

Trends

in Psychiatry and Psychotherapy

Trends in Psychiatry and Psychotherapy

ISSN: 2237-6089

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Associação de Psiquiatria do Rio Grande
do Sul
Brasil

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Trends in Psychiatry and Psychotherapy, vol. 39, núm. 3, julio-septiembre, 2017, pp. 158-
164

Associação de Psiquiatria do Rio Grande do Sul
Porto Alegre, Brasil

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Trends in the prescription of clozapine in a psychiatric hospital: a 5-year observational study

Tendência na prescrição de clozapina em um hospital psiquiátrico: estudo observacional de 5 anos

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Abstract

Introduction: Clozapine is a well-recognized effective treatment for some patients with treatment-resistant schizophrenia (TRS). Although it has potential benefits and approximately 30% of patients have a clinical indication for clozapine use, prescription rates are low.

Objective: To evaluate clozapine prescription trends over a 5-year period in a tertiary psychiatric hospital.

Methods: In this observational study, data prospectively collected by the Medical and Statistical File Service (Serviço de Arquivo Médico e Estatístico) and the Pharmacy Division of Instituto de Psiquiatria de Santa Catarina between January 2010 and December 2014 were summarized and analyzed by investigators blinded to data collection. The number of 100 mg clozapine pills dispensed by the Pharmacy Division to the inpatient units was the outcome and considered a proxy measure of clozapine prescriptions. The number of occupied inpatient unit beds and the number of patients admitted with F20-F29 (ICD-10) diagnoses during the study period were considered to be possible confounders.

Results: A multiple linear regression model showed that time in months was independently associated with an increase in the number of clozapine pills dispensed by the Pharmacy Division (β coefficient = 15.82; 95% confidence interval 10.88-20.75).

Conclusion: Clozapine prescriptions were found to have increased during the 5-year period studied, a trend that is opposite to reports from several other countries.

Keywords: Clozapine, inpatient psychiatry, pharmacoepidemiology.

Resumo

Introdução: Clozapina é um medicamento reconhecidamente eficaz para alguns pacientes com esquizofrenia refratária ao tratamento. Apesar dos seus potenciais benefícios e de sua indicação clínica para aproximadamente 30% dos pacientes, a frequência de prescrição de clozapina é baixa.

Objetivos: Avaliar a tendência na prescrição de clozapina durante um período de 5 anos em um hospital psiquiátrico.

Métodos: Neste estudo observacional, dados coletados prospectivamente pelo Serviço de Arquivo Médico e Estatístico e pela Divisão de Farmácia (DF) do Instituto de Psiquiatria de Santa Catarina foram analisados por pesquisadores cegos para a coleta de dados. O número de comprimidos de clozapina 100 mg dispensados pela DF às enfermarias foi considerado a variável dependente e a medida de prescrição de clozapina. Número de leitos de internação ocupados e número de pacientes admitidos com diagnósticos F20-F29 (CID-10) durante o período de estudo foram considerados possíveis confundidores.

Resultados: Após análise com modelo de regressão linear múltipla, tempo em meses foi independentemente associado com aumento do número de comprimidos de clozapina 100 mg dispensados pela DF (coeficiente β = 15,82; intervalo de confiança de 95% 10,88-20,75).

Conclusão: Houve um aumento na prescrição de clozapina durante o período de 5 anos estudado, uma tendência oposta à relatada em vários outros países.

Descritores: Clozapina, farmacoepidemiologia, internação psiquiátrica.

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Submitted Jul 18 2016, accepted for publication Apr 03 2017.

Suggested citation: Niehues GD, Balan AB, Prá VB, Pellizzaro RS, da Silva PR, Niehues MD, et al. Trends in the prescription of clozapine in a psychiatric hospital: a 5-year observational study. Trends Psychiatry Psychother. 2017;39(3):158-164. Epub 31 July 2017. <http://dx.doi.org/10.1590/2237-6089-2016-0053>

Introduction

Clozapine is a well-recognized effective treatment for some patients with treatment-resistant schizophrenia (TRS).^{1,2} In a study by Stroup et al., national data were used to compare several outcomes between adults with TRS on clozapine therapy and those on other antipsychotics. The results showed that clozapine treatment was associated with lower rates of psychiatric admission, antipsychotic discontinuation, and use of additional antipsychotic medications.³ Even though it has potential benefits and approximately 30% of the patients have a clinical indication for clozapine use, prescription rates are low. In a retrospective analysis of data from 45 U.S. states, Stroup et al. found that among almost 630,000 antipsychotic treatments, only 5.5% of patients with treatment resistance were under clozapine treatment. In addition, among all newly prescribed antipsychotic treatments, only 2.5% were for clozapine.⁴ Prescription rates are not homogeneous across the country, but even in regions with higher levels of prescription, rates are lower than 20%.⁵ Not only is clozapine underused; its prescription is decreasing in some countries, and initiation is delayed.⁶⁻¹⁰ The reasons for this reduction range from the life-threatening risks of agranulocytosis¹¹ and myocarditis¹² to highly disturbing hypersialorrhea¹³ and constipation.¹⁴ In addition, the special care needed to monitor for possible blood dyscrasias may discourage psychiatrists from prescribing clozapine.¹⁵ As a result, many patients and their relatives are deprived of the potential benefits of clozapine therapy.^{3,16}

In this study, we evaluated 5-year trends in clozapine prescription (between January 2010 and December 2014) in a Brazilian tertiary psychiatric hospital. We also evaluated the number of beds occupied and the number of patients admitted with diagnoses of schizophrenia, schizotypal disorder, and delusional disorder in the same period and whether these variables were associated with the number of clozapine prescriptions dispensed.

Methods

Overall study design

This was an observational study that used data obtained longitudinally between January 2010 and December 2014 from the Medical and Statistical File Service (Serviço de Arquivo Médico e Estatístico, SAME) and the Pharmacy Division (PD) of the Instituto de Psiquiatria de Santa Catarina (IPQ/SC), located in São José, state of Santa Catarina, Brazil. The objective was to assess trends in clozapine prescriptions in the

period assessed. The number of beds occupied, first hospitalizations, and rehospitalizations of patients diagnosed with schizophrenia, schizotypal disorder or delusional disorder (F20-F29), identified according to the ICD-10 Classification of Mental and Behavioural Disorders¹⁷ at the time of admission to the emergency unit, were also analyzed as independent variables and considered possible confounders in a multiple linear regression model. The disorders covered by F20-F29 diagnoses were chosen because clozapine is mainly prescribed for TRS, given its superior efficacy.¹⁰

Data collection

The IPQ/SC is the only public psychiatric hospital in the metropolitan region of Florianópolis, capital of the state of Santa Catarina. Thus, it is the referral hospital for a population of approximately 1 million inhabitants who need acute tertiary psychiatric inpatient treatment and urgent care. The total number of beds available in the hospital is 160, 40 of which are reserved for male patients requiring substance use disorder detoxification. Of the remaining 120 beds, 80 are designated for male patients and 40 for female patients. No outpatient treatment is provided by the hospital.

Monthly, the SAME of the IPQ/SC organizes data collected daily in reports that summarize a wide range of information, including number of consultations at the emergency service, number of first admissions, number of readmissions, mean length of stay, patient origin (by city), and diagnosis upon admission. These monthly reports do not disclose any information that could lead to patient identification. Additionally, the PD of the IPQ/SC registers the number, dosage and type of medication dispensed to each inpatient unit and also provides monthly reports of this information. Medications are distributed daily and strictly according to the psychiatrist's prescriptions. Thus, the number of clozapine pills dispensed by the PD was considered a proxy of clozapine prescription for the aims of this study.

The study received ethical approval via Plataforma Brasil system submission.

Statistical analysis

In addition to descriptive statistics, a linear regression model was applied to verify the association between time in months and absolute number of 100 mg clozapine pills dispensed by the PD (which directly reflects psychiatric prescriptions). The absolute number of beds occupied and number of admissions and readmissions associated with F20-F29 diagnoses at the emergency unit were also analyzed as independent variables, and those presenting $p \leq 0.20$ in the former analysis were

included in a multiple linear regression model. In the final model of the multiple linear regression analysis, $p < 0.05$ was considered statistically significant. The normal distribution of the standardized residuals was analyzed to verify the extent to which the model fit the data.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 17.0.

Results

From January 2010 to December 2014, there were a total of 4,115 admissions with F20-F29 diagnoses at the emergency unit of IPQ/SC. Male patients accounted for 969 of the first admissions and 2,032 of the readmissions; the remaining 1,114 were female patients, comprising 462 first admissions and 652 readmissions. Considering the number of beds available for male (80) and female patients (40), during 87% of the study period, the female inpatient unit had an occupation rate above its capacity, compared to 38% of the time for the male inpatient unit.

Regarding the prescription of 100 mg clozapine pills, 57,427 pills were dispensed by the Pharmacy Division during the 5-year study period. Evaluation of the annual number of pills dispensed from 2010 to 2014 revealed a total increase of 141% in clozapine prescriptions in the hospital, corresponding to an increase of 117% in the male inpatient unit and 229% in the female inpatient unit.

Table 1 shows the results of the descriptive analysis (mean and standard deviation); Figures 1, 2, and 3 show these trends graphically over time. All continuous variables failed to reject the null hypothesis of a normal distribution.

A linear regression analysis was applied to test the trends in clozapine prescriptions between January 2010 and December 2014. Additionally, we assessed the association of clozapine prescriptions with the number of F20-F29 diagnoses upon admission and the number of patients in beds. In the simple linear regression analysis, time in months and number of F20-F29 diagnoses were associated with number of 100 mg clozapine pills dispensed (Table 2). However, in the multiple regression analysis, only time in months remained associated with clozapine prescription ($p < 0.001$) (Table 3). According

Table 1 - Descriptive analysis of the number of 100 mg clozapine pills dispensed, beds occupied, and F20-F29 diagnoses upon admission to the emergency unit by year (mean and standard deviation)

	2010	2011	2012	2013	2014
Clozapine dispensed					
Total	544.67 (192.92)	711.92 (264.42)	987.75 (295.77)	1230.08 (352.46)	1311.17 (415.36)
Male	428.58 (118.51)	606.25 (192.23)	673.50 (153.20)	816.08 (196.79)	929.67 (284.56)
Female	116.08 (114.82)	105.67 (122.82)	314.25 (242.07)	414 (276.41)	381.50 (230.32)
F20-F29 diagnoses					
Total	75.50 (11.59)	72.17 (7.53)	65.92 (11.48)	60.67 (6.60)	68.67 (8.71)
Male	56.33 (9.25)	52.67 (4.40)	49.33 (9.09)	43.08 (5.90)	48.67 (7.15)
Female	19.17 (4.09)	19.50 (5.18)	16.58 (3.75)	17.58 (4.25)	20 (4.78)
Beds occupied					
Total	112.75 (8.61)	138.25 (4.77)	146 (8.52)	132.58 (7.25)	126.92 (7.90)
Male	69.58 (4.76)	80.42 (3.73)	84.75 (4.83)	82.50 (6.95)	77.75 (4.86)
Female	43.17 (4.76)	57.83 (3.21)	61.25 (5.43)	50.08 (3.87)	49.17 (5.08)

Table 2 - Simple linear regression analysis with independent variables (number of admissions with F20-F29 diagnoses, number of beds occupied, and time) and a dependent variable (number of 100 mg clozapine pills dispensed by the hospital pharmacy)

Variables	R	R ²	F	β coefficient (95%CI)	p
Number of clozapine pills dispensed					
Admission with a F2X diagnosis*	0.31	0.09	6.02	-12.43 (-22.58 to -2.29)	0.02
Beds occupied	0.15	0.02	1.32	4.70 (-3.48 to 12.88)	0.25
Time (by month)	0.68	0.47	50.70	16.56 (11.90 to 21.21)	< 0.001

95%CI = 95% confidence interval.

* According to evaluation by the physician on call at the time of admission: schizophrenia, schizotypal disorder, and delusional disorder (F20-F29) according to the ICD-10 Classification of Mental and Behavioural Disorders.¹⁷

to the results, for each month, there was an increase of almost 16 100 mg clozapine pills prescribed (Table 3).

Discussion

In this study, we found an increase in clozapine prescriptions between January 2010 and December 2014, totaling 60 months of observation. This trend remained even after controlling for number of admissions with F20-F29 diagnoses according to the ICD-10 Classification of Mental and Behavioural Disorders.¹⁷ Thus, this finding suggests that the increase was more likely due to a rise in the proportion of patients receiving clozapine than a consequence of an increase in the absolute number of patients diagnosed with psychotic disorders. Although we cannot ignore the possibility that the clinical severity of patients admitted increased over time, it is implausible that either this or clozapine indications for aggressive and suicidal behavior, included in the prescription guidelines especially from 2010, would be responsible for a 140% increase in clozapine prescriptions.^{18,19}

Despite its known superior efficacy, clozapine prescriptions have decreased in the United States, from

11% of the total atypical antipsychotic prescriptions in 1999 to approximately 5% in 2002. In addition to the United States, New Zealand and the UK also seem to underutilize clozapine.¹⁰ The association of clozapine use with risks of neutropenia, agranulocytosis, seizures, and myocarditis could explain the reluctance of psychiatrists to prescribe it.²⁰ Moreover, the need for careful and continuous blood monitoring could also discourage adherence by patients.²¹ The possibility of these severe adverse events could also be related to the reported delay in clozapine prescription to patients with appropriate clinical indications – this could be one of the reasons why psychiatrists and pharmacists are reluctant to prescribe and dispense it, respectively, in some hospitals.²² The main concern related with this phenomenon is that patients who could benefit from the therapeutic effects of clozapine, especially those with TRS, may not receive the appropriate treatment for their illness. In a review by Warnez & Alessi-Severini, the authors estimated that only 25% of patients with TRS were treated with clozapine in 1999.¹⁰

Specific policies that combine guidelines for prescription and monitoring for side effects could help change this scenario and allow patients who could benefit from clozapine therapy to receive this

Table 3 - Multiple linear regression analysis showing independent associations with number of 100 mg clozapine pills dispensed by the hospital pharmacy

Variables	R	Adj. R ²	F	β coefficient (CI 95%)	p
Number of clozapine pills dispensed	0.69	0.46	25.71		< 0.001
Admissions with F2X diagnostic				-3.81 (-12.06 to 4.44)	0.36
Time (by month)				15.82 (10.88 to 20.75)	< 0.001

95%CI = 95% confidence interval.

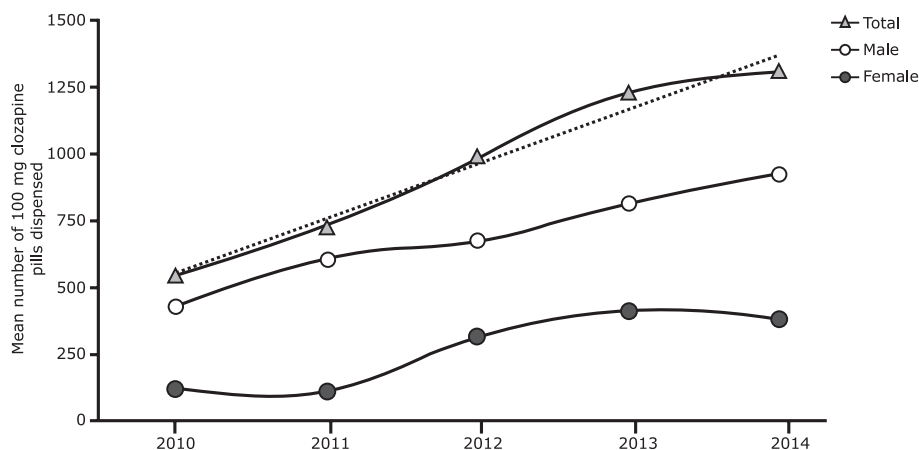


Figure 1 - Trends in the number of clozapine prescriptions from January 2010 to December 2014

treatment. Malalagama et al. evaluated the patterns of clozapine prescription in Australia over 10 years. Based on the amount of clozapine imported into Australia, they calculated a rate per 1,000 people over 16 years old. Their results showed an increase of 77% in clozapine imported into the country from 2000 to 2009. This increase was disproportionately higher than the growth of the population in the same period, suggesting a change in the prescription pattern; in other words, more patients took clozapine. The rationale behind this change may be related to compliance with scientific protocols for prescription, as the major peaks of clozapine importation during this period coincide with

the release of guidelines, in 2002 and 2005.²³ Similarly, following low rates of clozapine prescription in New York, the New York State Office of Mental Health released the “Best Practices Initiative – Clozapine” in 2010 to stimulate its prescription by supporting evidence-based practices. This initiative played a fundamental role in the increase in clozapine prescriptions, which nearly doubled at state-operated facilities.²⁴

There are at least three possible reasons that might explain the rise in the number of clozapine prescriptions at IPQ/SC. First, the state of Santa Catarina defrayed the cost of the medication. Second, an intern medical residence program in psychiatry was established and

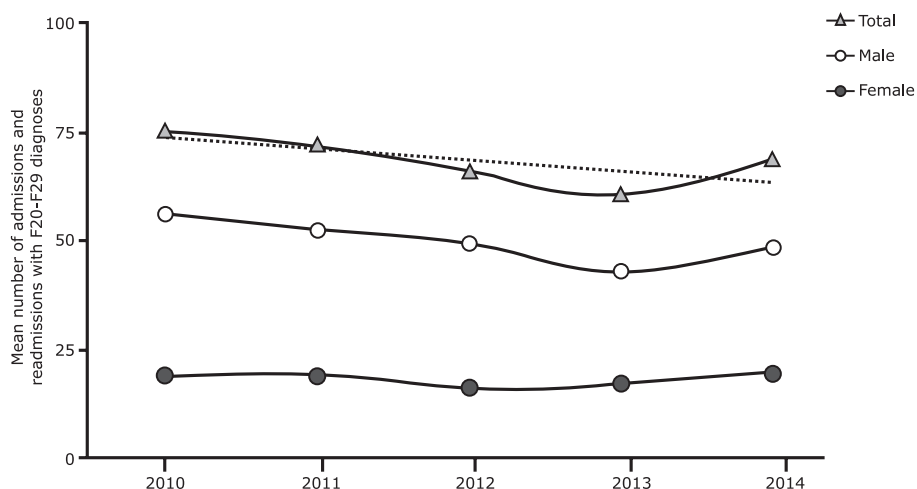


Figure 2 - Trends in the number of patients admitted to the emergency unit with F20-F29 diagnoses from January 2010 to December 2014

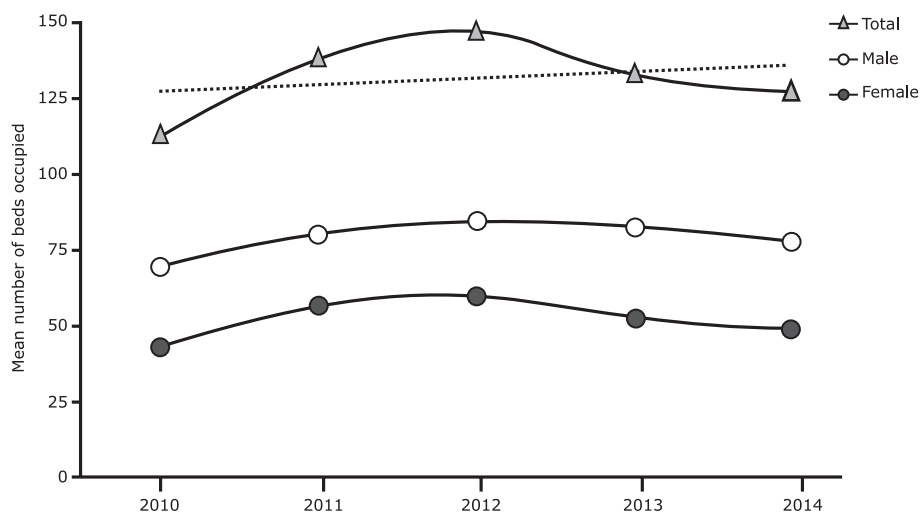


Figure 3 - Trends in the number of beds occupied from January 2010 to December 2014

based its interventions on evidence-based guidelines. Finally, there may have been a learning curve for the staff related to the management of side effects, blood monitoring, and careful instruction of patients and their relatives about the necessary precautions after discharge, including a written report on outpatient medical assistance (discharge summary).

Our study has several limitations. We were not able to determine whether there was an increase in the mean dosage of clozapine per patient, which could increase the absolute number of pills dispensed without necessarily raising the total number of patients under clozapine therapy. In addition, despite suggested by our results, we cannot assure that new patients were under clozapine treatment. The diagnosis made upon admission to the emergency unit may not agree with the assistant psychiatrist's diagnosis. The lack of patient sociodemographic and clinical information also prevents the identification of other variables that could be associated with the increased prescription of clozapine. Another limitation is that these results are related to inpatient treatment; thus, we are unable to determine whether the same trend is found in outpatient care. Finally, our results suggest only a rise in the number of clozapine pills dispensed between 2010 and 2014, but do not give any information about the efficacy and safety of the medication. However, to our knowledge, there were no reports of severe side effects related to the clozapine therapy during treatment at IPQ/SC.

Conclusion

Despite its efficacy – supported by vast scientific evidence – and safety – under close and careful monitoring –, clozapine prescriptions are both low and delayed for TRS patients in many health care systems. This may be explained by reluctance to prescribe due to the risk of serious hematological adverse events, the need for close monitoring and side effects that could lessen patient adherence. Greater compliance with evidence-based guidelines for prescription and monitoring can help improve the access of patients to clozapine treatment. Even though the present study was conducted at a state referral psychiatric hospital, these results cannot be considered generalizable to the country.

As a final note, although it was not an objective of our study, it is important to note that the reduced availability of beds for female patients at IPQ/SC can be hardly justified by epidemiological differences. This issue should be an urgent focus of specific policies.

Acknowledgements

The authors are thankful to the staff of IPQ/SC for their essential cooperation during the study, especially to Ledemir Geraldo Alegre, chief of the Pharmacy Division, and those responsible for the SAME, on behalf of José Medeiros.

Disclosure

No conflicts of interest declared concerning the publication of this article.

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