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

Can antipsychotic use protect from COVID-19?

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Canal-Rivero et al. (2021) recently reported in Schizophrenia Research counterintuitive results of an epidemiological retrospective study on the prevalence of COVID-19 and its complications in individuals older than 18 years with severe mental disorders (SMD) receiving long-acting injectable (LAI) antipsychotics. They found individuals with SMD on antipsychotics, who had good adherence to treatment, were less likely to contract COVID-19, and had better outcomes following infection, than the general population.

This study is an important contribution to the on-going debate on the interplay between COVID-19, mental illness and the psychotropic drugs we use for its treatment. Two prior epidemiological studies, using data from national patient databases in the United Kingdom (Yang et al., 2020) and South Korea (Lee et al., 2020), found that patients with psychotic disorders were at increased risk of severe complications of COVID-19. Unlike Canal-Rivero et al. (2021), however, neither study looked specifically at patients' antipsychotic treatment status at time of infection. Commenting on Yang et al.'s (2020) findings, Ferraris et al. (2021) argued that the use of antipsychotics could be the main reason for an association of poor outcomes of COVID-19 and psychotic disorders, but this was not confirmed. Canal-Rivero's results now provide evidence that antipsychotics may in fact protect against COVID-19 complications.

Interestingly, clinical reports arising from acute inpatient psychiatric services seem to support Canal-Rivero's observations. This has been the case in our own inner-London unit where, against our worst predictions, patients with SMD under our care who contracted COVID-19, many of whom had major risk factors for poor outcomes, all fully recovered without any complications or need for medical intervention (Boland and Dratcu, 2020; Dratcu and Boland, 2020). Despite their differing clinical profiles, they all shared in common the regular use of antipsychotic medication, adherence to which was ensured in the inpatient setting. Effective symptom control with antipsychotics may, in and of itself, counter-balance the vulnerabilities to severe COVID-19 associated with untreated SMD. However, antipsychotics may also confer direct protection against COVID-19, a hypothesis which is compatible with the pathophysiology of COVID-19 itself.

Cytokine storms seem to contribute to severe COVID-19 (Mehta et al., 2020). In the lungs, the ACE2 receptor, the principal receptor for the SARS-CoV-2 virus, is highly expressed on epithelial cells, through which the virus enters the organism. The ensuing innate cellular and cytokine inflammatory response in the infected lungs is capable of clearing the virus but can cause severe impairment of lung function. The overproduction of pro-inflammatory cytokines, together with the activation of the coagulation cascade and microthrombi formation in the lung vasculature, can lead to acute respiratory distress syndrome and later to multiorgan failure and death. Importantly, there is mounting evidence that antipsychotics are endowed with anti-inflammatory properties that may attenuate the normal defensive function of the immune system and possibly reduce uncontrolled inflammatory responses such as seen in severe COVID-19.

Evidence that cytokines could be influenced by antipsychotic treatment, perhaps in a dual mode (short- and long-term), has lent support to the notion that the anti-inflammatory action of antipsychotics may contribute to the treatment of schizophrenia itself (Mondelli and Howes, 2014). Zhou et al. (2021) further suggested that anti-inflammatory effects of antipsychotics may play a part in the treatment of psychotic symptoms. In a recent meta-analysis of 12 studies (961 patients with schizophrenia *vs* 729 controls) on the impact of antipsychotics on the production of serum interleukin-6 (IL-6), a pro-inflammatory cytokine, they found that antipsychotic treatment was associated with a decrease of IL-6 in patients. Conversely, trifluoperazine, a conventional antipsychotic, has been identified as a potential treatment option for microbe-induced septic shock after it was found to reduce inflammatory response by suppressing pro-inflammatory cytokines in mice (Park et al., 2019). More recently, Crespo-Facorro et al. (2021) suggested that aripiprazole, an atypical antipsychotic, could also be repurposed as a treatment for COVID-19 after a transcriptomic analysis revealed that it could revert effects induced by COVID-19 on gene expression in patients.

COVID-19 remains a novel disease which is not fully understood and for which no effective treatment is available. This makes it all the more pressing to further investigate the effects of antipsychotic use on COVID-19, as patients with SMD are a vulnerable group and this question remains largely unanswered. Additional epidemiological studies testing the replicability of Canal-Rivero's results would be welcome.

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Supplementary analysis of Canal-Rivero's data would also be helpful to examine whether any differences of outcome could be associated with the class of antipsychotics received (1st or 2nd generation) or the duration of treatment with LAI antipsychotics. Finally, further research is also warranted to ascertain the association, if any, of the anti-inflammatory effects of antipsychotics with COVID-19 outcomes.

Poor adherence to antipsychotic therapy is the most common cause of relapse in SMD, itself a major risk factor for contracting COVID-19. If, in addition to preventing relapse, antipsychotics are found to offer protection against COVID-19 and its complications, adherence to antipsychotic treatment could thus be doubly protective against the SARS-CoV-2 virus in SMD. This would give clinicians even more compelling reasons to ensure patients with SMD receive the treatment they require throughout the pandemic and beyond.

CRediT authorship contribution statement

Conceptualization: Luiz Dratcu
Writing- original draft: Xavier Boland
Writing - review and editing: Luiz Dratcu.

Declaration of competing interest

None.

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Luiz Dratcu*, Xavier Boland
Maudsley Hospital, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom

* Corresponding author.
E-mail addresses: Luiz.dratcu@slam.nhs.uk (L. Dratcu), XBoland@slam.nhs.uk (X. Boland).