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

Covid-19 treatment-induced neuropsychiatric adverse effects

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Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) was first notified in Wuhan, China, in December 2019, and has rapidly spread worldwide, due to its high transmission rate. It has been identified as the causative agent of the now termed coronavirus disease (COVID-19), which can range from mild condition to potentially fatal respiratory distress syndrome [1]. There is no vaccine or specific antiviral drug regime used to treat ill patients. However, the therapeutic potential of certain drugs used for other diseases has led to their off-label use for COVID-19, such as antiretroviral drugs (lopinavir-ritonavir, darunavir, remdesivir), corticosteroids, biological treatments (tocilizumab), antiparasitics (hydroxychloroquine and nitazoxanide) and antibiotics (azithromycin) [2]. COVID-19 represents a major challenge in the field of psychiatry, as both the virus and the medications used to treat it may induce neurologic and psychiatric symptoms [3]. The main aim of this letter is to briefly review COVID-19 treatment-induced neuropsychiatric adverse effects.

Steps in coronavirus replication are potential targets for Antiretroviral drugs. These drugs may produce undesirable effects on the central and peripheral nervous systems, highly variable in frequency and severity, depending on the biological mechanism involved. Cytochrome p450 enzymes are affected by protease inhibitors (lopinavir, ritonavir, darunavir) which could lead to neurotoxicity by altering plasma concentrations of multiple psychotropic drugs. Despite their poor penetration through the blood-brain barrier they are inherently neurotoxic, showing perioral (25%) and peripheral (7%) paresthesias, as well as changes in taste (12%) since the first month of treatment [4]. The lopinavir-ritonavir combination has been associated with bilateral sensorineural hearing loss after 4 weeks of treatment, and with the appearance of depressive symptoms. Darunavir, however, has not shown increased neurotoxicity [4].

Corticosteroids modulate hyper inflammation and inhibit immune responses that are vital for the host defense against the virus. However, side-effects are common, appearing in up to 90% of patients with more than 60 days of treatment, according to the dose range and route of administration. Memory deficits and cognitive impairment have been described, probably in relation to the high number of corticosteroid receptors in the hippocampus. Short course high-dose corticosteroid treatment, as occurs in COVID-19, may cause delirium and changes in mood (with a frequency of up to 52% of patients treated with more than 20 mg a day of prednisone during 3 months) [5], being mania and hypomania more frequently observed than depression.

Azithromycin is an antibiotic that has been proven to be active in vitro against Zika and Ebola viruses by interfering with their protein synthesis. The distinctive feature of azithromycin is its high and sustained concentration in brain tissue, presumably due to its amphipathic properties and high volume of distribution. Neurological adverse events reported in premarketing clinical trials were mild, occurring in less than 1% of patients. Serious adverse neuropsychiatric effects such as delirium have been rarely reported in adults [6].

Despite there is no clear evidence of its efficacy it seems relevant to mention chloroquine and related agents, whose compassionate use is based on the role that they could have in stopping the cytokine storm which contributed to acute respiratory distress caused by SARS-CoV-2. These treatments are able to induce neuropsychiatric symptoms from mild (mood lability, nervousness) to severe degree (psychosis, suicidal tendencies) and the high dose administration is a predictor of complications [7].

Tocilizumab is a humanized monoclonal antibody approved for the treatment of rheumatoid arthritis (RA). It plays a significant role in IL-6 blockade, which could contribute to reduce the inflammatory cascade in COVID-19. Inhibition of IL-6 may also be responsible for improvements in depression, fatigue and pain, common extra-articular features of RA [8]. Improvements in cognition have also been demonstrated in psychotic disorders such as schizophrenia, although no changes in psychopathology have been described [9].

Treatments with interferon, remdesivir and nitazoxanide are also being repurposed. In particular, remdesivir, a nucleotide analogue prodrug, is considered a promising antiviral agent in the treatment of critically ill patients, as it causes a blockade in viral RNA polymerases reducing the viral load and alleviating pathological damage to lung tissue. Although there is no evidence of neuropsychiatric side-effects, a close monitoring is necessary in order to minimize risks [10].

Therapeutic recommendations and guidelines for covid-19 are still constantly changing. With several ongoing clinical trials at this time, it is expected that some drugs will be discarded while new ones will increase the available therapeutic arsenal. Given the increasing spread of COVID-19, it is important that psychiatrists stay up-to-date on treatments and remain aware of the occurrence of neuropsychiatric side effects, even not previously described.

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Declaration of competing interest

The authors declare they have no competing conflicts of interest regarding this paper.

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C.A. Carrajo García*, E.B. Alonso Sánchez, D. Hernández Huerta, J. Gómez-Arnau
Department of Psychiatry, University Hospital Ramón y Cajal, Madrid, Spain
E-mail address: carmenaldara@hotmail.com (C.A.C. García).

* Corresponding author at: Department of Psychiatry, University Hospital Ramón y Cajal, Ctra. Colmenar Viejo, km 9.100, 28034 Madrid, Spain.