This is a peer-reviewed, accepted author manuscript of the following article: Barbosa, W. B., Gomes, R. M., Godman, B., Acurcio, F. D. A., & Guerra Júnior, A. A. (2020). Real world effectiveness of olanzapine and risperidone in the treatment of schizophrenia in Brazil over a 16-year follow-up period; findings and implications. *Expert Review of Clinical Pharmacology*. https://doi.org/10.1080/17512433.2021.1865799

Real world effectiveness of olanzapine and risperidone in the treatment of schizophrenia in Brazil over a 16-year follow-up period; findings and implications

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Abstract

Introduction: Antipsychotics are widely prescribed for patients with schizophrenia. The Brazilian public health system provides these patients free of charge to patients and it is pertinent to evaluate their benefits. **Objective:** To evaluate the effectiveness of olanzapine and risperidone in the treatment of patients with schizophrenia in the real world and assessing risk factors for their discontinuation through a national non-concurrent cohort with 16 years of follow-up. **Methods:** Three SUS administrative databases were integrated by deterministic-probabilistic linkage. After, patients were matched (1:1) for psychiatric hospitalization, year of receiving the antipsychotic, sex and age, considering either olanzapine or risperidone at study entry. Kaplan-Meier was used to estimate the cumulative probabilities of discontinuation of treatment and associated factors were identified. Sensitivity analyzes were performed. **Results:** 3416 pairs of patients were included. Olanzapine had a longer time until discontinuation of treatment (p = 0.021), and risperidone had a higher risk of discontinuation (p = 0.021). Among patients persistent for at least 24 months, there was no statistically significant difference. **Conclusion:** Olanzapine demonstrated superior real-world effectiveness over risperidone, in terms of survival and psychiatric hospitalization. This superiority was not sustained in all analyzes.

Keywords: Antipsychotics, Brazil, databases, olanzapine, real world effectiveness, risperidone, schizophrenia.

1. INTRODUCTION

Schizophrenia is a complex mental health disorder that is associated with appreciable morbidity despite relatively low but growing prevalence rates [1, 2]; consequently, patients with schizophrenia must be carefully managed. In 2010, mental and behavioral disorders accounted for 7.4% of total global disability associated life years (DALYs), which comprised principally major depressive disorders (2.5%), anxiety disorders (1.1%), drug use disorders (0.8%), alcohol use disorders (0.7%), and schizophrenia (0.6%) [3]. However, others believe this is an underestimate [4]. In 2016, it was estimated that there were 20.9 million cases of schizophrenia globally, up from 13.1 million in 1990, giving an estimated point prevalence rate of 0.28% [1], with schizophrenia contributing 13.4 million years of life lived with disability globally [1]. Patients

with severe mental illness such as schizophrenia also have up to a 60% higher chance of dying prematurely from non-communicable diseases (NCDs), which their treatment often neglected due to underlying mental health conditions [4-6]. Schizophrenia is also associated with a high economic burden, estimated to range from 0.02% to 1.65% of a country's gross domestic product [7].

Antipsychotics remain the principal medicines to treat patients with schizophrenia [2, 8-10]. This includes atypical antipsychotics, or second generation antipsychotics (SGA), which include olanzapine and risperidone [9, 11-13]. However, there are concerns with the extent of antipsychotic polypharmacy, which is typically not recommended as this increases side-effect rates including extrapyramidal side-effects, QT prolongation and the metabolic syndrome, reduces adherence rates, as well as increasing mortality and costs [10, 14-18].

Several studies have now compared typical and atypical antipsychotics, and concluded that there are few differences in efficacy between them apart from potentially clozapine; however, there are differences between them in terms of safety and tolerability impacting on usage in practice [11, 19-25]. The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) studies were fundamental to better understand these differences and used the discontinuation of treatment (discontinuation of antipsychotic use) for any cause as a measure of efficacy, safety and tolerability, as they considered that interrupting or changing the antipsychotic in use occurs frequently and represents a major problem in the treatment of schizophrenia. Among the causes for discontinuation of treatment, CATIE studies considered hospitalization for exacerbation of schizophrenia, intolerability to the antipsychotic and the presence of serious adverse events, such as ideation or attempted suicide [25-27]. Despite methodological challenges, and through large secondary databases, some observational studies have also used discontinuation of treatment for any reason to measure the effectiveness and safety of antipsychotics in routine clinical care, i.e. in the real world, considering urgent psychiatric care and psychiatric hospitalizations as the main outcomes [28-30].

In Brazil, the public health system [*Sistema Único de Saúde* (SUS)] provides both typical antipsychotics, i.e. chlorpromazine and haloperidol, in both oral and injectable presentations as well as oral atypical antipsychotics, clozapine, olanzapine, quetiapine, risperidone and ziprasidone, free of charge for patients with schizophrenia [31,32]. Previous studies conducted in Brazil among patients in the SUS reported that atypical antipsychotics were responsible for most of the direct medical expenditures in a cohort of eleven years follow-up. Olanzapine and risperidone were the most prescribed antipsychotics, with olanzapine the most used despite being the most expensive with lower costs for risperidone [32]. However, there are concerns with equity of access to atypical antipsychotics in Brazil [31]. Consequently, we wanted to expand our original research in Brazil [32] by assessing the efficacy of olanzapine and risperidone in the real world and assess the risk factors for discontinuation of treatment in patients with schizophrenia to provide future guidance using a nationwide cohort with 16-year follow-up period. This is in line with an increasing tendency to use real-world evidence to assist society and decision-makers with health policies and resource allocation decisions although there are still challenges [33-37]. We believe this is particularly welcomed in this situation as there have been concerns with the reliability of comparative studies sponsored by respective pharmaceutical companies [38].

2. METHODS

2.1 Data source, study design and population

This study was performed with an open, non-concurrent, paired and nationwide cohort of adult patients diagnosed with schizophrenia, who received an atypical antipsychotic between January 2000 and December 2014. The follow-up period of this population occurred from January 1, 2000 to December 31, 2015 and was determined by the availability of the SUS databases.

SUS is the Brazilian public health system nationwide and serves all individuals, without depending on the individual's socio-economic status (SES), covering both complex and simple medical procedures as well as authorized medicines including high cost medicines. These medicines are provided free-of-charge provided that patients meet the agreed prescribing criteria every three months [31-33]. However, patients are free to purchase their medicines privately, either by paying out of pocket or through private health plans. Currently, in Brazil,

approximately 22% of the population have private health plans; however, these individual can also use SUS yet.

A national health database, centered on the individual, was developed through the deterministic and probabilistic integration of existing records in three SUS administrative databases: (i) Hospital Information System [*Sistema de Informações Hospitalares* (SIH/SUS)], (ii) Outpatient Information System [*Sistema de Informações Ambulatoriais* (SIA/SUS)] and (iii) Mortality Information System [*Sistema de Informação sobre Mortalidade* (SIM)]. In Brazil, notification of mortality through SIM is mandatory. Atypical antipsychotics dispensed monthly for patients, and outpatient procedures are registered with SIA/SUS, and hospital procedures are registered with SIH/SUS [32, 39, 40]. In addition, as mentioned, SUS needs to authorize the prescription every three months else 100% co-pay. In this way, maintain good follow-up of patients.

From this national health database, patients were extracted who: (i) received one or more of the atypical antipsychotics including clozapine [Anatomical Therapeutic Chemical code (ATC: N05AH02)], olanzapine (N05AH03), quetiapine (N05AH04), risperidone (N05AX08) and ziprasidone (N05AE04) (41); (ii) were diagnosed with one of the following diagnoses [International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10)]: paranoid schizophrenia (F20.0), hebephrenic schizophrenia (F20.1), catatonic schizophrenia (F20.2), undifferentiated schizophrenia (F20.3), post-schizophrenic depression (F20.4), residual schizophrenia (F20.5), simple schizophrenia (F20.6) or other schizophrenias (F20.8) and (iii) were prescribed atypical antipsychotics between January 1 2000 and December 31 2014. The choice of these atypical antipsychotics was due to their availability through SUS. The period of entry into the cohort was established so that each patient was followed up for at least 12 months. The excluded patients were those who: (i) received atypical antipsychotics following other ICD-10 diagnoses; (ii) under the age of 18 and (iii) who have not received any atypical antipsychotic for at least six months. We subsequently principally concentrated on olanzapine and risperidone when assessing discontinuation and related factors as these were the most prescribed atypical antipsychotics. The date of entry into the cohort was defined as the date of the first record of dispensing an antipsychotic recorded in SIA between 2000 and 2014.

Posteriorly, a paired analysis was established (1:1), of pairs matched for the presence of psychiatric hospitalization, year of first receipt of an atypical antipsychotic, gender and age in years at the time of first receipt of an atypical antipsychotic among patients who entered the cohort receiving either olanzapine or risperidone during the period follow-up. When more than one patient in any group was a therapeutic candidate for matching by the five variables, the pair allocation was selected at random.

2.2 Events

The discontinuation of treatment was the main outcome analyzed in this study, defined by psychiatric hospitalization or death for any reason during the follow-up period. The entry of an atypical antipsychotic, i.e. either olanzapine or risperidone, was defined as the first used by the patient with a minimum duration of six consecutive months. Consequently, from the perspective of intention to treat (ITT), the time until discontinuation of treatment with the therapeutic regimen based on olanzapine or risperidone was measured. Psychiatric hospitalization was used as an event assuming that the patient was hospitalized to obtain better control of schizophrenia symptoms, which suggests a possible treatment failure. Death from any cause was adopted as an event due to the impossibility of defining, in most cases, whether this occurred due to the consequences of schizophrenia and its management. The date of the event was defined as the date of psychiatric hospitalization or death, whichever came first, and censorship was characterized as loss of follow-up, defined as the date of the patient's last registration with the SIA, SIH, SIM or December 31, 2015, the final date for follow-up this cohort (right censorship).

2.3 Statistical analysis

The variables collected at the beginning of the study were: demographic variables (gender, age group, geographic region of residence and study entry period) and clinical variables [primary diagnosis (ICD-10), atypical antipsychotic use intensity, persistence in using atypical antipsychotics for 24 months, occurrence of previous psychiatric care and presence of any comorbidity]. The atypical antipsychotic use intensity (clozapine, olanzapine, quetiapine, risperidone and ziprasidone) was calculated by dividing the number of months in which the antipsychotic was dispensed by the patient's time in the cohort. Previous psychiatric care considered procedures performed on outpatient or hospital level or the provision of an atypical

antipsychotic through other ICD-10 diagnoses different from those of schizophrenia, prior to the use of some atypical antipsychotics that defined the beginning of patient monitoring in this cohort.

Comorbidities were identified using the indicators developed by Charlson *et al.* [42] and updated by Quan *et al.* [43]. Finally, the persistence in using an atypical antipsychotic for 24 months, occurrence of events (psychiatric hospitalization or death), and censorship, were monitored during the follow-up period of this study.

Discrete variables were described by means of absolute numbers and frequency distribution and continuous variables by means of measures of central tendency (mean and median) and of variability [standard deviation (SD) and interquartile range (IQR)]. The cumulative probability of time until the discontinuation of treatment in the 16-year of follow-up period, according to the therapeutic regimen, was assessed by the Kaplan-Meier estimator and the survival curves were compared using the log-rank test. In addition, exploratory analysis of the cumulative probability of the time until the discontinuation of treatment was undertaken considering: persistence in the use of an atypical antipsychotic for at least 24 months, previous psychiatric care, presence of comorbidities, and the first 24 months of follow-up of individuals in this cohort.

The factors that influenced the discontinuation of treatment with an atypical antipsychotic [hazard ratio (HR)] were assessed using univariate analysis. The progression risk ratio for the event, adjusted by the multivariate model, was also calculated using the Cox proportional hazards model and the Wald test, considering the clinically relevant variables or with a $p < 0.20$ in the univariate analysis. A 95% confidence interval (95% CI) was adopted for univariate and multivariate analysis. The adequacy of the multivariate model was assessed by Schoenfeld residues.

Finally, a sensitivity analysis was conducted considering the events psychiatric hospitalization and death separately (psychiatric hospitalization + censorship and death + censorship) and another sensitivity analysis considering patients who persisted in using an atypical antipsychotic for at least 24 months.

All statistical analyzes were conducted with Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), MySQL 5.5 database management system (Oracle Corporation, Redwood, CA, USA) and R Program 4.0.1 (R Core Team 2020, Vienna, Austria).

This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE - 44121315.2.0000.5149).

3. RESULTS

3.1 Patient characteristics

Of the 3,416 pairs of patients included in the study where data was available, 1,708 were prescribed a therapeutic regimen based on olanzapine and 1,708 based on risperidone. Among the therapeutic regimens, 2,952 patients (86.4%) remained with records of exclusive use of the same atypical antipsychotic of entry throughout the follow-up period, being 1,457 (85.3%) with olanzapine and 1,495 (87.5%) with risperidone. The other patients used other atypical antipsychotics provided by SUS at some point in time during the follow-up period (Figure 1).

Insert Figure 1

Most patients (53.4%) were between 18 and 45 years old, with a mean of 44.8 (16.9) years and a median of 44 (30; 58) years; lived in the southeast region (64.5%) of the country and were diagnosed with paranoid schizophrenia - F20.0 (74.3%) at the time of entry into the cohort (Table 1). The annual average of patients who were prescribed atypical antipsychotics increased during the follow-up period.

Insert Table 1

3.2 Time until the discontinuation of treatment

The median time until the discontinuation of treatment due to psychiatric hospitalization or death of patients was 63 months (five years and three months). Patients prescribed olanzapine had a

median time of 66 months (five years and six months), whereas this was 59 months (approximately five years) for those prescribed risperidone. Graphical representations of time until the discontinuation of treatment, according to which atypical antipsychotic, and with clinically relevant and statistically significant explanatory variables, can be seen in Figure 2.

At the end of the follow-up period, 84.4% of patients discontinued treatment. This was 82.1% for individuals prescribed olanzapine and 86.8% for those prescribed risperidone (p = 0.02). Considering the first 24 months of follow-up, 19.2% patients discontinued treatment. This percentage was 19.1 for those prescribed olanzapine and 19.3 for risperidone (Figure 2).

Insert Figure 2

3.3 Factors associated with the discontinuation of treatment

3.3.1 Univariate analysis

The univariate analysis indicated a higher risk of the discontinuation of treatment among patients prescribed risperidone (HR = 1.13; 95% CI = 1.02 – 1.25). On the other hand, there was a lower risk for patients who persisted in using atypical antipsychotics for 24 months (HR = 0.38; 95% CI = 0.34 – 0.43); who had previous psychiatric care (HR = 0.43; 95% CI = 0.38 – 0.48) and for those who did not present a comorbidity during the follow-up period of the cohort (HR = 0.70; 95% CI = 0.59 – 0.83) (Table 2).

Among the intensity of use of an atypical antipsychotic, risperidone presented a higher risk for discontinuation of treatment (HR = 1.19; 95% CI = 1.04 – 1.36). On the other hand, olanzapine (HR = 0.80; 95% CI = 0.71 – 0.91), quetiapine (HR = 0.42; 95% CI = 0.26 – 0.68) and clozapine (HR = 0.40; 95% CI = 0.20 – 0.80) indicated a lower risk for patients (Table 2).

Insert Table 2

3.3.2 Multivariate analysis

In the multivariate analysis, risperidone presented a higher risk of discontinuation of treatment (HR = 1.13; 95% CI = 1.02 – 1.25). On the other hand, the intensity for using clozapine (HR = 0.40; 95% CI = 0.20 – 0.80) and the absence of comorbidities (HR = 0.70; 95% CI = 0.59 – 0.83) were associated with a lower risk of an event (Table 3).

Insert Table 3

Finally, Schoenfeld residues demonstrated a good suitability of the multivariable model, with an average close to zero and without violation of the homoscedasticity premise.

3.3.3 Sensitivity analysis

Considering exclusively psychiatric hospitalization, the median time until the event was 67 months (five years and seven months). Individuals who were prescribed olanzapine had a median time of 74 months (six years and two months) and those prescribed risperidone 62 months (five years and two months). At the end of the follow-up period, 79.4% of the patients discontinued treatment due to psychiatric hospitalization. This was 77.1% for those prescribed olanzapine and 82.0% for those prescribed risperidone (p = 0.006). The risk for psychiatric hospitalization was higher among patients prescribed risperidone and the difference was statistically significant (HR = 1.17; 95% CI = 1.05 – 1.31; p = 0.006). Considering only death, 40.1% of patients discontinued treatment, 36.3% were prescribed olanzapine and 44.4% risperidone (p = 0.8). The risk for death was lower among patients prescribed risperidone but without any statistically significant difference (HR = 0.97; 95% CI = 0.76 – 1.24; p = 0.808) (Table 4).

Insert Table 4

In the analysis considering patients who had at least 24 months of persistent use of any atypical antipsychotic, the median time until an event was 96 months (eight years); 106 months (eight years and ten months) for those prescribed olanzapine and 89 months (eight years and three months) for those prescribed risperidone. At the end of the follow-up period, 74.3% of patients discontinued treatment. This was 72.7% for those prescribed olanzapine and 76.5% for those prescribed risperidone (p = 0.06). In this analysis, the risk of psychiatric hospitalization or death

was also higher among those prescribed risperidone, but with no statistically significant difference (HR = 1.22; 95% CI = 0.99 – 1.51; p = 0.06).

4. DISCUSSION

In this real-world, non-concurrent and nationwide study, where it was possible to evaluate the performance of technologies already incorporated into SUS, olanzapine was more effective than risperidone in the long-term with respect to time until the discontinuation of treatment. The risk of this event for patients prescribed risperidone was greater compared to those prescribed olanzapine, both in the univariate and multivariate analysis. When the main outcome was separated, the analyzes confirmed a higher risk with risperidone compared to olanzapine for psychiatric hospitalization but not for death. However, for those patients who had persistent use of an atypical antipsychotic for at least 24 months, there was a higher risk of discontinuation of treatment with risperidone compared to olanzapine; however, this was not statistically significant.

The choice of outcomes in health research must be clinically relevant and based on long-term results as well as considering the natural history of the disease and the challenges faced by decision makers [44, 45]. Through the prescribing of antipsychotics and psychosocial approaches, the treatment of schizophrenia aims to reduce patients' symptoms and prevent them from developing long-term disability, thereby helping them to lead a productive and independent life [2, 8, 46]. This is the strategy that Brazil has pursued in the care of patients with mental health disorders in recent decades, through the de-hospitalization of these patients and the encouragement of community treatment, with an emphasis on outpatient care [47-50]. Consequently, the choice of discontinuation of treatment due to psychiatric hospitalization or death as an event is relevant and timely, and reflects the concern with the treatment of patients with schizophrenia and other mental health disorders that use atypical antipsychotics in their therapeutic strategy.

Similar to some clinical trials [27, 51] and observational studies [28, 30, 52], the findings of this cohort also point to a longer time for discontinuation of treatment among patients prescribed olanzapine. Similar results were observed in the analyzes considering psychiatric hospitalization as an outcome. However, unlike the studies cited, the time until the event in this study was longer. A probable explanation for this difference is because the choice of events, i.e. psychiatric hospitalization or death for some reason, was more conservative and because the patients included, at some point in time, had psychiatric hospitalization in SUS, suggesting that they were patients who spent more time in public psychosocial services and were therefore more stable. It was observed that the majority of individuals in this cohort (84.1%) had a record of previous psychiatric care and having this condition presented a lower risk for discontinuation of treatment. It is reasonable to assume that individuals with previous psychiatric hospitalization were more motivated to maintain outpatient follow-up and persistence to treatment. In fact, psychosocial monitoring tends to provide a better quality of life for the patient and, consequently, more independence and less hospitalizations. SUS has several strategies for monitoring outpatients with mental health disorders on an outpatient basis, which range from infrastructure to qualified and dedicated multidisciplinary teams, to help in this regard [53].

The persistence in using an atypical antipsychotic for at least 24 months favored both antipsychotics in this study, with no statistically significant difference in risk until the discontinuation of treatment between olanzapine and risperidone. This is in line with the findings of a recent study with real-life data which evaluated several atypical antipsychotics and found that treating patients with schizophrenia for a longer time with antipsychotics had more clinical benefits for patients than not using them [54]. Our finding reinforces the relevance of monitoring patients with schizophrenia over time and assessing the importance of a possible superiority of one antipsychotic over the other, except for the possible adverse events of each one. This hypothesis was verified in the study by Noordsy *et al.* where olanzapine and risperidone showed similar efficacy among stable patients and in outpatient follow-up study, with no statistically significant differences between the causes for discontinuation of treatment [55]. In addition, there was also no significant difference between olanzapine and risperidone in some analyzes performed in the CATIE studies regarding all causes of discontinuation of treatment, including lack of effectiveness, in patients with schizophrenia [56, 57]. In fact, it seems that there is still no consensus about the relative effectiveness of these two antipsychotics as some studies have pointed out that both antipsychotics are similar in efficacy,

i.e. improvement in symptomatic scores) [58], while in CATIE there are results suggesting otherwise [27]. Hence the importance of studies like ours with a long follow-up time and based on real life practice. It is worth noting that in SUS the costs of outpatient psychiatric follow-up are considerably lower than those associated with psychiatric hospitalizations suggesting greater efficiency in the outpatient approach [32]. However, as already stated, public policies and decision-making should always consider spending together with health outcomes and indicators [32].

In the 16-year of follow-up period, the percentage of discontinuation of treatment among patients in this cohort (84.4%) was consistent with a number of experimental [27, 51, 57, 59] and observational studies [28, 30], both for those prescribed olanzapine (82.1%) and those prescribed risperidone (86.8%). However, the follow-up period for these studies ranged from 18 to 36 months and all adopted a greater number of causes of discontinuation, i. e. including lack of effectiveness, adverse reactions, and lack of adherence. For comparison, when considering the first 24 months of follow-up in our cohort, the percentage of patients discontinuing treatment were well below those of these cited studies, with 19.2% for the entire population, 19.1% for those prescribed olanzapine and 19.3% for those prescribed risperidone. This may also be related to the hypothesis that patients in this cohort are being monitored more continuously, especially in outpatient care, and are more stable. Reinforcing this possibility, the analysis performed considering individuals persisting for at least 24 initial months with an atypical antipsychotic, which showed, at the end of the follow-up period a reduction to 74.3%, 72.7% and 76.5%, respectively. Another aspect that draws attention is that, in the analysis among patients in this cohort, the difference between the percentages of discontinuation of treatment between olanzapine and risperidone was statistically significant ($p = 0.02$), which did not occur in the analysis among individuals persisting for at least 24 initial months with an atypical antipsychotic ($p = 0.06$). Likewise, some CATIE studies have also shown no statistical significance between olanzapine and risperidone in terms of the percentage of patients who discontinued treatment [57, 59].

The use of clozapine at some point in time and without comorbidities presented a lower risk for psychiatric hospitalization or death and are in line with the literature. Some studies have suggested that clozapine has superior efficacy in the treatment of psychopathological symptoms among patients with schizophrenia resistant to pharmacotherapy with other antipsychotics, which may reduce relapses and psychiatric hospitalizations [25, 29, 57]. However, monitoring during the use of clozapine is strongly recommended, aiming to detect and mitigate its possible serious adverse effects [22, 57, 60]. Consequently, guidelines typically reserve the use of clozapine for refractory cases although this is being challenged [46, 61-63]. With regard to comorbidities, it is known that they are appreciably more common among individuals with schizophrenia than among others, with a greater potential to worsen health over time and enhance mortality among these patients [46]. Consequently, the atypical antipsychotic chosen needs to principally take into account the patient and comorbidities especially with patients with schizophrenia increasingly managed in the community [64, 65].

We are aware that the study has a number of limitations. Firstly, the patients are from a non-concurrent cohort from administrative databases allowing some information to be incomplete or inconsistent, common in secondary databases. This situation made it impossible for us to have access to some clinical data such as time of diagnosis, data from the Positive and Negative Syndrome Scale (PANSS), the Global Clinical Impressions scale (CGI), or the British Psychiatric Rating Scale and Safety (BPRS), among others, which would help to better understand the reasons of treatment discontinuation. In addition, for this study, we do not have information about the doses of atypical antipsychotics during treatment including the extent of defined daily doses, which would have helped to better understand some findings. Possible demographic and clinical differences between the two arms of the study may have occurred, but an attempt was made to minimize this selection bias by matching five of the main variables available in this cohort and subsequently through sensitivity analyzes. Another limitation is the lack of information on the possible use of typical antipsychotics by patients in this cohort, a record not included in this database. In addition, when we were conservative and we considered the minimum time of use of atypical antipsychotic for six months we underestimated the potential discontinuation of treatment during the early months. However, despite these limitations we believe these findings are robust as they come from a large national database, with a long follow-up period and clinically relevant outcomes (that is, psychiatric hospitalization and death) for the condition providing real-world evidence. The results presented here may

corroborate with findings from experimental studies, which generally work with selected samples, a controlled research environment and a shorter follow-up time. In addition, this database has been used in a number of studies to help guide treatment, investment and disinvestment decisions within the Brazilian healthcare system [32, 66-71].

5. CONCLUSION

In this nationally matched cohort with a long follow-up period, olanzapine demonstrated superior real-world effectiveness in relation to risperidone, considering the entire study population and also only when patients who had psychiatric hospitalization after entering the cohort were included. However, this superiority was not sustained in all analyzes. In addition, there was no difference among those patients who had an initial persistence of 24 months with atypical antipsychotics. Consequently, the choice of atypical antipsychotic should be principally determined by the requirement of the patients and any current comorbidities including metabolic syndrome or diabetes.

The results suggest that the patients in this study could be continuously monitored on an outpatient basis and be more stable, which is beneficial for the future to help conserve costs. However, the large percentage of these individuals who have discontinuation on treatment demonstrates how much attention and care patients with schizophrenia or other mental health disorders need, and we will be following this up. Lastly, observational studies from large real-world databases appear to corroborate experimental studies in the consolidation of knowledge and they need to be encouraged as patients become more complex.

Author Contributions

Conceptualization, W.B.B. and A.A.G.J.; Data curation, W.B.B. and A.A.G.J.; Formal analysis, W.B.B., R.M.G. and A.A.G.J.; Investigation, W.B.B. and A.A.G.J.; Methodology, W.B.B., R.M.G. and A.A.G.J.; Project administration, A.A.G.J.; Software, A.A.G.J.; Supervision, W.B.B. and A.A.G.J.; Validation, W.B.B., B.G. and A.A.G.J.; Writing—original draft, W.B.B., R.M.G., B.G. and F.d.A.A.; Writing—review and editing, W.B.B., R.M.G., B.G., F.d.A.A. and A.A.G.J. All authors have read and agreed to the published version of the manuscript.

Study funding

WBB received a PhD scholarship from Financial support from CAPES, in Brazil (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).

Acknowledgments

The authors are grateful for the institutional support of the CCATES/UFMG (SUS Collaborating Centre ‐Technology Assessment and Excellence in Health/College of Pharmacy, Federal University of Minas Gerais, Brazil).

Conflicts of interest

The other authors have nothing to declare.

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Table 1. Characteristics of the study population (Brazil, 2000-2015; n = 3416)

Characteristics	Total (n = 3416)		Olanzapine (n = 1708)		Risperidone (n = 1708)	
	n	%	n	%	n	%
Patient Gender						
Female	1704	49.9	852	49.9	852	49.9
Male	1712	50.1	856	50.1	856	50.1
Age group at study entry (years)						
18-25	526	15.4	263	15.4	263	15.4
26-35	672	19.7	336	19.7	336	19.7
36-45	626	18.3	313	18.3	313	18.3
46-55	594	17.4	297	17.4	297	17.4
56-65	510	14.9	255	14.9	255	14.9
>65	488	14.3	244	14.3	244	14.3
Geographic origin *(study entry)*						
Midwest	278	8.1	187	10.9	91	5.3
Northeast	385	11.3	192	11.2	193	11.3
North	53	1.6	36	2.1	17	1.0
Southeast	2203	64.5	1054	61.7	1149	67.3
South	497	14.5	239	14.0	258	15.1
Study entry period						
2000-2003	488	14.3	244	14.3	244	14.3
2004-2007	786	23.0	393	23.0	393	23.0
2008-2011	1114	32.6	557	32.6	557	32.6
2012-2014	1028	30.1	514	30.1	514	30.1
Primary diagnosis (ICD-10) at study entry						
Paranoid schizophrenia (F20.0)	2539	74.3	1269	74.3	1270	74.4
Hebephrenic schizophrenia (F20.1)	87	2.5	45	2.6	42	2.5
Catatonic schizophrenia (F20.2)	17	0.5	10	0.6	7	0.4
Undifferentiated schizophrenia (F20.3)	65	1.9	37	2.2	28	1.6
Post-schizophrenic depression (F20.4)	15	0.4	8	0.5	7	0.4
Residual schizophrenia (F20.5)	151	4.4	78	4.6	73	4.3
Simple schizophrenia (F20.6)	319	9.3	148	8.7	171	10.0
Other schizophrenias (F20.8)	223	6.5	113	6.6	110	6.4
Previous psychiatric care	2874	84.1	1419	83.1	1455	85.2
Persistence in using AA for 24 months	978	28.6	527	30.8	451	26.4
Presence of comorbidity	320	9.4	153	9.0	167	9.8

Note: AA = atypical antipsychotic; ICD = international disease classification.

Table 2. Univariate analysis: hazard ratio for discontinuation of treatment, according to demographic and clinical characteristics of the study population (Brazil, 2000-2015; n = 3416).

Variable	Total	Event						HR (95% CI)	P value
		Total		Death		Psychiatric hospitalization			
	n	n	%	n	%	n	%		
Gender									
Male	1712	783	45.7	137	8.0	646	37.7	1.06 (0.95-1.17)	0.296
Female	1704	721	42.3	123	7.2	598	35.1	1.0	-
Study entry period									
2000-2003	488	349	71.5	45	9.2	304	62.3	1.0	-
2004-2007	786	448	57.0	103	13.1	345	43.9	0.93 (0.80-1.07)	0.302
2008-2011	1114	543	48.7	82	7.4	461	41.4	1.10 (0.95-1.26)	0.213
2012-2014	1028	164	16.0	30	2.9	134	13.0	0.90 (0.74-1.10)	0.301
Primary diagnosis (ICD-10) at study entry									
Paranoid schizophrenia (F20.0)	2539	1082	42.6	180	7.1	902	35.5	1.09 (0.97-1.22)	0.144
Hebephrenic schizophrenia (F20.1)	87	40	46.0	5	5.7	35	40.2	0.90 (0.66-1.23)	0.514
Catatonic schizophrenia (F20.2)	17	9	52.9	2	11.8	7	41.2	0.97 (0.50-1.87)	0.929
Undifferentiated schizophrenia (F20.3)	65	21	32.3	5	7.7	16	24.6	0.84 (0.54-1.29)	0.416
Post-schizophrenic depression (F20.4)	15	8	53.3	0	0	8	53.3	1.25 (0.62-2.51)	0.528
Residual schizophrenia (F20.5)	151	75	49.7	21	13.9	54	35.8	0.93 (0.74-1.17)	0.540
Simple schizophrenia (F20.6)	319	183	57.4	33	10.3	150	47.0	0.93 (0.79-1.08)	0.323
Other schizophrenias (F20.8)	223	86	38.6	14	6.3	72	32.3	0.99 (0.80-1.23)	0.939
Atypical antipsychotic study entry									
Risperidone	1708	756	44.3	118	6.9	638	37.4	1.13 (1.02-1.25)	0.021
Olanzapine	1708	748	43.8	142	8.3	606	35.5	1.0	-
Atypical antipsychotic use intensity									
Clozapine	98	46	46.9	8	8.2	38	38.8	0.40 (0.20-0.80)	0.010
Olanzapine	1708	748	43.8	142	8.3	606	35.5	0.80 (0.71-0.91)	<0.001
Quetiapine	267	115	43.1	15	5.6	100	37.4	0.42 (0.26-0.68)	<0.001
Risperidone	1708	756	44.3	118	6.9	638	37.3	1.19 (1.04-1.36)	0.014
Ziprasidone	137	80	58.4	9	6.6	71	51.8	0.54 (0.28-1.05)	0.069

Persistence in using an atypical antipsychotic for 24 months									
Yes	978	349	35.7	84	8.6	265	27.1	0.38 (0.34-0.431)	<0.001
No	2438	1155	47.4	176	7.2	979	40.2	1.0	-
Previous psychiatric care									
Yes	2874	1101	38.3	250	8.7	851	29.6	0.43 (0.38-0.48)	<0.001
No	542	403	74.4	10	1.8	393	72.5	1.0	-
Presence of comorbidity									
No	3096	1363	44.0	204	6.6	1159	37.4	0.70 (0.59-0.83)	<0.001
Yes	320	141	44.1	56	1.8	85	26.6	1.0	-

Note: HR = hazard ratio; CI = confidence interval.

Table 3. Hazard ratio for discontinuation of treatment: Cox multivariate logistic regression in a cohort of 16-year of follow-up (Brazil, 2000-2015; n = 3416).

Variable	HR (95% CI)	P value
AA study entry (Risperidone)	1.13 (1.02-1.25)	0.017
AA use intensity (Clozapine)	0.40 (0.20-0.80)	0.009
Presence of comorbidity (No)	0.70 (0.59-0.83)	<0.001

Note: AA = atypical antipsychotic; HR = hazard ratio; CI = confidence interval.

Table 1. Sensitivity analysis: hazard ratio for discontinuation of treatment measured separately for event in the study population (Brazil, 2000-2015; n = 3416).

Atypical antipsychotic	Event			
	Death	P value	Psychiatric hospitalization	P value
	HR (95% CI)		HR (95% CI)	
Risperidone	0.97 (0.76-1.24)	0.808	1.17 (1.05-1.31)	0.006
Olanzapine	1.0	-	1.0	-

Note: HR = hazard ratio; CI = confidence interval.

Figure 1. Study flowchart (Brazil, 2000-2015; n = 3416).

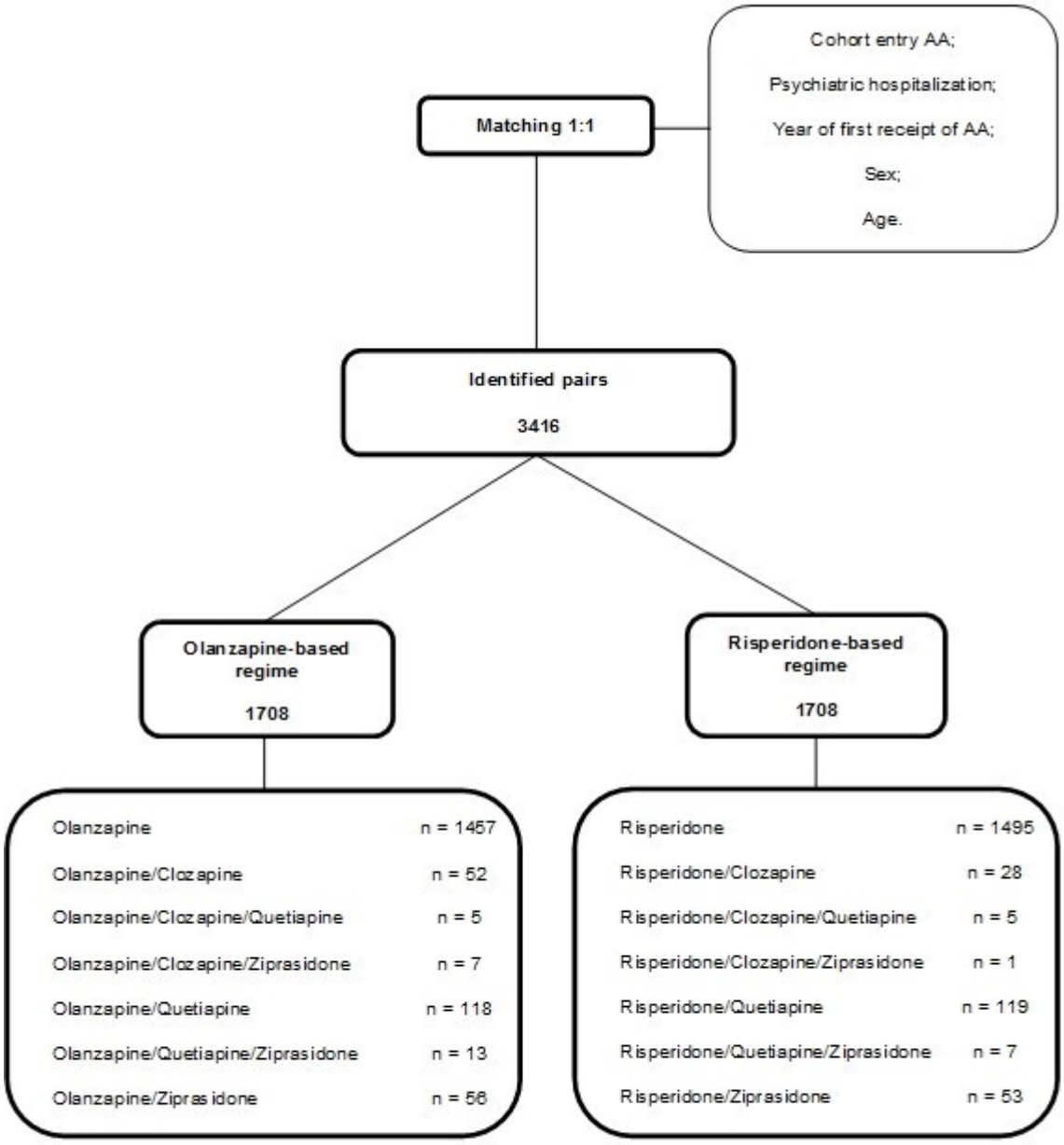

Figure 2. Kaplan-Meier estimator for the time until discontinuation of treatment after using an atypical antipsychotic, in a 16-year cohort, according to: a) total population; b) antipsychotic at study entry; c) persistence of 24 months; d) previous psychiatric care and e) presence of a comorbidity (Brazil, 2000-2015; n = 3416).