Clozapine treatment and risk of COVID-19
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The antipsychotic clozapine is known to have immune-modulating effects. Clozapine treatment has been reported to be associated with increased risk of COVID-19 infection. However, it remains unclear whether this is because of increased testing of this patient group, who are closely monitored. We linked anonymised health records from mental health services in Cambridgeshire (UK), for patients taking antipsychotic medication, with data from the local COVID-19 testing hub. Patients receiving clozapine were more likely to be tested for COVID-19, but not to test positive. Increased testing in patients receiving clozapine suggests prudent judgement by clinicians, considering the overall health vulnerabilities of this group.

Keywords
Antipsychotics; psychotic disorders; schizophrenia; COVID-19; clozapine.

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Clozapine is one of the most effective antipsychotic medications, and the only medication licensed for treatment-resistant schizophrenia in the UK.1 In this population, clozapine can improve positive symptoms, hospital admissions and all-cause mortality.2 However, in a subgroup of patients clozapine treatment is associated with immune-mediated side-effects, notably neutropenia,3 requiring mandatory neutrophil count monitoring in most countries.4 Meta-analysis shows increased risk of COVID-19 mortality associated with psychotic disorder and exposure to antipsychotics.5 A previous study of National Health Service (NHS) electronic mental health records reported increased risk of COVID-19 infection in patients with schizophrenia who received clozapine.6 It has been speculated that the immune-modulating effects of clozapine might account for this association. However, it remains unclear whether such patients are more likely to be tested for COVID-19 in the first place, given the close clinical monitoring offered to this patient group. It also remains unclear whether patients with schizophrenia taking clozapine are more likely to test positive for COVID-19 after considering testing frequency.

Results
A total of 13 726 patients were prescribed an antipsychotic during the study period (January 2013 to April 2021) and were included in the study. Of these, 1943 (14%) had a COVID-19 test, 2123 (15.5%) had a coded diagnosis of schizophrenia and 778 (6%) were prescribed clozapine.

The odds ratio for patients receiving clozapine being tested for COVID-19 was 1.99 (95% CI 1.70–2.33, P < 2×10⁻¹⁶) versus patients on other antipsychotics, after adjusting for age, gender and ethnicity. After adding a coded diagnosis of schizophrenia as a predictor, the odds ratio reduced to 1.32 (95% CI 1.10–1.59, P = 0.002) (Supplementary Table 1).

Among patients tested for COVID-19, clozapine use was associated with an odds ratio of 1.22 (95% CI 0.68–2.07, P = 0.48) for a positive test result, after adjusting for age, gender and ethnicity. The odds ratio adjusted further for a coded diagnosis of schizophrenia was 1.06 (95% CI 0.56–1.91, P = 0.84) (Supplementary Table 2).

Finally, the odds ratio for patients receiving clozapine (versus others) having a positive test for COVID-19 irrespective of testing rates was 2.09 (95% CI 1.18–3.48, P = 0.007), after adjusting for age, gender and ethnicity. The odds ratio further adjusted for a coded diagnosis of schizophrenia was 1.25 (95% CI 0.67–2.26, P = 0.46) (Supplementary Table 3).

Sensitivity analyses of 13 268 patients ‘currently’ prescribed antipsychotic medications yielded similar findings. Patients receiving clozapine had higher odds of being tested for COVID-19, but...
Our findings suggest that, compared with secondary healthcare patients treated with other antipsychotics, patients receiving clozapine were more likely to be tested for COVID-19, but they were not more likely to test positive if tested. However, our results also show that patients receiving clozapine were more likely to test positive for COVID-19 irrespective of the difference in testing rates, if a schizophrenia diagnosis was not taken into account.

Our findings are compatible with previous work, and extend it in various ways. We show that the potential association between clozapine treatment and an increased risk of testing positive for COVID-19 could, at least in part, be attributed to increased rates of testing in this patient group, who are under greater surveillance, and appropriately so. Furthermore, we use two sets of complementary analyses based on either patients treated with antipsychotics over a longer 7-year period or current treatment limited to the latest 24 months, yielding compatible findings. Limitations of the work include reliance on electronic health record data, which depends upon clinicians recording information and thus is prone to missing information, a common problem for electronic health record-based studies. For example, schizophrenia was likely significantly undercoded in this data-set, rendering tentative conclusions about diagnosis. Our study period captures the first 12 months of the COVID-19 pandemic in the UK, and so may not be generalisable to other countries or time frames. Further, COVID-19 testing data did not include community testing results, or tests carried out at the other Cambridgeshire hospital (Peterborough City Hospital); therefore, the EpiCov data-set included all emergency department and in-patient tests performed at the CUH, covering approximately half of CPFT’s catchment area by population. Finally, PCR test availability for SARS-CoV-2 varied considerably over time: initially only available for in-hospital testing of high-risk cases, it became gradually available for home self-testing of any symptomatic member of the public over the course of the pandemic. However, we do not believe that availability would have differentially affected secondary healthcare patients treated with other antipsychotics versus patients receiving clozapine.

We conclude that increased testing for COVID-19 in patients receiving clozapine, as observed in our results, shows prudent clinical judgement by clinicians and should continue, considering the notable health vulnerabilities of this patient group, which include multimorbidity and the immune-mediated effects of clozapine.

Discussion

Our findings suggest that, compared with secondary healthcare patients treated with other antipsychotics, patients receiving clozapine were more likely to be tested for COVID-19, but they were not more likely to test positive if tested. However, our results also show that patients receiving clozapine were more likely to test positive for COVID-19 irrespective of the difference in testing rates, if a schizophrenia diagnosis was not taken into account.

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