Patterns of clozapine and other antipsychotics prescriptions in patients with treatment-resistant schizophrenia in community mental health centers in São Paulo, Brazil

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Abstract

Background: Despite of its global underuse, clozapine is still the golden standard antipsychotic for patients with treatment-resistant schizophrenia (TRS). **Objective:** To evaluate the patterns of clozapine and other antipsychotic drugs prescription in TRS in community mental health centers in São Paulo, Brazil. **Methods:** A multiple-choice questionnaire was applied to fifteen psychiatrists at five centers inquiring about patients' clinical condition, adherence to oral treatment and current antipsychotic treatment. History of previous and current antipsychotic treatment was collected through medical chart review. **Results:** Out of 442 schizophrenia patients, 103 (23.3%) fulfilled the criteria for TRS. Fifty-eight patients (56.3%) were receiving polypharmacy; 30 (29.1%) were on atypical antipsychotic monotherapy, 14 (13.6%) were on typical antipsychotic monotherapy, 25 (24.3%) were taking depot antipsychotic medication and only 22 (21.4%) were receiving clozapine. **Discussion:** As well as in other parts of the world, many TRS patients (78.6%) receive other drugs instead of clozapine in São Paulo, the best evidence-based medication for patients with TRS. The government should make every effort to provide medical training and the equipment and logistic support to adequately serve those who could benefit from clozapine treatment at the community health centers.

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Keywords: Schizophrenia, drug resistance, drug prescriptions, clozapine, antipsychotic agents.

Introduction

Antipsychotic drugs are the mainstay of the treatment of schizophrenia, but although they are effective in the majority of patients, approximately 30% of this population has little or no benefit from conventional antipsychotic treatment[1]. These patients have more severe levels of psychopathology, greater number of episodes of illness and hospitalizations, and poorer quality of life compared to those who respond to treatment[2,3]. Their care also requires a disproportionately high proportion of the total cost of treating schizophrenia[4]. The term treatment-resistant schizophrenia (TRS) is currently applied to patients with persistance of moderate to severe levels of psychotic symptoms after at least two optimal treatments with different antipsychotic drugs[5].

Brazil's Constitution establishes health as a right for all and a duty of the State, thus in our country most of the patients with TRS are treated in public community mental health centers, named *Centros de Atenção Psicossocial* (CAPS), (Psychosocial Care Centers). These centers are located nationwide and assist people with the most severe mental disorders, providing intensive and multidisciplinary care, with focus on medical treatment and social reinsertion through access to labor, civil rights and leisure.

Clozapine, the first atypical antipsychotic agent, is the medication of choice when TRS is confirmed, and many studies have demonstrated its superiority over other antipsychotic compounds in such cases[6-8]. There are, however, drawbacks to the use of clozapine, foremost the need for regular blood counts, due to the increased risk for agranulocytosis, limiting the prescription of this medication. In fact, studies conducted worldwide have shown that clozapine prescription is less than the actual number of patients resistant to the antipsychotic treatment[9]. In Brazil, there is no study addressing neither the local population of TRS schizophrenic patients nor the pattern of antipsychotic prescription to these patients.

A Brazilian federal law advocating for the rights and protection of people with mental disorders states that the mentally ill person must be granted to the best treatment available, according to his/her needs[10]. Since clozapine is the best treatment for TRS patients, the aim of the present study is to investigate wether clozapine is actually and adequately prescribed for patients with TRS as well as to evaluate the patterns of antipsychotic drugs prescription for patients with TRS in the CAPS of São Paulo.

Methods

Study design

A cross-sectional study was conducted in six CAPS of São Paulo.

Study population and assessment

By the time of the study, São Paulo Municipality counted with 20 CAPS specialized in assisting adults with severe mental disorders and six of them entered the research. Although these CAPS's catchment area did not cover the whole city, the equipments appertained to the five different Regional Health Coordinations areas existing in São Paulo. This choice was made in order to involve the different realities of this megalopolis. The CAPS that entered the study were the first ones from which we had an acceptance in participate on it, which characterizes a convenience sample. We proceeded with the identification of all the patients with diagnoses ranging from F20 to F29 (schizophrenia, schizotypal and delusional disorders), according to the 10th Edition of the International Classification of Diseases

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(ICD-10). All centers allowed us access to their files, which identified all attending patients with their respective diagnoses.

Psychiatrists were invited to answer a multiple-choice questionnaire whereby they ranked, for each patient under their care, their current clinical condition, their adherence to antipsychotic treatment and their current antipsychotic treatment, using the following instruments:

a. Current Clinical Condition was evaluated using the Clinical Global Impression – Severity Scale (CGI-S). This scale assesses the clinician's subjective impression of the current state of the patient's illness. The rater is asked to "consider his total experience with the given population". The time span considered is the week prior to the rating, and the following scores can be given: 1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = among the most extremely ill patients. We have chosen this scale because it is frequently used to evaluate the psychopathological state of patients with schizophrenia[11], is easy to administer, is brief (it takes 1-2 min to be complete), has a good reliability in the clinical context and its results can be interpreted intuitively[12].
b. Adherence to antipsychotic treatment was defined according to the following criteria: 1. Totally Adherent: patient takes virtually all the doses of the prescribed antipsychotic drugs; 2. Partially Satisfactory: patient takes the majority of the doses of the prescribed medication; 3. Partially Unsatisfactory: patient takes less than half of the doses of the prescribed antipsychotic drug; and 4. Completely Non-adherent: patient takes very few doses or no medication at all.
c. Information on current antipsychotic treatment was evaluated according to psychiatrists' answers to the questionnaire and classified into the following cathegories: 1. Typical Antipsychotic Drug Monotherapy; 2. Atypical Antipsychotic Drug Monotherapy; 3. More than one Antipsychotic Drug; 4. Clozapine Therapy (single or concomitant use with other drug); and 5. No Antipsychotic Drug Use.

The questionnaire ended with an open question asking psychiatrists which would be the most important obstacle to prescribe clozapine.

To find out which patients could be diagnosed with TRS, we first selected patients rated with a level of severity of at least moderately ill on CGI-S, i.e., CGI-S ≥ 4. They were considered poor responders and had their medical charts extensively reviewed. The CGI-S cut-off was the same used by Kane *et al.*[13] to establish the cross-sectional criteria for TRS in a landmark study that demonstrated clozapine's superiority compared to chlorpromazine in TRS patients. The severity level defined as "moderately ill" in the CGI-S corresponds to approximately 75 in the Positive and Negative Syndrome Scale (PANSS)[14] which is a threshold degree of severity which is generaly accepted for inclusion criteria in studies that evaluate antipsychotic drug efficacy.

All antipsychotic drugs previously and currently prescribed to the poor responder patients, including doses and length of treatment, were retrieved from the charts. Socio-demographic and clinical data such as number of previous hospitalizations and period of treatment in CAPS, amongst others, were also obtained.

All patients considered poor responders who have had at least two adequate antipsychotic drug trials with different agents were defined as TRS patients, according to the recommendations of the Schizophrenia Algorithm of the International Pharmacological Algorithm Project[5]. An adequate trial was defined as a period of at least 8 weeks treatment with antipsychotic with doses at or above the drug therapeutic range[15].

All patients taking clozapine also had their charts reviewed.

Inclusion and exclusion criteria for treatment-resistance

Inclusion criteria:

a) Patients diagnosed with schizophrenia or schizoaffective disorder (ICD-10: F20 or F25);
b) Poor responder patients that had, at least, two adequate antipsychotic drug trials with different agents or;
c) Patients on clozapine therapy, independent of the CGI-S score.

Exclusion criteria:

a) Patients with a concomitant diagnosis of mental retardation (ICD-10: F70 to F79) or organic mental disorder (ICD-10: F06), in order to avoid misdiagnosis;
b) Partially unsatisfactory adherent and non-adherent patients and;
c) Patients whose last psychiatric evaluations were written more than 90 days prior, since changes in clinical status in this period could not be ruled out.

Statistical analysis

Descriptive statistics were used to describe the study sample, psychiatrist's responses and the chart findings. Statistical analysis was conducted using the SPSS 18.0 for Windows.

Ethical aspects

This study was approved by the research ethics committees of the Universidade Federal de São Paulo and the Municipal Health Office of São Paulo.

We initiated the study after obtaining written consent from the directory board of each CAPS and from psychiatrists that agreed to participate in the research.

Results

Six CAPS were invited to participate in the study with a total of 2,191 patients: CAPS Pirituba-Jaraguá (n = 389); CAPS Itaim Paulista (n = 976); CAPS Jardim Lídia (n = 45); CAPS Jabaquara (n = 188); CAPS Lapa (n = 192) and CAPS Perdizes (n = 401).

Psychiatrists from the CAPS Itaim Paulista were not able to cooperate with the study due to time constraints; therefore we have worked with a total of 1,215 patients (Figure 1). Fifteen out of 16 psychiatrists in the five remaining CAPS agreed to answer the questionnaire. A total of 442 (40.1%) patients had the diagnosis of schizophrenia or schizoaffective disorder without comorbidities like Mental Retardation and Organic Mental Disorder and were investigated in order to determine whether they fulfilled TRS inclusion criteria.

Thirty-six patients were excluded of the study because psychiatrists had not completed the screening questionnaire regarding their clinical condition. A total of 171 patients (160 with scores ≥ 4 on CGI-S and 11 taking clozapine with scores < 4 on CGI-S) had their charts reviewed. Fifteen patients whose last psychiatric evaluations were performed more than 90 days were excluded.

The chart review showed that 53 of the patients not taking clozapine did not fulfill the TRS criteria, due to the fact that 42 had not received adequate antipsychotic drug trials and 11 had an unsatisfactory adherence to oral treatment.

Finally we found that 103 (23.3%) out of the 442 patients from the CAPS fulfilled the TRS inclusion criteria.

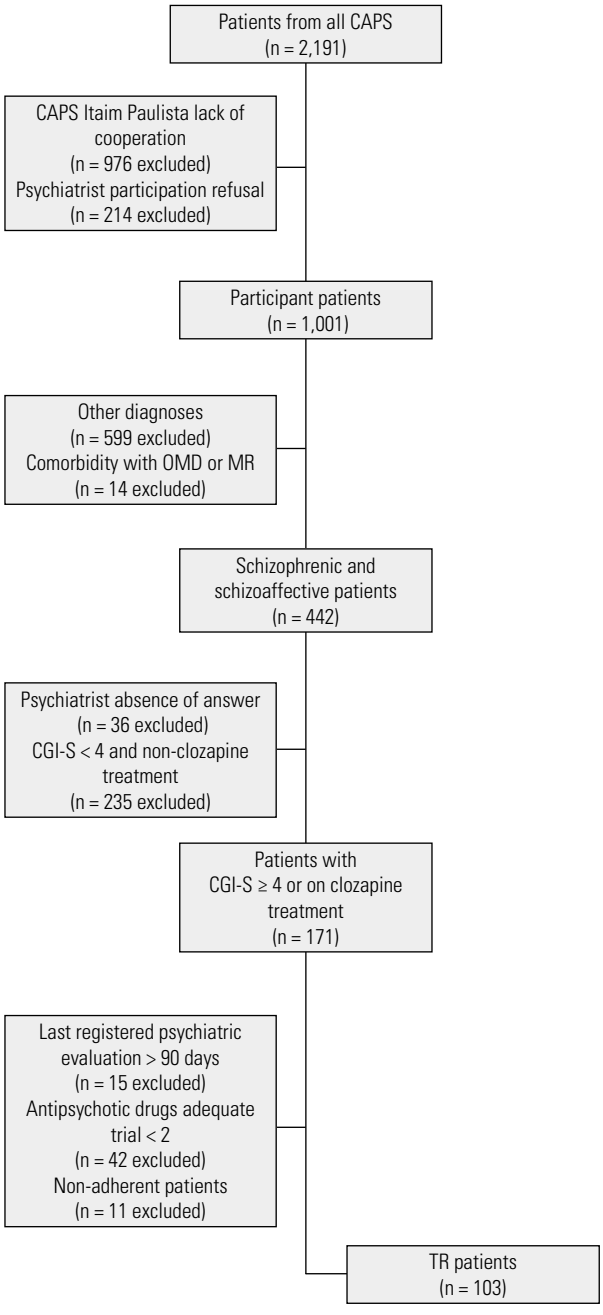
The mean age of this group (n = 103) was 41.8 (SD: 12.78) years and 65 (63%) were men, with a mean duration of disease of 17.5 years (SD: 11.02). Schizophrenia was the diagnosis of the great majority (92.2%) of these patients. See table 1.

Figure 2 shows the antipsychotic drugs prescribed for the TRS group. The most frequently prescribed drugs were, in decreasing order, haloperidol (oral = 38, 36.9%; decanoate = 25, 24.3%), olanzapine (n = 32; 31.1%), chlorpromazine (n = 31; 30.1%) and clozapine (n = 22; 21.4%). Fifty-eight patients (56.3%) were taking more than one antipsychotic drug, 8 were taking 3 antipsychotic drugs and 1 was taking 4 antipsychotic drugs; thirty (29.1%) were on atypical antipsychotic monotherapy and 14 (13.6%) were on typical antipsychotic monotherapy. Six patients were taking clozapine in association

with another antipsychotic agent. In four cases the other drug was haloperidol, in the others, one was taking quetiapine and one was taking levomepromazine.

Altogether, psychiatrists prescribed 100 typical and 81 atypical drugs. One patient (1.0%) was not taking any antipsychotic drug. The lifetime mean number of antipsychotic trials was 2.66 (SD: 1.69), but this number is probably underestimated, due to the difficulty of tracking antipsychotic prescriptions prior to the CAPS admission.

Nine psychiatrists (60%, *n* = 15) prescribed clozapine at least for one patient. Table 2 shows main obstacles associated to clozapine prescription according to psychiatrists.



CAPS: Centro de Atenção Psicossocial; OMD: organic mental disorder; MR: mental retardation; CGI-S: Clinical Global Impression – Severity Scale; TR: treatment-resistant.

Figure 1. Study population - from all patients to treatment-resistant patients.

Table 1. Treatment-resistant schizophrenia patient's characteristics (n = 103)

Variable	Treatment-resistant schizophrenia patients (n = 103)
Diagnosis – % (N)	92.2% (95) Schizophrenia, 7.8% (8) Schizoaffective Disorder
Gender – %(N)	36.9% (38) Female, 63.1% (65) Male
Age (Years) – Mean, (SD)	41.84 (12.78)
CGI-S – Mean (SD)	4.44 (1.10)
First Episode Age (Years) – Mean, (SD)	24.39 (10.32)
Disease Duration (Years) – Mean (SD)	17.58 (11.02)
First Treatment Age (Years) – Mean (SD)	26.97 (10.00)
Delay from First Episode and Treatment Initiation (Years) – Mean (SD)	2.14 (4.14)
Treatment Duration (Years) – Mean (SD)	15.04 (10.34)
Number of Antipsychotic Drugs adequately used through life – Mean (SD)	2.66 (1.70)
CAPS Treatment (Months) – Mean (SD)	92.18 (97.17)
Number of Hospitalizations – Mean (SD)	4.29 (6.06)
Number of Hospitalizations in the Past Year – Mean (SD)	0.18 (0.50)

SD: standard deviation; CGI-S: Clinical Global Impression – Severity Scale.

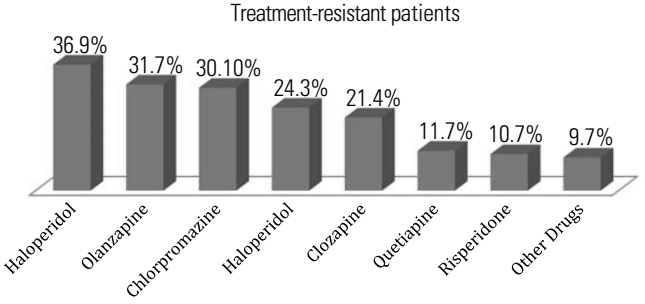


Figure 2. Antipsychotic drug treatment prescribed to treatment-resistant patients in CAPS.

Table 2. Obstacles to prescribe clozapine according to psychiatrists

Obstacles to prescribe clozapine	%	N
Patients low adherence to blood counts	53.33%	8
Laboratory delay in providing results and/or low reliability	26.67%	4
Psychiatrist lack of experience	13.33%	2
Dificulty in dosis titration	6.67%	1
Patients clinical comorbidities	6.67%	1
Lack of family support	6.67%	1

Discussion

In this study, which evaluated the antipsychotic drug prescription to 103 patients who fulfilled criteria for TRS attending community centers in São Paulo, it was found that psychiatrists frequently prescribed antipsychotic polypharmacy for these patients and clozapine was offered for only a small percentage of them. Of these 103 individuals, fifty-eight (56.3%) were on a polypharmacy regimen of treatment. It is well known that combining antipsychotic drugs is a very common therapeutic practice[16-18] in psychiatry, with some studies showing that the proportions of antipsychotic polypharmacy in United States of America and Canada are as high as 50%[19,20]. Nevertheless, its efficacy is not proven. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that antipsychotic combination was more prescribed to patients with high levels of symptoms, but in the end, it did not differ in terms of improving efficacy measures

compared to antipsychotic monotherapy[21]. Howes *et al.*[22] and Alessi-Severini *et al.*[23] carried out studies at Mental Health Centers in England and Canada, respectively, and found out that polypharmacy and three or more tries of antipsychotic treatment was a common feature before the initiation of clozapine.

Regarding the patients with TRS, some meta-analyses support combining another antipsychotic with clozapine in patients who do not respond fully to this medication[16,24,25] but the evidence of efficacy of these augmentation strategies is also scarce[24].

As a group, atypicals were more prescribed in monotherapy (30%), but typicals were more prescribed in general (100 typical prescriptions against 81 atypical prescriptions at the time of the research), with haloperidol as the most prescribed agent, both in monotherapy and in polypharmacy. Social-economic conditions may play a role in the high prevalence of typical antipsychotic prescription. People who attend CAPS usually have low income, and the low cost of typical antipsychotic drugs makes them more affordable. Moreover, prescribing a typical antipsychotic drug requires minimal paperwork in comparison to atypical agents. In Brazil, the government subsidizes treatment with several existing antipsychotic drugs, but while typical drugs can be obtained for free in public pharmacies, placed in numerous neighborhoods and thus easily accessible to everyone, in exchange of a regular prescription in duplicate, prescribing the atypical medications requires more paperwork because it is also necessary to fulfill a large protocol. These atypical antipsychotic drugs are listed in the Brazilian Program of High Cost Medications and are only available in Special Pharmacies, which exist in a number of two in São Paulo, a city of more than 11 million inhabitants. Therefore, even if the individual cost of the medications does not weigh in the choice of prescribing typical antipsychotics, the paperwork and the scantiness of Special Pharmacies probably contributes for the high prescription rates of haloperidol.

The use of clozapine varies enormously according to different countries and settings, with higher prescription rates in China[26] and Oceania[27] and lower in North America[28,29]. The rates of clozapine prescription for TRS patients found in Brazilian community centers were similar to rates found in studies carried out in the United States[28,29], an especially low proportion when compared to other countries[26,27,30]. Clozapine was only prescribed for 22 individuals, which represents 21.4% of the TRS patients, or 5% of the total number of schizophrenia patients, despite the abundant evidence of clozapine's superior efficacy and effectiveness compared with other antipsychotic drugs in the treatment of TRS patients[6,7,8,13,31,32]. Current clinical practice guidelines for the treatment of schizophrenia recommend that a trial of clozapine should be offered after the identification of resistance to antipsychotic treatment[1,15,33,34], which suggests that the major part of the psychiatrists participating in our study do not follow strictly to guideline recommendations, a feature also observed in other parts of the world[22,35].

Perhaps this scenario could be even worse in other parts of Brazil, since unlike São Paulo, the country's richest city, many cities do not have Special Pharmacies where people have access to high-cost medications. A generic clozapine formulation exists in Brazil for some years now, which allowed a cost reduction for consumers, but not enough to the very low-income stratum of our society.

There are several obstacles to the use of clozapine that may impact negatively in its prescription rate, some of them related to the patients and their families, like refusal to take blood counts and fear of potential side effects, some of them related to its special treatment regime, since clozapine requires slow dose titration and close monitoring during the initiation phase and careful management of treatment emergent side-effects. However, some studies underline that clinician-related factor are a main contribuitor to the low rates of clozapine prescription, as consultant psychiatrists may have little knowledge about certain aspects of clozapine, like its capacity to reduce suicide or drug abuse in patients with schizophrenia, and few experience in treating patients with this drug, since a significant number of the psychiatrists interviewed claimed to have had less than five patient on clozapine therapy[36,37].

The majority of psychiatrists identified patients' low adherence to blood routines as the main obstacle to prescribing clozapine. Psychiatrists tend to overestimate the patients' annoyance with hematologic control[36], which is in contrast with studies that focused on patient's opinion and identified that blood tests are not an usual cause of concern among patients on clozapine[38,39] and that they feel clinically better and prefer clozapine therapy over previously prescribed antipsychotic drugs[7,40,41]. It is remarkable that only two of the participating CAPS can run the blood tests in their own facilities, while the other centers refer their patients to primary care units in order for them to obtain hematological exams. Psychiatrists beliefs also interfere since they may think that if the patients have to move to another care unit to get blood routines, this could affect their adherence to treatment.

Problems with the blood tests were also pointed as obstacles to prescribe clozapine. Psychiatrists reveal that there is a long delay from the taking of the blood sample until they receive their results. This delay, which may take one week, could represent the difference between a rapid identification of a mild neutropenia and its adequate management, or a missed neutropenia that progresses into a severe agranulocytosis.

This study has some limitations, mainly regarding the diagnostic of TRS. The number of drug trials was established retrospectively, relying on the information retrieved from medical records. We cannot assure that all of the changes in drug prescription were based on treatment failure, since some medication changes might have had the goal of improving tolerability. However, the pattern of prescription among psychiatrists clearly shows an emphasis on polypharmacy, which, as discussed above, increase concerns about the risk of medication side effects. We believe, therefore, that the psychiatrists participating in our study are not primarily driven by tolerability concerns when prescribing antipsychotic drugs.

In addition to the number of adequate antipsychotic trials, we used the CGI-S to establish the diagnosis of TRS. This scale provides a global judgment of a patient's overall state and it cannot determine what psychopathological aspect, in terms of positive or negative symptoms, the study clinicians were considering while rating their patients and how that influenced their decision on which drug to prescribe. For example, negative symptoms are prevalent throughout the disease[42] and less responsive to antipsychotic treatment[43], thus psychiatrists may consider that there is little advantage in changing antipsychotic drug regimen on the basis of negative symptoms. However, if the use of CGI-S lacks in psychopathological specificity, it allowed us to obtain psychiatrists' opinion about the clinical status of their own patients in routine clinical practice, in a not burdensome or time-consuming manner.

Adherence to treatment was presumed by addressing psychiatrists about their perception. Byerly *et al.*[44] demonstrated a drastically underestimated antipsychotic non-adherence by clinicians when comparing antipsychotic adherence rates of outpatients assessed by electronic monitoring and by clinician rating. Therefore, we may also have underestimated non-adherence, leading to some inadequate TRS results.

This study endorses the low-adherence to treatment guidelines also found in other parts of the world. Its results can be potentially helpful in alerting psychiatrists and authorities of the low use of evidence-based treatments in São Paulo, which is demonstrated by the high prevalence of antipsychotic polypharmacy and the enormous gap between the prevalence of TRS in patients ordinarily treated in CAPS and clozapine prescription. Government authorities, legally committed to provide the most appropriate treatment to mentally ill people, should make every effort to supply the CAPS with the necessary equipment and logistic assistance to adequately serve patients who could benefit from Clozapine treatment. They also need to provide organizational and educational support in order to allow clinicians and staff to have the proper expertise for the identification of TRS and for the optimum management of clozapine, including the safest and most efficient monitoring of hematologic status.

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Conflict of interest

Dr Cecília Attux has received grant research from Roche.

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All other authors declare no conflict of interest inherent to this article.

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