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Clozapine Therapy and COVID-19: A Systematic Review of the Prevalence Rates, Health Outcomes, Hematological Markers, and Patient Perspectives

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***Background/Objectives*: There have been concerns that clozapine treatment may undermine the capacity of the body to fight infection and increase the vulnerability to contracting COVID-19. This review of recent cohort studies investigated (1) whether people with a severe psychiatric disorder are at increased risk of COVID-19 and complications, (2) the immunological response of clozapine-users who contract COVID-19, and (3) patients' perspectives on COVID-19 and the pandemic response. *Methods*: A systematic search of EMBASE, Medline, Pubmed, and PsycINFO databases using PRISMA guidelines using "COVID-19", "clozapine", and "vaccination" terms. *Results*: 18 studies (out of 330 identified) met all criteria (*N* = 119 054 including 8045 on clozapine). There was no strong evidence that clozapine users may be at increased risk of contracting COVID-19 or developing complications after adjusting for medical comorbidities. Hematological studies showed temporary reductions in neutrophils in COVID-19-positive patients and vaccination suggesting a clozapine effect in defence against infection. Vaccination studies did not report major adverse effects. Increased plasma levels of clozapine and neutropenia however point to COVID-19-related interference of clozapine metabolism. Patient surveys reported limited impact on mental health and positive attitudes regarding pandemic response. *Conclusion*: This review did not find compelling evidence that the immune system of clozapine users put them at risk of COVID-19 and further complications. Evidence of drug–infection interactions however points to the importance of adhering to consensus guidelines about clozapine therapy during the pandemic. More evidence using longitudinal designs is required to examine the longer-term effects of COVID-19 and vaccination in this vulnerable population.**

Key words: COVID-19/coronavirus/clozapine/schizophrenia

Introduction

Schizophrenia is a chronic psychiatric condition requiring life-long treatment. One in three individuals diagnosed with schizophrenia will develop treatment resistance as defined as the failure to respond to two or more antipsychotic medications.[1] Clozapine, a dibenzodiazepine derivative, is the antipsychotic medication of choice for treatment-resistant schizophrenia[2,3] with evidence of clinical benefits on positive symptoms alongside a reduction in rehospitalization, all-cause mortality, and violent offending.[4–6] Adverse reactions to clozapine can include increased susceptibility to infections and pneumonia[7–9] raising concerns that clozapine users may be more likely to contract COVID-19 and suffer from worse outcomes due to health complications.[10–13] Recent studies have sought to examine the role of the immune system as a potential mechanism linking clozapine to greater risks of, and from, COVID-19.[7,14,15] There have been suggestions that clozapine's immunosuppressive effects could undermine the body's ability to defend itself against infections,[7,14] and that COVID-19 might further aggravate hematological abnormalities in clozapine users and/or increase the risk of side-effects of clozapine by reducing efficient metabolism of clozapine.[10–13,16] These issues have introduced challenges for clinicians when making decisions about the prescription of clozapine[10,17] although interrupting treatment during the course of COVID-19 infection is not a recommended course of action.[10–13] Earlier reviews have attempted to describe the association between clozapine and COVID-19[13] but a limitation of these earlier reviews

includes a paucity of data from cohort studies using rigorous methodology and control groups, and with laboratory confirmation of COVID-19.

COVID-19 is a disease caused by severe acute respiratory syndrome coronavirus (SARS-COV-2).[18] Many cases of COVID-19 infection are mild and self-limiting, although adverse outcomes can include pneumonia, acute respiratory distress, sepsis, cardiac failure, and death in vulnerable populations.[19] Approximately one in six will suffer a severe form of COVID-19 usually secondary to concurrent comorbidities. Risk factors for severe forms of COVID-19 infection include older age, obesity, smoking, metabolic disorders, and chronic respiratory disease all of which are more commonly found in those with severe mental illness.[20–22] Studies have demonstrated that people with severe mental illness are particularly vulnerable to contracting COVID-19.[21,23]

Furthermore, clozapine is one of the most cited antipsychotic medications in relation to its interaction with COVID-19.[24] There have been suggestions that clozapine users may be more susceptible to contracting COVID-19 and to experience severe symptoms resulting in an increased risk of hospitalization, morbidity, and mortality.[7,25] The relationship between clozapine and COVID-19 is complex but there are several factors that make interaction more likely. Illness-related factors include greater exposure to potentially infectious hospital services as well as difficulties adhering to social distancing and infection control measures.[15] In addition, a major hypothesis relates to clozapine's effect on hematological and immunological function.[7,14,26,27] Maintaining an adaptive immune response is important not only for protection against the virus but also for infected patients to suppress inflammation to maintain a healthy response[16] and there are concerns that the pharmacological properties of clozapine may affect immune response. Clozapine, at concentrations within the therapeutic range, causes disruption to adaptive immunity through the suppression of white blood cells, through an increase in pro-inflammatory cytokine levels,[7,8] especially interleukin-6 (IL-6),[28] decrease in secondary antibody deficiency, and a decrease in B-cells.[8] Clozapine's immunosuppressive and pro-inflammatory effects have been observed during clozapine initiation and in long-term clozapine users,[8] and have led to suggestions that clozapine may undermine the capacity of the body to fight infection and make patients more vulnerable to contracting COVID-19.[7,14]

In addition to increased risks of infection, there are concerns that those who contract COVID-19 will suffer worse health complications because of compromised immune response and/or increased serum clozapine levels and toxicity.[29] One recent suggestion is that COVID-19 may initiate an immune reaction that could aggravate the hematological and immunological dysfunction already caused by clozapine,[29,30] although this view has been disputed.[15] Another concern, which is not necessarily mutually exclusive from the immune dysfunction hypothesis, relates to a risk of clozapine toxicity due to the inhibitory effects of COVID-19 infection on clozapine metabolism. There is evidence that COVID-19 causes acute inflammation which interrupts the functions of cytochrome P450 1A2 (CYP1A2) enzymes resulting in rising clozapine plasma levels and a risk of clozapine toxicity,[29] perhaps linked to the active metabolite norclozapine.[31] Overall, these effects may cause a lower-than-normal white cell count (WCC) count and conditions such as neutropenia along with clozapine side-effects such as hypersalivation, difficulties swallowing and sedation raising the risk of severe infection, and aspiration pneumonia.[7,32,33]

The views of mental health consumers are also important to consider. Government approaches to control infections during the COVID-19 pandemic have included vaccinations and home restrictions, but the views of patients prescribed clozapine have rarely been specifically documented. Given recent efforts to increase rates of vaccine uptake among mental health clients,[34] a discussion of patients' views regarding their medication and COVID-19 is of special importance.

In this paper, we undertook a systematic review of studies that examined the relationship between clozapine and (1) the risk of contracting COVID-19 infection, (2) COVID-19 infection severity indicators (hospitalization, intensive care (ICU) treatment, and all-cause mortality), (3) hematological changes caused by COVID-19; and (4) perspectives from clozapine users about COVID-19.

Method

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[35] A systematic search was conducted of four electronic databases including EMBASE, Medline, Pubmed, and PsycINFO and a cross-reference of the publications cited in the selected articles. Combinations of MeSH search terms and keywords "COVID", "COVID-19", "Coronavirus", "clozapine", "vaccination" were utilized. The search of the electronic databases was conducted on three separate occasions between November 2021 to July 2022 with final search conducted on July 7, 2022. All search results were reviewed by title and abstract and screened according to inclusion and exclusion criteria. A search of the Cochrane register, scientific literature, and reference lists from included studies was performed to ensure that no relevant studies were missed. Inclusion criteria comprised cohort, experimental, or observational human studies, peer-reviewed journal articles since 2019, English language, laboratory-confirmed COVID-19 infection in the context of clozapine treatment, and psychiatric illness. Exclusion criteria comprised reviews, opinions, theoretical discussions, single case studies, no

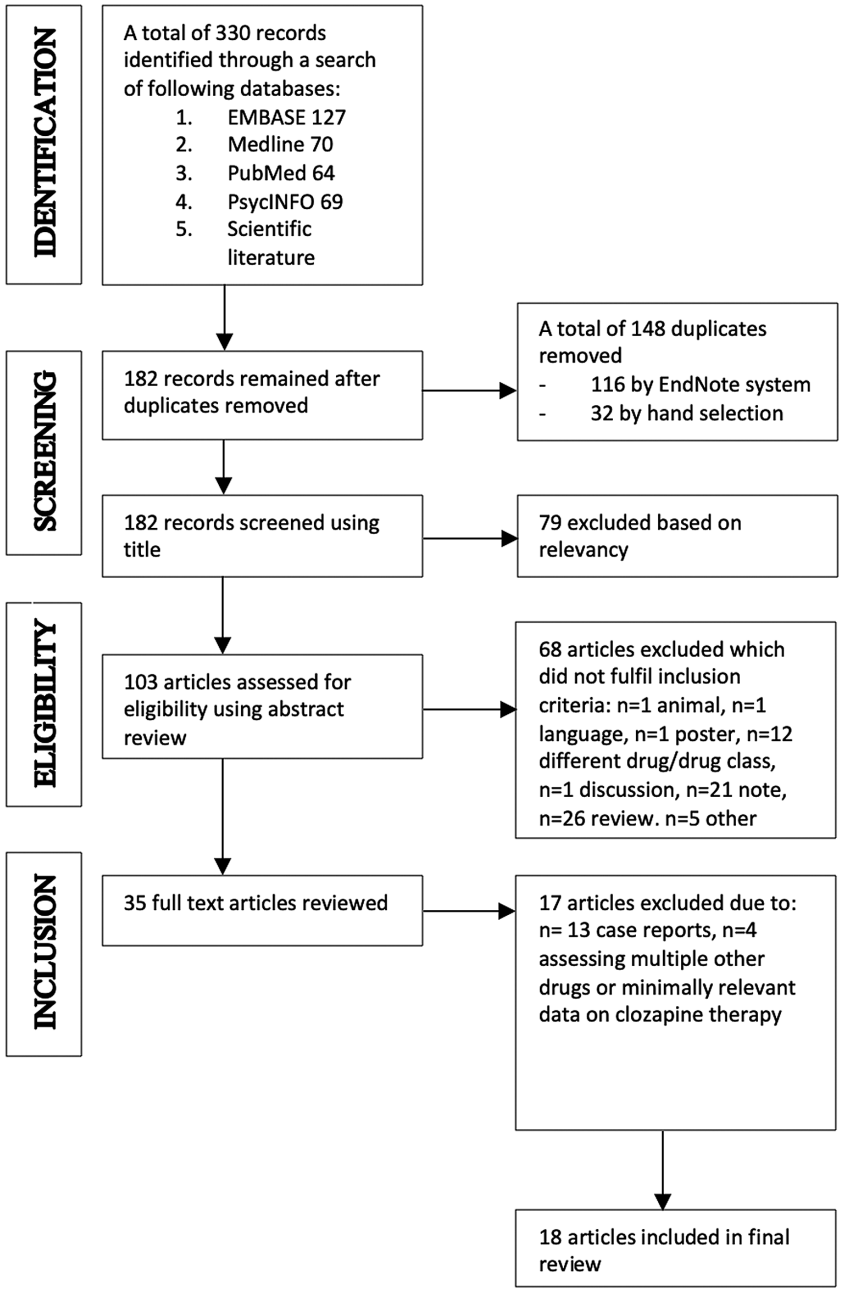

Fig. 1. Flowchart of systematic literature review.

laboratory confirmation of COVID-19, treatment other than clozapine, and nonpsychiatric populations.

Results

Search Results

A total of 330 records were identified (see figure 1); 182 articles remained after removal of duplicates. A further 79 articles were removed following evaluation of titles. A total of 103 abstracts were reviewed for relevancy and from this, a further 68 articles were removed. In total 35 full-text articles were selected for review. 17 Articles did not meet inclusion criteria leaving a total of 18 articles to be reviewed.

Study Quality and Risk of Bias

The best available National Health and Medical Research Council (NHMRC) level of evidence available was III-2 (controlled cohort studies). An assessment of the study quality and risk of bias in the articles included in the review was conducted using the Newcastle–Ottawa Scale (NOS),[36] and included in tables 1–4.

Table 1. Summary of Studies Exploring the Risk of COVID-19 Infection

Author	Study Design	*N* Total	Measurement of Outcome	Limitations	Findings	NOS
Govind et al[37]	Retrospective cohort study	6309	Clinical record of COVID-19 infection	Observational study design Risk of residual confounding factors eg HTN, obesity, DM, increased contact of clozapine group with healthcare professionals	Of 6309 patients 102 tested positive for COVID. Individuals who were using clozapine were at increased risk of developing COVID compared to other antipsychotics: unadjusted hazard ratio HR = 2.62 (95% CI 1.73–3.960) which was attenuated after adjusting for potential confounders adjusted HR = 1.76 (95% CI 1.14–2.72)	8
Okusaga et al[38]	Cross-sectional study	101 032	Clinical record of COVID-19 infection	Observational study design Risk of residual confounding factors eg smoking status, frequency of clinical contact, inpatient status. May have ceased clozapine prior to end of study	Odds of testing positive were higher in the clozapine group (44 veterans, 1%) compared to nonclozapine group (675, 0.7%) Unadjusted OR = 1.47 (95% CI 1.08–1.99) Adjusted OR = 1.77 (95% CI 1.29–2.41)	6
Sheng et al[17]	Retrospective cohort study	504	COVID-19 infection confirmed by PCR swab (n = 58) or Imaging + clinical symptoms (n = 26)	Observational study design Missing clinical data for some cases included in the study. Approximately one-third did not have a laboratory confirmed diagnosis of COVID-19. Inadequate follow up	504 Schizophrenia patients in total. 84 of these tested positive for COVID-19. Randomly sampled 174 cases who were uninfected and used this group as a comparison group. No. of infected clozapine users = 15 (17.9% of the infected group), 55 clozapine users were in the noninfected group (31.6%). Those with COVID-19 infection were less likely to be treated with clozapine (P = .03).	5
Nemani et al[39]	Retrospective cohort study	1958	Clinical record review for documented COVID-19 infection (PCR or antibody result) and secondary outcome of COVID-19 related death	Observational design Lack of generalization	49.5% (n = 969 patients) tested positive for COVID-19 infection during their hospital admission. Among the infected patients, 3.9% (n = 38) had a COVID-19 related death. Clozapine (n = 712 patients on clozapine therapy in total, 36.3%) was the only medication associated with decreased odds of mortality. The odds ratio was significant in the unadjusted model (OR, 0.25, 95% 0.10–0.62), but failed to retain significance after adjusting for demographic and medical risk factors including BMI, chronic respiratory disease, diabetes, and heart disease.	3
Prokopez et al.[40]	Case-control study	242	COVID-19 infection confirmed by PCR swab	Observational study design Small sample size Risk of residual confounding factors eg smoking status	Clozapine was the only drug to show potential protective effect against COVID-19, probability of positive diagnosis was 60% less than those who did not use it (OR 0.40, CI 95% 0.19–0.80). The absolute risk reduction was 22%.	5

Table 2. Summary of Studies Exploring Adverse Health Outcomes

Author	Study Design	*N* Total	Measurement of Outcome	Limitations	Findings	NOS
Govind et al.[42]	Retrospective cohort study	157	Clinical record review using software algorithms examining rate of COVID-related hospitalization, ICU treatment, and all-cause mortality during the follow up period	Limited generalization Missing patients during search process due to algorithm error Some bias attributed to clozapine treated patients being in more contact with services Some deaths may not have been related to COVID infection BMI data was often not recent	In the clozapine group 25% had COVID related hospitalizations, 7% had COVID related ICU treatment and 7% died. No significant association between clozapine and adverse outcomes compared to other antipsychotics with adjusted OR hospitalizations = 1.12, ICU care = 0.71, and all-cause mortality = 1.38 (95% CI)	8
Ohlis et al[43]	Cohort study	8233	Clinical record review for documented COVID-19 related hospitalization, COVID-19 related ICU care, or death due to COVID-19	Observational study design Small sample size Type 2 error risk Lack of information obtained regarding if treatment was stopped during inpatient admission and duration of clozapine treatment	No statistically significant findings observed between clozapine vs alternative antipsychotics in terms of COVID-19 adverse clinical outcomes (adjusted HR 0.96 for inpatient care, 1.69 for care in intensive care unit, and 0.86 for death)	6
Butler et al[41]	Retrospective case series	8	Clinical record review for documented COVID-19 infection (PCR) & current clozapine therapy admitted to a medical ward	Observational study design Small sample size Short follow-up duration Lack of patient perspectives	8 Consecutive hospital patients on long-term clozapine treatment who contracted COVID-19 and with an average age of 62 years. 6 of the 8 patients developed complications including COVID-19 pneumonia or delirium. Three required intensive care for average of 34 days. Three patients died.	4
Nemani et al[39]	Retrospective cohort study	1958	Clinical record review for documentedCOVID-19 infection (PCR or antibody result) and secondary outcome of COVID-19 related death	Observational design Lack of generalization	49.5% (n = 969 patients) tested positive for COVID-19 infection during their hospital admission. Among the infected patients, 3.9% (n = 38) had a COVID-19 related death. Clozapine (712 patients on clozapine therapy in total) was the only medication associated with decreased odds of mortality. The odds ratio were significant in the unadjusted model (OR, 0.25, 95% 0.10–0.62), but failed to retain significance after adjusting for demographic and medical risk factors including BMI, chronic respiratory disease, diabetes, and heart disease.	3

Table 3. Summary of Studies Exploring Hematological Effects Including Vaccination(*)

Author	Study Design	*N* Total	Measurement of Outcome	Limitations	Findings	NOS
Gee and Taylor[14]	Observational cohort study	13	Baseline ANC + WCC values ANC + WCC values day 0–7 post positive COVID-19 diagnosis ANC + WCC values day 8–14 post positive COVID-19 diagnosis	Observational study design Small sample size No control group No accounting for variables eg age, sex, ethnicity	Mean ANC at baseline 4.83 × 10^9/L, reducing to 4.24 × 10^9/L in the first week following a positive swab and second week mean ANC was 5.70 × 10^9/L. 3 deaths within first week post positive diagnosis (all taking clozapine >1 year). No statistically significant differences between mean ANC baseline and day 0–7 (P = .240), between mean ANC days 0–7 and days 8–14 (P = .155), or between mean baseline ANC and mean ANC days 8–14 (P = .509)	5
Gee et al.[10]	Retrospective chart review	56	Baseline ANC, Lymphocyte count, WCC vs values during COVID-19 infection at day 1–7 and day 8–14.	Small study size Clozapine levels not measured Majority were inpatients	Reduction in ANC (P = .005), lymphocyte count (P = .03) and WCC (P < .001) between baseline and first 7 days of COVID-19. All cell counts returned to baseline levels by days 8–14. 6 patients (11%) had neutropenia in total. Mild neutropenia during acute phase of COVID-19 infection is likely a consequence of COVID not clozapine in well-established clozapine patients	6
Hata et al.[45]	Retrospective chart review	19	Clinical record review for adverse psychiatric or hematological event	Observational study design Small sample size Selection bias Lack of generalization	19 Patients on clozapine underwent extended monitoring periods beyond the regulated 14 days. No adverse psychiatric or hematological adverse events were observed among these patients	5
Bonaccorso et al.[44]	Retrospective chart study	10	PCR positive test for COVID-19, baseline ANC + WCC pre-COVID-19 infection, ANC + WCC approx. 3 days post positive PCR, post-COVID-19 ANC + WCC approx. 1 month post positive PCR	Observational design Small sample size Results not adjusted to consider variables	ANC during COVID infection was 4.13 (SD = 2.70) which constituted a significant drop from a baseline value of 5.2 (SD = 2.24). Mean relative reduction in ANC was −0.2729 (SD = 0.1666). ANC values return to 95% of baseline post-COVID-19 infection indicating the neutrophil drop is only transient.	3
Vallecillo et al.[47]	Retrospective cohort study	31	Baseline ANC data and ANC during acute phase of COVID-19 infection	Observational design Small sample size Results not adjusted to consider variable including comorbidities	Significant increase in clozapine plasma levels during acute phase COVID-19 infection (P = .04). Significant decrease in total leucocytes 4.510 × 10^9/L, ANC 3 × 10^9/L, lymphocytes 1.280 × 10^9/L during COVID-19 compared to baseline (P < .01 for all). Significant increase in total leucocytes 7.2 × 10^9/L (P < .01), ANC 4.150 × 10^9/L (P < .01) and lymphocytes 1.705 × 10^9/L (P < .03) post COVID-19 compared to during acute infection	6
Moga et al.[46,68]	Retrospective cohort study	105	ANC values measured pre-COVID-19 infection, during COVID-19 infection, and 1 month after resolution	Observational design Small sample size	Small reductions in neutrophil count during active COVID-19 infection compared to baseline (ANC = 4.41 × 109/L, S.D. = 2.22 vs 4.66 × 109/L, S.D. = 2.34). 10 patients developed neutropenia (9.5% patients). In one of the 10 patients it was moderate leading to discontinuation of clozapine. One month after the first negative PCR test, ANC values had returned to normal levels.	6

Table 3. Continued

Author	Study Design	*N* Total	Measurement of Outcome	Limitations	Findings	NOS
Veerman et al[13,48]*	Prospective cohort study	133	WCC and differentials and serum clozapine levels collected pre and post COVID-19 vaccine doses	Observational design Small sample size Lack of control group Varying methods to monitor clozapine serum levels	Serum clozapine levels increased significantly after second vaccination (effect size = 0.28, P = .003), clinically relevant increases in serum clozapine level occurred in 22% (n = 20) and 29% (n = 16) patients after first & second doses respectively. Clozapine alert levels (ie >1000 µg/L) occurred in 1% (n = 1) and 5% (n = 3) patients after first & second doses respectively. Changes in WBC had no clinical implications for any patient	5
Lim et al[49]*	Prospective cohort study	127	Full blood count data collected pre and post mRNA Pfizer/BioNTech vaccinations	Observational design Small sample size Limited follow-up length	N = 127 prevaccination, n = 127 one dose, n = 124 two doses. No changes in blood parameters between prevaccinations and first or second vaccinations. One (0.8%) and two cases (1.7%) of asymptomatic mild neutropenia after the first and second dose respectively (two of whom had a history of neutropenia).	5

Study Description Overview

There were five studies examining the risk of contracting COVID-19 among patients on clozapine therapy[17,37–40] (table 1), four studies investigating adverse effects in clozapine users who contracted COVID-19[39,41–43] (table 2), six studies examining the hematological changes associated with COVID-19 in clozapine users[14,27,44–47] with a further two addressing vaccination response[48,49] (table 3) and two studies investigated patient perspectives[50,51] (table 4) resulting in a total sample size of 119 054 participants including 8045 on clozapine.

Risk of COVID-19 Infection in Clozapine Users

We found five studies that examined whether clozapine-users are at an increased risk of contracting COVID-19[17,37–40] (table 1, total N = 110 045, comprising 6418 on clozapine).

Only two studies found a higher risk of COVID-19 infection in clozapine treatment vs other antipsychotics.[37,38] Govind et al[37] examined the type of antipsychotic medications taken by patients who contracted COVID-19 amongst a cohort of 6309 patients with schizophrenia-spectrum disorders (n = 1282 taking clozapine, 20.3%). They found a higher proportion of clozapine-users in COVID-19-positive patients (41.1%), and a lower proportion of clozapine-users in patients who were not infected (19%). After adjusting for socio-economic status and service contact, the hazard ratio for clozapine users testing positive for COVID-19 was 1.76 (95% CI 1.14–2.72) which was interpreted as evidence that clozapine treatment is associated with a significantly higher risk of COVID-19 infection compared to other antipsychotics. Similar conclusions were drawn by Okusaga et al[38] who examined COVID-19 results of 101 032 veterans with a diagnosis of schizophrenia-spectrum disorders treated with clozapine (n = 4313, 4.2%) or other antipsychotics. They found higher odds of testing positive for COVID-19 in the clozapine group (n = 44, 1%) compared to the group taking other medications (n = 675, 0.7%), with OR for clozapine = 1.7, 95% CI 1.29–2.41 after adjusting for demographic factors, BMI, and risk of long-term mortality. They concluded that clozapine treatment is associated with an increased risk of contracting COVID-19, although they urged caution given the 12-month gap between the medication dates, and COVID-19 results during which time medication may have changed.

Opposite results were found by Sheng et al[17] who examined the medication history of inpatients with schizophrenia who contracted COVID-19. They observed that patients who tested positive for COVID-19 (n = 84 from original 504 inpatients), were less likely to be on clozapine (n = 15, 17.9%) than other antipsychotics (82.1%), although the results were no longer statistically significant after Bonferroni correction.

Table 4. Summary of Studies Exploring Patients' Perspectives

Author	Study Design	*N* Total	Measurement of Outcome	Limitations	Findings	NOS
Fahy et al[50]	Cross-sectional study	63	Semi-structured interviews, Beck Anxiety Inventory Scale (BAI), Hamilton Anxiety Rating Scale (HAM-A)	Qualitative study design Lack of generalization due to small cohort size Lack of data regarding effect on psychotic symptomatology Lack of healthy control group Use of nonvalidated Likert scale	Anxiety symptoms were low with median BAI score of 4.0 and HAM-A score of 4.0. Likert scale measurements showed only minimal adverse impact of COVID-19 restrictions on anxiety and depressive symptoms, quality of life, and occupational and social functioning. 5 themes from free-text comments: neutral impact (n = 22), negative psychological impact (n = 13), negative social impact (n = 11), positive psychological impact (n = 5) and media coverage inducing anxiety (n = 4)	5
Rainford et al.[51]	Cross-sectional study	54	Semistructured interviews, Beck anxiety inventory scale (BAI), Hamilton anxiety rating scale (HAM-A)	Qualitative study design Lack of generalization due to small cohort size Lack of data regarding effect on psychotic symptomatology Lack of healthy control group Use of nonvalidated Likert scale	Minor increase in anxiety symptoms by HAM-A (P = .03), nonsignificant increase in BAI scores. Likert scale data noted a minor increase in depressive symptoms of 0.82 points (P = .034). Main free-text themes: looking forward to a return to normality (n = 19), positive impact of COVID-19 (n = 15), positive views regarding vaccination (n = 12), negative impact of COVID-19 (n = 5) and negative views regarding being vaccinated (n = 7). 85.4% were fully vaccinated at time of study.	5

A common limitation of the above studies includes a risk of selection bias because of their analysis of patients who had already contracted COVID-19. The number of clozapine patients may be higher due to an increased need for monitoring requirements of clozapine which might have led to increased COVID-19 detection. Overcoming this limitation, Nemani et al[39] examined outcomes of patients who were routinely tested for COVID-19. They investigated the association between different medications and the risk of contracting COVID-19 in a consecutive group of inpatients (N = 1958, including 712 or 36.3% on clozapine). They found that clozapine was associated with significantly decreased odds of infection (OR = 0.79, 95% CI 0.64–0.98), and nonsignificant differences from second-generation antipsychotic medications, although these effects were not statistically significant after adjusting for demographics and medical risk. In a separate study, Prokopez et al[40] conducted a case-control study including two patient groups on different medications (N = 252, 51 with clozapine) and showed using regression analyses that clozapine may have a protective effect for COVID-19 with a 60% lower risk of COVID-19 infection (OR 0.40, CI 0.19;0.80).

In summary, the available evidence demonstrates mixed findings. While the two earlier results show an increased risk of COVID-19 in clozapine patients[37,38] more recent studies either fail to find such an association or suggest that clozapine may, in fact, confer some protection again COVID-19.[17,40,52]

Risk of COVID-19 Complications in Clozapine Users

All four studies which reported on the outcomes of clozapine users who contracted COVID-19 failed to demonstrate adverse clinical outcomes compared to other antipsychotic treatments on infection severity indicators such as hospitalization, intensive care (ICU) treatment and all-cause mortality[39,41–43] (table 2, Total N = 10 356 including 1743 clozapine).

Three studies comprised larger cohort studies and a comparison of clozapine against other medications.[39,42,43] Ohlis et al[43] examined 8233 people with a psychotic disorder who contracted COVID-19 and compared the outcomes of patients on different medications (n = 966, 11.7% on clozapine). At a follow-up of 9 months, they found nonsignificant differences between groups in the number of patients receiving COVID-19 inpatient care or with more severe course of infection (clozapine group hazard ratio of 0.96, 95% CI 0.54–1.70); ICU care (HR 0.69, 95% CI 0.48–5.93), or death due to COVID-19 (0.86, 95% CI 0.26–2.80), after adjusting for socioeconomic status and comorbid medical illnesses. Similarly, Govind et al[42] compared the outcomes of 157 patients on antipsychotics and infected with COVID-19 (n = 57, 36% on clozapine therapy). Rates of adverse outcomes

were similar between patients on clozapine treatment vs other antipsychotics on episodes of COVID-related hospitalization (24% vs 28%, adjusted clozapine OR 1.12, 95% CI 0.48–2.60), COVID-related ICU care (7% vs 9%, OR 95% CI 0.18–2.77), and all-cause mortality within 28 days of infection (7% vs 8%, OR 1.38, 95% CI 0.33–5.71) suggesting that clozapine treatment did not carry a significantly higher risk of complications compared with other antipsychotics. In Nemani et al's[39] study, the 6–9 month outcome of 969 inpatients who become infected with COVID-19 (from an initial $N = 1958$ routinely tested for COVID-19) was examined. When comparing the mortality rates associated with different psychotropics, clozapine was the only medication associated with decreased odds of mortality. The odds ratio was significant in the unadjusted model (OR 0.25, 95% 0.10–0.62), although failed to retain significance after adjusting for demographic and medical risk. The final study presented the results of a naturalistic observational design with eight consecutive hospital patients on long-term clozapine treatment (Butler et al[41]). Six of the eight patients had developed complications including pneumonia or delirium and three patients died. While this shows evidence of poor outcomes, pneumonia occurs at elevated rates in clozapine treatment possibly linked to side-effects such as hypersalivation and swallowing difficulties,[7,32,33] and a lack of a comparison group limits the type of conclusions that can be made about this study on clozapine specifically.

In conclusion, available evidence from cohort studies does not confirm the notion that COVID-19 infection in clozapine-users leads to additional health complications when compared to other antipsychotics, and adding to findings from case studies that suggest an absence of complications.[53] Limitations of studies include increased risk of type II errors, a lack of comparable patient selection criteria, and follow-up durations. Of future interest, fine-grain analyses of medical complications which did not result in hospitalization and longer-term outcomes of people infected with COVID-19 would add substantially to this literature.

Hematological Effects of COVID-19 and COVID-19 Vaccination in Clozapine Users

This section examines the hematological effects of COVID-19 in patients treated with clozapine and the effects of COVID-19 vaccination. Hematological testing usually includes measurement of blood parameters including white blood cell count (WCC), neutrophil count (absolute neutrophil count, ANC), and lymphocyte count which assesses the early peripheral immune response. A specific immunological marker of COVID-19 is a reduction in lymphocyte count together with elevated neutrophil count.[54] However, clozapine can lower neutrophil count (which can cause neutropenia and agranulocytosis) raising questions about the immunological response of clozapine-users who contract COVID-19.[27,55]

Hematological Effects of COVID-19. We identified six studies with small cohorts and a retrospective observational design[14,27,44–47] (table 3, Total $N = 234$ including 219 clozapine), with the most common finding showing a reduction in neutrophil counts following the onset of COVID-19 together with increased incidence of neutropenia.

Three observational studies comprised clozapine-users without control groups, two of which were conducted by Gee and Taylor.[14,27] In their first study, Gee and Taylor[14] examined the clinical records of 13 clozapine patients during acute COVID-19 infection, with bloods taken prior to testing positive for COVID-19 ("baseline", 14 days pre-infection), and again at 0–7 and 8–14 days post-positive PCR results. The results showed nonsignificant reductions in neutrophil count during days 0–7 of COVID-19 when compared to baseline values (Mean ANC = 4.24×10^9/L vs 4.83×10^9/L) and which resolved during the second week. Comparisons using other hematological markers were similarly non-significant. In 2021, Gee and Taylor[27] replicated their study using a larger cohort of 56 clozapine patients with a mean treatment duration of 4.6 years. Notable findings were significant decreases in WCC, neutrophils (ANC counts), and lymphocyte counts between pre-infection baseline measurements and days 0–7, although cell counts had returned to baseline values within days 8–14. Furthermore, six patients (11%) developed neutropenia (neutrophil count < 1500 cells/mcL), including 4 subjects undergoing clozapine cessation. The authors concluded that the mild neutropenia observed only in the early phase of COVID-19 infection was more likely evidence of acute infection rather than clozapine treatment. While their lack of control group and lack of adjustment for confounding variables make it difficult to draw strong conclusions, the reductions in neutrophil levels were independently replicated in the two other studies. Moga et al[46] examined the change in neutrophil levels between pre-infection, during acute COVID-19, and after the resolution of infection. In a large sample of 105 patients on clozapine, they reported small non-significant reductions in neutrophil count during active COVID-19 infection compared to baseline (ANC = 4.41×10^9/L, S.D. = 2.22 vs 4.66×10^9/L, S.D. = 2.34). Ten patients (9.5%) developed neutropenia. One month after the first negative PCR, ANC values had normalized. Using a similar design and 10 inpatients treated with clozapine and with COVID-19, Bonaccorso and colleagues[44] reported similar results showing a temporary drop in neutrophils which were temporally related to acute COVID-19 infection. The main difference is that the drop in neutrophil levels between baseline and acute infection was statistically significant and with mean relative reduction in ANC of −0.27 with average ANC levels

at baseline period averaged from the previous three years. The only study with a comparison group was conducted by Vallecillo and colleagues[47] which included a group of patients taking antipsychotic medications other than clozapine. They assessed hematological parameters in 31 psychiatric patients who tested positive for COVID-19 (51% or $n = 16$ on clozapine). They found statistically significant reductions in median values of WCC, neutrophil, and lymphocyte counts during the period of COVID-19 infection ($P < .01$ for all three markers) which did not differ between clozapine vs other medication groups. Within two weeks, all measures reverted to baseline value, except for lymphocyte values which remained lower than baseline. Three patients developed neutropenia during the study, two from clozapine group (both had a history of neutropenia during initial clozapine titration) and which resolved after clozapine cessation. The authors concluded that the transitory drop in hematological markers was likely related to COVID-19 infection and was not specific to clozapine since it was observed in patients taking other antipsychotics. They also pointed to an antecedent of previous neutropenia in the clozapine patients who developed neutropenia during COVID-19 infection, suggesting it could be used as a future risk factor. Finally, a study by Hata et al[45] reported a lack of adverse hematological effects in 19 clozapine patients who were regularly monitored for extended periods, although insufficient details were provided to compare with previous studies.

Overall, results are generally consistent in showing reductions in neutrophils during acute COVID-19 infection in people treated with clozapine. None of the studies showed the hematological profile typically associated with COVID-19 suggesting a drug–interaction effect in immune defence against infection.[15] Common limitations of the above however include small sample sizes with a lack of comparison group. The interpretation is therefore difficult because of the possibility of interference from multiple medications and comorbidities, and different periods used in the calculation of baseline and COVID-19 periods.

Effects of COVID-19 Vaccination. There were only two studies that investigated the effects of COVID-19 vaccine on the immune response of people on clozapine treatment (Total $N = 260$, including 260 on clozapine, in table 3). Lim et al[49] examined hematological changes and adverse effects after a hospital vaccination schedule consisting of two doses of mRNA Pfizer/BioNTech vaccines administered 21 days apart in people treated with clozapine ($n = 127$ prevaccination, $n = 127$ one dose, $n = 124$ two doses). They reported no significant changes in blood parameters between prevaccination and first or second vaccinations. Additionally, no major adverse effects were observed. Three patients developed mild neutropenia after the second dose (two of whom had history of neutropenia). Veerman et al's[48] study consisted of 133 people on clozapine vaccinated with four different mRNA vaccines ($n = 133$ prevaccination and one dose, and $n = 56$ after 2 doses). The results showed no significant change in neutrophils between baseline and after the first vaccine. However, small and temporary decreases in neutrophils and WCC were reported after the second vaccine, together with a rise in serum levels of clozapine of greater than 100 ug/L (in 22% and 29% of the cohort after the first and second dose of vaccination respectively), although these effects were not clinically relevant after the exclusion of people vaccinated with Johnson and Johnson vaccine. Mild granulocytopenia cases occurred in 3% and 5% after the first and second dose respectively but no significant adverse effects were reported.

The lack of larger cohort studies detailing adverse effects of vaccination is reassuring in light of the large numbers of clozapine users who have been vaccinated worldwide.[13]

Perspectives of Clozapine Users About COVID-19. To date, there has been a paucity of quantitative or qualitative research on the impact of the pandemic and subsequent government-mandated restrictions and vaccination on individuals treated with clozapine. This review identified two studies reporting on the same cohort of patients attending a clozapine clinic in Ireland[50,51] (table 4, Total $N = 117$).

Fahy et al[50] measured the impact of COVID-19 restrictions on clozapine patients with schizophrenia-spectrum disorders using a study-designed measure that assessed adverse impact on a Likert scale ranging from 0 to 10. They also included measures of anxiety, socio-occupational functioning, and quality of life using the Beck Anxiety Inventory (BAI), Hamilton Anxiety Rating Scale (HAM-A), and semi-structured interviews. There was no baseline measurement, but cross-sectional data pointed to low levels of anxiety, depression, and social-occupational functioning. Thematic analyses of free-text showed a largely neutral response to the pandemic ($n = 22$, 40%). By contrast, 20% to 23% ($n = 11$ and 13) revealed they had suffered a negative psychological or social impact from the isolation associated with the pandemic response. The negative impact was significantly elevated with anxiety symptoms as measured on the BAI and HAM-A and was linked to media coverage in 4 patients who completed the interviews. Twelve months after initial engagement with the study, the same group was approached for a follow-up study using the same measures. Rainford et al[51] found small but significant increases in symptoms of anxiety (HAM-A change of 1.9 points, $P = .003$). All participants demonstrated relative stability with regards to their mental health with only 3 participants requiring an increase in their clozapine doses within the 12 months and no patients requiring hospitalization

due to mental health relapse. Free-text responses identified that a larger proportion of patients were favorable to vaccination (n = 12, 28% of respondents, vs n = 7, 17% against vaccination) and mandatory restrictions (n = 15, 36%) and that only a minority expressed negative psychosocial impact (n = 5, 12%). 85.4% of participants were fully vaccinated at the time of completion of both studies.

Discussion

This systematic review explores available data on the association between COVID-19 infection and clozapine therapy. Specifically, we queried whether individuals on clozapine treatment might be more vulnerable to contracting COVID-19 and severe health complications, and examined the findings on the immune response triggered by COVID-19 in people treated with clozapine.

The results were as follows: First, the results were not fully supportive of the notion that clozapine treatment increases the vulnerability to COVID-19. Three studies (out of 5 cohort studies) failed to support this notion of increased risk of COVID-19, instead showing that patients taking clozapine may be at lower risk.[17,39,40] This conclusion is also supported by an independent study comprising 32 patients (23 on clozapine) who developed COVID-19.[56] Second, there was no evidence that COVID-19-positive clozapine patients were at risk of more serious adverse clinical outcomes[39,41–43] and nonsignificant differences compared to other antipsychotics after adjustments for potential confounders. While these results initially appear at odds with studies in schizophrenia which show increased risk of severe COVID-19 when compared to nonpsychiatric and other psychiatric groups,[21,23,52,57–59] the effects are largely mediated by medical comorbidities. Third, results of hematological studies were generally consistent with reductions in neutrophils in COVID-19-positive clozapine users.[14,27,44–47] No study showed the hematological profile typically associated with COVID-19, suggesting instead that immune response may be altered by clozapine treatment, which has been interpreted as a drug–interaction effect in defence against infection.[15] Results of vaccination studies[48,49] showed no major changes in hematological markers following mRNA vaccine, except for mild and temporary decrease in neutrophils and WCC, and raised clozapine plasma levels, which were not linked to major adverse effects. These results provide a cautious level of reassurance given case studies that have drawn attention to potential adverse clinical outcomes in clozapine patients following vaccination.[48,60–62] Finally, the perspectives of patients provided important insights into the dual challenges of living with clozapine and COVID-19. The two studies[50,51] by the same authors reported that patients on clozapine therapy have remained relatively stable with regards to their mental health during the pandemic with only a minimal increase in anxiety and depressive symptoms and minimal clozapine dose adjustments among those who did not require hospitalization. Views regarding the pandemic response were mixed although largely positive, both in their support of vaccination and travel restrictions.

A common factor between clozapine and COVID-19 infection is that both have been associated with compromised immune function. The results of this review failed to find compelling evidence that clozapine increases vulnerability to contracting COVID-19. Hematological findings showed reductions in neutrophil counts which were temporarily related to the acute onset of infection. The results have been interpreted to suggest a complex relationship between clozapine and COVID-19 and that of an active immune response defence against infection.[15,17,39] Jeong and Kim[15] suggested that clozapine's immunosuppression and anti-inflammatory effects might in fact offer protection against viruses such as COVID-19 by dampening the body's acute reaction to infections. They argue that anti-inflammatory effects increase with the duration of clozapine (unlike temporary rises in cytokine levels which are associated with early phase of clozapine initiation) and that the combined immunosuppression and anti-inflammatory effects of clozapine may be the most effective way to mount an antiviral defence. This conclusion is supported by studies reviewed here.[17,39,40]

Another interesting finding amongst the studies reviewed was increased plasma levels of clozapine during COVID-19 infection[47] and after vaccination with mRNA vaccines, and common reports about neutropenia.[27,46–49] These findings confirm previous reports of patients established on clozapine,[63–67] although some negative findings exist.[41,53] Moga et al[46] observed that the incidence of neutropenia in clozapine patients appears substantially higher than reported prior to the pandemic. While the risk of neutropenia is greatest during the first few weeks/months of clozapine initiation, it is relatively infrequent in patients on long-term clozapine treatment (approximately 2%–3%), yet they estimated that neutropenia has been reported in approximately 10.6% of COVID-19 clozapine patients. They suggested that neutropenia might confirm the notion of interference between clozapine and COVID-19 perhaps from clozapine toxicity from COVID-19-related interruptions of clozapine metabolites or other immunological effects.[68] This notion of clozapine intoxication from COVID-19 due to elevated plasma levels of clozapine has received strong support amongst other studies[29] including group and case-studies studies demonstrating elevated clozapine levels at the onset of COVID-19[47,65,69] and even in the context of normal neutrophil counts.[70] There is evidence from other infections that the severity of inflammation may determine the risk of clozapine intoxication[71] and that in the absence of available serum clozapine levels, CRP values may prove useful.[67] This interpretation is consistent with the above studies showing increases in plasma levels during acute

Issues	Recommendations
Suspected/Confirmed COVID-19 infection	• Urgent physical exam and investigations to include: FBC, CRP (available rapidly to identify inflammation and help prevent clozapine intoxication[48]), troponin, LFT, serum clozapine level, coronavirus PCR testing[12,45]. • Consider differential diagnoses including but not limited to neutropenic sepsis, myocarditis[10,17] • Clozapine dose adjustment: preferably to be guided by plasma concentration o Cessation should only be considered as a last resort and following discussion with the treating psychiatrist o Dose reduction of up to 50% can be considered especially in those with high CRP as inflammation can cause cytokine storm (inhibits CYP1A2 function which can cause clozapine toxicity)[71] o Consider that altered smoking habits during active infection may affect serum levels[10,72] o Once nil evidence of fever in the past 3 days consider re-commencing clozapine titration following consultation with the treating psychiatrist[71]
Routine haematological monitoring	• Patients on clozapine therapy > 1 year and nil history of neutropenia: This review is in agreement with consensus guidelines which suggest the extension of haematological monitoring intervals to 3 months with the dispensation of a 90-day supply of clozapine[10,12]. • Patients on clozapine therapy < 1 year: extension of haematological monitoring intervals should be considered on a case-by-case basis
Prevention	• Ensure up-to-date COVID-19 vaccination • Recommend pneumococcal and influenza vaccination • Consider vitamin D supplementation[14] • Smoking reduction or cessation should be encouraged[73] • Reduce face-to-face contact where possible between healthcare professionals and facilities and patients on clozapine therapy[10,72] • Consider home delivery of medication[73] • Provide psychoeducation regarding signs of clozapine intoxication[48] • Address any noted side effects particularly hypersalivation as it can precipitate aspiration pneumonia[73]

Fig. 2. Recommendations regarding COVID-19 and patients on clozapine therapy.

infection only, and which resolved after the infection had resolved (eg Vallecillo et al.[47]).

This review demonstrates the importance of careful consideration of clozapine patients during the COVID-19 pandemic. While the results did not find strong support for increased vulnerabilities of clozapine users, the documented changes in clozapine serum levels and other medical comorbidities suggest that close monitoring of clozapine users remains important. Figure 2 summarizes the current recommendations and previous consensus guidelines which are vital to ensure the safe treatment and outcomes of patients. Transient neutropenia and lymphocytopenia are likely to be observed within the acute phase of COVID-19 infection in this patient population but are more likely to be of viral origin as opposed to as a result of clozapine therapy, especially in those well-established on clozapine. The clinical presentation of neutropenic sepsis, agranulocytosis, or cardiac side effects due to clozapine therapy are often rare but can be of higher frequency in certain populations[72,73] and can be similar to that of COVID-19 infection thus clinicians should always take caution to consider all possible diagnoses. Similarly, adverse cardiac side effects following COVID-19 immunization have been of concern due to the dilemma of distinguishing between clozapine-induced myocarditis and myocarditis post-mRNA vaccination. Typically, clozapine-induced myocarditis occurs within the first four weeks of clozapine initiation and while specific risk factors have not been identified, concurrent treatment with sodium valproate, cumulative dose, and rapid titration may be of significance.[74] There have been reports of myocarditis within a week following the second dose of mRNA vaccination, more commonly occurring in males and young adults.[75] To date, global data suggests that the benefits of receiving COVID-19 vaccination outweigh the risk of myocarditis for all age groups. This review would advise clinicians to proceed with encouraging immunization in clozapine users but encouraging them to seek medical attention when indicated.

The main limitations of this review include the small number of studies available, the lack of data comparing people on clozapine therapy and other treatments, as well as the lack of data available to distinguish whether the outcomes for patients are due to clozapine therapy, the underlying illness, or its comorbidities. The assessment of studies in the English language only may preclude analyses of other data available around the world.

In conclusion, this is a fast-developing area of research interest and there is still a paucity of high-quality evidence. While the studies await independent replication, these initial results point to a need for services to consider how to maximize COVID-19 identification and early intervention. Future studies with longer follow-up periods and investigation of the reasons for all-cause hospital admissions would be of interest. However, given the large number of patients who have already contracted, and/or who have been vaccinated for, COVID-19, the results allow a cautious level of optimism about the lack of adverse effects, although we await the results of studies on "long-term" COVID-19. In the meantime, those who are COVID-19 positive should, where possible, continue clozapine therapy following a discussion with their treating psychiatrist and COVID-19 vaccination should be encouraged.

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