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Letter to the Editor

An overall protective effect of antipsychotic drugs against COVID-19 seems implausible

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To the editors,

We read with interest the study published by Canal-Rivero and colleagues (Canal-Rivero et al., 2021), which examined the prevalence and prognosis of COVID-19 in an epidemiological cohort of severe mental disorder (SMD) population treated with long-acting injectable (LAI) antipsychotics and compared them with a non-SMD sample. The study main finding was that SMD patients receiving LAI-antipsychotic treatment showed a lower risk of SARS-CoV-2 infection and a likely better COVID-19 prognosis. However, the classification as "antipsychotic drugs" is of clinical-pharmacological nature, but their biological effects and physical-chemical properties are heterogeneous. In our opinion, it appears unlikely to observe similar effects across different compounds, so the risks of COVID-19 should be variable (Gordon et al., 2020). The comparison among different antipsychotic medications would be relevant to clarify this issue (Ferraris et al., 2021).

In a previous letter (Ruiz de Pellon Santamaría, 2020), we called to conduct observational studies assessing the hypothesis of a protective effect of phenothiazine drugs against COVID-19. In this regard, a study comparing the electronic data of a SMD cohort exposed to different LAI antipsychotic treatments (unpublished data; publication in progress) was conducted. Our cohort study (approved from Euskadi Medications Ethics Research Committee on 9 March 2021; EOM2021002) included all adults aged 18 years or over with SMD (ICD-10 codification: F20-F29; F30-F31) who had been treated on LAI antipsychotic drugs from 1 February 2020 to 1 February 2021 (first COVID-19 case in Spain was detected on 24 February 2020) in all the Basque Country region (Spain). All patients not adequately receiving treatment were excluded. Finally, some potential confounding factors were considered (see Supplementary material).

Because of the analogous characteristics of both cohorts, our critical view towards the plausibility of their postulates and the interesting debate around the relationship of the SMD, antipsychotic drugs and COVID-19 (Toubasi, 2021); we tried a secondary analysis of our main study sample, with a similar approach to the study of Canal-Rivero. The public epidemiologic data of the entire population of the Basque Country concerning COVID-19 during the same study period (Basque Government Department of Health, 2021) were used as a comparator to our SMD sample data. We calculated odds ratios and confidence intervals stratified by age group with a Mantel-Haenszel adjustment. As a limitation, several potential confounders could not be adjusted in the analysis due to the unavailable data in the general population sample. Finally, we included a description of the residency under institutionalized or semi-institutionalized conditions in the SMD cohort, which we considered relevant to the discussion. All data were summarized together on Table 1.

A reduced incidence of COVID-19 among younger groups in the SMD sample relative to the general population was observed (similar findings to Canal-Rivero), but also an increased proportion in the older group (≥70 years). Both associations were statistically significant. The inconsistent results obtained among age groups did not suggest a general biological effect of the drugs. These differences could be better explained by other hidden risk factors of SARS-CoV-2 infection related to age and different from antipsychotic treatment which require further study. For example, we could speculate that the reduced social contact of the SMD individuals (Giacco et al., 2016) could act as a protective factor against the SARS-CoV-2 infection in the younger groups. In the older group, there were a large proportion of COVID-19 cases in our SMD sample among those residing in institutions. Perhaps the facilities with limited mobility and lack of interpersonal distance were related to a higher exposure to SARS-CoV-2 (Fallon et al., 2020; Vila-Corcoles et al., 2020). Moreover, COVID-19 related deaths were similar in SMD and general population cohorts, which did not suggest a protective effect of antipsychotic treatment. Almost all of the deaths occurred in the older group (≥70 years) and, in the SMD sample, mainly in institutionalized participants.

Since the complexity of COVID-19 infection is extensive, numerous confounding factors could be involved. Our study cannot clarify the role of antipsychotics in COVID-19 due to methodological limitations similar to those discussed by Toubasi (Toubasi, 2021). Nevertheless, the findings are relevant to the interpretation of the results of Canal-Rivero and colleagues. First, we suggest that age acted as a confounding factor in the

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Table 1
Comparison between the COVID-19 data of the general population of the Basque Country (Spain) and our SMD population sample on LAI-antipsychotic treatment:

	COVID-19 data of the Basque Country population ($n = 1,798,182$)[a]			COVID-19 data of the SMD sample on LAI treatment ($n = 3168$)		
Age group *(years)*	**20–49**	**50–69**	**≥70**	**18–49**	**50–69**	**≥70**
SARS-CoV-2 infections, *n (%)*	57,870/ 816836 (7.08%)	36,797/ 614088 (5.99%)	22,167/ 367258 (6.03%)	69/1803 (3.83%)	49/1136 (4.31%)	28/229 (12.23%)
Adjusted OR by age group (95% CI); *p*	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	**0.52 (0.41–0.66); <0.001**	**0.71 (0.53–0.94); 0.018**	**2.17 (1.46–3.22); <0.001**
Deaths related to COVID-19, *n (%)*	43/57870 (0.074%)	317/36797 (0.86%)	3116/22167 (14.06%)	0/69 (0%)	1/49[b] (2.04%)	5/28 (17.86%)
Adjusted OR by age group (95% CI); *p*	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	–	2.4 (0.3–17.4); 0.39	1.3 (0.5–3.5); 0.56
COVID-19 cases among institutionalized residency[c], *n (%)*	–	–	–	4/69 (5.80%)	14/49 (28.57%)	20/28 (71.43%)
COVID-19 related deaths among institutionalized residency[c], *n (%)*	–	–	–	0 (0%)	0 (0%)	4/5 (80.00%)

· SMD: Severe Mental Disorder; · LAI: Long-Acting Injectable Antipsychotic Treatment.

[a] Adapted from original: *["The epidemiological situation of COVID-19 in the Basque Country: Data accumulated until 31 January 2021"]* (in Spanish language) (Basque Government Department of Health, 2021). We excluded the age groups: "*0–19*" and "*Unknown age*". Follow-up period included from 1 February 2020 to 31 January 2021.

[b] The deceased was a 68-years-old man.

[c] The variable included several institutions where people reside stably, with reduced mobility and in a close proximity environment; from closed psychiatry units, nursing homes, residential apartments to charitable facilities. The short-stay social shelters were excluded.

risk of SARS-CoV-2 infection. Age is a key risk factor for COVID-19 severity (Williamson et al., 2020) and its influence on infection risk should also be considered. Second, regarding the severe implications of COVID-19, the infrequency of deaths in younger groups (<0.1% and <1%, respectively) and the low number of COVID-19 cases in their SMD population ($n = 9$; only 2 participants >65 years old) did not allow to study this association properly. Furthermore, the differences observed in severe COVID-19 outcomes were not statistically significant. Thus, despite the cautiousness of the authors in interpreting their results, we felt that the conclusion achieved about a likely better COVID-19 prognosis was insufficiently supported.

To conclude, further research is needed to clarify the role of antipsychotics on COVID-19. Future studies should concentrate on certain compounds with shared biological properties (Hoertel et al., 2021), rather than on antipsychotics as pharmacological group. We call for collaboration between international researchers to unify criteria and share data to clarify these controversies.

CRediT authorship contribution statement

All the authors have made substantial contributions for this paper.

Ethical statement

Ethical approval was obtained from Euskadi Medications Ethics Research Committee.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.12.020.

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