Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

An analysis of the possible protective effect of antipsychotics for SARS-CoV-2 in patients under treatment for severe mental illnesses

Since the Severe Acute Respiratory Syndrome coronavirus type 2 (SARS-CoV-2) pandemic has sparked, it was supposed that inpatients with severe mental illnesses (SMI) could be at higher risk of developing the infection, as a consequence of their long stay in closed institutions, adding to the difficulty that SMI entails for compliance with prevention measures, like social distancing or mask wearing. Moreover, people with SMI usually tend to have unhealthy habits, including the use of high amounts of tobacco, a sedentary lifestyle, and an inappropriate diet. These factors, added to the metabolic adverse effects associated with the use of atypical antipsychotics, predispose to respiratory, cardiovascular, and metabolic diseases (Rossler et al., 2005). It is well known that all these conditions are associated with a severe course of SARS-CoV-2 disease (Chen et al., 2020; Grasselli et al., 2020; Zheng et al., 2020). Since the pandemic started in Argentina, we expected a growing number of infected inpatients among mental health hospitals. To prevent the SARS-CoV-2 spread among patients in closed institutions, a SARS-CoV-2 unit was created to receive all inpatients with a positive test and the absence of symptoms, or the presence of mild symptoms. To our surprise, these units received few patients, and even fewer patients required to be transferred to more complex general hospitals because of the disease severity. These events led us to ask if antipsychotics could have a protective effect on the disease.

It was reported that many psychotropics have antiviral properties, leading to consider psychotropic drugs as potentially effective in preventing either infection, or a poor SARS-CoV-2 disease outcome (Javelot et al., 2020; Villoutreix et al., 2020). Recently, Gordon et al. identified haloperidol as a candidate with an antiviral effect through its interaction with Sigma receptors (Gordon et al., 2020). Furthermore, it was proposed that phenothiazines could have an anti-SARS-CoV-2 effect as a consequence of their immunomodulatory effects (de Pellón Santamaría, 2020).

We conducted a case-control study across two closed mental health hospitals. We aimed to analyze if treatment with certain antipsychotics is associated with a protective effect for SARS-CoV-2 infection and/or with a better SARS-CoV-2 disease outcome in a group of inpatients with similar risk of contagion. Both hospitals have several units, and patients under each unit, share the bedroom, toilets and the dining room. Cases were defined as all inpatients who were positive for SARS-CoV-2 infection through the Polymerase Chain Reaction (PCR) test. These included, the index cases of each unit and closer contacts of the cases with a positive test carried out 7 days after a case detection if they did not have symptoms, or a positive test carried out before if a patient had symptoms. Closer contacts were defined as all patients staying at the same unit where a case was detected. Controls were defined as closer contacts with a negative PCR test, carried out 7 days after a case detection. All patients included in the study underwent antipsychotic treatment at least 4 weeks prior the PCR test. More information was obtained for both groups, such as sex, age, and type and number of risk factors for SARS-CoV-2. We also found out the antipsychotic treatment and we classified among 3 groups depending on the type of antipsychotic received: haloperidol, clozapine, or phenothiazines, in which patients under treatment with thioridazine, trifluoperazine, promethazine, chlorpromazine or levomepromazine were grouped. We also found out the daily dose (in mg) for each drug. Additional data were collected for cases, such disease severity, among asymptomatic, mild (patients with symptoms that did not require transfer to a general hospital), moderate (patients that required transfer to a general hospital because the equipment at the SARS-CoV-2 unit of the mental health hospital was not enough for the clinical manifestations), and severe/critical disease (patients admitted to an intensive care unit).

To analyze the possible association between the use of different antipsychotics and a positive diagnosis of SARS-CoV-2, univariate logistic regression models were adjusted and the odds ratio and its 95% confidence interval (CI95%) were estimated. To analyze the relationship between the use of different antipsychotics and the characteristics of the disease in patients with a positive diagnosis of SARS-CoV-2 the chi-square or Fisher's exact test was used for the qualitative variables and the t-student test for the quantitative variables. The Institutional Review Board of both hospitals approved the study protocol. This study did not require written informed consent as it did not involve a direct contact with subjects since the information was obtained from clinical records. One hundred twenty-one cases and 121 controls were recruited (Table 1). As a result, we found that patients under treatment with haloperidol did not have a protective effect for the infection, as the probability of a positive diagnosis of SARS-CoV-2 was 2.09 times higher in patients on haloperidol (CI95%: 1.21;3.66) compared to those who did not use this drug (Suppl. Table 2). Further analysis showed that higher doses of haloperidol were associated with less probability of infection compared to lower doses of this drug. However, the higher doses under study (30 mg) were not enough to obtain a protective effect (Suppl. Fig. 1). In our study, clozapine showed a protective effect for SARS-CoV-2 infection, as the probability of a positive diagnosis was 60% lower among users of this drug, compared to those who did not use it (OR:0.40, CI95%: 0.19;0.80), and this effect was dose-independent (Suppl. Fig. 1). Based on the incidence of SARS-CoV-2 among clozapine users and nonusers, the absolute risk reduction was 22%, and it was estimated that on average, 4.5 patients would have to receive clozapine treatment for one additional patient to not have SARS-CoV-2 infection. No statistically significant associations were found with phenothiazines. Regarding the course and outcome of the disease, only patients under treatment with clozapine were 2 times less symptomatic than patients without this drug (69.2% vs. 30.6%) (Suppl. Table 3).

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Table 1
Characteristics of the participants under study.

Characteristic	Cases (n = 121)	Controls (n = 121)	p
Age (mean (SD))	53.50 (15.96)	55.87 (13.50)	0.213
Sex = Male (%)	53 (43.8)	51 (42.1)	0.897
Number of risk factors (%)			
0	54 (44.6)	53 (43.8)	0.382
1	40 (33.1)	38 (31.4)	
2	21 (17.4)	17 (14.0)	
3 or more	6 (5.0)	13 (10.7)	
Type of risk factor			
Age 60 or more = Yes (%)	43 (35.5)	49 (40.5)	0.508
COPD[a] = Yes (%)	6 (5.0)	8 (6.6)	0.783
Other lung disease = Yes (%)	0 (0.0)	3 (2.5)	0.245
Cardiovascular[b] = Yes (%)	1 (0.8)	13 (10.7)	**0.002**
Diabetes = Yes (%)	19 (15.7)	18 (14.9)	0.999
Hypertension = Yes (%)	23 (19.0)	19 (15.7)	0.611
Immunosuppression[c] = Yes (%)	8 (6.6)	1 (0.8)	**0.042**
Type of antipsychotic			
Haloperidol = Yes (%)	48 (39.7)	29 (24.0)	**0.013**
Clozapine = Yes (%)	13 (10.7)	28 (23.1)	**0.016**
Phenothiazines = Yes (%)	54 (44.6)	51 (42.1)	0.795

Bold values statistically significance at $p<0.05$.
[a] Chronic obstructive pulmonary disease.
[b] heart failure, coronary heart disease (CHD), arrythmias and peripheral arteriopathy.
[c] Patients with HIV infection, or under corticosteroid or other immunosuppressant agents.

Based on our results, we found a protective effect for the infection and for the course of the disease in patients under treatment with clozapine. In the absence of previous data, it was assumed that patients developing SARS-CoV-2 who were under treatment with antipsychotics, especially with clozapine, could be at particular risk of suffering pneumonia. However, our results show less risk of infection and less symptoms severity, although the possible mechanism is unknown. We did not find a protective effect in a clinical sample under treatment with haloperidol, as it was previously reported at the in vitro study conducted by Gordon et al. Our findings make an important but preliminary observation and many questions on this topic remain unclear and need to be addressed with more studies with greater number of participants and replicated in other populations.

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CRediT authorship contribution statement

CR Prokopez and M Alomo designed the study and wrote the protocol. CR Prokopez, M Vallejos, R Farinola, LS Lopredo, LE Sfriso, RM Corral, and C Arce done the fieldwork. CR Prokopez and MJ Cuesta managed the literature search and analyses. L Chiapella undertook the statistical analysis, and CR Prokopez and MJ Cuesta wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

No author or immediate family member has financial relationships with commercial entities that might appear to represent a potential for conflict of interest.

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Appendix A. Supplementary data

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