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Early treatment resistance in a Latin-American cohort of patients with schizophrenia

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ABSTRACT

Background: Failure to respond to antipsychotic medication in schizophrenia is a common clinical scenario with significant morbidity. Recent studies have highlighted that many patients present treatment-resistance from disease onset. We here present an analysis of clozapine prescription patterns, used as a real-world proxy marker for treatment-resistance, in a cohort of 1195 patients with schizophrenia from a Latin-American cohort, to explore the timing of emergence of treatment resistance and possible subgroup differences.
Methods: Survival analysis from national databases of clozapine monitoring system, national disease notification registers, and discharges from an early intervention ward.
Results: Echoing previous studies, we found that around 1 in 5 patients diagnosed with schizophrenia were eventually prescribed clozapine, with an over-representation of males and those with a younger onset of psychosis. The annual probability of being prescribed clozapine was highest within the first year (probability of 0.11, 95% confidence interval of 0.093–0.13), compared to 0.018 (0.012–0.024) between years 1 and 5, and 0.006 (0–0.019) after 5 years. Age at psychosis onset, gender, dose of clozapine used, and compliance with hematological monitoring at 12 months, was not related to the onset of treatment resistance. A similar pattern was observed in a subgroup of 230 patients discharged from an early intervention ward with a diagnosis of non-affective first episode of psychosis.
Conclusions: Our results highlight that treatment resistance is frequently present from the onset of psychosis. Future studies will shed light on the possible different clinical and neurobiological characteristics of this subtype of psychosis.

1. Introduction

Treatment-resistance to antipsychotic medications in schizophrenia has been defined as the failure to respond to two or more trials of antipsychotic medication at appropriate doses (>600 mg/day of chlorpromazine equivalents) given for an appropriate length of time (>6 weeks) (Howes et al., 2017; Suzuki et al., 2012). Previous reports suggest that treatment resistance is relatively common in clinical practice, being described in 20% to 60% of patients (Conley and Kelly, 2001; Hassan and De Luca, 2015; Kane et al., 1988; Kennedy et al., 2014). It has a considerable impact on the quality of life of patients and has significant societal economic costs (Kennedy et al., 2014).

Clozapine is the most effective drug in treatment-resistance schizophrenia (Kane et al., 1988; Siskind et al., 2016). This is reflected on the widespread recommendation of its use in this population in treatment guidelines (Warnez and Alessi-Severini, 2014). However, it is not the only clinical indication. Clozapine also decreases suicidal ideation (Meltzer et al., 2003), and should be considered in those patients at high risk of suicide. It also has a very low risk of extrapyramidal side effects (Claghorn et al., 1987); yet, most clinicians would nowadays use another atypical antipsychotic if they were looking for an antipsychotic with that profile. Clozapine has even been proposed as a first-line treatment in first-episode patients (Remington et al., 2013). Although there are other indications for clozapine use apart from treatment-resistance, in practice its hematological (Alvir et al., 1993) and metabolic side effects (De Hert et al., 2011) have largely restricted its use to treatment-resistant cases. This is also the case in Chile, where clozapine is

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exclusively recommended for treatment-resistant cases (Ministerio de Salud, 2009).

Based on the idea that clozapine is mostly used in treatment-resistant cases of schizophrenia in clinical practice, previous studies have used clozapine prescription as a proxy marker of treatment-resistance (Wimberley et al., 2017b, 2016). This has obvious advantages, since it is easy to identify in case-registers, and is a 'real world' clinical dichotomous definition. But it also has important limitations, since clozapine prescription patterns might be affected by other factors such as clinicians' perceptions, how services are organized, or how clozapine use is regulated (Nielsen et al., 2016, 2010) All these factors contribute to the observed differences in prescription patterns in different regions and countries (Bachmann et al., 2017; Downs and Zinkler, 2007), and to the known delay in clozapine initiation (Howes et al., 2012; Wheeler et al., 2014).

The timing in which resistance to treatment appears in the course of the disorder is a potentially significant specifier (Howes et al., 2017). A recent study has highlighted a subgroup of distinct patients who present treatment-resistance already from the onset of the illness (Lally et al., 2016). This early lack of response to antipsychotics potentially indexes a subgroup of patients with a non-dopaminergic psychosis from the onset (Demjaha et al., 2012). With this in mind, we here examined the timing of emergence of treatment-resistance as indexed by clozapine prescription patterns in a cohort of patients with schizophrenia in Chile.

2. Methods

2.1. Study sample

We included all patients diagnosed with schizophrenia between 1st of January 2007 and 31st December 2014 at the Psychiatric Institute "Dr. Jose Horwitz Barak" in Santiago, Chile (both inpatients and outpatients). This is a tertiary public hospital located in Santiago, Chile, with a catchment area of over 1,000,000 inhabitants. Diagnosis was obtained from the National Register of "Health Conditions under Explicit Guarantees", a governmental programme to guarantee universal access to care and treatment to patients (Letelier and Bedregal, 2006). This programme responds to a prioritization of the resources in the context of their limited availability in the country, and schizophrenia has been included since its beginning. To avoid including chronic cases of schizophrenia registered at a later stage than first diagnosis, we excluded the first year of the programme (2006) from the analyses. Notification of the disorder is compulsory for the treating physician as a way of ensuring the rights of patients.

In order to examine whether our results might be biased due to the inclusion of chronic cases, we also examined a smaller second cohort of patients who were admitted to the early intervention ward at the Psychiatric Institute "Dr. José Horwitz B.", received on discharge a diagnosis of a non-affective psychosis (DSM-IV schizophrenia or schizophreniform disorders), and were described as being their first episode. This is an 18-bed mixed-gender unit providing care for patients with psychosis aged between 16 and 25 years old (González-Valderrama et al., 2017).

2.2. Identification of treatment-resistant cases

We here used the initial prescription of clozapine as a proxy indicator for treatment-resistance, as it is the only medication with evidence supporting its efficacy in treatment-resistant schizophrenia, and the one recommended by clinical guidelines. We used the National Clozapine Monitoring Register, run by the Public Health System. Registration in this service is mandatory for patients receiving clozapine in the public health system. 5379 patients had been registered between 2004 and 2016.

We also identified the last known dose of clozapine prescribed, which arguably is informative about the responsiveness of a patient to clozapine. We also examined the compliance with hematological monitoring for clozapine at 12 months, with a view that it can also be used as a proxy for all-cause discontinuation - an outcome frequently used in effectiveness trials (Lieberman et al., 2005).

2.3. Statistical analyses

Probability of becoming resistant to treatment as indexed by clozapine prescription was analyzed using survival curves, with the Greenwood formula used for calculating its variance (Bland and Altman, 1998). We divided the examined period into three as suggested by a recent consortium (Howes et al., 2017): early onset period (within 1 year of treatment onset), medium-term onset (1 to 5 years of treatment), and late onset (>5 years). Probability of clozapine initiation for each of these periods was calculated, defined as (1-probability (end of period)) – (1-probability (beginning of period)). In other words, it represents the probability of someone entering this period of being prescribed clozapine by the end of it. To account for the longer duration of certain periods, we divided the probability for the whole period by the number of years it includes. To provide a measure of variance to this estimate, we used the 95% confidence intervals calculated by the Greenwood formula. Significance level was established at $P < 0.05$. Data were analyzed using MATLAB (Mathworks USA).

This study was approved by the ethics committee of the Servicio de Salud Metropolitano Norte, Santiago.

3. Results

3.1. Description of the two included cohorts

1195 patients from the Psychiatric Institute "Dr. Jose Horwitz B." received a notification of a diagnosis of schizophrenia between 2007 and 2014 and were included in this analysis. The second cohort was composed of 230 patients who were discharged from the Early Intervention ward of the hospital with a diagnosis of first episode of non-affective psychosis between 2008 and 2014. As Table 1 shows, the cohort of patients discharged from the ward had a larger proportion of males than those notified with a diagnosis of schizophrenia (77.8% compared to 59.6%, Chi-square $P < 10^{-5}$). Considering that the ward included in this study only admits patients aged between 16 and 25 years old, it is not a surprise that patients discharged from the ward were younger (median age of 19 compared to 27, $P < 10^{-59}$ Wilcoxon ranksum test).

3.2. Clozapine prescription patterns in patients notified with a diagnosis of schizophrenia

Table 2 shows that 258 subjects of the 1195 patients notified with a diagnosis of schizophrenia (21.6%) were subsequently enrolled in the

Table 1
Characteristics of the two cohorts included.

	Patients notified with a diagnosis of schizophrenia	Patients discharged from ward with the diagnosis of first-episode of non-affective psychosis	Statistical test	Statistical significance
Number of patients	1195	230	n.a.	n.a.
Gender (% male)	59.6%	77.8%	Chi-square statistic 27.17; d.o.f. 1	$P < 10^{-5}$
Age (median, inter-quartile range)	27 (21–38)	19 (17–21)	Wilcoxon ranksum test	$P < 10^{-59}$

n.a. = not applicable; d.o.f. = degrees of freedom.

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Table 2
Clinical variables associated with clozapine use.

	Clozapine users	Non-clozapine users	Statistical test	*P*-value
A. Patients notified with a diagnosis of schizophrenia				
- Included in analyses, *N* (%)	258 (21.6)	937 (78.4)	n.a.	n.a.
- Age at diagnosis (median, interquartile range)	24 (20–32)	28 (21–39)	Wilcoxon	<0.0001
- Gender (% male)	66.7	58	Chi-square test: 6.3, d.o.f. 1	0.012
- Last known clozapine dose (mean and standard deviation)	346 mg (164 mg)	n.a.	n.a.	n.a.
- All-cause clozapine discontinuation at 12 months (compliance with hematological monitoring)	5.2%	n.a.	n.a.	n.a.
B. Early intervention ward sub-sample				
- Included in analyses *n* (%)	42 (18.3)	188 (81.7)		
- Age at diagnosis (median, interquartile range)	19 (17–21)	19 (17–21)	Wilcoxon	$P = 0.7$
- Gender (% male)	81%	77%	Chi-square test: 0.29, d.o.f. 1	$P = 0.59$
- Last known clozapine dose (mean and standard deviation)	305 mg (177 mg)	n.a.	n.a.	n.a.
- All-cause clozapine discontinuation at 12 months (compliance with hematological monitoring)	4.8%	n.a.	n.a.	n.a.

n.a. = not applicable; d.o.f. = degrees of freedom.

National Clozapine Monitoring System. Patients who subsequently received clozapine were younger when diagnosed compared to those who were not prescribed this medication (median age 24 years old, compared to 28 years old; Wilcoxon rank sum $P < 0.0001$). Clozapine-treated group also had a larger proportion of males (66.67% compared to 58.02%; chi-square test 6.3, d.f. = 1, $P = 0.012$).

Patients were prescribed on average 345 mg of clozapine (164 mg standard deviation). All-cause clozapine discontinuation at 12 months, as indexed by the continuing hematological monitoring, was 5.2%.

We then looked at the timing of the prescription after notification of the diagnosis (Fig. 1A). Of the 258 subjects prescribed clozapine, 45 were notified after registration with clozapine services, and were excluded from this analysis. Median prescription time after diagnosis was 7.4 months in this population. Fig. 1 shows the probability of clozapine prescription after diagnosis, showing a clear early steep increase. When using a recently recommended subdivision of the timing of treatment-resistance into early (<1 year), medium (1 to 5 years), and late (>5 years) (Howes et al., 2017), we found that the average annual probability of clozapine initiation was highest in the early stage (0.11; 95% CI 0.093–0.13), compared to medium (0.018; 95% CI 0.012–0.024) or late (0.006; 0–0.019) (Fig. 2A).

Subsequently we examined the potential relationship between age, gender, dose, and compliance with hematological monitoring at 12 months, with the onset of treatment-resistance (Table 3). Age at diagnosis did not have a significant effect on the timing of subsequent clozapine prescription ($r_s = 0.004$, $P = 0.96$, Spearman correlation). Logistic regression looking at the effect of gender was not statistically significant either ($P = 0.4322$). Average doses used were slightly higher for those with an early onset, however this was not statistically significant (Pearson correlation $R = -0.13$, $P = 0.06$). Discontinuation rates were higher in those with an early-onset, but this was not statistically significant when tested within a logistic regression ($P = 0.062$).

3.3. Analyzing prescription pattern in subjects discharged from early intervention ward

We then repeated the analysis looking only at those patients who had been discharged from the Early Intervention ward with a first-episode of non-affective psychosis. 42 of the 230 patients included (18%) were subsequently prescribed clozapine. In this subgroup of patients, who are selected by their need of hospital admission during their first-episode and being aged between 16 and 25 years old, there were no differences in age or gender between those who subsequently started clozapine and those that did not (Table 2B).

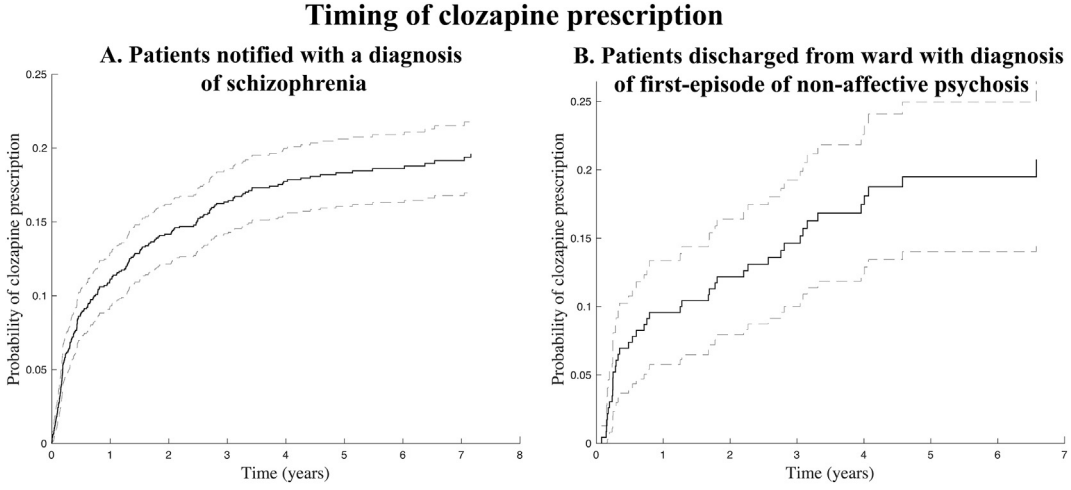

Fig. 1. Probability of clozapine initiation. Kaplan-Meier estimates with 95% confidence intervals calculated using Greenwood's formula for all patients notified with a diagnosis of schizophrenia (A) and those discharged from the early intervention ward (B).

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Patients who subsequently started clozapine received an average dose of 305 mg (standard deviation 177 mg). 4.8% of patients did not comply with the hematological monitoring at 12 months.

When analyzing the timing of clozapine initiation, survival curves showed a similar form in this cohort, with an early steep increase in clozapine prescription within the first two years which flattens down later (Fig. 1B). Average annual probability of clozapine was 0.096 (95% CI 0.06–0.013) during the early period (<1 year), 0.025 (95% CI 0.01–0.04) during the medium stage (1 to 5 years), and 0.006 (95% CI 0–0.004) at the late stage (>5 years) (Fig. 2B).

There was no statistically significant effect of age ($r_s = 0.084$, $P = 0.6$, Spearman correlation), gender (logistic regression $P = 0.43$), clozapine dose (Pearson correlation $R = -0.087$, $P = 0.58$) or compliance with hematological monitoring at 12 months (Logistic regression $P = 0.76$) on the timing of the clozapine prescription (Table 3).

4. Discussion

Treatment resistance is a significant clinical challenge which has a big impact on our patients and society in general. Using clozapine prescription rates as a proxy marker for treatment-resistance, and in line with previously reported literature, we here show that treatment resistance is relatively common in a Latin American cohort, with around 1 in 5 patients diagnosed with schizophrenia being subsequently prescribed clozapine. Our main finding was that the emergence of resistance was highest within the first year after diagnosis, suggesting that treatment-resistance is present since the onset of the disease in a significant number of patients.

There is significant interest in the group of patients who are treatment resistant from the onset of the disease (Demjaha et al., 2017). This is undoubtedly an important clinical question. Previous studies have shown that between 10% to 20% of first-episode patients are resistant to treatment (Agid et al., 2011; Lally et al., 2016; Yoshimura et al., 2017), which is in line with the observed probability of clozapine initiation within the first year in our sample. Our results will help highlight to clinicians to be ready to prescribe clozapine within the first year of treatment (Williams et al., 2017). It also raises interesting biological questions about a psychotic disorder in which dopamine does not seem to be the core dysfunction, as shown by its lack of response to dopaminergic antagonists and its PET correlates (Demjaha et al., 2012). This would support the idea that at least some subtypes of treatment-resistant psychosis are categorically distinct and not part of a continuum within schizophrenia (Mouchlianitis et al., 2016; Wimberley et al., 2017a). Other studies using other approaches such as biomarkers or imaging will shed further light on this group (Kapur et al., 2012).

Unlike a previous study (Lally et al., 2016), we did not find demographic differences between those with early onset and the rest of treatment-resistant patients. This potentially complicates the identification of these subjects. We did not have standardized clinical assessments from these subjects to explore further differences in clinical presentation, which is a potentially promising approach (Demjaha et al., 2017). However, we also examined the last-known dose of clozapine patients were receiving, arguably an indirect measure of how well patients responded to that medication. We also explored the rate of compliance with hematological monitoring at 12 months, which might be taken as an indirect measure of all-cause discontinuation as used in effectiveness trials. Overall, we did not find any statistical differences in these two outcomes in patients acquiring treatment-resistant at an early stage, which suggests that these patients also benefit from clozapine use. Further studies formally examining the clinical response to clozapine in these patients will be able to corroborate this.

Similar to previously published literature on treatment resistance, we found that patients who failed to respond and were prescribed clozapine were more likely to be male and had an earlier onset of psychosis (Henna et al., 1999; Meltzer et al., 1997). This was not significant in the smaller cohort of patients discharged from the ward, although this was likely due to the smaller sample size, the narrower age range of the patients included, and the higher prevalence of males in inpatient units (Walker and Lewine, 1993).

The main limitation of our study is the use of clozapine as a proxy marker of treatment resistance. Previous studies have shown that there is resistance to prescribe clozapine to individuals given its side effect profile and position as a 'treatment of last resort' (Nielsen et al., 2010), with patients receiving instead antipsychotic polypharmacy or high dose treatment (i.e. over the maximum licensed) (Howes et al., 2012). As a result, there is a significant delay in prescribing clozapine once needed, reported to range between 2.5 and 6 years in different cohorts (Howes et al., 2012; Najim et al., 2013; Ucok et al., 2015; Wheeler et al., 2014). This bias would lead to an under-estimation of the burden of treatment-resistance, particularly in those with an early-onset. The delay in clozapine prescription is not universal, possibly responding to different practices in different countries (Bachmann et al., 2017) and

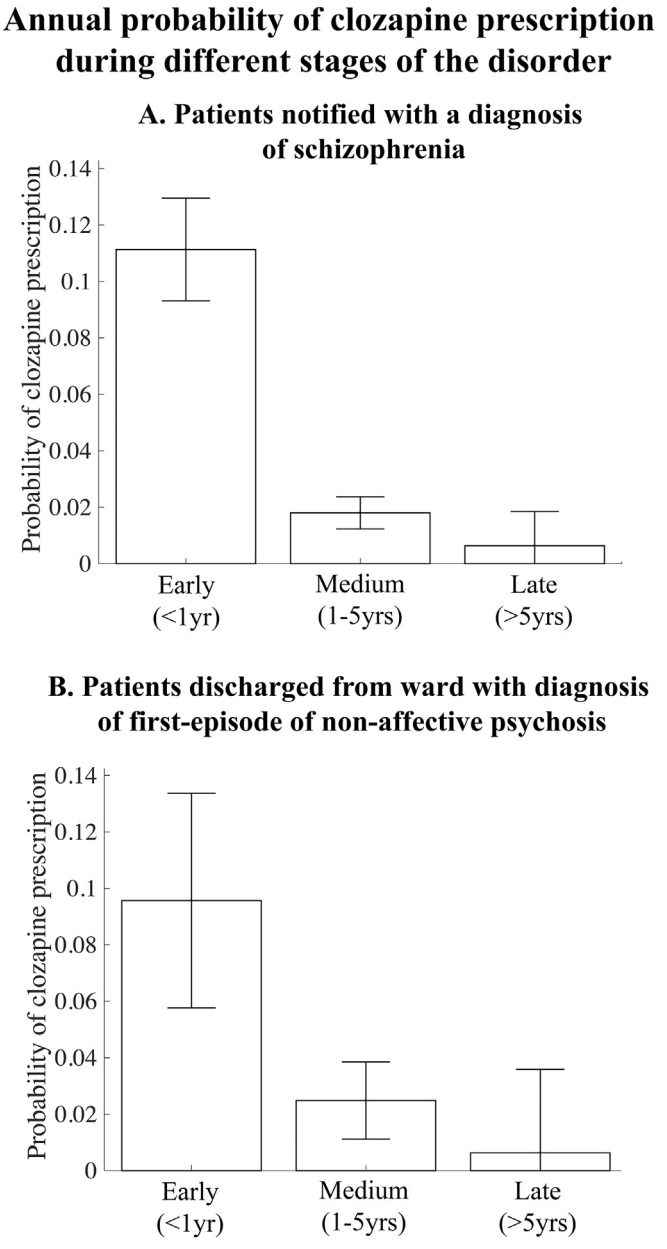

Fig. 2. Annual probability of clozapine initiation for the different stages of the disorder for the two cohorts. Stages are based on recent recommendations (Howes et al., 2017).

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Table 3
Clinical variables associated with timing of subsequent clozapine prescription.

	Early-onset TR (<1 year)	Medium-onset TR (1 to 5 years)	Late onset TR (>5 years)	Statistical test	*P*-value
A. Patients notified with a diagnosis of schizophrenia					
- Included in analyses *n* (%)	128	78	7	n.a.	n.a.
- Age at diagnosis (median and interquartile range, in years)	25.5 (21–32.5)	24 (20–30)	23 (20.5–30.25)	Spearman correlation $r_s = 0.006$	$P = 0.96$
- Gender (% male)	68.75%	62.8%	71.4%	Logistic regression	$P = 0.66$
- Last known clozapine dose (mean and standard deviation)	348 mgs (165)	343 mgs (171)	343 mgs (53)	Pearson correlation $R = -0.13$	$P = 0.06$
- All-cause clozapine discontinuation at 12 months (compliance with hematological monitoring)	8.6%	0%	0%	Logistic regression	$P = 0.062$
B. Early intervention ward sub-sample					
- Included in analyses *n* (%)	22	19	1	n.a.	n.a.
- Age at diagnosis (median and interquartile range, in years)	18 (17–21)	19 (18–21)	19	Spearman correlation $r_s = 0.084$	$P = 0.6$
- Gender (% male)	77.3%	89.5%	0%	Logistic regression	$P = 0.43$
- Last known clozapine dose (mean and standard deviation)	308 mgs (193)	307 mgs (166)	200 mgs	Pearson correlation $R = -0.087$	$P = 0.58$
- All-cause clozapine discontinuation at 12 months (compliance with hematological monitoring)	4.6%	5.3%	0%	Logistic regression	$P = 0.76$

TR = treatment resistance; n.a. = not applicable; d.o.f. = degrees of freedom.

even in different institutions (Nielsen et al., 2012). The number of patients receiving clozapine at an early stage in our study, suggest that this is less of a problem in our institution. However, we cannot rule out this significant confounder. Even when taking this into account, our main result describes an early onset of treatment-resistance in a significant number of our patients, which possibly might be still an underestimate of the real impact. Another limitation of our study is that a proportion of patients initially seen in the public hospital might have subsequently been prescribed clozapine in the private sector, without registering in the clozapine monitoring system included in this study. We also did not consider patients who died after being diagnosed, which although they were likely to be only a few, they were still considered as population at risk of becoming treatment resistance. Again, these two confounders would tend to under-estimate the number of treatment-resistant cases. The diagnoses of subjects were based on notification to the public health system, which might not be entirely accurate, with many subjects potentially notified after years of treatment. The replication of the findings with our secondary analyses using the subgroup of patients who had an inpatient admission and a diagnosis of first-episode non-affective psychosis shows that our results are robust. Notified diagnoses did not specify subtypes of psychosis, preventing us to examine the role of different clinical presentations.

Our study benefits from a relatively large cohort of patients in a real-world scenario. Furthermore, the setting and population studied is under-represented in the published literature (Patel and Sumathipala, 2001). Thus, our study will help link findings from the developed world into more deprived settings, allowing the existing evidence to shed light and relieve the burden caused by treatment-resistance on the other 90% of the world.

Data statement

Information about 1195 patients diagnosed with schizophrenia between 2007 and 2014 were obtained from the National Register of Diseases, including demographic characteristics and time of diagnosis. This was cross-linked with clozapine hematological surveillance systems which contained the date of clozapine initiation. A further cohort of 230 subjects was also included. These subjects were discharged from an early intervention ward between 2008 and 2014 with a diagnosis of a first episode of non-affective psychosis.

Conflict of interest

None.

Contributors

CM, AGV and NAC designed the study and wrote the protocol. CM, AGV, BI and NAC retrieved the data and performed the analyses. NAC wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Role of the funding source

Funding source did not have any role in the design, analysis or drafting the manuscript.

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