

ORIGINAL ARTICLE

Clozapine treatment and risk of severe COVID-19 infection

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Abstract

Objective: To investigate whether patients with clozapine treatment are at an increased risk of a more severe COVID-19 infection as compared with patients on other antipsychotic drugs.

Methods: In this register-based cohort study, all residents (age 18 or older) in the Stockholm Region with a psychotic disorder diagnosis and antipsychotic treatment were included ($N = 8\,233$) and followed from 1 March 2020 to 14 January 2021. The exposure was defined as clozapine treatment and the outcome measures (indicating a more severe COVID-19 infection) were: inpatient care, care within intensive care unit or death due to COVID-19 infection. Differences in outcome rates between exposed ($n = 966$) and unexposed (other antipsychotics; $n = 7\,267$) were examined using Cox proportional hazards models and expressed as hazard ratios (HR) with 95% confidence intervals (CI).

Results: No statistically significant differences in outcome rates were found between the two groups of patients after adjusting for age, sex and residence in retirement homes. The adjusted HR for the exposed compared to the unexposed was 0.96 (95% CI: 0.54, 1.70) for inpatient care; 1.69 (0.48, 5.93) for care in intensive care unit (ICU); and 0.86 (0.26, 2.80) for death. Regarding inpatient care, additional adjusting for country of birth, living in socioeconomically vulnerable areas, number of care visits during the previous year, and comorbid medical illnesses did not alter the results.

Conclusions: Our results may add support to the present guidelines, recommending sustained clozapine treatment during the current COVID-19 pandemic with careful monitoring and readiness to alter drug doses as needed.

KEYWORDS

antipsychotics, clozapine, COVID-19, psychotic disorder, side effects

1 | INTRODUCTION

Clozapine is the only evidence-based antipsychotic for treatment-refractory schizophrenia (ie not responding to two or more trials of antipsychotic treatment in adequate

dose and duration), which occurs in up to one third of patients with schizophrenia.¹ Clozapine has been shown to reduce violent offences,² hospitalisation and all-cause mortality,³⁻⁵ including risk of suicide.⁶⁻⁸ However, clozapine may affect the innate immune system, which may

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increase the risk of developing neutropenia and agranulocytosis.⁹ As a result of these serious side effects, clozapine treatment requires close blood monitoring. Furthermore, concomitant viral infection may contribute to neutropenia in clozapine-treated patients.¹⁰ Recent findings by Ponsford et al. suggest that clozapine may also affect the adaptive immune system, as clozapine treatment has been found to be associated with reduced levels of immunoglobulins, specifically IgG, IgA and IgM.^{11–13}

Patients with schizophrenia tend to adopt a lifestyle that increase the risk of infections and of excess mortality, such as poor diet, inactivity, tobacco smoking and substance use.^{14–16} Clozapine patients seem to have a higher risk of infections, such as pneumonia, as compared with patients treated with other antipsychotics,^{17–19} and pneumonia seems to be highly lethal in clozapine patients.^{20,21} The underlying mechanisms remain poorly understood but could be due to side effects of the drug, such as hypersalivation, and the treatment's adverse effects on the immune system.^{11,20} However, this increased infection risk may partly be due to confounding by indication since clozapine is prescribed to treatment-refractory patients who are likely to have more severe and chronic psychosis, and greater comorbidities.^{20,22} In fact, it has been suggested that behavioural and biological factors associated with treatment-refractory schizophrenia, such as higher smoking prevalence, lack of treatment adherence and medical comorbidities, may have a larger impact on a patient's pneumonia risk than their clozapine treatment.²³

The majority of COVID-19 infected individuals show mild symptoms, but in severe cases the infection can cause pneumonia, acute respiratory distress syndrome and death. Since clozapine patients are more susceptible to viral infection and pneumonia, they may in theory be more susceptible to either increased risk of COVID-19 infection or severe outcomes.²⁰ In addition, clozapine patients tend to be older and are at greater risk of diabetes and cardiovascular diseases compared to patients treated with other antipsychotics. Notably, older age, diabetes and cardiovascular diseases are considered risk factors for a severe COVID-19 infection.²⁴

Attempts have been made to better understand if clozapine treatment is associated with a greater risk for COVID-19 infection and severe outcomes. In a study of 6 309 patients of which 102 tested positive for COVID-19, Govind and colleagues found that clozapine patients had a higher risk for COVID-19 infection compared to patients on other antipsychotics.²² However, a closer monitoring among clozapine patients may have led to increased testing for COVID-19, resulting in higher reports of COVID-19 infection among clozapine patients.²² Thus, as the authors put forward, further studies in larger samples are needed.

Significant outcomes

- Patients on clozapine treatment were not found to be at an increased risk of a more severe COVID-19 infection as compared with patients on treatment with other antipsychotics.
- Our results support present guidelines to sustain clozapine treatment during the current COVID-19 pandemic.

Limitations

- The number of cases was small and the statistical power to detect risk differences was therefore low.
- Misclassification is a possibility as we lack information on treatment adherence and treatment given within psychiatric inpatient care, and only included patients with prescribed and dispensed antipsychotics in 2020.

Notably, in an internal outbreak of COVID-19 at a psychiatric clinic, 20 out of 46 patients with schizophrenia and COVID-19 were on clozapine treatment. No clozapine toxicity was reported. Four patients required hospital treatment for pneumonia – all of whom were on clozapine treatment. All patients recovered, and no patient needed intensive care unit (ICU) treatment. Clozapine treatments were sustained throughout the infection.²⁵

Research is continuing to emerge on the interactions between clozapine use and COVID-19 infection. Albeit Rendon-Quintero and colleagues' study in which patients on clozapine developed pneumonia upon an internal COVID-19 outbreak within a psychiatric clinic,²⁵ and therefore, may indicate an increased susceptibility among clozapine patients, no previous study has as far as we know examined whether clozapine treatment is associated with increased risk of a more severe COVID-19 infection as compared with other antipsychotic drugs.

1.1 | Aims of the study

The aim of this study is to examine whether patients on clozapine treatment are at increased risk of a more severe COVID-19 infection as indicated by inpatient treatment, intensive care or death following infection with COVID-19 as compared with patients on treatment with other antipsychotics.

2 | MATERIAL AND METHODS

2.1 | Setting

Within this cohort study, we utilised data from a regional health care register (VAL-databaserna) within the Stockholm Region, which is a metropolitan area with approximately 2 million inhabitants. The register holds data on all out- and inpatient care, diagnoses according to the International Classification of Disease [ICD] version 10, prescribed and dispensed drugs. From Statistics Sweden,²⁶ data on demographics and social factors were collected. Ethical approval was granted by the Swedish Ethical Review Authority (original approval: Dnr 2020-03122, and update: Dnr 2021-00810).

2.2 | Study cohort

Included in this study were all residents in the Stockholm Region who were of age 18 and older by 1 March 2020 and fulfilled the following two inclusion criteria: (1) a psychotic disorder diagnosis (ICD-10, F20-29) registered between 1 January 2019 and 29 February 2020 and (2) prescribed and dispensed antipsychotics (see Supplement for included drugs) at any time during year 2020.

2.3 | Exposure

Exposure was defined as treatment with clozapine (ie having been prescribed and dispensed clozapine at any time during 2020). Those who had been prescribed and dispensed other antipsychotics (see Supplement for included drugs), not including clozapine, at any time during 2020 constituted the unexposed group (ie the comparison group).

2.4 | Main outcomes

The main outcome measures included: (1) inpatient care with diagnosed COVID-19 (ICD-10 U07.1-07.2), (2) care in intensive care unit (ICU) with diagnosed COVID-19 (ICD-10 U07.1-07.2) or (3) death due to COVID-19 (ICD-10 U07.1-07.2) according to the Cause of Death Register²⁷ at any time during the follow-up period between 1 March 2020 and 14 January 2021.

2.5 | Covariates

The possible confounding effect of age, sex and residence in retirement homes were considered in all analyses.

Regarding the outcome measure inpatient care with COVID-19, the analyses were further adjusted for the potential effect of: country of birth (divided into three options: (a) Sweden, (b) Denmark, Finland or Norway and (c) other countries including unknown origin); living in a socioeconomically vulnerable area (ie about 10% of 68 areas in Stockholm Region, characterised by high rates of unemployment, social benefits and benefits for sickness and disability); number of care visits (0, 1-9, 10-19 or ≥ 20) from the study baseline to censoring, not including visits <5 days before outcome event or visits with diagnosed COVID-19, and any or several comorbid medical illnesses (ie diabetes, ICD-10: E10-14; cardiac disease/failure, ICD-10: I20-25, I42-43, I50; chronic renal failure, ICD-10: N18; cancer ICD-10: C00-07) registered between 1 January 2018 and 29 February 2020.

2.6 | Statistical analysis

Data were analysed using SAS 9.4. Differences in outcome rates between the exposed (ie clozapine treatment) and the unexposed (ie other antipsychotics) were analysed. The hazard ratio (HR) with 95% confidence intervals (CI) for each outcome were estimated with Cox proportional hazards model, starting 1 March 2020, with moving outside of the Stockholm Region (ie last day in month before moving date) or death due to any cause during follow-up or the end of follow-up as censoring time (ie 14 January 2021). The proportional hazard assumption was not violated in any analyses, tested by using Kaplan-Meier curves.

3 | RESULTS

Sample characteristics and distribution of confounding variables among the patients are described in Table 1. Between 1 January 2019 and 29 February 2020, a total of 8 233 inhabitants age 18 and older ($M = 51.3$ years, $SD 16.2$) in the Stockholm County had been diagnosed with a psychotic disorder and received antipsychotic drugs during 2020, of them 966 (12%) had received clozapine treatment. Only a small number of individuals on antipsychotic drugs needed inpatient or ICU care, or died due to COVID-19 infection between 1 March 2020 and 14 January 2021. The HRs of inpatient care (HR, 0.96 [95% CI: 0.54, 1.70]), ICU care (1.69 [0.48, 5.93]) or death (0.86 [0.26, 2.8]) due to COVID-19, for clozapine patients as compared to patients on other antipsychotic drugs, after adjusting for age, sex and residence in retirement homes, showed no altered risks for the outcomes. Further adjustments for country of birth, living in a socioeconomically vulnerable area, number of care visits and comorbid medical illnesses for the

TABLE 1 Sample characteristics and distribution of confounding variables among patients with clozapine treatment and patients treated with other antipsychotics

	Clozapine (n = 966)	Other antipsychotics (n = 7266)
	n (%)	n (%)
Gender		
Female	375 (39)	3479 (48)
Male	591 (61)	3788 (52)
Age[†]		
18–49	468 (48)	3 181 (44)
50–69	445 (46)	2971 (41)
70+	53 (5)	1 078 (15)
Residency[‡]		
Retirement home	34 (4)	473 (7)
Socioeconomically vulnerable area	165 (17)	1 263 (17)
Country of birth		
Sweden	731 (76)	4717 (65)
Denmark, Finland, Norway	36 (4)	326 (5)
Other countries	199 (21)	2,187 (30)
Number of care contacts		
0	105 (11)	823 (11)
1–9	529 (55)	4284 (59)
10–19	190 (20)	1348 (19)
20+	142 (15)	775 (11)
Medical illnesses[‡]		
Cardiovascular	29 (3)	367 (5)
Diabetes	184 (19)	1188 (16)
Cancer	29 (3)	299 (4)
Renal failure	26 (3)	287 (4)

[†]Age is entered as a continuous variable in the statistical model but categorised in the table to show the distribution between the groups.

[‡]The subcategories under the variables residency and medical illnesses, respectively, were not exclusive categorisations thus capturing individuals who had multiple comorbidities as well as individuals who met multiple residential categorisations.

outcome measure, inpatient care, did not alter the results. See Table 2.

4 | DISCUSSION

In this study, we examined whether patients on clozapine treatment have an increased risk of severe COVID-19 infection as indicated by inpatient care, care at ICU or death related to COVID-19 infection, as compared with

patients on treatment with other antipsychotics. We found no indication of a more severe course of the infection in terms of these outcomes among patients on clozapine treatment after adjusting for age, sex and residence in retirement home. Regarding inpatient care, additional adjusting for country of birth, living in socioeconomically vulnerable areas, number of care visits during follow-up, and comorbid medical illnesses did not alter the results. However, the number of cases was small and the statistical power to detect risk differences was consequently low.

Previous studies have described the course of COVID-19 in clozapine-treated patients, as well as possible mediators of a more severe COVID-19 infection or other complications during clozapine treatment and simultaneous COVID-19 in order to guide whether there are special risks associated with clozapine during the pandemic. To the best of our knowledge, five cases of suspected clozapine toxicity have occurred in patients with a concurrent COVID-19 infection and furthermore, a single case of elevated clozapine levels was described after a COVID-19 vaccination,^{28–31} whilst others have reported no such findings.²⁵ In addition, previous case series have reported no identified increased risks associated with COVID-19 infection and concurrent clozapine treatment indicated by a significant reduction in neutrophil counts, which can forebode agranulocytosis,^{32,33} or by additional complications associated with clozapine treatment when having mild symptoms of COVID-19 infection.³⁴ Our findings are in line with these previous studies in that no increased risk for a more severe COVID-19 infection in terms of inpatient care, ICU or death were found among clozapine patients as compared with patients on other antipsychotic drugs.

The comprehensive measures within our study allowed for many potential risks to be covered, such as number of care visits, comorbid medical illnesses and all additional risks leading to the need for inpatient care, care within an ICU or death despite lacking data on specific risk factors associated with infection and clozapine treatment. However, our results are based on a small number of cases and need to be interpreted with great caution. Given our sample size, we had an 80% power to detect a HR of 1.58 for inpatient care, 3.97 for care in ICU and 2.23 for death. That is, the risk of type II error is high. We included only patients with a dispensed antipsychotic in 2020 and made the assumption that this was similar to treatment adherence. In addition, misclassification is a possibility. Furthermore, there was potential for medications that were received within psychiatric inpatient care to be antipsychotics, however since data on medications delivered within psychiatric inpatient care was unavailable, it was not included as dispensed or prescribed antipsychotics.

TABLE 2 Number of patients with clozapine treatment or other antipsychotic treatment receiving inpatient care, or care at an intensive care unit, or death related to COVID-19 infection and risk estimates for COVID-19 related inpatient care, treatment in ICU or death between 1 March and 14 January 2021, among patients with Clozapine treatment as compared to treatment with other antipsychotics

Clozapine versus other antipsychotics [§]					
	Full sample N (%)	Clozapine n (%)	Other antipsych. n (%)	HR (95% CI)	
				Adjusted [¶]	Adjusted ^a
Individuals	8233 (100)	966 (12)	7267 (88)	–	–
Number with COVID–19 related inpatient care, ICU or death					
Inpatient care	147 (1.8)	13 (1.3)	134 (1.8)	0.96 (0.54, 1.70)	0.94 (0.53, 1.67)
ICU	17 (0.2)	3 (0.3)	14 (0.2)	1.69 (0.48, 5.93)	n/a
Death	53 (0.6)	3 (0.3)	50 (0.7)	0.86 (0.26, 2.80)	n/a

^aAdjusted for age, sex, residence in retirement homes, country of birth, living in a socioeconomically vulnerable area, number of care visits and comorbid medical illnesses (ie diabetes; cardiac disease/failure; chronic renal failure; cancer).

[§]See supplement for included drugs.

[¶]Adjusted for age, sex and residence in retirement homes.

Moreover, we lacked information on treatment length or whether treatment was terminated as the patient tested positive for COVID-19 infection. Information on treatment length may be of importance since clozapine-induced neutropenia and agranulocytosis mainly occurs at the initiation of treatment, with the risk diminishing greatly over time.¹⁰ Consequently, it is possible that a potential increased risk of neutropenia associated with clozapine treatment and a concurrent COVID-19 infection is dependent on whether the patient recently initiated treatment. In addition, we cannot reject the possibility that clozapine or other antipsychotics were withheld upon a positive COVID-19 test or earlier as a precaution due to the pandemic outbreak. Yet, it is plausible to surmise that due to the potential drawback of drug withdrawal, treatment termination prior to developing more severe symptoms, which require inpatient or ICU care or cause death, is less likely.

Despite this study's substantial limitations, our results may add support to the present guidelines, recommending sustained clozapine treatment during the current COVID-19 pandemic with adapted monitoring and readiness to alter drug doses as needed in case of infection, or treatment cessation if neutrophil counts are significantly decreasing.^{24,35} Further case reports and larger studies regarding COVID-19 infection and concurrent clozapine treatment are needed. To the best of our knowledge, no findings have so far supported the termination of ongoing clozapine treatment albeit theoretical risks. The likely relapse of psychotic symptoms in patients who discontinued clozapine could, in addition to the distress caused to the patient and their relatives, make both controlling the spread of the virus in this psychiatric population as well as delivering life-saving COVID-19 treatment to this population difficult.²⁴ Overall, it is our opinion that the

dangers of discontinuing clozapine treatment likely outweigh the risks of continued clozapine treatment under careful monitoring.

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CONFLICT OF INTEREST

None.

PEER REVIEW


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DATA AVAILABILITY STATEMENT

Derived data supporting the findings of this study are available from the corresponding author on request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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