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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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