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LETTER TO THE EDITOR

Comment on: "Fluvoxamine for the Early Treatment of SARS-CoV-2 Infection: A Review of Current Evidence"

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Dear Editor,

We read with great interest the Current Opinion paper by Facente et al. [1], who promptly reviewed the available literature assessing fluvoxamine administration as a repurposed drug for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The current evidence [2–4] supports the promising role of fluvoxamine as an effective early treatment option for preventing clinical deterioration, hospitalization, mortality, and long-term morbidity due to SARS-CoV-2 infection. This protective effect over severe coronavirus disease 2019 (COVID-19) outcomes can result from potential anti-inflammatory, immune-modulatory, and antiviral mechanisms related to fluvoxamine. Fluvoxamine is a selective serotonin reuptake inhibitor antidepressant, commonly used to treat major depressive disorder and obsessive-compulsive disorder with an efficacy, tolerability, and a side-effect profile similar to other selective serotonin reuptake inhibitors [5]. Even if all the reviewed studies [2–4] have a sound methodology and provide pivotal findings for the clinical management of COVID-19, none of them has investigated if the beneficial effect of fluvoxamine on COVID-19 prognosis may be mediated by its direct antidepressant effect.

SARS-CoV-2 infection is associated with an immediate psychopathological distress, resulting in clinical depression in one in three patients during the early phases of the disease [6]. The underlying mechanisms are most likely related to the COVID-19-associated systemic inflammation. High interleukin-1β and C-reactive protein levels, and neutrophil-to-lymphocyte ratio and systemic immune-inflammation index contribute to the pathophysiological onset of depressive symptoms soon after infection [7, 8]. Notably, depressive symptomatology is independently associated with an increased risk of hospitalization, intensive care unit admission, need for mechanical ventilation, and in-hospital mortality in pneumonia and respiratory diseases [9–11]. Even in COVID-19, comorbid depression was found to be associated with an increased risk of hospitalization, intensive care unit admission, and mortality [12, 13]. In contrast, antidepressant treatments have been associated with reduced all-cause mortality in the general population, and interventions for depression integrated into medical care settings have been shown to reduce hospitalization and related healthcare costs [9, 14].

In this context, we believe that the effect of fluvoxamine on depressive symptomatology should be investigated as a parallel relevant mechanism in improving COVID-19 hospitalization and severe outcome. A rapid improvement of depressive symptoms can be observed already in the first week of fluvoxamine administration [15]. In COVID-19, fluvoxamine serotoninergic (5-HT) and anti-inflammatory properties can be particularly effective in counteracting the depression onset rapidly triggered by SARS-CoV-2 infection-related systemic inflammation. Moreover, fluvoxamine could directly neutralize the indoleamine 2,3-dioxygenase-mediated detrimental effects of inflammation by potentiating

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5-HT neurotransmission, modulating tryptophan metabolism, and reducing the excitotoxic quinolinic acid [16]. In line with these hypotheses, we found preliminary evidence of a rapid antidepressant effect of a wide range of selective serotonin reuptake inhibitors in post-COVID depressive episodes [17]. We also observed that treatment with cytokine-blocking agents during acute COVID-19 showed a protective effect against depression, proportional to the dampening of systemic inflammation [18]. Moreover, while our recent meta-analytic evidence showed a higher risk of COVID-19 severe outcome in mood disorders, pre-existing antidepressant treatment was not significantly associated with a worse prognosis [12].

Given the importance of the topic, further investigations are needed to explore whether the direct antidepressant effect of fluvoxamine could reduce the risk for a vicious cycle of infection, inflammation, depression, hospitalizations, and poor prognosis not only in COVID-19, but also in other medical conditions involving similar pathopsychological processes. Thus, considering that several studies exploring the efficacy of fluvoxamine for the treatment of SARS-CoV-2 infection are still ongoing [1], we recommend all clinical trials of serotonergic compounds repurposed against COVID-19 to assess depressive symptomatology at baseline and follow-up assessments.

Declarations

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Conflicts of interest/competing interests MGM, BV, LDP, FB, and RZ have nothing to declare.

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Author contributions All authors contributed equally to this letter.

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