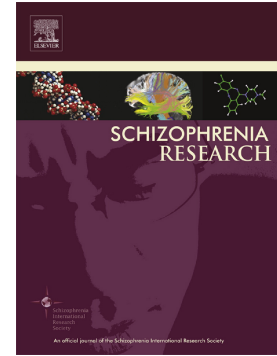


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Olanzapine, Risperidone and Quetiapine: Do these atypical antipsychotics have a protective effect for SARS-CoV-2?

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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, Jang et al. 2020, Javelot, Petriguet et al. 2020, Plaze, Attali 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, Hiatt et al. 2020, Gordon, Jang et al. 2020). Another mechanism proposed by which antipsychotics could have antiviral properties is through the inhibition of clathrin-mediated endocytosis (de Pellón Santamaría 2020, Villoutreix, Beaune 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, Bielecka-Wajdman 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, Riesco-Dávila 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, Vallejos 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, Ruiz-Veguilla 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. Table 2 and Suppl. Table 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, Hiatt et al. 2020, Gordon, Jang et al. 2020). 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 was proposed a possible protective effect because of its chemical similarity with clozapine, its CAD properties (Villoutreix, Beaune et al. 2020) and its affinity for ACE2 (Lu, Hou 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 arinipazole and its anti-SARS-CoV-2 properties (Crespo-Facorro, Ruiz-Veguilla et al. 2021), however, we could not include this drug because it is not available in our institutions.

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 ¹ = Yes (%)	5 (5.0)	8 (6.6)	0.783
Other lung disease = Yes (%)	0 (0.0)	3 (2.5)	0.245
Cardiovascular ² = 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 ³ = 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

¹Chronic obstructive pulmonary disease²heart failure, coronary heart disease (CHD), arrhythmias and peripheral arteriopathy³Patients with HIV infection, or under corticosteroid or other immunosuppressant agents.

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Disclosures

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

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Contributors

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 conducted the interviews. 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.

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