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.

Schizophrenia Research 241 (2022) 140–141

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Olanzapine, risperidone and quetiapine: Do these atypical antipsychotics have a protective effect for SARS-CoV-2?

It was proposed that antipsychotics drugs (APDs) could have anti SARS-CoV-2 properties and different mechanisms were described to explain this antiviral effect (Gordon et al., 2020b; Javelot et al., 2020; Plaze et al., 2020). Two articles using the comparative viral-human protein-protein interaction map revealed that the sigma-1 receptor (SIGMA1R), located in the endoplasmic reticulum, caused reductions in SARS-CoV-2 replication, and proposed haloperidol as a potential anti SARS-CoV-2 for its effect on this receptor (Gordon et al., 2020a, 2020b). Another mechanism proposed by which antipsychotics could have antiviral properties is through the inhibition of clathrin-mediated endocytosis (de Pellón Santamaría, 2020; Villoutreix et al., 2020). Also, it was described that cationic amphiphilic drugs (CAD), like numerous APDs, may have antiviral effects (Vaugeois, 2020). On the other side, antipsychotics suppress the expression of pro-inflammatory cytokines and these anti-inflammatory effects are elicited through the reduction of pro-inflammatory cytokines production, like IL-1A, IL-6, and TNF-α (Obuchowicz et al., 2017). Growing evidence suggests that antipsychotics have anti-inflammatory properties that may attenuate the normal defensive function of the immune system and possibly reduce the uncontrolled inflammatory responses, such as seen in severe SARS-CoV-2 (Juncal-Ruiz et al., 2018). In recent years, it has been proposed that second-generation APDs, may enhance brain function in schizophrenia beyond the capability of these drugs to modulate microglia and astrocyte activation, reducing the levels of pro-inflammatory mediators (Tendilla-Beltrán and Flores, 2021). Second-generation APDs have anti-inflammatory, antioxidant, and neurotrophic properties, which can ameliorate neuroinflammation and improve neuroplasticity. For all of the above mentioned, it is being analyzed whether treatment with antipsychotics would exert an antiviral effect against SARS-CoV-2. Recently, we conducted a case-control study across two closed mental health hospitals located in the Autonomous City of Buenos Aires, Argentina. "*Braulio A. Moyano*" Neuropsychiatric Hospital is a mental health hospital which cares for female patients between 18 and 65 years old, and "*José T. Borda*" Hospital has similar characteristics but assists male patients. Both care for low-income and uninsured patients. Each of these hospitals has several inpatients units and when the pandemic started, and before the first inpatient case was detected, these units were locked. Inpatients only had contact with other inpatients from the same unit and with health personnel. Inpatients with acute or chronic psychosis were included. The study was carried out between May, when the first case was detected, until November 2020. It is important to note that no vaccines were available at that time. Cases were defined as all inpatients who were positive for SARS-CoV-2 infection through the Polymerase Chain Reaction (PCR) test, since the first case was detected in each hospital. Controls were defined as closer contacts of the cases and were obtained from the same unit where at least one case was detected. We assumed a similar risk of contagion for patients from a unit where a case was detected, as patients under each unit, share the bedroom, toilets and the dining room, and they are closed units. Controls were confirmed with a negative PCR test, carried out 7 days after the case detection. All patients included in the study were hospitalized and underwent treatment with one or more antipsychotics at least 4 weeks prior to the PCR test. In this study, we aimed to analyze the possible protective effect of phenothiazines, haloperidol and clozapine on the prevention of SARS-CoV-2 infection and/or on the clinical outcome of the disease (Prokopez et al., 2021). We included 121 patients with SARS-CoV-2 and 121 patients without the infection. We decided to study typical antipsychotics because it has been previously reported that they could have anti SARS-CoV-2 properties. We also included clozapine in our analysis because there were many concerns about the use of this drug and the risk of developing a worse course of SARS-CoV-2 because of its known risk of pneumonia as a side effect. In our study, we found a protective effect on the infection only in patients under treatment with clozapine. Taking into account this finding on an atypical antipsychotic and also a CAD, and later suggestions that atypical antipsychotics could have anti-SARS-CoV-2 effects (Crespo-Facorro et al., 2021; Tendilla-Beltrán and Flores, 2021), we conducted a further analysis of our database, exploring if others atypical antipsychotics could have a protective effect on SARS-CoV-2 infection and/or a better clinical outcome. We explored the possible protective effect of quetiapine, olanzapine and risperidone, which are the atypical antipsychotics available at the public mental health hospitals included. To analyze the possible association between the use of different antipsychotics and a positive diagnosis of SARS-CoV-2, taking into account the existence of polypharmacy, multivariate logistic regression models were used 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. Considering that 28 statistical tests were performed, with an initial significance level of 0.05, the significance level considered by Bonferroni correction was $0.05/28 = 0.0018$. Characteristics of the patients under study are shown in Table 1. As a result, we did not find a protective effect on the infection with none of these drugs. We also did not find differences in the course of the disease between none of these drugs (Suppl. Tables 2 and 3). Regarding our findings, it was previously reported that atypical antipsychotics, such as olanzapine, aripiprazole, paliperidone, risperidone, and quetiapine, do not bind SIGMA1R and they did not show antiviral activity in vitro (Gordon et al., 2020a, 2020b). However, clozapine does not bind SIGMA1R and its possible protective effect could be explained by a different mechanism, like being a CAD. Regarding quetiapine, it

https://doi.org/10.1016/j.schres.2022.01.035
Received 19 November 2021; Received in revised form 16 January 2022; Accepted 16 January 2022
Available online 24 January 2022

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
Essential hypertension = Yes (%)	23 (19.0)	19 (15.7)	0.611
Immunosuppression[c] = Yes (%)	8 (6.6)	1 (0.8)	0.042
Type of antipsychotic			
Olanzapine = Yes (%)	22 (18.2)	20 (16.5)	0.865
Risperidone = Yes (%)	43 (35.5)	34 (28.1)	0.270
Quetiapine = Yes (%)	23 (19.0)	21 (17.4)	0.868

[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.

was proposed a possible protective effect because of its chemical similarity with clozapine, its CAD properties (Villoutreix et al., 2020) and its affinity for ACE2 (Lu et al., 2021). However, we obtained negative results and, to our knowledge, there are not previous studies either on quetiapine or on risperidone in clinical populations.

Our findings make an important but preliminary observation and more studies on this topic are needed. Recently, Crespo-Facorro et al. conducted an exploratory investigation that provided further support to aripiprazole and its anti-SARS-CoV-2 properties (Crespo-Facorro et al., 2021), however, we could not include this drug because it is not available in our institutions.

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 has financial relationships with commercial entities that might appear to represent a potential for conflict of interest.

Acknowledgments

We thank Yanina Rojo, and Ayelen Noziglia and we also want to thank the authorities of both hospitals for allowing to carry out this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.01.035.

References

Crespo-Facorro, B., Ruiz-Veguilla, M., Vázquez-Bourgon, J., Sánchez-Hidalgo, A.C., Garrido-Torres, N., Cisneros, J.M., Prieto, C., Sainz, J., 2021. Aripiprazole as a candidate treatment of COVID-19 identified through genomic analysis. Front. Pharmacol. 12, 346.
Gordon, D.E., Hiatt, J., Bouhaddou, M., Rezelj, V.V., Ulferts, S., Braberg, H., Jureka, A.S., Obernier, K., Guo, J.Z., Batra, J., 2020. Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms. Science 370 (6521).
Gordon, D.E., Jang, G.M., Bouhaddou, M., Xu, J., Obernier, K., White, K.M., O'Meara, M. J., Rezelj, V.V., Guo, J.Z., Swaney, D.L., 2020. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 1–13.
Javelot, H., Petrignet, J., Addiego, F., Briet, J., Solis, M., El-Hage, W., Hingray, C., Weiner, L., 2020. Towards a pharmacochemical hypothesis of the prophylaxis of SARS-CoV-2 by psychoactive substances. Med. Hypotheses 144, 110025.
Juncal-Ruiz, M., Riesco-Dávila, L., de la Foz, V.O.-G., Martínez-Garcia, O., Ramírez-Bonilla, M., Ocejo-Viñals, J.G., Leza, J.C., López-Hoyos, M., Crespo-Facorro, B., 2018. Comparison of the anti-inflammatory effect of aripiprazole and risperidone in 75 drug-naïve first episode psychosis individuals: a 3 months randomized study. Schizophr. Res. 202, 226–233.
Lu, J., Hou, Y., Ge, S., Wang, X., Wang, J., Hu, T., Lv, Y., He, H., Wang, C., 2021. Screened antipsychotic drugs inhibit SARS-CoV-2 binding with ACE2 in vitro. Life Sci. 266, 118889.
Obuchowicz, E., Bielecka-Wajdman, A.M., Paul-Samojedny, M., Nowacka, M., 2017. Different influence of antipsychotics on the balance between pro-and anti-inflammatory cytokines depends on glia activation: an in vitro study. Cytokine 94, 37–44.
de Pellón Santamaría, Á.R., 2020. Psychosis treatment during COVID-19 pandemic and the potential role of phenothiazines: a call for research studies. J. Clin. Psychopharmacol. 40 (6), 641–642.
Plaze, M., Attali, D., Petit, A., Blatzer, M., Simon-Loriere, E., Vinckier, F., Cachia, A., Chrétien, F., Gaillard, R., 2020. Repurposing of chlorpromazine in COVID-19 treatment: the reCoVery study. Encéphale S35–S39.
Prokopez, C.R., Vallejos, M., Lopredo, L.S., Sfriso, L.E., Chiapella, L.C., Arce, C., Corral, R.M., Cuesta, M.J., Farinola, R., Alomo, M., 2021. An analysis of the possible protective effect of antipsychotics for SARS-CoV-2 in patients under treatment for severe mental illnesses. Schizophr. Res. 233, 99–100.
Tendilla-Beltrán, H., Flores, G., 2021. Due to their anti-inflammatory, antioxidant and neurotrophic properties, second-generation antipsychotics are suitable in patients with schizophrenia and COVID-19. Gen. Hosp. Psychiatry 71, 137–139.
Vaugeois, J.-M., 2020. Psychotropics drugs with cationic amphiphilic properties may afford some protection against SARS-CoV-2: a mechanistic hypothesis. Psychiatry Res. 291, 113220.
Villoutreix, B.O., Beaune, P.H., Tamouza, R., Krishnamoorthy, R., Leboyer, M., 2020. Prevention of COVID-19 by drug repurposing: rationale from drugs prescribed for mental disorders. Drug Discov. Today 25 (8), 1287–1290.

Cintia R. Prokopez[a,b,*], Romina Farinola[c], Miguel Vallejos[c], Lorena S. Lopredo[a], Luciano E. Sfriso[a], Luciana C. Chiapella[d,e], Claudio Arce[a], Ricardo M. Corral[c], Manuel J. Cuesta[f,h], Martín Alomo[a,g]
[a] *Braulio Aurelio Moyano Neuropsychiatric Hospital, Buenos Aires, Argentina*
[b] *Institute of Pharmacology, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina*
[c] *José Tiburcio Borda Hospital, Buenos Aires, Argentina*
[d] *National Scientific and Technical Research Council (Gordon, Jang et al.), Buenos Aires, Argentina*
[e] *Pharmacology Area, Faculty of Biochemical and Pharmaceutical Sciences, National University of Rosario, Santa Fe, Argentina*
[f] *Department of Psychiatry, Complejo Hospitalario de Navarra, Pamplona, Spain*
[g] *Faculty of Psychology, University of Buenos Aires, Buenos Aires, Argentina*
[h] *IdiSNA, Navarra Institute for Health Research, Pamplona, Spain*

[*] Corresponding author at: Paraguay 2155, Buenos Aires City, Argentina.
E-mail address: cprokopez@gmail.com (C.R. Prokopez).