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Do the Selective Serotonin Reuptake Inhibitor Antidepressants Fluoxetine and Fluvoxamine Reduce Mortality Among Patients With COVID-19?

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In a large, multicenter, retrospective cohort study of 83 584 patients with laboratory-confirmed COVID-19 who had an emergency department or urgent care visit or were admitted for observation or hospitalized across 87 health care centers in the US, Oskotsky et al[1] observed an association between selective serotonin reuptake inhibitor (SSRI) administration and reduced mortality in 3401 patients with COVID-19 compared with 6802 matched control patients who were not given SSRIs but shared similar sociodemographic characteristics, medical comorbidities, and medication indication. Interestingly, among SSRIs, a significant association between treatment and reduced mortality was observed for fluoxetine and for fluoxetine or fluvoxamine. These results confirm and expand on prior findings from observational, preclinical, and clinical studies suggesting that certain SSRI antidepressants, including fluoxetine or fluvoxamine, could be beneficial against COVID-19.[2,3]

First, a prior multicenter, retrospective, observational study involving patients who were hospitalized for COVID-19 in Paris, France, indicated that antidepressant use—particularly fluoxetine use—was associated with reduced risk of intubation or death.[2] Second, several preclinical studies support a substantial in vitro efficacy of different SSRI- and non-SSRI antidepressants—particularly fluoxetine—against SARS-CoV-2 with different host cells (eg, Vero E6, Calu-1, Calu-3, HEK293T-ACE2-TMPRSS2) and human lung epithelial cells as well as with different variants of the virus.[4] Finally, 3 clinical trials, including 2 randomized, placebo-controlled trials, found an association between the use of fluvoxamine for 10 to 15 days and a reduced risk of clinical deterioration among outpatients with COVID-19. In a double-blind, randomized, placebo-controlled trial involving 152 outpatients with COVID-19, patients who were treated with fluvoxamine had a significantly lower risk of clinical deterioration over 15 days of treatment than those who received a placebo.[5] The results of a prospective, real-world evidence study of 113 outpatients with COVID-19 also support this observation.[6] Finally, the preliminary results of the multicenter randomized placebo-controlled TOGETHER trial showed a significant and substantial reduction in risk of hospitalization or retention in a COVID-19 emergency setting due to COVID-19 associated with fluvoxamine use vs placebo in 1472 outpatients with COVID-19 who were at a high risk for developing severe complications.[7]

Taken together, these convergent results from observational, preclinical, and clinical studies performed by different research teams call into question the mechanisms that underlie this potential positive effect of certain antidepressants against COVID-19. Several studies have led to a substantially improved understanding of those potential multiple and likely interrelated mechanisms.[3,4,8]

First, most SSRI antidepressants, including fluoxetine and fluvoxamine, belong to the group of functional inhibitors of acid sphingomyelinase (FIASMA).[4] In addition to SSRI antidepressants, FIASMA comprises other medications frequently used in clinical practice, including certain non-SSRI antidepressants (eg, amitriptyline), antihistamines (eg, hydroxyzine), calcium channel blockers (eg, amlodipine), cholesterol medications (eg, fenofibrate), and mucolytics (eg, ambroxol). In vitro and in vivo, these pharmacological compounds inhibit acid sphingomyelinase (ASM), an enzyme that catalyzes the hydrolysis of sphingomyelin into ceramide and phosphorylcholine.[4] Preclinical data indicate[4] 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, and the release of proinflammatory cytokines. The inhibition of the ASM-ceramide system by FIASMA antidepressants prevents infection of Vero E6 cells with

SARS-CoV-2. Importantly, the reconstitution of ceramides in cells treated with these antidepressants restores the infection.[4] In healthy volunteers, oral use of the FIASMA antidepressant amitriptyline prevents infection of freshly isolated nasal epithelial cells, which is also restored after the reconstitution of ceramides in these cells. In an observational multicenter retrospective study, use of a FIASMA medication upon hospital admission was associated with a substantially reduced risk of intubation or death.[9] Finally, plasma levels of ceramides were found to correlate with disease clinical severity and with inflammation markers in patients with COVID-19.[4] Interestingly, among SSRIs, the magnitude of the in vitro inhibition of ASM, which varies across molecules (eg, fluoxetine > paroxetine > fluvoxamine > other SSRIs), appears to correlate with the magnitude of the in vitro antiviral effect against SARS-CoV-2.[4] The findings of Oskotsky et al,[1] which suggest that use of fluoxetine and fluoxetine or fluvoxamine is significantly associated with reduced mortality compared with other SSRIs, are consistent with the results of a prior observational study[2] and seem to provide further support for this potential mechanism. Taken together, these results show the potentially crucial importance of the ASM-ceramide system as a treatment target in COVID-19.[2,9]

Second, the anti-inflammatory properties of SSRIs may underlie their potential action against COVID-19 and could be explained by (1) the high affinity of certain SSRIs (such as fluvoxamine or fluoxetine) for sigma-1 receptors (S1Rs), which have been shown to restrict the endonuclease activity of an endoplasmic reticulum stress sensor inositol-requiring enzyme 1 (IRE1) and to reduce cytokine expression without inhibiting classical inflammatory pathways; (2) the effects on non–S1R-IRE1 pathways, such as nuclear factor κ B, inflammasomes, Toll-like receptor 4, or peroxisome proliferator-activated receptor γ; and/or (3) the inhibition of ASM in endothelial cells and the immune system.[3,4,8] Interestingly, as highlighted by Oskotsky et al,[1] a prior study by Creeden et al,[10] which compared differential gene expression signatures from drug-treated cell lines with those from genetic knockdown of select cytokine storm-related inflammatory genes, found greater concordance in these signatures with fluoxetine compared with dexamethasone, a steroid widely used to treat COVID-19 patients with severe illness.

Finally, other potential mechanisms may include reduction in platelet aggregation, decreased mast cell degranulation, increased melatonin levels, interference with endolysosomal viral trafficking, and antioxidant activities.[3,8]

Because most of the world's population is currently unvaccinated and the COVID-19 pandemic is still active, effective treatments of COVID-19—especially those that are easy to use, show good tolerability, can be administered orally, and have widespread availability at low cost to allow their use in resource-poor countries—are urgently needed to reduce COVID-19–related mortality and morbidity. In this context, short-term use of fluoxetine or fluvoxamine, if proven effective, should be considered as a potential means of reaching this goal. Given the urgent need for an easily administered, effective treatment against COVID-19, especially in resource-poor countries, and increasing evidence of efficacy of these medications for this indication, both fluoxetine (which is on the World Health Organization's Model List of Essential Medicines and has the greatest in vitro inhibitory effect on the ASM-ceramide system among SSRIs) and fluvoxamine (which has shown very encouraging results in 3 clinical trials) should be prioritized in large-scale phase 3 clinical trials at different stages of the disease, either alone or in combination with other medications. This approach could enrich the current therapeutic arsenal with an inexpensive, well-tolerated, and easily administered medication in the global fight against COVID-19.

ARTICLE INFORMATION

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