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

Due to their anti-inflammatory, antioxidant and neurotrophic properties, second-generation antipsychotics are suitable in patients with schizophrenia and COVID-19

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One year after the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic, there have been almost 3 million deaths reported, and more than 130 million people infected. In addition to gastrointestinal and hematological complications, approximately one-third of patients with COVID-19 have presented neurological or psychiatric symptoms, such as anxiety, depression, dementia, and psychosis, during their recovery period [1].

Psychosis is the core symptom of schizophrenia, which has neuroinflammatory imbalance and its oxide-nitrosative consequences as prevalent neurobiological mechanisms (Fig. 1). Initial reports described increased risk for mortality in hospitalized COVID-19 patients with schizophrenia [2,3]. This phenomenon was attributed to the lack of adherence to public health measures (social distancing, hand washing, and the use of face masks) by patients, the limited availability of health services for patients with mental disease because of hospital saturations, or the delayed medical attention or treatment-seeking. Also, other comorbidity factors including obesity and diabetes which are prevalent in patients with schizophrenia [4], have been reported as risk factors to developing severe symptoms and increasing mortality in patients with COVID-19. However, neuroinflammation due to COVID-19 may be associated with disease outcomes in patients with schizophrenia. SARS-CoV-2 requires interaction with the angiotensin-converting enzyme 2 (ACE2) for cell docking, and the transmembrane serine protease 2 (TMPRSS2) for cell infection (Fig. 1). The nasal epithelium and the olfactory bulb may represent the gateway for SARS-CoV-2 to the brain [5], whose infection mechanisms are summarized in Fig. 1. Moreover, Wang et al., [6] demonstrated that apolipoprotein E4 (ApoE4), a glycoprotein involved in cholesterol metabolism highly expressed in the brain, increases SARS-CoV-2 infection susceptibility in neurons and astrocytes derived from human induced pluripotent stem cells (iPSC) and in brain organoids. In such a manner, the brain is an organ that is susceptible to SARS-CoV-2 infection, and neuroinflammation due to COVID-19 can generate neurologic or psychiatric symptoms or even aggravate them in diseases in which neuroinflammation is part of their pathophysiology, such as schizophrenia.

A couple of recent reports suggest that second-generation antipsychotic drugs (APDs) may prevent and protect against COVID-19 [7], and specifically aripiprazole seems to be a strong candidate [8]. Awaiting the replication of these results, and the elucidation of the mechanisms which contribute to the observed effects, Crespo-Facorro and colleagues suggest that second-generation APDs may have anti-inflammatory, antioxidant, and neurotrophic properties [9].

In recent years, it has been proposed that second-generation APDs, including risperidone, paliperidone, olanzapine, aripiprazole, and others, may enhance brain function in schizophrenia beyond their monoaminergic effects. This hypothesis is supported by the capability of these drugs to modulate microglia and astrocyte activation, reduce the levels of pro-inflammatory mediators, and enhance antioxidant systems such as the one regulated by nuclear factor E2-related factor 2 (Nrf2). Moreover, second-generation APDs stimulate neurotrophin activity, including brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) and enhance structural neuroplasticity in key brain regions for schizophrenia pathophysiology such as the prefrontal cortex (Fig. 1). The aforementioned effects have been demonstrated in vitro, in peripheral blood of patients with schizophrenia, and in the brain in animal models relevant for the study of the disease [9].

Despite second-generation APDs having lower rates of extrapyramidal side effects compared to first-generation APDs, these drugs still produce a myriad of side effects. Chronic treatment with second-generation APDs induces weight gain and alterations in carbohydrate metabolism, which lead to obesity and diabetes and generate cardiovascular complications, which are prevalent risk factors for severe outcomes and increase mortality in COVID-19. Moreover, clozapine (a second-generation APD) can induce neutropenia, which can be severe if the absolute neutrophil count (ANC) is not periodically assessed in patients [4]. Clozapine is the APD with the best efficacy outcome and the one prescribed for treatment-resistant schizophrenia which appears in approximately 34% of the patients [10]. Also, in respiratory tract infections, such as COVID-19, clozapine treatment may worsen the outcome by increasing the risk of pneumonia due to sialorrhea and subsequent aspiration [4]. However, since viral infections commonly

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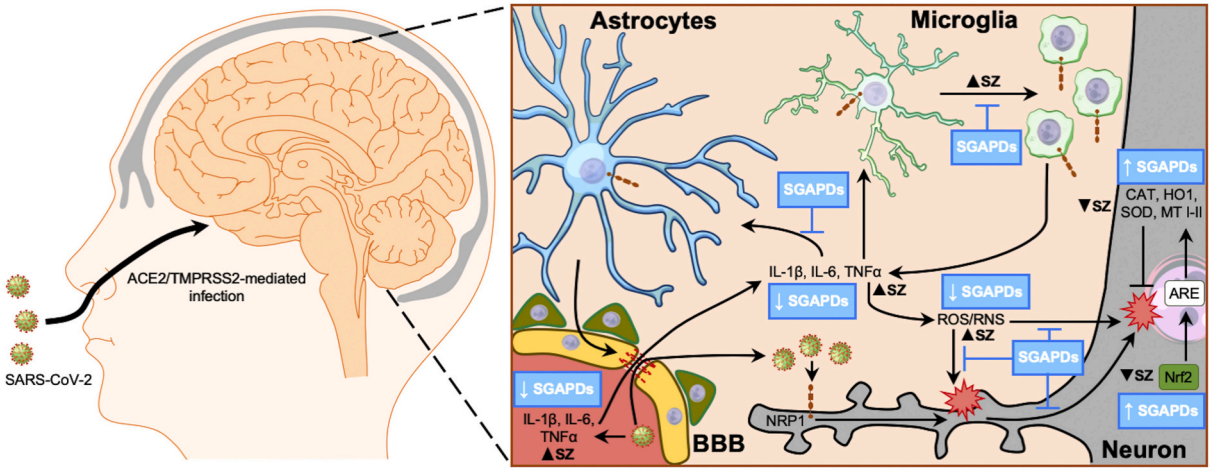

Fig. 1. SARS-CoV-2 brain infection, neuroinflammation, and the crosstalk with schizophrenia pathophysiological mechanisms.
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) requires interaction with the angiotensin-converting enzyme 2 (ACE2) for cell docking, and the transmembrane serine protease 2 (TMPRSS2) for cell infection via nasal-olfactory bulb infection or via systemic circulation breaking through the brain-blood barrier (BBB). Pro-inflammatory cytokines such as interleukin 1β (IL-1β), IL-6, and tumor necrosis factor α (TNFα) as an inflammatory response to a SARS-CoV-2 infection increases BBB permeability. In the brain, SARS-CoV-2 infects vascular endothelial cells through basigin (BSG) or neurons, astrocytes, and microglia through a neuropilin-1 (NRP1)/cathepsin-mediated mechanism. SARS-CoV-2 infection in astrocytes compromises BBB function, allowing blood immune cell infiltration, pro-inflammatory cytokine diffusion to the brain, and the facilitation of SARS-CoV-2 entry into the brain. Activated microglia change from ramified to ameboid morphology and stimulate the synthesis of pro-inflammatory mediators which consequently increase the reactive oxygen and nitrogen species (ROS/RNS). ROS and RNS damage membranes and DNA, leading to cell death. In schizophrenia, there are also increased levels of pro-inflammatory mediators, increased microglial activation, and increased levels of ROS/RNS. Moreover, in schizophrenia, there are reduced levels of antioxidant molecules modulated by the nuclear factor E2-related factor 2 (Nrf2) activity such as catalase (CAT), heme-oxygenase 1 (HO1), superoxide dismutase (SOD), and metallothionein I-II (MT I-II). This compromises antioxidant response and favors oxidative/nitrosative stress, which disrupts neuroplasticity. Second-generation antipsychotic drugs (SGAPDs) decrease IL-1β, IL-6, and TNFα, and may not only reduce astrocytes and microglia activation, but also the ROS/RNS levels. Moreover, SGAPDs increase antioxidant Nrf2-related molecules. Consequentially, SGAPDs ameliorate oxidative/nitrosative stress and enhance neuroplasticity.

induce neutropenia, further studies must analyze whether neutropenia aggravates COVID-19 in patients with schizophrenia and how second-generation APDs treatment modulates it.

It is important to clarify that the COVID-19 pandemic may increase the possibilities of schizophrenia pharmacotherapy changes, interruptions, or suspension (because of medicine shortage, logistic delivery impediments, presence of side effects, etc.). In such a manner, clinicians must be careful in how the second-generation APDs dose is gradually reduced for these purposes, since this is crucial for the best outcome of the disease.

In conclusion, COVID-19 and schizophrenia share neuroinflammation as relevant pathophysiological mechanisms, which may synergically worsen the outcome of both diseases. Second-generation APDs have anti-inflammatory, antioxidant, and neurotrophic properties which can ameliorate neuroinflammation and improve neuroplasticity. Thus, second-generation APDs seem to be suitable in patients with schizophrenia and COVID-19. However, chronic treatment with second-generation APDs is associated with the development of some risk factors for severe COVID-19 such as obesity and metabolic syndrome. This highlights the importance of adhering to the guidelines for the use of APDs, as well as constant monitoring of side effects, for effective pharmacotherapy.

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