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Predictors of clozapine discontinuation at 2 years in treatment-resistant schizophrenia

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ABSTRACT

Introduction: Little is known about predictors of clinical response to clozapine treatment in treatment-resistant psychosis. Most published cohorts are small, providing inconsistent results. We aimed to identify baseline clinical predictors of future clinical response in patients who initiate clozapine treatment, mainly focusing on the effect of age, duration of illness, baseline clinical symptoms and homelessness.

Methodology: Retrospective cohort of patients with treatment-resistant schizophrenia, aged between 15 and 60 years, that initiated clozapine between 2014 and 2017. Sociodemographic characteristics, years from illness diagnosis, and clinical presentation before the initiation of clozapine were collected and analyzed. All-cause discontinuation at two years follow-up was used as the primary measure of clozapine response.

Results: 261 patients were included with a median age at illness diagnosis of 23 years old (IQR 19-29) and a median age at clozapine initiation of 25 (IQR: 21–33). 72.33% (183/253) continued clozapine after two years follow-up. Being homeless was associated to higher clozapine non-adherence, with an OR of 2.78 (95%CI 1.051–7.38) ($p = 0.039$, controlled by gender). Older age at clozapine initiation and longer delay from first schizophrenia diagnosis to clozapine initiation were also associated with higher clozapine non-adherence, with each year increasing the odds of discontinuation by 1.044 (95%CI 1.018–1.071; $p = 0.001$) and OR 1.093 (95%CI 1.008–1.19;$p = 0.032$) respectively.

Conclusion: Starting clozapine in younger patients or shortly after schizophrenia diagnosis were associated with better adherence.

1. Introduction

Treatment-resistant schizophrenia has been defined as lack of a satisfactory clinical improvement despite the sequential use of two antipsychotics at recommended doses (i.e. 600 mg chlorpromazine equivalent per day) for at least six weeks (Howes et al., 2017; Suzuki et al., 2011a). Approximately one-third of patients with schizophrenia will fulfil the criteria for treatment-resistance (Conley and Kelly, 2001; Hassan and De Luca, 2015). These subjects score the highest among patients in psychopathology scales (Elkis, 2007), and have the worst outcomes in terms of everyday functioning and quality of life (Lasevoli et al., 2016). The economic burden in direct healthcare costs alone is 4 to 11 times higher than the cost of those who respond to antipsychotics (Kennedy et al., 2014).

The most effective pharmacological treatment for improving the clinical outcome in these patients is clozapine, reducing hospital admissions, suicidality, aggressive behaviour, and even improving survival (Kane et al., 1988; Meltzer et al., 2003; Siskind et al., 2016; Vermeulen et al., 2019). However, we know there are significant delays worldwide in the initiation of treatment (Howes et al., 2012), and a large group of

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patients that might benefit from it are never offered the medication (Bachmann et al., 2017). This could be due to fear of possible known complications of clozapine, such as agranulocytosis or myocarditis, and its requirement of regular blood tests (Daod et al., 2019; Mena et al., 2018; Mena et al., 2019; Nielsen et al., 2013). Furthermore, a recent metanalysis shows that approximately 60% of patients are resistant to clozapine, falling in the category of ultra-resistant schizophrenia patients (Siskind et al., 2017). Predicting who would benefit from clozapine use would have a significant clinical impact, potentially increasing its prescription for those that would benefit (including at an earlier stage), as well as avoiding the exposure to significant side effects to those that would not.

A few studies have examined potential clinical and social predictors of response to clozapine treatment in treatment-resistant schizophrenia (Köhler-Forsberg et al., 2017; Samanaite et al., 2018; Suzuki et al., 2011b). Higher baseline symptoms and better functioning in the previous years have been described as reliable markers (Chung and Remington, 2005), although some studies contest those findings (Umbricht et al., 2002). One suggested reason why a clear picture has not yet emerged, is that many reports have assessed characteristics after clozapine initiation (Suzuki et al., 2011b), or are based on a relatively small sample of patients. Poor social support has also been linked previously to poorer mental health outcomes in patients with schizophrenia (Tempier et al., 2012) and described as a predictor of clozapine response (Köhler-Forsberg et al., 2017). A more recent study has highlighted data from several observational studies that support a shorter delay in its initiation as a prognostic marker (Shah et al., 2018). This interesting clinical observation was also recently replicated by Chan et al. in a first episode cohort (Chan et al., 2020). The age effect (younger age, which could be related with a shorter delay) also seems consistent across observational studies (Smart et al., 2019) and metanalysis (Okhuijsen-Pfeifer et al., 2020). However, it was not observed in a meta-regression analysis of a recent systematic review of randomized controlled trials (Jones et al., 2020), possibly considering the limitations of exploring pooled (average) data. The possibility of an effect in the delay of clozapine has significant clinical implications. Mirroring the long-term impact of duration of untreated psychosis in first presentation (Marshall et al., 2005; Penttilä et al., 2014), the duration of untreated treatment-resistant psychosis also could have an impact regarding future response to treatment.

In order to contribute further data to this literature, we aimed to explore sociodemographic and clinical predictors of clozapine response. We focused on the effect of age at clozapine start, duration of illness prior to clozapine initiation, baseline clinical symptoms and homelessness (as a proxy of baseline functioning and social support). We examined records of 261 patients who initiated clozapine treatment in one psychiatric institution in Chile, looking at baseline predictors of future response. Following previous effectiveness trials in real-world settings (Davis et al., 2011), we used clozapine discontinuation at two years as a composite marker of effectiveness from the clinicians' and patients' perspective, as well as tolerability. We hypothesized that higher positive symptomatology and a shorter duration of illness would predict higher adherence at two years.

2. Methodology

We conducted a retrospective cohort study including all patients with treatment-resistant schizophrenia, aged between 15 and 60 years, that initiated clozapine between 2014 and 2016 in a public psychiatric institute in Santiago, Chile ("Dr José Horwitz Barak."). This psychiatric institute is a quaternary care referral hospital for the public health service (service which provides care for 80% of the Chilean population). It is the hospital which most frequently initiates and follows-up patients on clozapine in Chile. Namely 20% of patients who initiated clozapine in Chile are started in this hospital, and 13.8% of patients using clozapine continue their follow up in this specialized centre. Subjects with diagnoses other than schizophrenia spectrum disorder (DSM-5) or with comorbid neurological disorders were excluded.

The study was approved by the Ethics and Research Committee of the North Metropolitan Health Service.

2.1. Data source

Clinical symptoms measured by the treating psychiatrist using the PANSS scale and sociodemographic data were extracted from the standardized clinical evaluation at registration for clozapine treatment, before the initiation of clozapine. Symptom dimensions were defined using PANSS items for subgroup analyses, including positive symptoms (P1-P7), negative symptoms (N1-N7), and disorganization symptoms (P2, G10, G11; as used previously in (Ortiz et al., 2013)).

Data on the year of diagnoses were obtained from records of the national disease notification register. Chilean law requires registration of cases of specific medical disorders in order to guarantee access to treatment (Letelier and Bedregal, 2006). Schizophrenia has been included since 2005, from the first psychotic episode, being a reliable source of information for the year of illness initiation (González-Valderrama et al., 2020; Mena et al., 2018). To avoid bias when assessing the duration of illness in chronic patients just registered when the law came to effect, we excluded from our estimate cases with diagnoses during 2005 and 2006 (n = 8). This information was available for only 220 cases, due probably to the fact that the other patients experienced their first episodes before 2005.

2.2. Outcome measures

We used all-cause discontinuation during the two years follow-up as our primary outcome reflecting efficacy as judged by the patient and clinician, as well as tolerability. We obtained these data from the electronic record of the national database of clozapine monitoring system. This is a government supported database which registers all subjects receiving clozapine. Subjects receiving clozapine need to be registered in this system for clozapine to be dispensed by the public health system. Every time the medication is dispensed to the patient (weekly or monthly according to clozapine pharmacovigilance calendar), the dose and results of the patient's latest blood test is registered by the corresponding nurse in the database. Discontinuation was defined as a gap in this record longer than three months, meaning the patient didn't received the medication for three months. Subjects in which discontinuation was due to death (n = 2) or hematologic adverse effect (n = 6) were excluded from the analysis. Hematologic adverse events described were mild (n = 1) and moderate neutropenia (n = 4), and severe leukocytosis (n = 1).

2.3. Independent variables

Based on the existing literature we here studied the effect on clozapine adherence of timing of initiation (delay in clozapine prescription, age at clozapine initiation), clinical presentation (total PANSS score at baseline, positive, negative and disorganization symptom subscores at baseline), and homelessness (a marker of social support and functioning).

2.4. Statistical analyses

Descriptive statistics and corresponding measures of variability were calculated for the sample, testing for normality of the distribution of numerical variables using Kolmogorov-Smirnov test. For the univariate analysis, T-student or Mann-Whitney tests were made for numerical variables and Chi-square test for categorical ones. Multivariate analysis was made using logistic and multiple linear regression, obtaining Odds Ratio (OR) adjusted for gender. ANOVA testing for interactions for gender and psychosis was also used. The formula used in each model is

y ~ gender + independent variable (time-related variables, baseline symptom severity or homelessness). All significant independent variables were posteriously included in a final model, controlled by gender.

Following a previous study (Chan et al., 2020), we also explored the effects of clozapine prescription timing on clozapine adherence using a Kaplan Mayer plot with log-rank and cox proportional hazard ratio analysis. The Kaplan Mayer survival analysis is a more appropriate analysis when studying the effect of a time variable as it considers the variable of time estimating the average constant hazard over a specific period, compared to the multiple regression model which estimates risk in a specific time-point. One Kaplan Mayer plot was constructed for each of the two time-related variables. Time variables measured were the age at clozapine initiation and the number of years from schizophrenia diagnosis to the date of clozapine prescription (referred on this study as delay in clozapine prescription).

All statistical analyses used two-tailed tests and a P value <0.05 was considered statistically significant. SPSS version 25.0 statistical package and Rstudio package version 1.3.1093 were used.

3. Results

The sample consisted of 261 treatment-resistant patients. Their sociodemographic, clinical and illness progression characteristics at the time of clozapine initiation are presented in Table 1. 2.4% of patients discontinued secondary to hematologic side effects and 0.8% due to death. These subjects were excluded from further analyses reported. Mean maximum clozapine dose was 403.43 mg (SD: 148.38). 51.2% were first-episode psychosis (FEP) patients at clozapine initiation, considering as FEP those within the first year since their illness had been notified. Only 28.4% of the sample were female, and 7.4% homelessness at the time of clozapine initiation. 72.33% (183/253) patients continued clozapine after two years follow-up.

3.1. Homelessness

7.3% of patients were homeless, which was associated with less adherence (p = 0.039, controlled by gender), OR 2.78 (95%CI 1.05–7.38) with only 50% of homeless patients being adherent vs 72.2% of non-homeless. The parameters of the model are described in Table 2.

Table 1
Sociodemographic, clinical and duration of illness characteristics of participants at clozapine initiation.

Participants	261
Sociodemographic	
Gender; n (% women)	75 (28.4%)
FEP at clozapine initiation; n (%)	108/211 (51.2%)*
Homeless; n (%)	19/261 (7.3%)
Illness progression	
Age at illness diagnosis; median (IQR)	23 (19-29)*
Age at first clozapine start; median (IQR)	25 (21−33)*
Time from diagnosis to clozapine start (years); mean (SD), median (IQR)	2.27 (3.89), 0 (0–3)*
Previous clozapine use; n (%)	53/261 (20.3%)
Severity of symptoms	
Total PANSS score; mean (SD)	101.73 (33.27)
Disorganization score; mean (SD)	8.88 (3.62)
Total positive score; mean (SD)	24.54 (9.59)
Total negative score; mean (SD)	28.8 (10.48)

Abbreviations: SD: Standard deviation, FEP: first episode psychosis: subjects within the first year the psychotic disorder is notified. Previous clozapine use: patients that have used clozapine in prior occasions. *excluding cases diagnosed during 2005–2006 (to avoid bias when assessing duration of illness in chronic patients just registered when the law came to effect).

Table 2
Independent variable's effect on clozapine adherence, controlled by gender.

Variable	B	Std error	P-value	OR	95% CI OR
Homelessness effect on adherence model.					
Homelessness	1.024	0.497	0.039	2.78	1.05–7.38
Gender	0.512	0.334	0.125	1.67	0.87–3.22
Model r^2 = 0.038					
Age at clozapine initiation effect on adherence model.					
Age at clozapine initiation	0.042	0.013	0.001	1.04	1.02–1.07
Gender	0.693	0.347	0.046	1.99	1.01–3.95
Model r^2 = 0.077					
Years from illness diagnosis to clozapine initiation effect on adherence model.					
Years from illness diagnosis to clozapine initiation	0.088	0.041	0.032	1.09	1.01–1.18
Gender	0.719	0.409	0.079	2.05	0.92–4.58
Model r^2 = 0.063					

3.2. Clinical variables

Clinical variables as total PANSS score (p = 0.918, adjusted by gender) and positive (p = 0.725, adjusted by gender), negative and (p = 0.616, adjusted by gender) disorganization (p = 0.42, adjusted by gender) subscales did not predict discontinuation.

3.3. Time related variables

Younger age at clozapine initiation was associated with lower risk of discontinuation in logistic regression (controlling for gender), with each year increasing the odds of discontinuation by 1.043 (95%CI 1.02–1.07; p = 0.001). 28.66 years was the mean age (SD: 10.26) in the continuation group compared to 33.72 (SD: 12.64) years in the discontinuation group. The model parameters are described in Table 2.

Fewer years from illness diagnosis to clozapine initiation was associated with lower all-cause discontinuation in a logistic regression (controlled by gender), with every year from illness onset increasing the odds with a ratio of 1.092 (95% CI 1.01–1.184; p = 0.032). 1.84 years was the mean time from diagnosis (SD: 3.21) in the continuation group vs 3.42 years (SD: 5.15) in the discontinuation group. The parameters of the model are described in Table 2.

3.4. Final model

We then performed analyses including the significant variables in previous models (homelessness and time related variables) to see their relationship. Both time variables were analyzed in different models since they were highly correlated in this sample (p < 0.001). Results showed that age at clozapine initiation (and not homelessness) maintained significance in its relation to adherence when corrected by homelessness and gender, with each year increasing the odds of discontinuation by 1.04 (95%CI 1.01-1.07; p = 0.004). The parameters of the model are described in Table 3.

Years from illness diagnosis to clozapine initiation when corrected by homelessness and gender was no longer significant (p = 0.059). The parameters of the model are described in Table 3. The homelessness group had significantly (p < 0.001) more years from illness diagnosis to clozapine initiation vs the non-homelessness group (mean (SD): 6.25 (8.54) vs 2.03 (3.32), median (IQR): 3 (0–9.5) vs 0 (0–3) respectively). The association between years from illness diagnosis to clozapine initiation, controlling by gender, remained significant when only considering the group of patients (93% of cases) that were not homeless OR 1.12 (IC95% 1.02–1.23, p = 0.02). The parameters of the model are described in Table 3.

Table 3
Homelessness and time related variables effect on adherence model.

Variable	B	Std Error	*P*-value	OR	95% CI OR
Homelessness and age at clozapine initiation effect on adherence model.					
Age at clozapine initiation	0.039	0.014	0.004	1.04	1.01–1.07
Gender	0.67	0.348	0.054	1.95	0.99–3.86
Homelessness	0.395	0.558	0.479	1.48	0.498–4.43
Model $r^2 = 0.08$					
Homelessness and years from illness diagnosis to clozapine initiation effect con adherence model.					
Years from illness diagnosis to clozapine initiation	0.08	0.043	0.059	1.09	0.997–1.18
Gender	0.76	0.413	0.066	2.05	0.95–4.81
Homelessness	0.792	0.676	0.242	2.21	0.59–8.30
Model $r^2 = 0.072$					
Years from illness diagnosis to clozapine initiation affect con adherence model, in the non-homeless group.					
Years from illness diagnosis to clozapine initiation	0.114	0.049	0.02	1.12	1.02–1.23
Gender	0.892	0.45	0.048	2.44	1.01–5.897
Model $r^2 = 0.083$					

3.5. Survival analysis

Kaplan Mayer survival analysis (Fig. 1) shows that in the whole sample the age at clozapine initiation was higher in the non-adherent group than in the adherent group (log-rank $\chi2 = 5.06$, $P = 0.024$). The y-axis represents the proportion of patients who continued (blue line) or discontinued (red line) clozapine, while de x-axis the age at clozapine initiation. Cox proportional hazard ratio analysis showed a hazard ratio of 1.405 (95% IC 1.04–1.903), taking the non-adherent group as reference. This can be interpreted as in a given time someone who discontinued clozapine is 40% more likely to be older at clozapine initiation as someone who continued clozapine.

Kaplan Mayer survival analysis (Fig. 2) shows that in the not homeless group (n = 244) the delay of clozapine prescription was significantly longer in the non-adherent group than in the adherent group (log-rank $\chi2 = 11.9$, $P < 0.001$). The y-axis represents the proportion of patients who continued (blue line) or discontinued (red line) clozapine, while de x-axis the years of illness before clozapine initiation. Cox proportional hazard ratio analysis showed a hazard ratio of 1.736 (95% IC 1.25–2.41), taking the non-adherent group as reference. This can be interpreted as in a given time someone who discontinued clozapine is 73% more likely to have a longer delay in clozapine start as someone who continued clozapine.

4. Discussion

Early identification of treatment-resistant patients who will benefit from clozapine, as well as potential interventions that might increase their chances of response, would have a significant impact in clinical practice. In order to contribute with this aim, we here present predictors of clozapine adherence at two years, a real-world composite outcome that probably includes tolerability and response, from a comparatively large cohort of patients. Our setting provided us with the opportunity to assess many patients in a relatively short period. We found that not being homeless, a shorter course of illness, and younger age at clozapine initiation were positively associated with remaining on clozapine through the follow up period, while higher levels of symptoms on presentation were not. With every year older at Clozapine initiation, and with every year passed since diagnosis to Clozapine initiation, there was a 4.3% and 8.9% respectively higher chance of discontinuation in the two-year follow-up. Kaplan Mayer survival analysis confirmed the effect of timing of clozapine initiation in clozapine adherence, with someone who discontinued clozapine being 73% more likely to have a longer delay in clozapine start, and 40% more likely of being older compared to someone who continued clozapine.

Our results echo the findings of two recent systematic reviews (Shah et al., 2018; Griffiths et al., 2021) where a delay in clozapine initiation predicted worse outcomes. They are also in line with two recent meta-analyses highlighting that lower age at clozapine initiation was associated to better clozapine response (Okhuijsen-Pfeifer et al., 2020; Smart et al., 2019). They also support the possibility that early use could prevent treatment failures, considering the duration of untreated treatment-resistant psychosis as toxic (Shah et al., 2018). However, our study – as well as many other observational studies - did not measure the duration of untreated treatment-resistance psychosis, rather using as proxy age or duration of illness. Thus, an alternative explanation to our findings could be that treatment-resistance psychosis is a heterogeneous group, in which those with an early onset could be a Clozapine responsive subgroup of psychosis (Demjaha et al., 2017; Mena et al., 2018). A recently published paper (Chan et al., 2020) studied patients from illness onset and monitored for the appearance of treatment-resistance, hence contributing to differentiate the effect of age from duration of illness. Their results are similar to our findings, both presenting Kaplan-Meier survival plots for the delay in clozapine

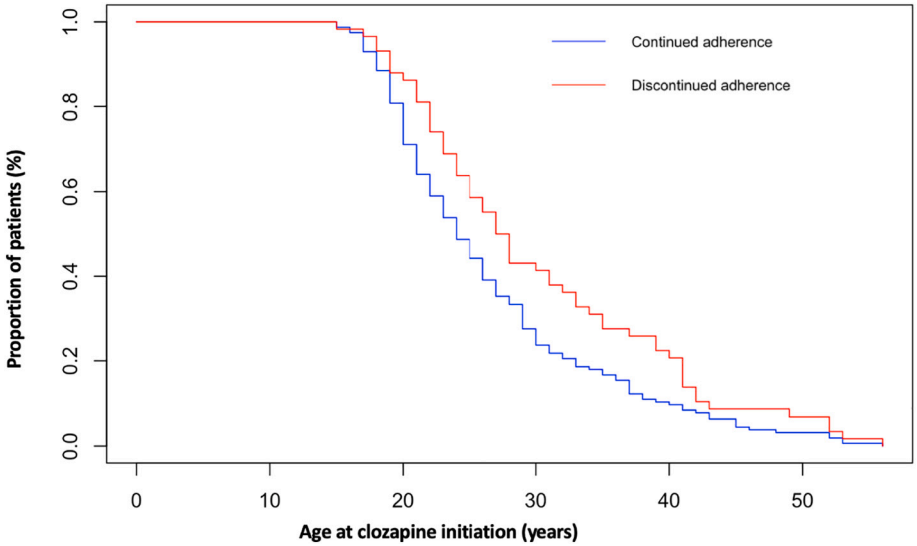

Fig. 1. Kaplan-Meier survival plot for age at clozapine initiation in adherent and non-adherent clozapine patients.

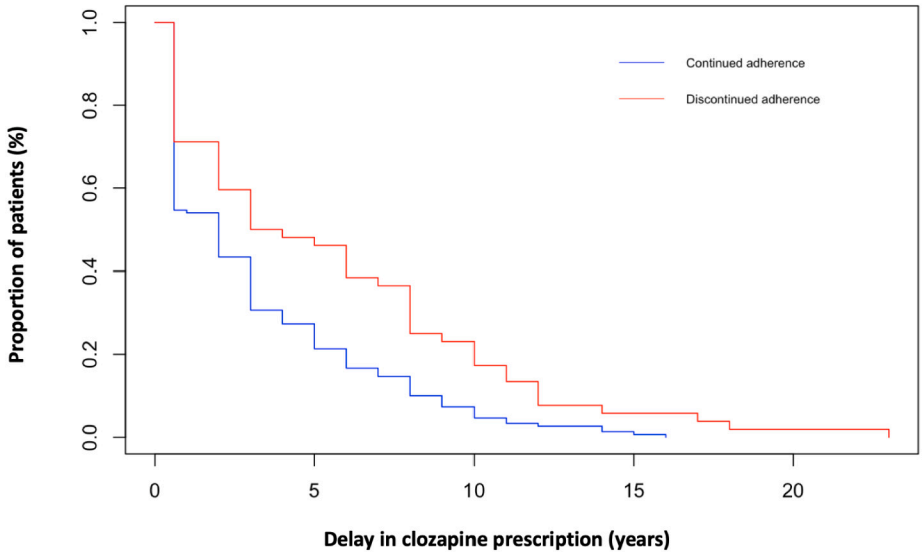

Fig. 2. Kaplan-Meier survival plot for delay in clozapine prescription in adherent and non-adherent clozapine patients.

prescription showing an early divergence in both curves.

Contrary to expected, the severity of symptoms at baseline measured with the PANSS scale (general, positive, negative or disorganization), did not predict adherence. Previous studies have found higher general symptomatology (Chung and Remington, 2005) and lower negative symptoms (Okhuijsen-Pfeifer et al., 2020) at baseline, predict better outcomes with Clozapine.

We also found homelessness as a possible predictor of future adherence. Poor social support has been described previously as a predictor of clozapine response (Köhler-Forsberg et al., 2017). Better adherence and pre-morbid functioning have been hypothesized as possible explanations of this association. The relationship between adherence and homelessness was no longer significant when considering variables related to a delay in the initiation of clozapine. This suggests that poor social support leading to a delay in clozapine initiation (older age at clozapine initiation or more years from illness diagnosis to clozapine start) could explain part of the high failure of treatment in this group.

In the final model analyzing homelessness and clozapine initiation delay relationship to adherence, both variables lost significance (homelessness ($p = 0.24$), clozapine initiation delay ($p = 0.059$)), with clozapine delay maintaining a trend to significance. To better understand the relation between these two variables, we controlled by homelessness through categorization. As a result, the homeless group (n = 19) although it concentrated the highest delay in clozapine initiation of the sample, the delay in this group was not related significantly to clozapine non-adherence (probably due to other variables influencing this relationship). However, the not homeless group (93% of the sample) did show an association of clozapine initiation delay to adherence ($p = 0.02$, controlled by gender).

A remarkable result was the low average delay to clozapine start from illness diagnosis found in this sample (mean of 2.27 years (SD: 3.89), and a median of 0 years (ICR 0-3)). Previous studies describe a considerable delay for commencing clozapine. A cross-sectional study showed in most countries the prevalence of clozapine use peaked in middle age, which is about 10 years later than the known average age of illness onset (Bachmann et al., 2017). Verdoux et al. systematic review studied institutional-related characteristics favouring clozapine prescription. Their results showed prescribers' adherence to evidence-based medicine principles and learning by modelling from experienced clozapine prescribers as significant factors (Verdoux et al., 2018). Our study was carried out in a quaternary care hospital setting, with a specialized clozapine pharmacovigilance unit, possibly explaining the difference with other samples.

Clozapine was successfully continued by 72.3% of the sample at a two-year follow-up, a relatively high rate. Previous studies on antipsychotic adherence describe rates from 47 to 95% depending on how it is defined and assessed (Sendt et al., 2015) . A recent study with a short follow up of 3 months showed a 72% of adherence (Takeuchi et al., 2020a, 2020b), proportion we would expect to lower in a 2 years follow-up. According to our results this could be related in part due to the low average delay of clozapine start in our sample, with 51.2% of patients still in their first year of illness at clozapine initiation. This needs to be considered in light of clozapine discussion in its position as third line antipsychotic. Relevant studies have already argued considering its use as second line antipsychotic (Remington et al., 2017), which is supported by expert consensus in cases of persistent problems such as suicidality, comorbid violence, and substance abuse (Moore et al., 2007).

Female patients were underrepresented in the sample, with only 28.4% of women. There is scarce evidence on gender differences in clozapine use, tolerance and response (Alberich et al., 2019). However, studies found in a recent systematic review usually include similar percentages of female patients (29.3- 38.9%), probably due to higher prevalence of schizophrenia and of treatment resistant psychosis described in men compared to women (Alberich et al., 2019).

Our study has several limitations. Our primary outcome is only a proxy of efficacy and tolerance. Remaining on clozapine does not necessarily reflect better efficacy as it may be secondary to other causes such as fewer adverse effects or better adherence. The lack of longitudinal assessments on psychopathology with a use of formal rating scales and of formal assessments on adverse effects is a limitation. As previously mentioned, we do not have the data on the duration of clozapine delay from the emergence of treatment-resistance. This would allow testing the hypotheses of a toxic duration of untreated treatment-resistance psychosis compared to the existence of a clozapine responsive subgroup of psychosis in those with early-onset treatment-resistance. Since age and delay in treatment initiation were correlated in our data, we could not evaluate their independent effect. Lastly, we excluded patients registered during the first years when the schizophrenia health plan came to effect in Chile, as well as those diagnosed many years ago who might have never been notified. By excluding the older cases, we also restricted the variability of duration of illness of included patients. However, this did not preclude the finding of associations.

It is also worth noticing that as with other observational studies, delay in clozapine initiation could have been due to other uncontrolled

factors which by themselves could predict worse treatment outcome (such as patients with worse functioning, lower insight into illness, poorer social support and access to healthcare, lower medication adherence). Such confounders could be addressed in future studies using a randomized controlled trial design.

It is important to pinpoint the ORs obtained represent the risk of clozapine non-adherence contributed by each year of delay and every year older of age before clozapine initiation, in the two year follow up. We don't have enough information to know if this risk continues increasing linearly with every year or if it is greater in the initial years of delay reaching a plateau posteriously. The Kaplan Mayer survival analysis, which considers the variable of time estimating the average constant hazard over a specific period of time, only shows the risk of a longer delay in the non-adherent group in this 2-year follow up. Further longer studies are needed to understand the effect of the delay in clozapine initiation over time.

In conclusion, higher clozapine continuation was particularly associated with shorter illness course and younger age at clozapine initiation. Therefore, initiating clozapine in treatment resistant patients earlier might be a recommendable practice for achieving better outcomes.

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1) Concept and design: Barbara Iruretagoyena, Carmen Paz Castañeda, Nicolas Crossley.
2) Provision of study materials or patients: Ruben Nachar, Cristian Mena, Camila Diaz.
3) Acquisition of data: Cristian Mena, Camila Diaz, Barbara Iruretagoyena, Carmen Paz Castañeda, Nicolas Crossley.
4) Statistical analysis: Barbara Iruretagoyena
5) Analysis and interpretation of results: Barbara Iruretagoyena, Carmen Paz Castañeda, Nicolas Crossley.
6) Drafting of Manuscript: Barbara Iruretagoyena, Carmen Paz Castañeda, Nicolas Crossley, Juan Undurraga, James A. Maccabe, Alfonso Gonzalez, Cristian Mena.
7) Critical revision of paper: Juan Pablo Ramirez-Mahaluf, Bárbara Iruretagoyena, Juan Undurraga, James A. Maccabe, Alfonso Gonzalez-Valderrama, Cristian Mena, Nicolas A. Crossley.
8) Supervision: Nicolas A. Crossley
9) Obtaining funding: Juan Pablo Undurraga, Nicolas Crossley.
10) Administrative, technical or logistical support: Ruben Nachar

Role of funding source

The funding source had no involvement in any stage of the study.

Declaration of competing interest

Dr. Crossley has received personal fees from Janssen, outside the submitted work. The other authors report no conflict of interests.

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