Analysis of the impact of antidepressants and other medications on COVID-19 infection risk in a chronic psychiatric in-patient cohort

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Background
During the first wave of the coronavirus disease 2019 (COVID-19) pandemic, patients with confirmed cases in New York State accounted for roughly 25% of total US cases, with psychiatric hospital in-patients at particularly high risk for COVID-19 infection.

Aims
The beneficial effects of mental health medications, such as selective serotonin reuptake inhibitors (SSRIs), on the severity of COVID-19 disease outcomes have been documented. Protective effects against infection have also been suggested for these medications. We therefore tested the hypothesis that medication use modifies the risk of COVID-19 infection in a long-stay, chronic in-patient psychiatry setting, where the potential for exposure was likely uniform across the facility, and where these medications were routinely prescribed.

Method
This was a retrospective cohort study of an adult psychiatric facility operated by the New York State Office of Mental Health. Current medication information and COVID-19 status was collected from electronic medical records for 165 people who were in-patients during the period January to July 2020, and logistic regression was employed to model the main effects of medication use on COVID-19 infection.

Results
A significant protective association was observed between antidepressant use and COVID-19 infection (odds ratio (OR) = 0.33, 95% CI 0.15-0.70, adjusted P < 0.05). Analysis of individual antidepressant classes showed that SSRI, serotonin-norepinephrine reuptake inhibitor and the serotonin-2 antagonist reuptake inhibitor classes of antidepressants, drove this protective effect. Exploratory analyses of individual antidepressants demonstrated an association between lower risk of infection and fluoxetine use (P = 0.023), as well as trazodone use (P = 0.001).

Conclusions
The novel finding of reduced COVID-19 infection risk for psychiatric in-patients taking antidepressants, suggests that antidepressants may be an important weapon in the continued fight against COVID-19 disease. This finding may become particularly salient for in-patient settings if vaccine-resistant strains of the virus appear.

Keywords
Antidepressants; fluoxetine; trazodone; psychiatric illness; COVID-19.

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many antiviral properties of antidepressants, in particular SSRIs and it has been theorised that antidepressants may be effective against SARS-CoV-2 infection.\textsuperscript{16,17}

Aims

Intriguingly, recent population cohort studies investigating medication effects on COVID-19 risk\textsuperscript{12,13,18} may be confounded by actual rates of viral exposure in the broad geographical communities studied. We propose that risk of infection could also be examined in an in-patient population setting, where the potential for exposure is likely uniform across the facility, and where these mental health medications/supplements are routinely prescribed. In the present study we tested the hypothesis that medication use, such as antidepressants or vitamin D supplementation, modifies the risk of COVID-19 infection in a long-stay, chronic in-patient psychiatry setting.

Method

We conducted a retrospective cohort study of the in-patient population at The Rockland Psychiatric Center (RPC), a large psychiatric facility for adults operated by the New York State Office of Mental Health (OMH). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the RPC institutional review board, using a waiver of authorisation for informed consent. The study followed the STROBE reporting guidelines for cohort studies.

During the period between June 2 to 31 July 2020, we collected patient data from the OMH online medical records system, across seven wards in entirety (approximately 50% of the RPC in-patient population). Demographic and clinical details were recorded, plus all current medication use (including PRN medications) within the first wave of the pandemic in New York State. COVID-19 infection was determined by a positive polymerase chain reaction diagnostic test or the presence of antibodies following an enzyme-linked immunosorbent assay. Testing was performed at RPC for all patients from the first wave of the pandemic in New York State. COVID-19 infection rates of viral exposure in the broad geographical communities likely uniform across the facility, and where these mental health medications/supplements are routinely prescribed. In the present study we tested the hypothesis that medication use, such as antidepressants or vitamin D supplementation, modifies the risk of COVID-19 infection in a long-stay, chronic in-patient psychiatry setting.

A total of 165 RPC in-patients were included (Table 1), of whom 91 (55%) were positive for COVID-19. Individuals with COVID-19 did not differ by gender, BMI or the presence of hypertension, respiratory illness or diabetes. There was a trend towards significance for COVID-19 positively to be associated with schizophrenia spectrum disorders (schizophrenia or schizoaffective disorder) when compared with

| Characteristic | COVID+ (n = 91) | COVID− (n = 74) | P* |
|----------------|----------------|-----------------|----|
| Gender, n (row %) | 0.327 | | |
| Female | 8 (12) | 11 (38) | |
| Male | 83 (57) | 63 (43) | |
| Ethnicity, n (row %) | 0.671 | | |
| African American | 43 (41) | 30 (59) | |
| White | 39 (52) | 36 (48) | |
| Other | 8 (47) | 9 (53) | |
| Age, years, n (row %) | 0.095 | | |
| 18–44 | 29 (45) | 36 (55) | |
| 45–54 | 22 (69) | 10 (31) | |
| 55–64 | 26 (55) | 21 (45) | |
| 65+ | 14 (67) | 7 (33) | |
| BMI, n (row %) | 0.534 | | |
| Normal (BMI ≤ 25) | 23 (59) | 16 (41) | |
| Overweight (BMI 26–30) | 40 (58) | 29 (42) | |
| Obese (BMI 31+) | 28 (49) | 29 (51) | |
| Psychiatric diagnosis,\textsuperscript{b} n (row %) | 0.062 | | |
| Schizophrenia spectrum disorder | 84 (58) | 61 (42) | |
| Mood disorder | 5 (31) | 11 (49) | |
| Hypertension, n (row %) | 0.160 | | |
| Yes | 29 (64) | 16 (36) | |
| No | 61 (51) | 58 (49) | |
| Respiratory illness, n (row %) | 0.756 | | |
| Yes | 7 (64) | 4 (36) | |
| No | 84 (55) | 70 (45) | |
| Diabetes (type 2), n (row %) | 0.185 | | |
| Yes | 10 (42) | 14 (48) | |
| No | 81 (57) | 60 (43) | |
| Heart disease, n (row %) | 0.062 | | |
| Yes | 5 (31) | 11 (69) | |
| No | 86 (58) | 63 (42) | |

| Medications | | | |
|----------------|------------------|------------------|
| CPZE, mean (s.d.) | 1729.4 (3365.8) | 737.8 (629.7) | 0.116 |
| Typical neuroleptic, yes: n (row %) | 54 (61) | 34 (39) | 0.084 |
| Atypical neuroleptic, yes: n (row %) | 85 (54) | 71 (46) | 0.733 |
| Mood stabiliser, yes: n (row %) | 52 (33) | 42 (45) | 1.000 |
| Benzodiazepine, yes: n (row %) | 43 (66) | 23 (35) | 0.039 |
| Antidepressant, yes: n (row %) | 13 (34) | 25 (66) | 0.002 |
| Anticholinergic, yes: n (row %) | 47 (59) | 32 (41) | 0.347 |
| Antihypertensive, yes: n (row %) | 21 (50) | 21 (50) | 0.475 |
| Antilipidemic, yes: n (row %) | 34 (60) | 23 (40) | 0.596 |
| Antidiabetic, yes: n (row %) | 3 (7) | 3 (7) | 0.282 |
| Steroid, yes: n (row %) | 12 (57) | 9 (43) | 1.000 |
| Supplement,\textsuperscript{c} yes: n (row %) | 54 (63) | 32 (37) | 0.043 |

BMI, body mass index; CPZE, chlorpromazine-equivalent daily dose. Significant differences bolded.

a. Fisher’s exact or Student’s t-test.
b. n = 161 (four participants with unspecified psychiatric diagnoses were excluded).
c. Vitamins B (B complex, B12, folic acid), C, D, multivitamin, fish oil, Calcium carbonate, magnesium, probiotics.
mood disorders (bipolar disorder or major depressive disorder) \( (P = 0.062) \), supporting data from a recent study. There was no difference in COVID-19 infection status when patient diagnoses were further classified into manic and depressive types (see Supplementary Tables 1 and 2 available at https://doi.org/10.1192/bjo.2021.1053).

We observed a significant association of CPZE dose with increasing COVID-19 risk (Table 2, odds ratio (OR) = 1.0007, 95% CI 1.0002–1.0013, Benjamini–Hochberg adjusted \( P < 0.05 \)), which was retained after adjustment for demographic and clinical variables. Interpreting CPZE quartile data from the adjusted model, the probability of being COVID-19 positive increased from 0.41 at the 25th percentile, to 0.44 at the 50th, 0.52 at the 75th, to 0.63 at the 90th percentile of the CPZE daily dose data. The use of benzodiazepines and supplements were also associated with COVID-19 positivity but did not remain significant following Benjamini–Hochberg adjustment.

There was a significant association with antidepressant use (OR = 0.33, 95% CI 0.15–0.70, Benjamini–Hochberg adjusted \( P < 0.05 \)); those treated with antidepressants had significantly reduced odds of COVID-19 infection, even after full adjustment for all demographic and clinical variables (fully adjusted OR = 0.28, Table 2). Results from sensitivity analyses using a stepwise selection of model variables yielded similar results. Analysis of individual antidepressant classes showed that patients treated with serotonin reuptake inhibitors (SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs)) or serotonin-2 antagonist reuptake inhibitors (SARI), both had a significantly decreased likelihood of COVID-19 infection (Table 2: unadjusted OR = 0.32, 95% CI 0.12–0.78 and OR = 0.06, 95% CI 0.008–0.51, respectively). Exploratory analyses of individual antidepressant use demonstrated a significant association between lower risk of infection and the SSRI antidepressant fluoxetine (\( P = 0.023 \)), as well as the SARI antidepressant trazodone (\( P = 0.001 \)), see Supplementary Table 3.

Discussion

Main findings

In this observational study of a long-stay hospital, psychiatric in-patient cohort, we found that patients who received antidepressant medication had a 72% lower odds of testing positive for COVID-19, compared with those not treated with antidepressants. The serotonin reuptake inhibitor (SSRI and SNRI) and the SARI classes of antidepressants appeared to drive the protective effect. Our findings augments recent studies documenting the beneficial effect of antidepressants (including both SSRIs and non-SSRIs) on reducing the risk of intubation or death in patients admitted to hospital with COVID-19, and taken together provides support for a randomised controlled trial to test the use of these antidepressants in the management of COVID-19 risk in psychiatric in-patient settings.

Interpretation of our findings

There are a number of plausible pathophysiological mechanisms that could explain the protective effects of antidepressant medication against COVID-19 infection. First, antidepressant use may directly impede viral host cell entry via inhibition of the ASM/ceramide system (\( 19,30,31 \) and references therein). Specifically, the ASM enzyme, present in lysosomes and the cell membrane, cleaves ceramide from sphingomyelin, resulting in the formation of ceramide-enriched membrane domains in the outer cell membrane. Preclinical studies have suggested that SARS-CoV-2 infection requires activation of the ASM/ceramide system, with viral entry into host cells facilitated by the clustering of ACE2 into these ceramide-enriched membrane domains. \( 19 \) Of relevance to our study finding, several antidepressants including the SSRI fluoxetine functionally inhibit ASM activity, and pharmacological in vitro studies have shown that treatment with a number of both SSRI, tricyclic and tetracyclic antidepressants directly block uptake of SARS-CoV-2 by epithelial cells, and with regards to fluoxetine, also dramatically reduced viral titers.

Studies of both cell culture systems and in vivo models have also highlighted the antiviral activity of particular antidepressants. For example, fluoxetine is a potent inhibitor of enterovirus replication, and the SSRI sertraline can inhibit Ebola virus cell entry both in vitro and in vivo. The SSRI citalopram inhibits HIV cell entry and replication, and citalopram and sertraline may reduce HIV replication in patient cerebrospinal fluid. Antidepressants can also act as anti-inflammatory agents, reducing levels of proinflammatory cytokines. For example, binding of fluoxetine to the sigma-1 receptor in the endoplasmic reticulum was shown to decrease cytokine activity and enhance survival in preclinical models of sepsis and inflammation, and human studies have supported the concept of a general decrease

| Table 2 | Odds ratios with 95% CIs of the unadjusted and adjusted medication models of COVID-19 infection |
| --- | --- | --- | --- |
| Medication | Unadjusted model | Adjusted model\( a \) | Fully adjusted model\( b \) |
| | OR (95% CI) | \( P \) | OR (95% CI) | \( P \) | OR (95% CI) | \( P \) |
| CPZE | 1.0007 (1.0002–1.0013) | 0.004 \( d \) | 1.0007 (1.0002–1.0014) | 0.044 | 1.0007 (1.0001–1.0015) | 0.046 \( e \) |
| Typical antipsychotic | 1.765 (0.947–3.287) | 0.073 | 1.765 (0.947–3.287) | 0.073 | 1.765 (0.947–3.287) | 0.073 |
| Mood stabiliser | 1.016 (0.547–1.888) | 0.960 | 1.016 (0.547–1.888) | 0.960 | 1.016 (0.547–1.888) | 0.960 |
| Benzodiazepine | 1.986 (1.046–3.773) | 0.036 | 1.986 (1.046–3.773) | 0.036 | 1.986 (1.046–3.773) | 0.036 |
| Anticholinergic | 1.402 (0.757–2.598) | 0.283 | 1.402 (0.757–2.598) | 0.283 | 1.402 (0.757–2.598) | 0.283 |
| Antilipidemic | 0.757 (0.375–1.528) | 0.438 | 0.757 (0.375–1.528) | 0.438 | 0.757 (0.375–1.528) | 0.438 |
| Antihypertensive | 1.322 (0.690–2.534) | 0.399 | 1.322 (0.690–2.534) | 0.399 | 1.322 (0.690–2.534) | 0.399 |
| Antibiotic | 0.811 (0.05–13.19) | 0.883 | 0.811 (0.05–13.19) | 0.883 | 0.811 (0.05–13.19) | 0.883 |
| Antiviral | 2.489 (2.03–24.436) | 0.434 | 2.489 (2.03–24.436) | 0.434 | 2.489 (2.03–24.436) | 0.434 |
| Steroid | 1.097 (0.426–2.763) | 0.844 | 1.097 (0.426–2.763) | 0.844 | 1.097 (0.426–2.763) | 0.844 |
| Supplement | 1.916 (1.029–3.567) | 0.036 | 1.916 (1.029–3.567) | 0.036 | 1.916 (1.029–3.567) | 0.036 |
| Antidepressant | 0.327 (0.153–0.698) | 0.004 \( d \) | 0.327 (0.153–0.698) | 0.004 \( d \) | 0.327 (0.153–0.698) | 0.004 \( d \) |
| SSRI/SSNRI | 0.302 (0.120–0.780) | 0.013 | 0.302 (0.120–0.780) | 0.013 | 0.302 (0.120–0.780) | 0.013 |
| SARI | 0.064 (0.008–0.505) | 0.009 | 0.064 (0.008–0.505) | 0.009 | 0.064 (0.008–0.505) | 0.009 |

Significant models are in bold. CPZE, chlorpromazine-equivalent daily dose; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SARI, serotonin-2 antagonist reuptake inhibitor.

a. Adjusted for age (categorical: 18–44 years (reference group), 45–54, 55–64, 65+); gender; ethnicity (categorical: African American (reference group), White, Other); psychiatric diagnosis (categorical: manic, depressive, mixed, other); and major depression (categorical: yes, no).

b. Adjusted as for footnote a, plus for the presence of diabetes, hypertension, respiratory illness or heart disease.

c. Benjamini–Hochberg adjusted \( P < 0.05 \).
d. Stepwise regression model \( OR = 1.0007 (1.0003–1.001) \), \( P = 0.049 \).
e. Stepwise regression model \( OR = 1.0007 (1.0003–1.001) \), \( P = 0.049 \).
of interleukin (IL)-1β and IL-6 in serum from patients taking antidepressants. Together these studies provide underlying mechanisms for the positive effect of antidepressant use on COVID-19 risk following potential exposure.

Typical antipsychotics have also been theorised to treat COVID-19 symptoms, but so far observational studies of antipsychotic treatment (chlorpromazine or haloperidol) have not demonstrated a beneficial effect of antipsychotic treatment on COVID-19 disease outcomes and overall mortality. In fact, one large cohort study of adult in-patients with a diagnosis of COVID-19 reported that antipsychotic treatment during COVID admission was significantly associated with a higher mortality rate. In our study, we observed a small, but significant association of increasing CPZE daily dose with increased COVID-19 infection, suggesting that use of some antipsychotics may also increase the risk of infection.

Consistent with a prior patient cohort study, we did not find an association between use of antihypertensive medication and COVID-19. Conversely, our findings do not support previous population cohort studies documenting a protective effect of vitamin D supplementation on COVID-19 risk. Intriguingly, Meltzer et al, recently reported data collected from a large urban medical centre, showing an increased risk for testing positive for COVID-19 in patients with a likely vitamin D deficiency, compared with those with sufficient levels. We and others have reported that vitamin D deficiency is frequent in psychiatric in-patient populations. Thus, an explanation for our finding of significantly more patients treated with supplements (including vitamin D) who were COVID-19 positive, may be because of underlying deficiencies that negatively have an impact on COVID-19 risk in this long-stay psychiatric facility.

**Limitations**

The main limitation of this study was the small size of the in-patient sample investigated. Additionally, severity outcomes following infection were not analysed, primarily because most patients with severe illness were transferred to local hospitals with limited ongoing status reporting in OMH records. Additionally, one of the main hypotheses of this study was that the potential for exposure to COVID-19 was uniform across the RPC facility. Although group programmes at RPC were discontinued in late March 2020, prior to this period we were not able to collect information on daily activities and interactions that could influence risk, which is a limitation of the retrospective chart review protocol. Of relevance to this point, we did not find a significant difference in COVID-19 infection status between patients with a current depressive episode, current mania or psychosis, suggesting that in this study there was not a significant impact on COVID-19 infection status by individual psychopathology.

**Implications**

A follow-on large cohort study that also evaluates characteristics of COVID-19 infection would be beneficial to confirm these initial but interesting findings, with the ultimate aim of developing medication-based COVID-19 prevention strategies for psychiatric in-patient settings.

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**Supplementary material**

Supplementary material is available online at https://doi.org/10.1192/bjp.2021.1053

**Data availability**

The data that support the findings of this study are available from the corresponding author (J.D.C.) upon reasonable request and approval by the Nathan S. Kline Institute institutional review board.

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**Author contributions**

Concept and design of the study was contributed to by C.L.C. and J.D.C. All authors contributed to the acquisition, analysis and interpretation of data. Statistical analysis was undertaken by C.L.C. Drafting of the initial manuscript was undertaken by C.L.C. and J.D.C. All authors contributed to the critical revision and review of the final manuscript.

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**Declaration of interest**

None.

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