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# Considerations before the decision-making including fluvoxamine as a treatment option in guidelines on the management of COVID-19

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A previous study found that due to the fear of coronavirus disease 2019 (COVID-19) contagion, severe clinical outcomes and the lack of effective treatments, many COVID-19 patients inevitably suffer from mental health effects [e.g. depression and post-traumatic stress symptoms (Bo et al., 2021)]. The possibility that this could suppress immune suppression function (Sperner-Unterweger, 2005) was however ignored in two recently published randomized control trials (RCTs) that found fluvoxamine was associated with reduced severity of COVID-19 and improved outcomes such as the risk of hospitalization (Lenze et al., 2020; Reis et al., 2021). These trials have received considerable attention, such as being mentioned in the NIH COVID-19 treatment guidelines in 2021 (Facente, Reiersen, Lenze, Boulware, & Klausner, 2021). However, before including fluvoxamine as a treatment option in any clinical guidelines on the management of COVID-19, two key questions remained to be addressed: is fluvoxamine the only psychotropic medication with anti-COVID-19 properties, and what is the underlying mechanism of such therapeutic action?

The first question was not examined by the RCTs (Lenze et al., 2020; Reis et al., 2021) as different COVID-19 treatment arms using fluvoxamine and other psychotropic medications to compare with placebo were not included. In contrast, two other cohort studies have partly addressed this concern. One cohort study (Oskotsky et al., 2021) found that compared with controls, the risk of mortality was significantly reduced among COVID-19 patients prescribed with any selective serotonin reuptake inhibitor (SSRI) antidepressants (14.6% v. 16.6%;  $p = 0.03$ ), particularly fluoxetine (9.8%;  $p = 0.03$ ), and fluoxetine or fluvoxamine (10.0%;  $p = 0.04$ ). The other cohort study (Hoertel et al., 2021) found that both SSRI (HR: 0.51;  $p < 0.001$ ) and non-SSRI antidepressants (HR: 0.65;  $p = 0.018$ ), particularly fluoxetine, paroxetine, escitalopram, venlafaxine, and mirtazapine, were significantly associated with reduced risk of intubation or death in COVID-19 patients. Therefore, it would appear that apart from fluvoxamine, at least several other antidepressants have potential anti-COVID-19 properties.

The mechanism of action of antidepressants in terms of improving COVID-19 outcomes is not clear. In the two RCTs comparing fluvoxamine and placebo (Lenze et al., 2020; Reis et al., 2021), the assumed reasons for its anti-COVID-19 action included the anti-inflammatory action through activating the S1R, increased melatonin plasma levels, antiviral effects via lysosomotropic properties, modulation of the IRE1 effects on autophagy, and SSRI inhibition of platelet activation. As other antidepressants also have the abovementioned anti-inflammatory properties, the anti-COVID-19 action is thus not limited to fluvoxamine (Hoertel et al., 2021; Oskotsky et al., 2021). Other possible mechanisms of action of antidepressants in improving COVID-19 outcomes included reduced acid sphingomyelinase activity and plasma levels of several inflammatory mediators (e.g. IL-6, IL-10, TNF- $\alpha$ , and CCL-2) (Hoertel et al., 2021; Oskotsky et al., 2021).

Further, the moderating effects of negative emotions on the immune function was not addressed in the previous fluvoxamine studies (Hoertel et al., 2021; Lenze et al., 2020; Oskotsky et al., 2021; Reis et al., 2021). Due to the fear of COVID-19 contagion, severe clinical outcomes and the lack of effective treatments, many COVID-19 patients inevitably suffer from mental health effects including depression, anxiety, distress, and post-traumatic stress symptoms (Zhao et al., 2021). Acute negative emotions could stimulate the hypothalamic-

pituitary–adrenal (HPA) axis and increase corticotropin levels, leading to immune suppression and dysfunction (Sperner-Unterweger, 2005). Antidepressants could ameliorate negative emotions effectively, which in turn could reverse the suppressed immune response (Schmidt, Kirkby, & Lichtblau, 2016) and result in better outcomes of COVID-19 compared to placebo. The moderating role of negative emotions on the anti-COVID-19 effect could be readily tested in RCTs. For example, standard scales of negative emotions could be used in the antidepressant and placebo groups, and their scores are controlled for as covariates when the primary outcomes between the two groups are compared. If the antidepressant demonstrates superiority, this would indicate its advantage in treating COVID-19 independent of the moderating effects of negative emotions.

Finally, other than antidepressants, certain antipsychotic medications (Kato et al., 2011) and mood stabilizers (Leu et al., 2017) also have anti-inflammatory actions as well as therapeutic effects on negative emotions. Therefore, their potential anti-COVID-19 properties should also be examined along with fluvoxamine and other antidepressants.

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