory and population-level rather than patient-level associations.

5) Mediation analysis: to investigate the mechanism underlying the association between HDI and clozapine dispensing rates, we tested a mediation model in which psychiatrist density was specified as a potential intermediary pathway between state-level HDI and clozapine dispensing per 100,000 inhabitants, rather than as a mere covariate. Mediation analysis was used to estimate the direct and indirect effects of HDI on clozapine dispensing. Indirect effects were estimated using bootstrap resampling with 10,000 samples and bias-corrected 95% confidence intervals. All analyses were performed using Jamovi version 2.7 and R Core Team version 4.5, with statistical significance defined as a two-sided $p < 0.05$.

Results

Descriptive analysis

Throughout 2024, a total of 3,240,406 antipsychotic dispensings were identified through the Specialized Component of Pharmaceutical Assistance (CEAF) across all 26 Brazilian states and the Federal District. The highest absolute number of antipsychotic dispensings occurred in São Paulo (n=1,157,013), the most populous state; the lowest were in less populous northern states: Amapá (n=2,318), Roraima (n=2,598), and Acre (n=2,884).

The geographic distribution of clozapine dispensing in 2024 is shown in Figure 1. The highest dispensing rates were observed in Rio Grande do Sul (361.24), Espírito Santo (310.40), Paraná (302.54), Federal District (296.16), and Minas Gerais (290.43). The lowest rates were observed in northern states, including Amapá (15.54), Roraima (49.63), Amazonas (50.08), Acre (50.48), and Pará (60.48).

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Figure 1. Clozapine dispensing per 100,000 inhabitants in Brazilian states

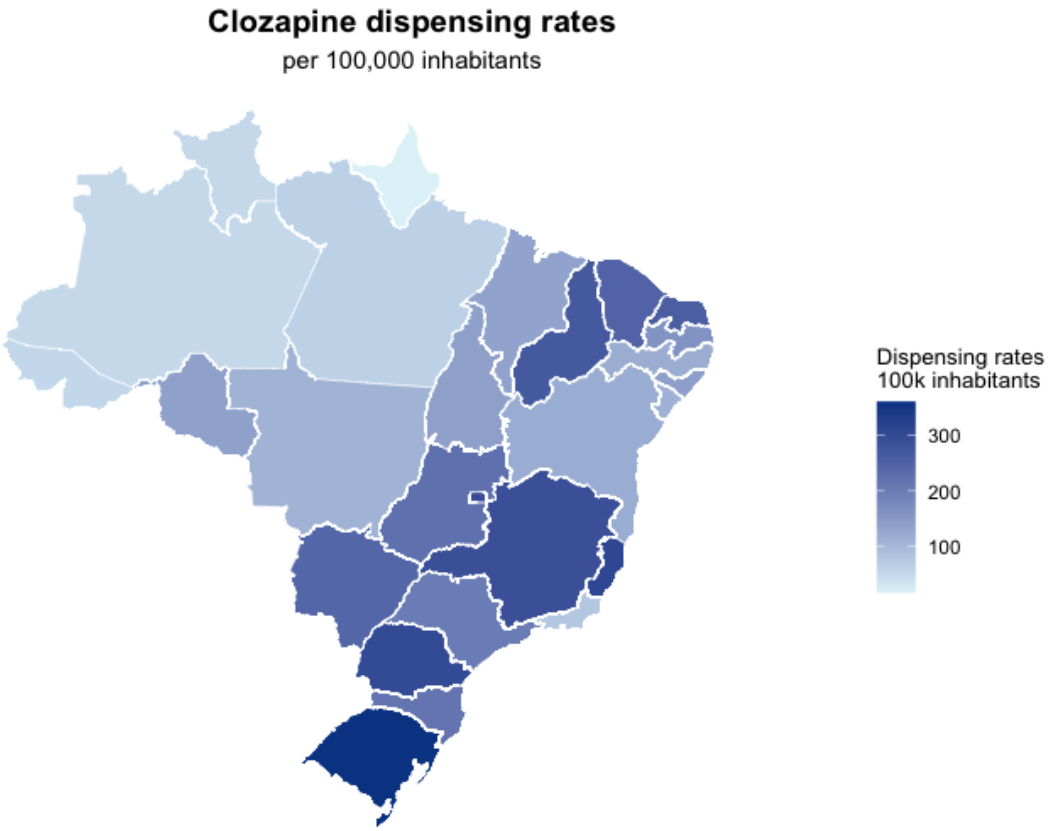


Figure 1. Clozapine dispensing per 100,000 inhabitants in Brazilian states

The mean prescribed dose of clozapine in Brazil was 351.94 mg/day. The highest mean doses were observed in Rio de Janeiro (437.02 mg/day), Amazonas (435.67 mg/day), and Pernambuco (400.67 mg/day). In contrast, Acre (255.35 mg/day), Amapá (263.16 mg/day), and Piauí (286.22 mg/day) had mean doses below 300 mg/day.

In 2024, Brazil had 3,448 CAPS (Psychosocial Care Centers), 28,625 psychiatric inpatient beds, and 54,350 FHT (Family Health Teams). The number of psychiatric inpatient beds varied across Brazilian states. The states with the highest numbers were São Paulo (n=8,372), Rio Grande do Sul (n=3,093), and Paraná (n=2,411). Northern states had the lowest numbers, including Roraima (n=2), Tocantins (n=15), Amapá (n=19), Amazonas (n=45), and Acre (n=67).

Primary health care coverage ranged from 69.81% in São Paulo to 150.33% in Piauí across states. Values exceeding 100% indicate that these teams' theoretical capacity, based on official parameters, surpasses the estimated resident population,

signaling high availability or relative oversupply of teams rather than literal over-coverage.[21] In Brazil, most regions have primary care potential coverage exceeding 100% of their estimated populations, except for São Paulo (69.81%), Distrito Federal (80.15%), Rio de Janeiro (84.60%), Goiás (93.17%), Paraná (95.90%), Amazonas (97.87%), Rio Grande do Sul (97.88%), and Mato Grosso (98.56%).

The national Human Development Index (HDI) in 2021 was 0.766 (high HDI category), varying from medium-HDI states such as Paraíba (0.676), Alagoas (0.684), Amapá (0.688), and Pará (0.690) to the highest-HDI jurisdictions, including São Paulo (0.806) and the Federal District (0.814). Detailed information on the data presented is available in Supplementary Table S1 and S2. Table 1 presents clozapine dispensing rates per 100,000 inhabitants, alongside psychiatric inpatient bed counts, numbers of CAPS (Psychosocial Care Centers), Family Health Teams (FHT), and the number of psychiatrists, normalized by state population.

Table 1. Clozapine dispensing and mental health service indicators by Brazilian states

State/Federal District	Clozapine dispensing rate (per 100,000)	Psychiatric inpatient beds (per 10,000)	CAPS (per 100,000)	FHT (per 10,000)	Psychiatrists (per 100,000)
Brazil (All states)	196.52	1.41	1.70	2.68	7.11
Rio Grande do Sul	361.24	2.84	2.18	2.38	17.08
Espírito Santo	310.40	1.90	1.12	2.81	6.96
Paraná	302.54	2.11	1.49	2.48	7.91
Distrito Federal	296.16	2.65	0.64	2.26	15.94
Minas Gerais	290.43	0.89	2.22	3.19	7.71
Piauí	269.26	0.60	2.05	4.27	4.52
Rio Grande do Norte	258.60	1.07	1.70	3.67	5.48
Ceará	248.36	1.24	2.22	3.56	5.03
Mato Grosso do Sul	242.84	1.28	1.49	2.80	6.78
Goiás	223.95	2.38	1.45	2.49	5.78

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Santa Catarina	215.31	1.74	1.64	3.15	8.80
São Paulo	201.22	1.89	1.49	1.61	9.38
Paraíba	161.57	1.30	3.30	4.16	5.01
Alagoas	140.68	1.77	2.27	3.10	4.86
Tocantins	138.21	0.10	1.59	4.11	3.24
Rondônia	136.97	0.59	1.40	2.85	3.12
Maranhão	133.04	0.98	1.64	3.95	1.77
Bahia	119.21	0.51	2.15	3.14	3.30
Pernambuco	117.54	1.65	1.87	3.19	4.05
Sergipe	111.04	0.89	1.99	3.43	4.21
Mato Grosso	106.90	0.74	1.45	2.73	3.66
Rio de Janeiro	75.40	1.03	1.40	2.21	8.02
Pará	60.48	0.18	1.44	2.69	1.64
Acre	50.48	0.81	1.45	3.01	2.17
Amazonas	50.08	0.11	0.94	2.39	1.70
Roraima	49.63	0.03	1.73	3.86	2.04
Amapá	15.54	0.26	1.36	3.31	1.91

CAPS, Psychosocial Care Centers; FHT, Family Health Teams. Rates are expressed per 100,000 inhabitants for clozapine dispensing, CAPS, and psychiatrists, and per 10,000 inhabitants for psychiatric inpatient beds and FHT.

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Correlation analysis

Table 2 shows the correlations between state-level clozapine dispensing rates (per 100,000 inhabitants) and clinical and sociodemographic variables. We observed strong positive Spearman correlations between clozapine dispensing rates per 100,000 inhabitants and the number of psychiatrists registered with regional medical boards (rho = 0.76; Supplementary Figure S1), psychiatric bed availability per state population (rho = 0.71; Supplementary Figure S2), and a moderate positive correlation with the Human Development Index (rho = 0.58; Supplementary Figure S3).

Table 2. Correlations between clozapine dispensing rates (per 100,000 population) and clinical and sociodemographic indicators

Clinical and sociodemographic variables	rho	95% CI	*p*-value
Psychiatrists registered in the medical councils/population	0.76	0.49-0.91	<0.01
Psychiatric Inpatient Beds/population	0.71	0.41-0.87	<0.01
HDI	0.59	0.26-0.77	<0.01
Psychosocial Care Centers (CAPS)/population	0.24	-0.20-0.65	0.22
Family Health Teams (FHT)/population	-0.10	-0.48-0.36	0.63
Coverage of primary health care services	-0.16	-0.50-0.25	0.45

Spearman's rank correlation coefficients are presented with 95% confidence intervals. CAPS, Psychosocial Care Centers; FHT, Family Health Teams; HDI, Human Development Index.

Exploratory multivariable linear regression

In the multivariable model (Table 3), specialized mental health service indicators explained approximately 55% of the variance in state-level clozapine dispensing rates within SUS [R^2 = 0.603; adjusted R^2 = 0.552; F (3, 23) = 11.7; p < 0.001]. Psychiatrist density remained independently associated with higher clozapine dispensing (B = 12.4; SE 5.64; 95% CI 0.77 to 24.1; p = 0.038; standardized β = 0.499), indicating that, after adjusting for the availability of psychiatric inpatient beds and CAPS, each additional psychiatrist per 100,000 inhabitants was associated with a mean increase of 12.4 clozapine dispensing events per 100,000 inhabitants.

Table 3. Multiple linear regression analysis of the association between specialized mental health service infrastructure and state-level clozapine dispensing rates (per 100,000 population)

Variable	*B* (SE)	95% CI	β	*p* value
Psychiatrists (per 100,000)	12.4 (5.64)	0.77 to 24.1	0.499	0.038
Psychiatric inpatient beds (per 10,000)	37.8 (27.59)	-19.27 to 94.9	0.309	0.184
CAPS (per 100,000)	25.9 (24.98)	-25.78 to 77.6	0.137	0.311

N = 27. *B*, unstandardized regression coefficient; SE, standard error; β, standardized regression coefficient; Model fit: R^2 = 0.603, adjusted R^2 = 0.552, F (3,23) = 11.7, p < 0.001. The dependent variable is the number of clozapine dispensing events per 100,000 inhabitants.

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The coefficients for psychiatric inpatient beds and CAPS did not reach statistical significance in this sample. Model residuals were approximately normally distributed, with no evidence of substantial heteroscedasticity, and variance inflation factors were 3 or lower for all predictors, indicating no multicollinearity. Given the strong correlation between psychiatrist density and HDI, as well as evidence of multicollinearity (rho = 0.85, VIF = 4.9, tolerance = 0.2), HDI was not entered into the multivariable linear regression model. Instead, the relationship between HDI, psychiatrist density, and clozapine dispensing was explored in a separate mediation analysis.

Exploratory mediation analysis

In the exploratory mediation analysis, psychiatrist density accounted for part of the association between state-level HDI and clozapine dispensing rates, with a significant indirect effect and no significant direct effect (Table 4).

Table 4. Mediation analysis of the association between Human Development Index and clozapine dispensing rates through psychiatrist density

Effect or path	Estimate (SE)	95% CI	*p* value
Indirect effect (a × b)	1326.0 (445.0)	617.0 to 2493.0	.004
Direct effect (c')	202.0 (613.0)	-1149.0 to 1312.0	.742
Total effect (c)	1528.0 (384.0)	859.0 to 3981.0	<.001
HDI → psychiatrist density (a)	79.1 (13.97)	52.94 to 107.1	<.001
Psychiatrist density → clozapine dispensing rate (b)	16.8 (7.94)	7.81 to 42.6	.035
HDI → clozapine dispensing rate, adjusted for psychiatrist density (c')	201.8 (613.12)	-1149.19 to 1311.7	.742

Values are unstandardized regression coefficients, with standard errors in parentheses. The indirect effect represents the product of paths a and b. The direct effect (c') represents the association between HDI and clozapine dispensing rates after accounting for psychiatrist density. The total effect (c) represents the overall association between HDI and clozapine dispensing rates before decomposition into direct and indirect components.

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Discussion

In this nationwide analysis, we found marked differences in clozapine dispensing rates across Brazilian states. At the state level, dispensing rates were associated with psychiatrist density, psychiatric inpatient bed availability, and the Human Development Index (HDI). In the exploratory multivariable regression model, psychiatrist density was the only predictor that remained significantly associated with clozapine dispensing after adjustment for psychiatric inpatient beds and CAPS. Further mediation analysis suggested that the association between higher HDI and greater clozapine dispensing may be partly explained by psychiatrist density. Once psychiatrist density was taken into account, HDI no longer showed an independent association with clozapine dispensing. This pattern suggests a possible relationship among psychiatrist density, and clozapine dispensing, but does not establish that psychiatrist availability explains regional variation or reflects patients' access to or clinical need for clozapine.

Although our analysis was conducted only in Brazil, our findings are consistent with recent international cross-country evidence. A longitudinal epidemiological study of 75 countries between 2014 and 2024 found that greater psychiatrist density was associated with higher clozapine prescription rates (rho = 0.60).[6] The same study also found that countries with higher human development indices and mental health infrastructure, such as New Zealand and Finland, have higher clozapine prescription rates than less developed countries.[6] A similar pattern was observed in our study when single bivariate correlations were performed.

Geographic variability in clozapine dispensing rates, both within and across countries, may reflect the availability, organization, and support of mental health services. In a study conducted in the United States, Bunting et al. found that clozapine was more frequently prescribed in psychiatric hospitals and specialized programs for severe mental disorders than in outpatient settings. The presence of on-site laboratory services was also associated with higher clozapine use, underscoring the importance of organizational infrastructure for clozapine availability.[25] Similarly, evidence from France suggests that regional differences in clozapine dispensing may be influenced not only by psychiatric resources themselves but also by the degree of coordination between mental health services and primary care.[26] Data from Latin

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America suggest that the availability of specialized mental health services does not necessarily correspond to greater clozapine use. For example, although Uruguay and Argentina meet the recommended psychiatric bed ratios (34.9 and 17 per 100,000 inhabitants, respectively), clozapine remains underutilized in the region, suggesting that psychiatric bed availability alone may not account for regional variation in clozapine use.[27]

We found no association between the number of Psychosocial Care Centers (CAPS), Family Health Teams (FHT), and coverage of primary health care services and clozapine dispensing across Brazilian states. In Brazil, CAPS are not staffed exclusively by psychiatrists. Under current regulations, some units may also include general practitioners or other non-psychiatrist physicians with training in mental health, alongside psychiatrists.[20] Although no recent national data are available on the composition of CAPS medical teams, a study in southern Brazil found that only 62% of CAPS physicians had specialized mental health training[28], suggesting that the number of CAPS alone may not capture differences in professional composition or other organizational characteristics potentially associated with clozapine dispensing.

States with the highest clozapine dispensing rates, such as Rio Grande do Sul, Espírito Santo, Paraná, and the Federal District, were characterized by higher HDI and greater availability of psychiatrists and psychiatric inpatient beds within the public health system. Notably, these states did not have higher primary care potential coverage, via Family Health Teams (FHT), suggesting that clozapine dispensing could be more related to mental health service capacity than to primary care density. However, the relative contribution of specialized and primary care services cannot be established from this analysis. In contrast, northern states with the lowest clozapine dispensing rates, like Amapá, Acre, Roraima, Pará, and Amazonas had substantially lower specialized mental health infrastructure, despite comparable or higher FHT density. These states displayed heterogeneous socioeconomic profiles, with two exhibiting high HDI (Amazonas 0.709; Acre 0.707) and three in the medium range (0.688 to 0.699), indicating that low clozapine dispensing rates were not uniformly attributable to low human development. However, some states with relatively high HDI and psychiatrist density, such as São Paulo and Santa Catarina, still showed

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lower clozapine dispensing than other high-resource states, suggesting that additional unmeasured factors may also contribute to regional variation.

Brazil's regional socioeconomic inequalities are also accompanied by documented racial disparities in healthcare access.[29, 30] Although these factors were not directly measured in the present study, their possible relationship with regional variation in clozapine dispensing should be examined in future research. Given Brazil has a unified public health system, future research may help guide public policies to reduce these inequalities, either by expanding specialist services across the country, improving referral pathways from general to specialist services, or enabling general services to prescribe clozapine with support from specialist teams.

This study has several strengths. It used nationwide administrative data from SUS, examined clozapine dispensing in all 26 Brazilian states and the Federal District, and incorporated both health service and socioeconomic indicators to explore geographic variation in clozapine dispensing. Our sample likely encompasses a large portion of antipsychotic dispensing for patients with psychotic disorders treated by the SUS, especially given that around 71.5% of the Brazilian population depends solely on this system for their healthcare needs.[19]

However, several limitations must be considered. First, this was an ecological cross-sectional study, and the unit of analysis was the state rather than the individual patient or service. Accordingly, the findings should not be interpreted as patient-level associations, and causal inferences cannot be made. Second, the outcome reflects clozapine dispensing events recorded within CEAF/SUS rather than the number of unique clozapine users or the proportion of patients with treatment-resistant schizophrenia receiving clozapine. Dispensing data provide an indirect indicator of treatment availability or utilization and should not be interpreted as a direct measure of patients' clinical need or actual access to appropriate treatment. In addition, because the database captures dispensing events rather than longitudinal treatment trajectories, we could not distinguish states with higher clozapine initiation and lower treatment persistence from those with lower initiation and higher persistence. Therefore, state-level dispensing rates and mean dispensed doses may reflect different combinations of treatment initiation, titration, maintenance, and discontinuation. Third, the dataset does not capture all antipsychotic use in Brazil,

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including treatment in the private sector and antipsychotics dispensed outside the CEAF reporting structure. Fourth, the use of administrative databases introduces the possibility of diagnostic misclassification and heterogeneous data quality across states, even though the first request for antipsychotics at CEAF can only be made by psychiatrists registered with the regional medical councils. Finally, we could not adjust for potentially important confounders such as state-level prevalence of schizophrenia or treatment-resistant schizophrenia, prescribing culture, availability of laboratory monitoring, or other organizational characteristics of local mental health networks. The associations observed in this study likely reflect broader differences in the organization and capacity of specialized mental health services rather than isolated effects of any single indicator.

Brazil is a continental country with marked socioeconomic, cultural, and health service heterogeneity across states, which may be associated with regional variation in clozapine dispensing. Moreover, differences across national healthcare systems may affect clozapine availability between countries. Future studies incorporating patient-level clinical information and broader healthcare, socioeconomic, organizational, and regional variables are needed to clarify the mechanisms underlying these differences and to assess potential inequalities in access to appropriate clozapine treatment.

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Disclosure

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Data availability

The dataset is based on anonymized data from the Brazilian Unified Health System (DATASUS). Aggregate data used in this study are available from the authors on reasonable request.

Author contributions

RM, LGP, and AG were responsible for conceptualization and methodology. RSMT, LGP, and RM were responsible for data curation. DFBC and RM were responsible for formal analysis and validation. DFBC and RM were responsible for writing – original draft. RM, ND, RSMT, HE, and NC were responsible for writing – review & editing and methodology. All authors have read and approved the final version submitted and take public responsibility for all aspects of the work.

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Supplementary Material

1. Methods

1.1. Data collection

To obtain data from Datasus, we used the microdatasus package[1], with the following R commands:

data <- fetch_datasus(year_start = 2024, month_start = 1, year_end = 2024, month_end = 12, information_system = "SIA-AM", vars=<colunas>)

also

data <- fetch_datasus(year_start = 2024, month_start = 1, year_end = 2024, month_end = 12, information_system = "SIA-PA", vars=<colunas>)

With the following columns (colunas) and their translation into parentheses:

- MVM (Processing/Movement Date)
- CODUNI (Establishment Code in National Registry of Health Establishments)
- AUTORIZ (Ambulatory Procedure Authorization number)
- CMP (Date of patient care / Competence)
- PRIPAL (Ambulatory Procedure Authorization main procedure)
- UFMUN (Federation Unit Code + Municipality of Establishment)
- CNSPCN (Codified Patient's National Health Card number)
- NUIDADE (Patient age)
- SEXO (Patient sex)
- RACACOR (Patient's skin color)
- MUNPCN (Patient's municipality of residence)
- UFNACIO (Patient's state of birth)
- CEPPCN (Postal code of residence)
- OBITO (Death indicator)
- CIDPRI (Main ICD-10)
- ETNIA (Patient's ethnicity)
- AM_PESO (Patient weight)
- AM_ALTURA (Patient height)

Data from Primary Care Reports[2]:

- Qt. eSF (Number of Family Health Teams)
- Qt. eAP 20hs (Number of Family Health Teams 20 hours)
- Qt. eAP 30hs (Number of Family Health Teams 30 hours)
- Qt. eCR (Number of Street Office Teams)
- Qt. Cadastro eCR (Number of patients registered in Street Office Teams)
- Qt. eAPP 20hs (Number of Prison Primary Care Teams 20 hours)
- Qt. Cadastro eAPP 20hs (Number of patients registered in Prison Primary Care Teams 20 hours)
- Qt. eAPP 30hs (Number of Prison Primary Care Teams 30 hours)
- Qt. Cadastro eAPP 30hs (Number of patients registered in Prison Primary Care Teams 30 hours)

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- Qt. eSFR (number of Riverine Family Health Teams)
- Qt. Cadastro eSFR (Number of patients registered in Riverine Family Health Teams)
- Qt. cadastros das eCR e eAPP (number of patients registered in Street Office and Prison Teams)
- Qt. capacidade da equipe (team capacity)
- Cobertura APS (primary care potential coverage)

The most relevant columns for data analysis were PRIPAL, which provided information regarding the antipsychotics used by the patients, and CIDPRI, which provided information regarding patient diagnoses based on ICD-10. Due to the large amount of data, results referring to individuals diagnosed with schizophrenia (ICD-10: F20) and schizoaffective disorder (ICD-10: F25) were extracted by regions of Brazil. These data were later compiled into a single database.

Atlas Brasil data was collected at both municipal and state levels, considering the following indicators:

- HDI
- HDI Income
- IDHM Longevity
- IDHM Education
- Total population

To obtain the translation of the municipal codes, the 2022 IBGE DTB (Divisão Territorial Brasileira) report was used. [3]

1.2. Interpretation of variables

When interpreting the variables below, it is necessary to consider that we obtained access to the number of atypical antipsychotics dispensed by the Specialized Component of Pharmaceutical Assistance (CEAF). Therefore, each medication dispensing record does not necessarily correspond to a single patient, since the same patient may have received more than one antipsychotic dispensing, either obtaining different antipsychotics or obtaining the same antipsychotic more than once throughout 2024.

- CLOZAPINE_TOTAL: total number of dispensings of the antipsychotic clozapine.
- DRUGS_TOTAL: total number of dispensings of any antipsychotic provided by state pharmacies.
- PERCENT_MASC: number of antipsychotic dispensings for male patients divided by the number of dispensings for both sexes.
- CLOZAPINE_DRUGS: corresponds to the division of CLOZAPINE_TOTAL by DRUGS_TOTAL. This represents the proportion of clozapine dispensing in relation to all antipsychotic dispensing. It is not exactly equal to the number of patients who used clozapine because the same patient can receive multiple antipsychotics or the same antipsychotic several times.
- CLOZAPINE_POP: CLOZAPINE_TOTAL divided by POPULATION. This represents a population-standardized clozapine dispensing rate (e.g., per

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100,000 inhabitants) and should not be interpreted as the percentage of individuals who used clozapine, because the same individual may receive multiple dispensing events.

- NUM_MEN: number of dispensings for male patients. Because the same patient may receive multiple medications or the same medication several times, this variable is not the same as the number of men with schizophrenia in that region. The NUM_WOMEN variable is analogous.
- NUM_MEN_CLOZAPINE: number of clozapine dispensings for men. Due to polypharmacy and multiple dispensings of the same antipsychotic for the same patient, it is not exactly equal to the number of men who use clozapine in that region. The NUM_WOMEN_CLOZAPINE variable is analogous.
- DIF_CLOZAPINE_SEX: corresponds to the division of the percentage of men by women who used clozapine.

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RESULTS

Descriptive analysis

Supplementary Table S1. Sociodemographic characteristics and antipsychotic dispensing indicators for Brazilian states and the Federal District

Region	State	Population	Antipsychotic Rx	Men on antipsychotics, n (%)	Clozapine Rx, n (%)	Men on clozapine, n (%)	Mean dose, mg/day (SD)
Brazil	All States	203,051,589	3,240,406	1,724,622 (53.22)	399,027 (12.31)	255,647 (64.07)	351.94 (200.16)
North	Acre	830,018	2,884	1,811 (62.79)	419 (14.53)	271 (64.68)	255.35 (188.59)
	Amapá	733,759	2,318	1,348 (58.15)	114 (4.92)	62 (54.39)	263.16 (122.84)
	Amazonas	3,941,613	12,738	6,473 (50.82)	1,974 (15.50)	1,190 (60.28)	435.67 (218.37)
	Pará	8,120,131	24,004	12,830 (53.45)	4,911 (20.46)	3,000 (61.09)	325.84 (175.45)
	Rondônia	1,571,872	20,566	11,346 (55.17)	2,153 (10.47)	1,361 (63.21)	311.22 (184.35)
	Roraima	636,707	2,598	1,525 (58.70)	316 (12.16)	180 (56.96)	395.58 (206.95)
	Tocantins	1,511,460	7,054	4,167 (59.07)	2,089 (29.61)	1,331 (63.71)	334.86 (158.49)
Northeast	Alagoas	3,127,683	28,221	13,961 (49.47)	4,400 (15.59)	2,608 (59.27)	350.30 (201.62)
	Bahia	14,141,626	131,988	71,415 (54.11)	16,858 (12.77)	10,414 (61.77)	332.22 (189.28)
	Ceará	8,794,957	231,706	123,645 (53.36)	21,843 (9.43)	14,103 (64.57)	330.92 (197.66)
	Maranhão	6,776,699	37,652	20,363 (54.08)	9,016 (23.95)	5,627 (62.41)	312.49 (171.41)
	Paraíba	3,974,687	76,565	41,545 (54.26)	6,422 (8.39)	4,128 (64.28)	341.75 (202.03)
	Pernambuco	9,056,843	76,006	43,971 (57.85)	10,645 (14.01)	6,641 (62.39)	400.67 (191.94)
	Piauí	3,271,199	51,392	27,709 (53.92)	8,808 (17.14)	5,351 (60.75)	286.22 (159.34)
	Rio Grande do Norte	3,302,729	91,266	46,315 (50.75)	8,541 (9.36)	4,926 (57.67)	311.70 (191.72)
	Sergipe	2,210,004	24,762	13,292 (53.68)	2,454 (9.91)	1,551 (63.20)	343.45 (191.06)
Midwest	Goiás	7,056,495	111,336	59,203 (53.18)	15,803 (14.19)	9,995 (63.25)	374.91 (182.09)
	Mato Grosso	3,658,649	38,340	20,178 (52.63)	3,911 (10.20)	2,195 (56.12)	311.55 (186.65)
	Mato Grosso do Sul	2,757,013	37,911	20,736 (54.70)	6,695 (17.66)	4,395 (65.65)	332.98 (202.27)
Southeast	Espírito Santo	3,833,712	115,730	58,606 (50.64)	11,900 (10.28)	7,534 (63.31)	354.24 (178.90)
	Minas Gerais	20,539,989	298,391	169,403 (56.77)	59,654 (19.99)	37,881 (63.50)	370.34 (197.66)
	Rio de Janeiro	16,055,174	79,571	45,092 (56.67)	12,105 (15.21)	7,758 (64.09)	437.02 (192.65)
	São Paulo	44,393,483	1,157,013	581,914 (50.29)	89,328 (7.72)	57,500 (64.37)	359.52 (203.72)
South	Paraná	11,444,380	319,141	172,047 (53.91)	34,624 (10.85)	21,994 (63.52)	340.54 (232.45)
	Santa Catarina	7,610,361	116,682	68,781 (58.95)	16,386 (14.04)	10,928 (66.69)	372.04 (201.83)
	Rio Grande do Sul	10,882,965	118,265	70,629 (59.72)	39,314 (33.24)	27,119 (68.98)	382.90 (188.47)
Federal District	Distrito Federal	2,817,381	26,306	16,317 (62.03)	8,344 (31.72)	5,604 (67.16)	368.76 (176.16)

Values are presented for Brazilian states and the Federal District. Antipsychotic prescriptions include dispensing events recorded in the Brazilian Unified Health System (SUS) for individuals with schizophrenia and schizoaffective disorder aged 16 years or older. Clozapine prescriptions are shown as absolute numbers and as a proportion of total antipsychotic prescriptions. Mean clozapine dose is expressed in mg/day.

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Supplementary Table S2. Health system indicators and socioeconomic context for Brazilian states and the Federal District

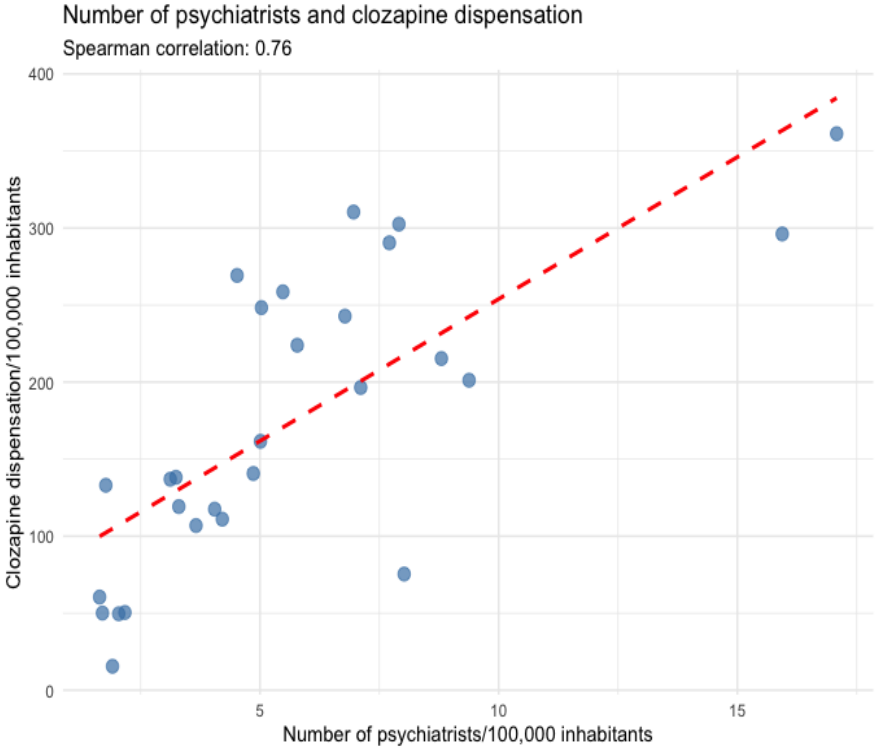
Region	State	CAPS	Psychiatrists	Psyc.beds	FHT	PHC coverage, %	HDI
Brazil	All States	3.448	14.427	28,625	54,350	101.24%	0.766
North	Acre	12	18	67	250	121.50%	0.710
	Amapá	10	14	19	243	127.21%	0.688
	Amazonas	37	67	45	942	97.87%	0.700
	Pará	117	133	145	2,181	102.53%	0.690
	Rondônia	22	49	93	448	104.89%	0.700
	Roraima	11	13	2	246	136.73%	0.699
	Tocantins	24	49	15	621	146.40%	0.731
Northeast	Alagoas	71	152	554	971	112.76%	0.684
	Bahia	304	466	723	4,442	114.84%	0.691
	Ceará	195	442	1,090	3,127	126.53%	0.734
	Maranhão	111	120	662	2,678	140.06%	0.676
	Paraíba	131	199	515	1,652	146.43%	0.698
	Pernambuco	169	367	1,496	2,886	114.86%	0.719
	Piauí	67	148	196	1,398	150.33%	0.690
	Rio Grande do Norte	56	181	354	1,213	132.04%	0.728
	Sergipe	44	93	197	758	122.95%	0.702
Midwest	Goiás	102	408	1,676	1,759	93.17%	0.737
	Mato Grosso	53	134	271	1,000	98.56%	0.736
	Mato Grosso do Sul	41	187	352	771	101.56%	0.742
Southeast	Espírito Santo	43	267	729	1,078	108.33%	0.771
	Minas Gerais	456	1.584	1,819	6,546	115.54%	0.774
	Rio de Janeiro	201	1.287	1,658	3,542	84.60%	0.762
	São Paulo	620	4.166	8,372	7,141	69.81%	0.806
South	Paraná	171	905	2,411	2,834	95.90%	0.769
	Santa Catarina	125	670	1,325	2,397	115.56%	0.792
	Rio Grande do Sul	237	1.859	3,093	2,590	97.88%	0.771
Federal District	Distrito Federal	18	449	746	636	80.15%	0.814

CAPS, Psychosocial Care Centers; FHT, Family Health Teams; HDI, Human Development Index. CAPS, psychiatrists, and clozapine dispensing rates are expressed per 100,000 inhabitants, whereas psychiatric inpatient beds and FHT are expressed per 10,000 inhabitants. Primary health care coverage values above 100% indicate that the theoretical capacity of Family Health Teams exceeds the estimated resident population and should be interpreted as relative oversupply rather than literal over-coverage.

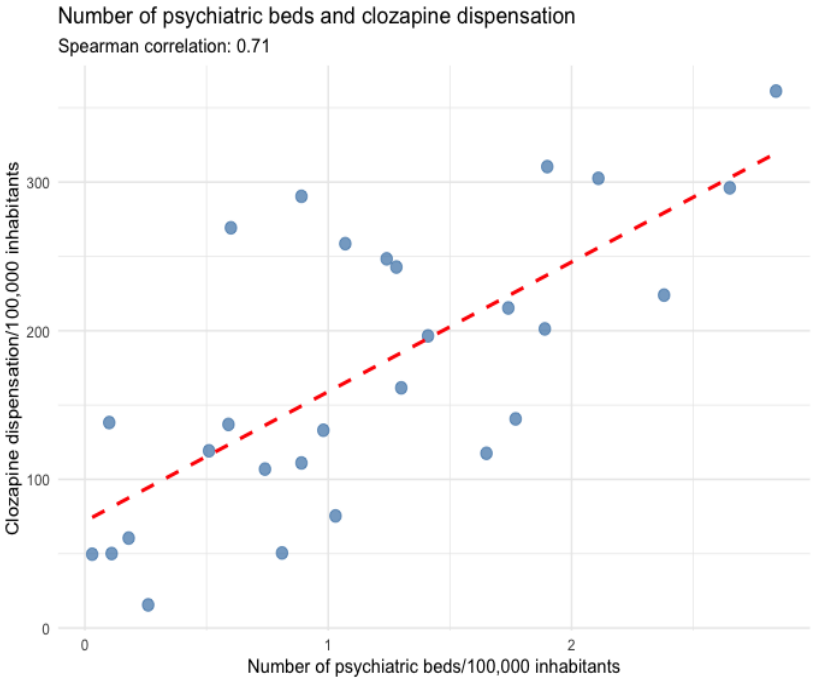
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Correlation analysis

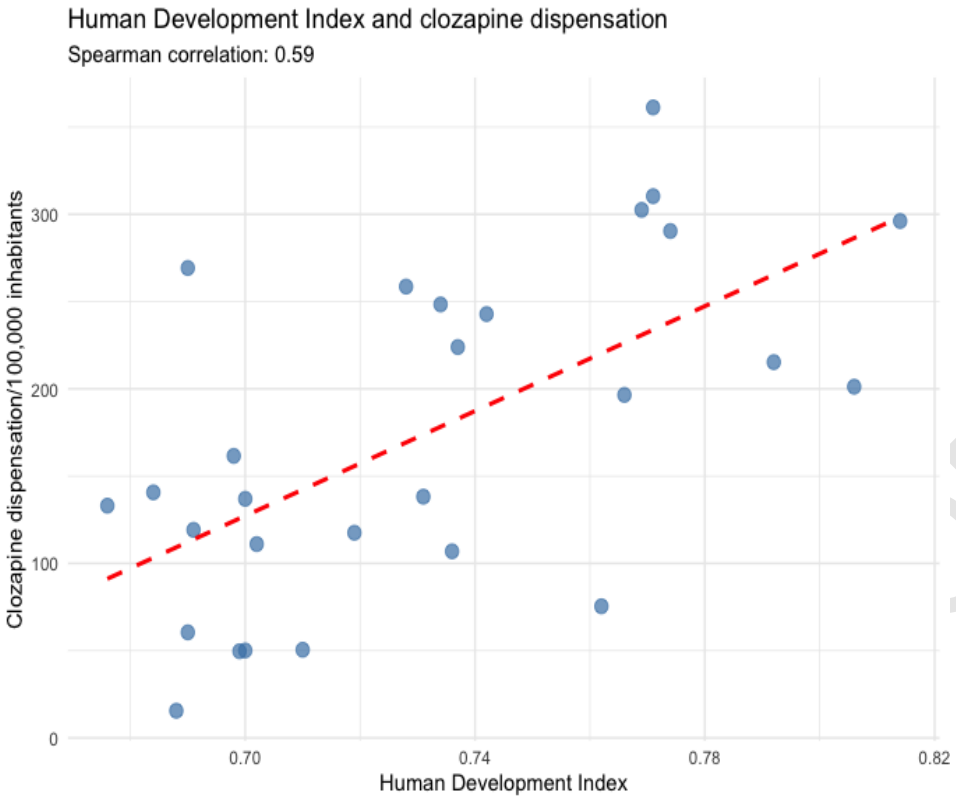
Supplementary Figure S1. Correlation between clozapine dispensing rates per 100,000 population and psychiatrists registered with medical councils per state population



Supplementary Figure S2. Correlation between clozapine dispensing rates per 100,000 population and psychiatric inpatient beds per 10,000 population



Supplementary Figure S3. Correlation between clozapine dispensing rates per 100,000 population and state Human Development Index (HDI)



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