

## CORRESPONDENCE



# Repurposing antidepressants inhibiting the sphingomyelinase acid/ceramide system against COVID-19: current evidence and potential mechanisms

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**TO THE EDITOR:**

We read with great interest the correspondence letters of Salles et al. [1] and Stip et al. [2], following our multicenter observational retrospective study that showed a substantial association between antidepressant use and reduced risk of intubation or death in 7230 patients hospitalized for COVID-19 [3]. Salles et al. suggest that combining an antidepressant such as fluoxetine with rimonabant, an inverse agonist of CB1 cannabinoid receptor, may be useful against COVID-19, thanks to the antiviral and anti-inflammatory effects of the former and the potentially complementary anti-inflammatory properties of the latter. Stip et al. significantly summarized the growing body of evidence of the potential benefit of different psychotropic medications in COVID-19 and their possible underlying mechanisms. They suggested further elucidation of ways that certain antidepressants may be acting in this indication. These two letters challenge us on the potential mechanisms that may underlie the potential positive effect of certain antidepressants on the course of COVID-19. This knowledge is crucial to help identify the more promising molecules for COVID-19 and help design trials evaluating these molecules.

Since the initial release of our results in July, 2020 [4], several important studies have led to a substantially improved understanding of the mechanisms that may underlie the potential positive effect of certain antidepressants.

First, molecules such as fluoxetine, fluvoxamine, paroxetine, escitalopram, or amitriptyline are antidepressants that belong to the group of functional inhibitors of acid sphingomyelinase (ASM), called FIASMA [5–7], that also comprises other medications commonly used in clinical practice, such as antihistamine medications (e.g., hydroxyzine, promethazine), calcium channel blockers (e.g., amlodipine, bepridil), and mucolytics (e.g., ambroxol [7]). These pharmacological compounds in vitro and in vivo inhibit ASM, an enzyme that catalyzes the hydrolysis of sphingomyelin into ceramide and phosphorylcholine [5–7]. Preclinical evidence indicates that SARS-CoV-2 activates the ASM/ceramide system, resulting in the formation of ceramide-enriched membrane domains that facilitate viral entry and infection by clustering ACE2, the cellular receptor of SARS-CoV-2 [6, 7]. The inhibition of the ASM/ceramide system by FIASMA antidepressants prevented infection of Vero E6 cells with SARS-CoV-2. Importantly, the reconstitution of ceramides in cells treated with these antidepressants restored the infection [6]. In healthy volunteers, oral

administration of a low dose of the FIASMA antidepressant amitriptyline prevented infection of freshly isolated nasal epithelial cells with SARS-CoV-2 spike protein pseudotyped particles within 2 h, which was also restored after the reconstitution of ceramides in these cells [6]. These preclinical data were confirmed by another study that demonstrated an inhibition by fluoxetine of SARS-CoV-2 infection in cultured epithelial cells [8]. The potential benefit of FIASMA treatments among patients hospitalized for severe COVID-19 was recently explored in an observational multicenter retrospective study [9]. Therein, it was reported that taking a FIASMA medication upon hospital admission was associated with substantially reduced likelihood of intubation or death. This association was not specific to one FIASMA class (e.g., FIASMA antidepressants) or medication (e.g., fluoxetine) [9]. A similar significant association was found in another observational multicenter retrospective study conducted in patients with psychiatric disorders and hospitalized for severe COVID-19 [10]. A retrospective observational study also established a positive association between chronic administration of FIASMA and reduced mortality in COVID-19 hospitalized patients that was significant for the FIASMA amlodipine [11]. In a double-blind randomized clinical trial, outpatients treated with the FIASMA antidepressant fluvoxamine compared with placebo had a lower risk of clinical deterioration over 15 days of treatment [12]. The results of a prospective real-world evidence study also support this observation [13]. Finally, plasma markers of ceramide metabolism were found to be associated with respiratory severity and to correlate with inflammation in 49 patients hospitalized for COVID-19 [14]. Taken together, these results show the potentially crucial importance of the ASM/ceramide system as a treatment target in COVID-19, a mechanism likely to be shared by all variants [15]. They also support the continuation of FIASMA medications during SARS-CoV-2 infection [9].

Second, anti-inflammatory properties of several antidepressants may have important value in regulating inflammation by inhibiting cytokine production in COVID-19. These anti-inflammatory effects might be explained (i) by the high affinity of certain antidepressants, such as fluvoxamine or fluoxetine, for Sigma-1 receptors [12, 16], which have been shown to restrict the endonuclease activity of an Endoplasmic Reticulum (ER) stress sensor called Inositol-Requiring Enzyme1 and to reduce cytokine expression without inhibiting classical inflammatory pathways, and/or (ii) by the inhibition of ASM in endothelial cells and the immune system [6, 7].

Finally, other potential mechanisms include reduction in platelet aggregation, decreased mast cell degranulation, interference with endolysosomal viral trafficking and increased melatonin levels [16].

These different but potentially interrelated mechanisms shared by several antidepressants such as fluvoxamine or fluoxetine,

might collectively lead to anti-SARS-CoV-2 effects while diminishing coagulopathy and cytokine storm consequences, which are known hallmarks of severe COVID-19.

Following these preclinical, observational and clinical converging findings, and as stated by Salles et al. [1] and Stip et al. [2], large-scale double-blind placebo-controlled randomized clinical trials of FIASMA antidepressants for COVID-19 at different stages of the disease, either alone or combined with medications that have shown preliminary evidence of potential efficacy and good tolerability, are urgently needed. Fluoxetine and fluvoxamine, which display high in vitro inhibition effect on ASM, showed potential positive effects at usual antidepressant doses, and are easy to use, including high safety margins, good tolerability, widespread availability and low cost, should be considered compelling treatments to prioritize for phase 3 trials against COVID-19 [9].

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## AUTHOR CONTRIBUTIONS

Writing—original draft: NH; Writing—review & editing: MS-R, CG, EG, JK, AC, KAB, AMR, EJJ, DS, CL, FL.

## COMPETING INTERESTS

NH, MS-R, EG, JK, AC, and FL are inventors on a patent application related to methods of treating COVID-19, filed by Assistance Publique—Hôpitaux de Paris in France. NH has received personal fees and nonfinancial support from Lundbeck, outside the submitted work. AMR and EJJ are inventors on a patent application related to methods of treating COVID-19, which was filed by Washington University in St. Louis. EJJ has received consulting fees from Johnson and Johnson, and Jazz Pharmaceuticals. AMR has received grant or research support from the McDonnell Center for Systems Neuroscience, the McDonnell Center for Cellular and Molecular Neurobiology, and the Taylor Family Institute for Innovative Psychiatric Research. DS is the Chief Medical Officer and CEO of Enable Biosciences, a CLIA certified Federal clinical reference laboratory that performs COVID-19 antibody testing. CL reports personal fees and nonfinancial support from Janssen-Cilag, Lundbeck, Otsuka Pharmaceutical, and Boehringer Ingelheim, outside the submitted work. FL has received speaker and consulting fees from Janssen-Cilag, Euthérapie-Servier, and Lundbeck, outside the submitted work. Other authors declare no competing interests related to this work.

## ADDITIONAL INFORMATION

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