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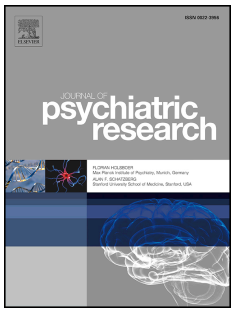

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Naturalistic study on the use of clozapine in the early phases of non-affective psychosis: a 10-year follow-up study in the PAFIP-10 cohort

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Abstract

Clozapine is seldom prescribed in treatment-resistant schizophrenia (TRS) patients during early phases of the illness. We aimed to examine the pathway and patterns and the impact of clozapine use in patients with TRS who were followed up for 10 years after the first outbreak of the illness. Data were obtained retrospectively from an epidemiological cohort of first episode schizophrenia patients (n = 218) who had been treated in a specialized intervention program (PAFIP). Out of 218, 35 (16%) individuals were on clozapine at 10-year assessment, while 183 (84%) were taking other antipsychotics. Among those 183 psychosis subjects who were not on clozapine, 13 (7.1%) met criteria for TRS. In the clozapine group, ten (28.6%) met criteria for early-TR and twenty-five (71.4%) met criteria for late-TR. Before clozapine treatment was initiated, the median number of days under other antipsychotic treatment was 1551 days (IQR = 1715) and the median time that subjects remained on clozapine was 6.3 years (IC95%: 5.49-7.20). At 10 years, we found that those individuals taking clozapine had higher CGI total scores ($F = 12.0$, $p = 0.001$) and SANS total scores ($F = 9.27$, $p = 0.003$) than subjects taking other antipsychotics after correcting for baseline values. Interestingly, when performing these analyses at 10 years between subjects taking clozapine (n = 35) and subjects who despite meeting TRS criteria were not taking clozapine (n = 13), we found that subjects taking clozapine had significantly lower total scores on all clinical scales compared with subjects who met TRS criteria and were not taking clozapine (p values <0.05). TRS patients who took the longest time to start clozapine (third tertile) showed significantly higher CGI scores at 10-year follow-up compared to those who initiated clozapine earlier (first tertile) ($t = 2.60$; $p = 0.043$). Our findings reinforce the need of a timely assessment of treatment-resistant criteria in early schizophrenia patients and highlight the long-term benefits of an early introduction of clozapine on those patients meeting treatment-resistant criteria.

Key words: first-episode psychosis, schizophrenia, treatment-resistant, clozapine, antipsychotics, metabolic syndrome

1. Introduction

Approximately 20% of schizophrenia patients receive only limited benefits from antipsychotic drugs for stable control of clinical symptoms of psychosis (A. Demjaha et al., 2017; Lally et al., 2016; Siskind et al., 2021). Clozapine has traditionally been prescribed as an alternative for patients who do not respond to standard antipsychotics (A. Demjaha et al., 2012, 2014; Szymanski et al., 1994; Thien et al., 2018), or for whom they seem to lose efficacy over time (Suzuki et al., 2015). Likewise, psychiatrists rarely prescribe clozapine in treatment-resistant schizophrenia (TRS) patients (Farooq and Taylor, 2011), with prescriptions ranging from 1% to 2% of total antipsychotics in many countries (Warnez and Alessi-Severini, 2014), and a delay in its initiation of up to five or nine years (Howes et al., 2012; Tang et al., 2016). In the interim, most patients may receive up to 13 different antipsychotics, in mono- or poly-therapies (Moore et al., 2007; Vera et al., 2012), likely worsening the disease's prognosis and increasing the risk of unnecessary side effects (Üçok et al., 2015). In spite of the availability of specialized resources for clozapine treatment, concerns about adherence, side effects, partial compliance with blood monitoring and lack of professional safety, lead many psychiatrists to resist its prescription (Daod et al., 2019). The clinical response rate to clozapine described in a recent meta-analysis is around 40% (Siskind et al., 2017).

Several clinical predictors have been significantly associated with treatment-resistant schizophrenia (TRS) and subsequent clozapine use, such as: the diagnosis of schizophrenia, younger age and early onset of psychosis, more insidious disease onset, more severe symptoms and greater negative symptoms at illness presentation, history of suicide attempts, affective symptoms, the use of antidepressant medications and a longer duration of untreated psychosis (DUP) (A. Demjaha et al., 2017; Wimberley et al., 2016).

However, the delayed onset of use that is linked to treatment for years with other antipsychotics that can likely lead to neurochemical alterations such as dopaminergic supersensitivity (Samanaite et al., 2018; Suzuki et al., 2015) elevated levels of glutamatergic metabolites in the anterior cingulate cortex (A. Demjaha et al., 2014), or serotonin dysregulation (Potkin et al., 2020) have also been reported as likely factors associated with clozapine non-

response.

Our objective is to examine the pathway and patterns of use and the impact of clozapine use in people with TRS in a cohort of individuals with a first episode of psychosis who have been followed for 10 years. The course of resistance (early or late), differences in sociodemographic and clinical characteristics at disease onset, and in long-term outcomes (10 years) between clozapine users and non-users were also analyzed.

2. Material and methods

2.1. Study setting

Data for the present study were obtained retrospectively from a large epidemiological cohort of patients who have been treated in a longitudinal intervention program of FEP called PAFIP (Programa de Atención a Fases Iniciales de Psicosis) conducted at the University Hospital Marqués de Valdecilla in Cantabria, Spain. The main procedures that are carried out in this program have been described previously (Pelayo-Terán et al., 2008).

The study was approved by the local ethics committee for clinical research (CEIC-Cantabria) in accordance with international standards for research ethics.

2.2. Study design

This is a retrospective analysis of the pattern of clozapine use during early phases of the illness and its outcome, in a large sample of first episode individuals (n=218) who had completed a 10 years follow-up assessment (PAFIP-10) (Ayesa-Arriola et al., 2019) and for which we had complete information on medication, adherence to treatment, and symptom severity (Flowchart is shown in *Figure 1*).

Patients analyzed in the present study were assigned to one of the 3 randomized, open-label, flexible-dose clinical trials that have been conducted in the PAFIP program from 2001 to 2018. More specifically, during the first clinical trial, from February 2001 to September 2005 (NCT02200588), patients with first-episode non-affective psychosis who entered the PAFIP program were randomly assigned to treatment with olanzapine, risperidone or haloperidol

(Crespo-Facorro et al., 2006). Consecutively, between October 2005 and January 2011 (NCT03481465), patients were randomly assigned to treatment with aripiprazole, ziprasidone, or quetiapine (Crespo-Facorro et al., 2013b). And finally, in the third clinical trial (NCT02305823), between February 2011 to October 2018 patients were randomly assigned to treatment with aripiprazole or risperidone (Son et al., 2021). An automated randomization list was drawn up to define the antipsychotic to be taken in each trial, respectively. During PAFIP II and PAFIP III trials, non-response was defined as lack of clinical response or lack of improvement (less than 40% of total BPRS score reduction and CGI total score of ≥4 (moderately ill) after treatment with a maximum therapeutic dose of first- or second-generation antipsychotics for at least 4 weeks (Crespo-Facorro et al., 2013a). During early years of the PAFIP I the criteria of clinical response were slightly different due to the recommendations of the clinical guidelines that existed at that time. Thus, lack of clinical response or improvement was defined according to the Leucht and Kane, 2006 criteria in which improvement is defined as a 20% reduction in baseline BPRS total score at 4 weeks compared to the severity level at baseline and/or a post-treatment CGI ≤3 or a BPRS ≤35. We define the TRS cases as those who did not respond to 2 sequential antipsychotic medication of adequate dose and duration and/or the documented reason for switching antipsychotic medication was due to a lack of therapeutic response. In those cases of non-response to two or more previous antipsychotics at adequate doses, a switch to clozapine was considered. Importantly, during the conduct of these three clinical trials, patients were allowed to switch medication due to lack of efficacy or tolerability without dropping out of the studies.

The group of patients on clozapine is compared to the group of psychosis individuals who were on other first and second-generation antipsychotics (haloperidol, quetiapine, ziprasidone, olanzapine, aripiprazole, risperidone and paliperidone) at 10 years assessment. Sociodemographic and clinical variables at baseline, as well as total score of clinical scales, adverse effects and number of relapses at 10-year of follow-up were compared. A comparison was also made between subjects with “early resistance” (E-TR) who did not present remission of symptoms after treatment trials with two or more antipsychotics, requiring treatment with clozapine, and those with "late resistance" (L-TR) who showed clinical worsening after initial

remission and who showed no clinical improvement despite increasing the antipsychotic dose or after switching to another antipsychotic, which eventually led to a switch to clozapine (A Demjaha et al., 2017). A second comparison was made between the clozapine group (n = 35) and patients considered resistant to treatment (TRS) who took antipsychotics other than clozapine (n = 13).

2.3. Subjects

All referrals to PAFIP (from February 2001 to July 2011) were screened against the following inclusion criteria: age 15-60 years; living in the catchment area; experiencing their first episode of psychosis; no prior treatment with antipsychotic medication or, if previously treated, a total life-time of adequate antipsychotic treatment of less than 6 weeks. DSM-IV criteria for drug or alcohol dependence, intellectual disability and having a history of neurological disease or head injury were exclusion criteria. The diagnoses were confirmed through the use of the Structured Clinical Interview for DSM-IV (SCID–I) (First et al., 1996), conducted by an experienced psychiatrist at 6 months from baseline visit. Only those PAFIP individuals who had completed the 10 years follow-up assessment were included in the current investigation.

2.4. Baseline socio-demographic, premorbid and clinical variables assessment

Baseline sociodemographic and clinical information was recorded from interviews with patients, their relatives and from medical records on admission.

Premorbid functioning was evaluated using the premorbid adjustment scale (PAS) (Cannon-Spoor et al., 1982), which includes sub-punctuations in childhood (up to 11 years), early adolescence (12-15 years), late adolescence (16 -18 years old) and adulthood (18 years and older).

The severity scale of the Clinical Global Impression (CGI) (Guy, 1976) scale, the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), the Expanded Brief Psychiatric Rating Scale (BPRS-E) (expanded version of 24 items) (Lukoff et al., 1986; Ventura et al., 1993), the Calgary

Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) were used to evaluate clinical symptomatology.

2.5. Clinical follow-up assessments

The duration of follow-up was defined as the period between the first contact with the PAFIP program and 10 years of follow-up (range between 8 and 12 years). During the intensive follow-up time of patients in the PAFIP program, clinical assessments were performed at inclusion, 6 weeks, 3 months, 1 year, 3 years (end of follow-up in the PAFIP program) and 10 years, as well as at any episode of relapse. These assessments points were used to assess the lack of response or tolerance to the treatments used, as described above.

Clinical information was obtained through clinical interviews with subjects, family members and computerized medical records. The beginning and end dates of all antipsychotics and concomitant treatments were recorded, as well as the dose, adherence to treatment and the reason for change or termination. Clozapine and other antipsychotics were used in a dose range of 50 to 900 mg/day (100-1000 mg/day of chlorpromazine) or 66.67-800mg/day of chlorpromazine, respectively. The mean dose of each antipsychotic is available upon request.

Relapse was defined as any of the following criteria that occurred during follow-up: (1) a rating of either 5 or above on any key BPRS symptom items, (2) CGI rating of ≥6 and a change score of CGI of "much worse" or "very much worse", (3) hospitalization for psychotic psychopathology, or (4) committed suicide (Andreasen et al., 2005). The key BPRS symptoms were unusual thought content, hallucinations, suspiciousness, conceptual disorganization, and bizarre behavior. Patients were considered to have a relapse if the re-emerged symptoms lasted for at least one week.

Adherence to treatment was defined as the degree to which a person's behavior regarding the follow-up of prescribed treatment (pharmacological treatment, psychotherapy, lifestyle changes, etc.) corresponds to the recommendations agreed with a provider of the healthcare. Adherence assessment was performed using indirect methods, such as the counting of the medication in the electronic prescription and the interview with patients and their relatives.

Parameters of physical health and the records of the measurement of blood pressure, weight, waist circumference and body mass index (BMI) were collected at the beginning and at 10-year of the follow-up period. According to the criteria of the National Cholesterol Education Adult Treatment Panel III (ATP-III) (Expert panel on detection evaluation and treatment of high blood cholesterol in adults, 2001) the presence of metabolic syndrome was also assessed.

The side effects of antipsychotic treatments were recorded using the Scale of Secondary Effects (UKU) scale (Lindström et al., 2001).

2.6. Statistical analysis

All data were tested for normality using Kolmogorov–Smirnov test, and equality of variances using Levene test.

Demographics and baseline clinical variables were analyzed using t-Student test, W-Wilcoxon rank-sum test, Kruskal-Wallis test or Chi-Square test as necessary.

Differences between groups in the degree of change regarding clinical scores from baseline to 10-year were evaluated using Analysis of Covariance (ANCOVA) after baseline scores were controlled.

For analyzing the effect sizes of the clinical scales variations within each antipsychotic group during the follow-up period, the correlation coefficient (r) was calculated dividing the Z value of the W-Wilcoxon signed-rank test by the square root of N (the number of observations over the two-time points), as it is described elsewhere (Fritz et al., 2012). r is a standardized measure of the strength and direction of linear relationship between two variables ranging from −1 for a perfect negative relationship and 1 for a perfect positive relationship. The follow cut-offs of the r co- efficient are considered by Cohen (Cohen J, 1988): r = 0.1 (small); r = 0.3 (medium); r = 0.5 (large). When these coefficients are compared between two groups, the difference may be considered to be significant when there is a change in level (e.g. from small to medium, from small to large, or from medium to large) (Cohen J, 1988).

STATA 16.1 was used for statistical analyses. Statistical tests were two-tailed with a 95% confidence interval.

3. Results

3.1. Comparison of sociodemographic, premorbid and clinical characteristics at baseline between clozapine-users and non-users

This study included 218 patients who completed a 10-year follow-up after their first episode of psychosis. Of 218 included individuals, 35 (16%) were taking clozapine, while 183 (84%) were taking other antipsychotics.

Sociodemographic, premorbid and clinical characteristics of individuals on clozapine and other treatments after 10 years are shown in *Table 1* and *Table 2*.

In the group of individuals on clozapine a significantly higher proportion of males (X^2 = 14.17; $p < 0.001$), single ($X^2 = 8.13$; $p = 0.004$), an earlier onset of psychosis ($t = -2.88$; $p = 0.004$), a lower education level ($X^2 = 4.84$; $p = 0.028$), a higher unemployed rate($X^2 = 7.74$; $p = 0.005$) and higher proportion of people living in urban areas ($X^2 = 4.06$; $p = 0.044$) were found. In addition, patients on clozapine showed higher total baseline scores on the SANS scale ($z = 2.29$; $p = 0.022$), as well as poorer premorbid adjustment during early adolescence ($z = 2.27$; $p = 0.023$).

The median of days until clozapine treatment was initiated1551 (IQR = 1715). The median time that subjects had been on clozapine was 6.3 years (IC95%: 5.49-7.20).

The 35 subjects in the clozapine group had been on different antipsychotics in monotherapy before switching to clozapine. The number of antipsychotics used before switching to clozapine is listed below: eleven subjects (31.4%) had been on two different antipsychotics before switching, seven subjects (20%) had tried three antipsychotics, ten subjects (28.6%) had tried four different antipsychotics, three subjects (8.6%) had tried five antipsychotics, two subjects (5.7%) had tried six antipsychotics and two subjects (5.7%) had tried during the follow-up period up to seven antipsychotics (see *Supplementary Table 1*) before switching to clozapine.

In the clozapine group, ten (28.6%) met criteria for E-TR and twenty-five (71.4%) met criteria for L-TR. Out of 183 subjects who did not take clozapine during the follow-up period, 13 (7.1%) met criteria for resistant schizophrenia based on the definition by Leucht and Kane (2006). Sociodemographic data of these subsamples are shown in *Supplementary Tables 2 and 3*.

3.2. Comparison of 10-year clinical outcome of clozapine users and nonusers

Table 2 shows the total scores of all clinical scales at baseline and at the 10-year follow-up, as well as ANCOVA analyses.

At 10 years, we found that those individuals taking clozapine had higher total CGI scores ($F = 12.0$; $p = 0.001$) and total SANS scores ($F = 9.27$; $p = 0.003$) than subjects who were taking other antipsychotics. Correlation coefficients after intrasubject analysis showed large effect sizes for all clinical scales except CDSS and SANS (medium effect sizes) in the two groups after 10-years of antipsychotic medication, with no statistically significant differences between groups.

Subjects with E-TR had higher total scores on baseline CDSS, baseline BPRS and baseline SAPS than individuals with L-TR ($F = 3.71$, $p = 0.079$; $F = 6.81$, $p = 0.014$; and $F = 4.58$, $p = 0.041$, respectively). However, no statistically significant differences were found between E-TR and L-TR individuals at 10 years (all p values > 0.05). Interestingly, if we compare the 13 patients who meet criteria for resistant schizophrenia but who did not receive clozapine with those who did receive it ($n = 35$), we see that the subjects with clozapine presented significantly lower total scores on all clinical scales at 10 years (all p values < 0.05).

A secondary analysis sought any clinical differences at baseline and after 10 years between subjects with different clozapine initiation patterns. In the clozapine group ($n = 35$), the median time between the first antipsychotic tried and the initiation of clozapine was divided by tertiles. The results were as follows (see *Table 3*): the median time until start of clozapine in the first tertile was 323 days (IQR = 805), in the second tertile was 1411.5 days (IQR = 1369) and in the third tertile was 2398 days (IQR = 1369). We did not find any differences in clinical scales between the three tertiles at baseline. At the 10-year follow-up, individuals who began clozapine later had higher total scores on the CGI ($F = 3.65$; $p = 0.038$) and on the YMRS ($F = 7.11$; $p = 0.003$) after controlling for baseline scores. After Bonferroni correction, the differences between the first and third tertile on the CGI scale and between the first and third tertile and the second and third tertile on the YMRS scale were statistically significant. We also observed a trend toward statistically significant differences in the BPRS between the three tertiles ($F = 2.67$; $p = 0.085$) in favor of the first and second tertiles with respect to the third (see *Table 3*).

We observed that of 183 individuals who were under other antipsychotics, 125 (68.3%) relapsed during the 10-year follow-up period, describing a multi-episodic pattern of relapses. On the other hand, individuals taking clozapine were subjects with a chronic, non-episodic course of psychosis. In this setting, we found that of 35 people taking clozapine, 10 (28.6%) relapsed after switching to clozapine.

3.3. Comparison of prevalence of side effects of clozapine and other antipsychotics at 10-year follow-up

No statistically significant differences in the increase in BMI were observed between the clozapine group (30.3kg/m^2) and the rest of the treatments (28.8 kg/m^2) after controlling for baseline BMI during the follow-up period (F = 0.63; p = 0.532). However, we did find a statistically significant higher prevalence of metabolic syndrome in the clozapine group (X^2 = 6.13; p = 0.013) than in the rest of antipsychotics (38.2% vs 18.7%). When the two groups were compared by UKU scale subgroups, there was a significant increase in daytime sleepiness (X^2 = 18.84; $p < 0.001$), sialorrhea (X^2 = 70.21; $p < 0.001$), weight gain (X^2 = 11.16; p = 0.011), fatigue (X^2 = 10.24; p = 0.017), orthostatic vertigo (X^2 = 9.36; p = 0.025) and constipation (X^2 = 10.26; p = 0.017) in clozapine users after 10 years.

Second, we specifically compared the side effects between clozapine and olanzapine considering both antipsychotics have a similar receptor profile. We found no difference in the increase in BMI (F = 0.48; p = 0.492) and the prevalence of metabolic syndrome (X^2 = 0.08; p = 0.773). The only UKU scale side effect that was more frequent in clozapine users than in olanzapine users at 10 years was sialorrhea (X^2 = 14.41; $p < 0.01$).

4. Discussion

Our findings could support the early use of clozapine, especially in those subjects who meet criteria for resistant schizophrenia. Although the individuals who took clozapine had more severe negative symptoms at the beginning of the study, we found no statistically significant differences in the effect sizes of the clinical scales between the two groups at 10 years, which presupposes

clinical benefit of long-term use of clozapine in resistant psychoses. Furthermore, the tolerance and prevalence of side effects of clozapine was very similar to that of olanzapine.

It was observed that 22% met criteria for treatment-resistant schizophrenia (TRS), a proportion similar to a recently published meta-analysis (Siskind et al., 2021), but only 16% of them were taking clozapine after 10 years. The median time to clozapine onset was 4 years, which is a shorter time than previously described (Correll and Howes, 2021; Howes et al., 2012; Tang et al., 2016). Despite this, about 60% of subjects eligible for clozapine initiation received more than two treatments (three to seven) before starting clozapine. In the efforts of psychiatric associations to redefine prescribing guidelines, the initiation of clozapine continues to be delayed for up to five to nine years in patients with early-onset schizophrenia (Doyle et al., 2017; Trinczek et al., 2016), and despite limited evidence supporting this clinical practice, most patients receive numerous antipsychotics, alone or in combination (Moore et al., 2007), worsening the prognosis and increasing side effects (Üçok et al., 2015).

Our study has identified several variables that could be associated with subsequent clozapine treatment during 10 years of follow-up, such as earlier age of onset of psychosis, poor premorbid adjustment in early adolescence, being male, being single, having received a lower educational level, living in urban areas, being unemployed and having a greater severity of negative symptoms (see *Table 1*). As in previous studies (Chan et al., 2021; Díaz et al., 2013; Friis et al., 2016; Lally et al., 2016; Smart et al., 2021), earlier age of onset of psychosis, poor premorbid adjustment, low educational level, being male and being single were identified as risk factors in clinical treatment resistance, although the effect of gender on treatment resistance has not been confirmed in other studies (Crespo-Facorro et al., 2013a; A Demjaha et al., 2017; Wimberley et al., 2016). In terms of clinical predictors, higher severity negative symptoms on FEP had also been associated with higher rates of resistance to treatment (Bozzatello et al., 2019; A Demjaha et al., 2017; Yoshimura et al., 2017). These findings, in line with previous studies, suggest that treatment-resistant schizophrenia could be a different subtype of schizophrenia.

Individuals taking clozapine had more severe negative symptoms at both the onset of the disease and at 10 years of follow-up (see *Table 2*). However, despite the fact that subjects who

will later take clozapine had initially greater clinical severity, we found similar effect sizes of treatment with clozapine regarding other antipsychotics at 10 years, which supports the hypothesis that clozapine is a treatment that would provide adequate clinical efficacy in subjects with greater initial clinical severity, especially in terms of negative symptoms. Furthermore, we observed that with regard the subjects who met criteria for TRS, those who took clozapine had statistically significant lower total scores on all clinical scales. In addition, individuals who subsequent started clozapine had higher total scores in CGI at 10 years. Minimizing the delay in the initiation of clozapine could be beneficial, improving long-term treatment results and quality of life in patients with resistant schizophrenia (A. Demjaha et al., 2017).

The fact that we only found statistically significant differences in terms of total scores of several clinical scales between E-TR and L-TR at the beginning of the disease but not at 10 years, could suggest that the pathophysiological basis that explains both types of resistance to treatment (early and late) is not so different. Regarding L-TR, we found a higher rate (71%) than the 50% described previously by Chouinard and Chouinard (Chouinard and Chouinard, 2008). These findings also contrast to previous literature (A. Demjaha et al., 2017; Lally et al., 2016) who reported that the majority of FEP patients with TRS were treatment resistant from illness onset (84% and 70%, respectively). This difference could be explained by the fact that the follow-up period of our study was longer and therefore there is a greater possibility of observing late resistance than in studies with shorter follow-up periods.

In addition, we observed a low rate of relapses after switching to clozapine (28.6%). This finding is in line what was observed by Tiihonen and colleges (2017) and more consistently supports the use of clozapine in resistant psychoses, as it could prevent relapse and rehospitalization. The exact causal mechanism that leads to the benefits of clozapine remains unclear, but this reduction in relapses may be justified by greater efficacy in the control of severely affected individuals and better adherence to the drug (Leucht et al., 2013; Üçok et al., 2015). Several studies indicate that clozapine directly reduces both hospitalizations and readmissions compared to other antipsychotics (Duggan et al., 2003; Masuda et al., 2019), despite both greater severity and chronicity of the disease in those individuals treated with clozapine.

Regarding tolerance, the most frequent side effects in the clozapine group regarding other antipsychotics at 10-year were a higher prevalence of weight gain, sialorrhea, fatigue, orthostatic vertigo, constipation, increased daytime sleep and development of metabolic syndrome. However, it is worth highlighting that the only difference found between clozapine and olanzapine was greater sialorrhea in patients on clozapine. This seems to be a key point, as olanzapine is one of the most widely used second generation antipsychotics, and one of the main reasons for the low use of clozapine is the fear of its metabolic side effects compared to other antipsychotics (Leucht et al., 2013; Nielsen et al., 2013). These findings coincide with the last Cochrane review, which showed heterogeneous results and weak evidence in favor of weight gain with clozapine versus olanzapine in only one study (Asenjo Lobos et al., 2010). Further studies are needed to better understand the predictors of antipsychotic-induced weight gain, including genetic markers (Pérez-Iglesias et al., 2014).

The strengths of this study include that it is a quasi-prospective study that allowed the follow-up of the first episodes of psychosis during the first 10 years of the disease, being able to observe the pattern of clozapine use in a cohort of TRS in a naturalistic environment and identifying possible clinical and sociodemographic predictors with initiation of clozapine. However, there are also several limitations of this study: the study includes a small sample of TRS and therefore it would be recommended to conduct studies with larger samples in order to check the replicability of our data; the fact that guidelines and prescribing protocols have changed during the 10-year follow-up time could explain the higher percentage of subjects with L-TR in our sample compared to other studies that have been conducted over a shorter follow-up time. Finally, medication adherence was self-reported and, therefore, may have been overestimated.

In conclusion, our findings reinforce the early evaluation of treatment-resistant schizophrenia in patients with a first episode of psychosis and support clozapine be quickly considered as a treatment in the first episode of schizophrenia, not differing greatly in side effects with respect to olanzapine. More studies based on larger samples are needed to replicate and progress in this area, as well as to better understand the possible biological differences among subjects with early or late resistance to treatment.

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Table 1. Comparison of sociodemographic, premorbid and clinical characteristics at baseline between patients on clozapine (n = 35) and on other treatments (n = 183) at the 10-year evaluation

	Clozapine users			
	Yes n = 35 (16%)	**No n = 183 (84%)**		
Characteristics	**n (%)**	**n (%)**	**Statistics**	**p**
Diagnosis (Schizophrenia)	33 (93.3)	118 (79.7)	$X^2 = 3.13$	0.077
Sex (male)	50 (78.2)	318 (53.5)	$X^2 = 14.17$	0.001
Education level (elementary)	22 (62.9)	78 (42.6)	$X^2 = 4.84$	0.028
Socioeconomic status of parents (not/low qualified worker)	21 (60)	90 (49.7)	$X^2 = 1.24$	0.266
Living in urban area (yes)	29 (82.9)	120 (65.6)	$X^2 = 4.06$	0.044
Living with family (yes)	28 (80)	133 (72.7)	$X^2 = 0.82$	0.366
Single (yes)	33 (94.3)	131 (71.6)	$X^2 = 8.13$	0.004
Unemployed (yes)	21 (60)	64 (35)	$X^2 = 7.74$	0.005
Family history of psychosis (yes)	9 (25.7)	41 (22.4)	$X^2 = 0.18$	0.670
Hospitalization at intake (yes)	20 (57.1)	120 (65.6)	$X^2 = 0.91$	0.340
Tobacco use at intake (yes)	21 (60)	101 (55.2)	$X^2 = 0.28$	0.600
Cannabis use at intake (yes)	16 (45.7)	64 (35)	$X^2 = 1.46$	0.227
Alcohol use at intake (yes)	21 (60)	90 (49.2)	$X^2 = 1.38$	0.241
Cocaine use at intake (yes)	8 (22.9)	28 (15.3)	$X^2 = 1.22$	0.270
	mean (sd)	**mean (sd)**	**Statistics**	**p**
Admission age in PAFIP	26.1 (8.36)	30.4 (9.01)	t = -2.59	0.010
Age of onset of psychosis	24.7 (6.28)	29.2 (8.73)	t = -2.88	0.004
	p50 (IQR)	**p50 (IQR)**	**Statistics**	**p**
Duration of untreated illness (DUI) (months)	17.5 (31)	11 (27.5)	U = 1.19	0.234
Duration of untreated psychosis (DUP) (months)	6.5 (17)	3 (11)	U = 1.44	0.151
Childhood PAS	2.1 (2.08)	2.1 (1.25)	U = 0.43	0.671
Early Adolescence PAS	3.0 (1.6)	2.3 (1.67)	U = 2.27	0.023
Late Adolescence PAS	3.0 (1.5)	2.3 (2)	U = 1.88	0.060
Adulthood PAS	2.2 (3.33)	1.11 (2.78)	U = 1.35	0.178
General PAS	4.4 (2.41)	2.2 (2.59)	U = 4.15	0.001

Abbreviations: DUI, duration of untreated illness; DUP, duration of untreated psychosis; PAS, premorbid adjustment scale; IQR, interquartile range.

Table 2. Comparison of psychopathological characteristics between clozapine users and users of other treatments at baseline and at 10-year

	Total N = 218		**Clozapine users n = 35**			**Users of other treatments n = 183**				
	Mean	**SD**	**Mean**	**SD**	**r**	**Mean**	**SD**	**r**	**Statistic**	**p**
CGI										
Baseline	6.31	0.75	6.37	0.81		6.30	0.74		U = 0.74[a]	0.460
						6[c]	1.15[c]			
10-year	2.62	1.64	3.49	1.60		2.46	1.60			
						4.85[c]	1.46[c]			
10-year change from baseline	-3.69	1.79	-2.89	1.81	0.60	-3.84	1.75	0.61	F = 12.01[b]	0.001
						-1.15[c]	1.21[c]		F = 10.12[c]	0.026
YMRS										
Baseline	12.77	5.65	13.37	5.86		12.66	5.62		U = 0.70[a]	0.482
						11.31[c]	4.99[c]			
10-year	1.72	3.35	2.51	4.27		1.56	3.14			
						5.92[c]	4.48[c]			
10-year change from baseline	-11.05	6.13	-10.86	6.28	0.62	-11.09	6.12	0.61	F = 2.07[b]	0.151
						-5.38[c]	3.48[c]		F = 8.79[c]	0.048
CDSS										
Baseline	2.51	3.49	3	3.69		2.41	3.45		U = 1.22[a]	0.221
						2.08[c]	2.90[c]			
10-year	0.81	2.14	0.77	1.65		0.82	2.22			
						3.15[c]	5.01[c]			
10-year change from baseline	-1.69	3.96	-2.23	4.33	0.32	-1.59	3.88	0.31	F = 0.04[b]	0.842
						1.08[c]	4.55[c]		F = 5.38[c]	0.025
BPRS										
Baseline	62.76	13.69	65.63	14.65		62.21	13.46		U = 1.58[a]	0.114
						56.34[c]	14.50[c]			
10-year	32.12	9.36	35.26	9.72		31.52	9.20			
						50.31[c]	11.21[c]			
10-year change from baseline	-30.64	15.02	-30.37	15.19	0.62	-30.69	15.02	0.61	F = 3.82[b]	0.052
						-6.23[c]	6.39[c]		F = 30.47[c]	0.001
SAPS										
Baseline	13.59	4.48	14.2	4.87		13.48	4.41		U = 1.19[a]	0.235
						12.38[c]	4.70[c]			
10-year	1.56	3.23	1.94	3.01		1.49	3.28			
						5.46[c]	4.77[c]			
10-year change from baseline	12.03	5.32	-12.26	4.94	0.62	-11.99	5.40	0.61	F = 0.49[b]	0.487
						-6.92[c]	3.88[c]		F = 12.29[c]	0.001
SANS										
Baseline	7.71	6.40	9.83	6.59		7.31	6.31		U = 2.29[a]	0.022
						8.85[c]	7.82[c]			
10-year	4.90	5.48	7.83	6.03		4.34	5.20			
						13.62[c]	6.27[c]			
10-year change from baseline	-2.81	7.14	-2	8.56	0.17	-2.96	6.85	0.28	F = 9.27[b]	0.003
						4.77[c]	5.23[c]		F = 24.08[c]	0.001

BPRS: Brief Psychiatric Rating Scale; CDSS: Calgary Depression Rating Scale for Schizophrenia; CGI: Clinical Global Impression; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms, YMRS: Young Rating Scale.

r: correlation coefficient ranging from -1 to +1; r = 0.1 (small); r = 0.3 (medium); r = 0.5 (large).

[a] Comparison between clozapine group and other antipsychotics at baseline (Wilcoxon rank-sum test for independent data).

[b] Comparison between clozapine group and other antipsychotics following the antipsychotic treatment at 10-year, using the total score of the clinical scales at baseline as covariate; analysis of covariance (ANCOVA).

[c] Comparison between the clozapine group (n = 35) and other antipsychotics in those subjects meeting criteria for treatment resistant schizophrenia (n = 13) as defined by Leucht and colleagues (2006).

Table 3. Comparison of clinical symptoms between the different tertiles according to the median time of initiation of clozapine, at baseline and at 10-year of follow-up.

	First tertile n = 11		**Second tertile n = 12**		**Third tertile n = 12**				
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Stadistics**	**p**	**Paired comparisons***
CGI									
Baseline	6.73	0.47	6.17	0.83	6.25	0.97	h = 3.09[a]	0.214	
10-year	3.73	1.85	2.58	1.16	4.17	1.40			
10-year change from baseline	-3	1.95	-3.58	1.31	-2.08	1.93	F = 3.65[b]	0.038	p = 0.203[c]; p = 1.000[d]; p = 0.043[e]
YMRS									
Baseline	12.91	6.11	12.67	5.02	14.5	6.69	h = 2.15[a]	0.342	
10-year	1.09	2.70	0.5	1.73	5.83	5.31			
10-year change from baseline	-11.82	6.15	-12.17	5.47	-8.67	7.04	F = 7.11[b]	0.003	p = 1.000[c]; p = 0.015[d]; p = 0.005[e]
CDSS									
Baseline	5.09	5.36	2.58	2.75	1.5	1.24	h = 1.70[a]	0.427	
10-year	0.73	1.49	0.08	2.89	1.5	2.28			
10-year change from baseline	-4.36	6.04	-2.5	2.65	0	2.76	F = 2.16[b]	0.133	
BPRS									
Baseline	74	10.04	59.58	16.92	64	13.14	h = 5.29[a]	0.071	
10-year	39	10.55	29.5	4.52	37.58	10.69			
10-year change from baseline	-35	13.21	-30.08	17.49	-26.42	14.50	F = 2.67[b]	0.085	
SAPS									
Baseline	16	5.18	13.75	4.94	13	4.41	h = 2.76[a]	0.252	
10-year	2.18	3.43	0.67	1.30	3	3.57			
10-year change from baseline	-13.82	5.53	-13.08	5.14	-10	3.52	F = 2.31[b]	0.116	
SANS									
Baseline	9.73	7.35	10.5	7.76	9.25	4.88	h = 0.07[a]	0.965	
10-year	9.27	7.62	6.17	4.41	8.17	5.92			
10-year change from baseline	-0.45	9.63	-4.33	8.95	-1.08	7.28	F = 0.80[b]	0.458	

BPRS: Brief Psychiatric Rating Scale; CDSS: Calgary Depression Rating Scale for Schizophrenia; CGI: Clinical Global Impression; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms, YMRS: Young Rating Scale.

[a] Comparison of the median clozapine onset time between tertiles at baseline (Kruskal-Wallis test).

[b] Comparison of the median clozapine onset time between tertiles at 10-year, using the total of the clinical scales at baseline as covariate; Covariance analysis (ANCOVA).

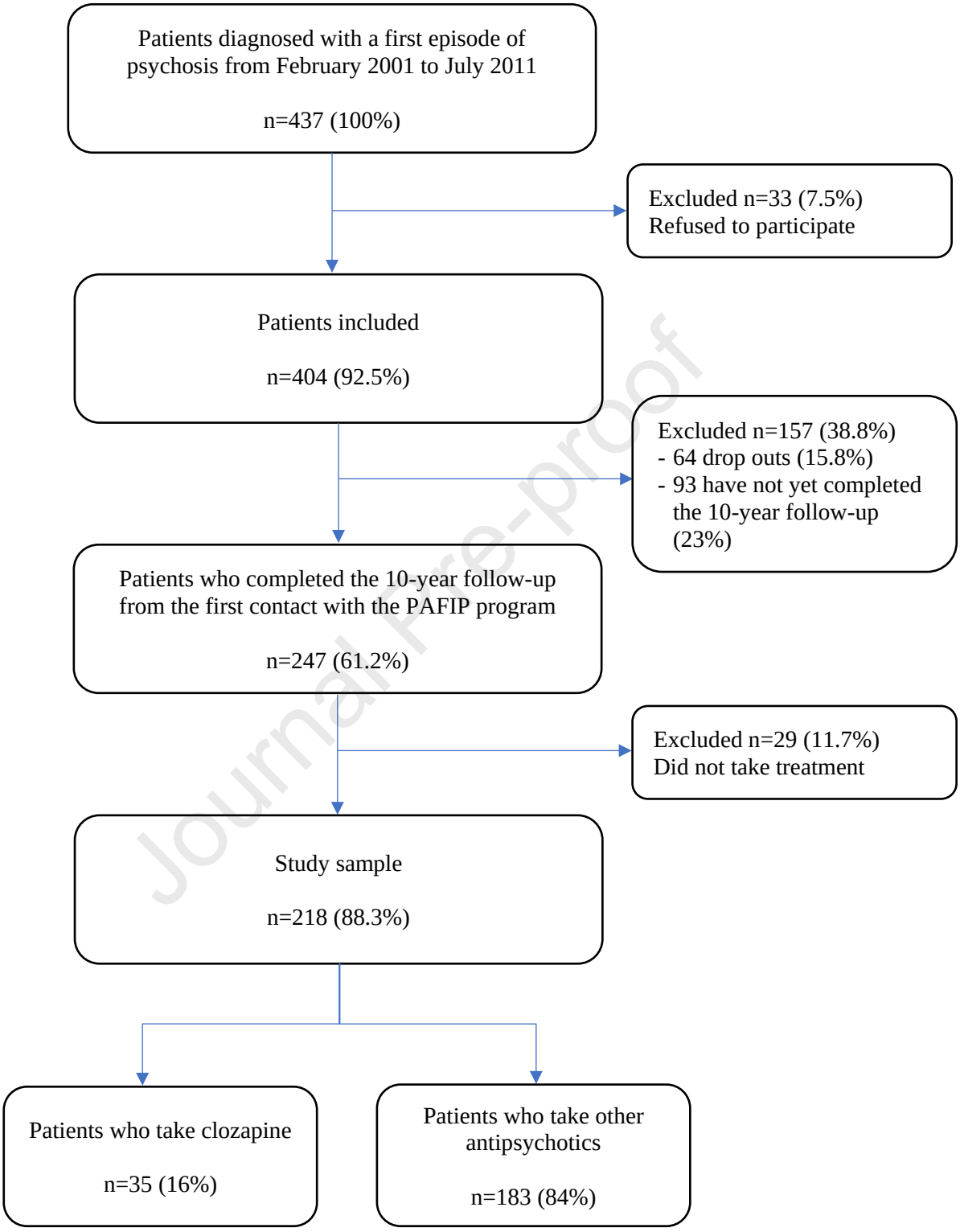
Significant after Bonferroni correction

[c]*: First tertile vs Second tertile*

[d]*: First tertile vs Third tertile*

[e]*: Second tertile vs Third tertile*

Figure 1. Study flowchart



Contributors:

Lara Moreno-Sancho designed the study protocol, collected the data, and co-wrote the manuscript. Maria Juncal-Ruiz designed the study protocol, analyzed the data, and co-wrote the manuscript. Javier Vázquez-Bourgón, Jacqueline Mayoral-Van Son, Diana Tordesillas-Gutierrez, Rosa Ayesa-Arriola and Esther Setien-Suero collected the data. Victor Ortiz-Garcia de la Foz collected and co-analyzed the data. Benedicto Crespo-Facorro designed the protocol, collected the data, and co-wrote the manuscript. All authors participated in the interpretation of the data, contributed and approved the final manuscript.

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