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Clozapine use decreases the number of hospitalizations per year in patients with treatment-resistant schizophrenia

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ABSTRACT

For years, the management of schizophrenia has represented a challenge for clinicians, with antipsychotic treatments usually resulting in relapses and new hospitalizations. Clozapine has been shown to be an effective medication for treatment-resistant schizophrenia (TRS), but is currently underused due to its potential side effects. Nevertheless, research has suggested that clozapine reduces future hospitalizations in patients with TRS. This study aims to verify the rates of hospitalizations in patients with TRS under long-term use of clozapine. We retrospectively analyzed clinical data from 52 individuals with TRS before and after the use of clozapine. The mean duration of treatment with and without clozapine was 6.6 (± 3.9) and 8.5 years (± 6.6), respectively. Patients had a median of 0.5 (0.74) hospitalizations per year before the use of clozapine and 0 (0.74) hospitalizations after it (p = 0.001). Therefore, the use of clozapine resulted in an expected reduction in the number of hospitalizations per year in individuals with TRS.

Keywords: *Schizophrenia; Treatment-resistant; Clozapine; Hospitalization*

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INTRODUCTION

Schizophrenia is a complex psychiatric disorder with multiple pharmacological treatment options. Despite a proven clinical efficacy, treatment with antipsychotics may not prevent patients with schizophrenia from relapsing, with rates as high as 80% within 5 years of discharge from the first episode[1]. Clozapine has been established as one of the most effective medications among antipsychotics and the first therapeutic option in patients with treatment-resistant schizophrenia (TRS)[2]. Nonetheless, potential side effects such as agranulocytosis, myocarditis, and metabolic syndrome may discourage clinicians from prescribing clozapine to patients with TRS[3], despite its association with lower mortality[4]. Clinicians may thus defer the initiation of treatment with clozapine, which has been associated with poorer long-term outcomes[5]. Additionally, clozapine has been shown to delay future hospitalization in patients with TRS[6,7]. However, only a few studies have assessed hospitalization rates in individuals with TRS who used clozapine in the long-term, usually ranging from 2 to 6-year reports[8-10]. Therefore, this study aimed to assess hospitalization rates among patients with TRS under long-term use of clozapine in a sample of a tertiary hospital in southern Brazil.

METHODS

This is a retrospective mirror-image observational study comparing hospitalizations of individuals with TRS before and after clozapine use. Patients were recruited from the schizophrenia outpatient facility of Hospital de Clínicas de Porto Alegre, Brazil. Inclusion criteria were: a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of schizophrenia, patients

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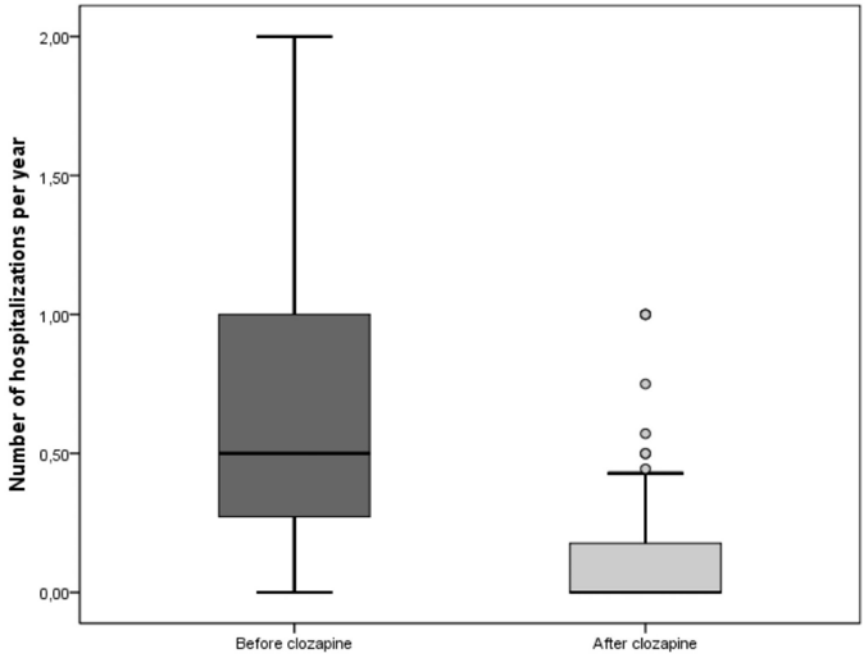
aged 18 years or older, and current clozapine use on a stable dose for at least 6 months. TRS was defined as a lack of response (ie, a reduction of less than 30% in the Brief Psychiatric Rating Scale) to at least 2 different classes of antipsychotics prescribed for 6 weeks each. All patients signed a consent form and the study was approved by the local ethics committee (project number 15-0282). Patient anonymity was preserved at all times. Our study was conducted in accordance with the latest declaration of Helsinki.

Clinical information was retrospectively gathered from patient records and family reports, including age of onset, duration of illness, and number of hospitalizations before and after clozapine use. A variable was created to verify the rates of hospitalizations per year before and after clozapine use. Data were analyzed using SPSS version 20.0. Demographic and clinical characteristics were analyzed using the Mann-Whitney test or Student's t-test. Descriptive analyses are presented as mean (standard deviation) or median (interquartile range), and p-values < 0.05 were considered significant.

RESULTS

Our sample consisted of 43 men and 9 women. The mean age was 37.5 years (± 8.8), and mean age of illness onset was 22.6 (± 6.5). Nearly half the patients (48.8%) were receiving sickness benefits, 20.9% of them were employed, 20.9% were unemployed, and 9.3% were either students or had unpaid occupations. The mean duration of illness was 14.9 years (± 7.8). Patients were using a mean clozapine dose of 561 mg daily (± 189 mg). Duration of treatment without clozapine was 8.5 years (± 6.6), and with clozapine it was 6.3 years (± 3.9). The total number of hospitalizations was a median of 3.5 (6.5). The median number of hospitalizations per year before clozapine was 0.5 (0.74), while after clozapine it was 0 (0.19) (p = 0.001) (Figure 1).

Figure 1: Box-plot of the number of hospitalizations per year before and after clozapine use in patients with treatment-resistant schizophrenia. Median values are indicated by horizontal lines. A Mann-Whitney test was performed to compare groups (p = 0.001).



DISCUSSION

This study supports previous findings of clozapine efficacy in TRS that showed reductions in hospitalization rates[11]. Clozapine use is also associated with important outcomes such as mortality reduction, low rates of treatment discontinuation[12], and treatment cost-effectiveness in TRS patients with a high level of hospital use[13].

Our findings highlight the important impact that the use of clozapine has on the treatment of schizophrenia, maintaining patients for longer periods in community settings; they also strengthen the choice of this drug among other antipsychotic medications, including atypical ones. In this sample, nearly 70% of the patients were either unemployed or on medical leave before clozapine use, evidencing a poor functional status. Considering that clozapine

has been shown to enhance employment status[14] and that these patients had a significant delay in its initiation, an earlier prescription might have prevented such poor outcomes. Therefore, clozapine should be used early in the treatment course, ideally within the critical treatment window of up to 2.8 years after TRS diagnosis, as proposed by Yoshimura et al.[15]. This may lead to higher functioning and occupational statuses by individuals with TRS, further reducing poor long-term outcomes and therapeutic costs.

The main limitation of this study is its retrospective design, which relied on medical records and the recollection of patients and/or their family members. However, this could reflect underestimated results, since patients and family members may have a higher probability of not precisely recalling events from several years ago when compared to more recent ones, implying that the number of hospitalizations before the use of clozapine may have been higher than reported. We also did not analyze possible confounding factors, such as additional medications or other treatments. Moreover, our small sample may have been subject to selection bias, as the patients' participation was dependent on their acceptance and availability for the study, which might limit our conclusions. Therefore, large prospective studies on long-term outcomes are further needed in order to ascertain the clinical efficacy of clozapine in TRS.

Conflicts of interest

The authors declare no conflicts of interest.

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