Antidepressant Helps Prevent Hospitalization in COVID Patients: Study

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A handful of studies have suggested that for newly infected COVID-19 patients, risk for serious illness may be reduced with a short course of fluvoxamine (Luvox), a decades-old pill typically prescribed for depression or obsessive-compulsive disorder (OCD). But those were small studies involving just a few hundred people.

This week, researchers reported promising data from a large, randomized phase 3 trial that enrolled COVID-19 patients from 11 sites in Brazil. In this study, in which 1472 people were assigned to receive either a 10-day course of fluvoxamine or placebo pills, the antidepressant cut emergency department and hospital admissions by 29%.

Findings from the new study, which have not yet been peer reviewed, were published August 23 in *MedRxiv.*

Around the globe, particularly in countries without access to vaccines, "treatment options that are cheap and available and supported by good-quality evidence are the only hope we've got to reduce mortality within high-risk populations," said Edward Mills, PhD, professor in the Department of Health Research Methods, Evidence and Impact, McMaster University, Ontario, Canada.

The new findings came from TOGETHER, a large platform trial coordinated by Mills and colleagues to evaluate the use of fluvoxamine and other repurposed drug candidates for symptomatic, high-risk, adult outpatients with confirmed cases of COVID-19.

The trial's adaptive format allows multiple agents to be added and tested alongside placebo in a single master protocol — similar to the United Kingdom's Recovery trial, which found that the common steroid dexamethasone could reduce deaths among hospitalized COVID-19 patients.

In platform trials, treatment arms can be dropped for futility, as was the case with hydroxychloroquine and lopinavir-ritonavir, neither of which did better than placebo at preventing hospitalization in an earlier TOGETHER trial analysis.

Study Details

In the newly reported analysis, patients were randomly assigned to receive fluvoxamine or placebo between January and August 2021. Participants took fluvoxamine 100 mg twice daily for 10 days. By comparison, the US Food and Drug Administration recommends a maximum daily dose of 300 mg of fluvoxamine for patients with OCD; full psychiatric benefits occur after 6 weeks.

For the primary outcome, the investigators assessed whether the conditions of patients with COVID worsened over a 28-day period so as to require either hospitalization or observation in the emergency department for more than 6 hours. In the placebo group, 108 of 733 patients' conditions deteriorated to this extent (14.7%); by contrast, only 77 of 739 patients in the fluvoxamine group (10.4%) met these primary criteria — a relative risk reduction of 29%.

The treatment effect was greater (34%) in the per protocol analysis of participants who completed their course of pills.

The investigators also collected data on vital signs, including temperature and oxygen saturation, as well as adverse events reported at clinic visits or through video conferencing, phone calls, or social media applications. Side effects were mild, most commonly nausea and fatigue, and did not differ significantly between active treatment and control groups, Mills told *Medscape Medical News.*

Amid scores of studies evaluating repurposed drugs for COVID-19, the data on fluvoxamine are "looking much more favorable than anyone could have guessed — at least anyone in infectious disease," said Paul Sax, MD, clinical director of the Division of Infectious Diseases at Brigham and Women's Hospital and professor of medicine at Harvard Medical School, Boston, Massachusetts.

The new TOGETHER trial results augment supportive data published in *JAMA* last November from a phase 2 randomized trial that was small but "very well done," Sax told *Medscape Medical News.*

Those results got a boost from a subsequent study of 65 racetrack workers who chose to take fluvoxamine during a COVID-19 outbreak in the San Francisco Bay area. Forty-eight persons opted against taking the drug. In this small, nonrandomized study, "the people who chose to be treated with fluvoxamine were sicker [at baseline] than the people who didn't go on it, and yet the [treated group] ended up better," said Sax, who discussed accumulating data on the use of fluvoxamine for COVID-19 in a recent *New England Journal of Medicine* blog post.

Anti-Inflammatory Effect?

After reviewing the new findings, Frank Domino, MD, professor of family medicine and community health at the University of Massachusetts Medical School, Worcester, Massachusetts, said he would encourage patients with high-risk COVID-19 to consider taking fluvoxamine to lower their risk of being hospitalized. "But I would make it clear this was not a 'cure,' " he said, "and we are unsure how it helps."

At this point, US treatment guidelines do not recommend fluvoxamine as the standard of care for nonhospitalized COVID-19 patients, but the National Institutes of Health (NIH) is "very aware of the data," Sax told Medscape.

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) — a class of drugs that includes the more commonly prescribed antidepressant fluoxetine (Prozac). If prescribed off-label to COVID-19 patients, fluvoxamine should not be used within 2 weeks of starting treatment with other SSRI or monoamine oxidase inhibitor antidepressants and should be used with caution with other QT-interval prolonging medications, Sax said.

In addition, fluvoxamine can enhance the effect of antiplatelet and anticoagulant drugs, potentially triggering bleeding.

On the basis of in vitro and mouse studies of fluvoxamine, "we think it has an anti-inflammatory effect," said child psychiatrist Angela Reiersen, MD, of Washington University, Seattle, Washington, who came up with the idea for testing fluvoxamine in last year's phase 2 trial and co-authored a recent article describing the drug's potential mechanisms of action in COVID-19.

She and other researchers believe fluvoxamine's anti-inflammatory effects derive from the molecule's binding to the sigma-1 receptor in the endoplasmic reticulum, which regulates cellular responses to stress and infection.

Fluvoxamine also inhibits the activation of platelets. "In COVID-19, there does seem to be a problem with hyperactivation of platelets and excessive blood clots forming, so it is possible this could be another mechanism where it might be helping," Reiersen said.

If sigma-1 activation turns out to be the main mechanism underlying fluvoxamine's benefits in COVID-19, other sigma-1 agonists, such as fluoxetine, may also help. In a retrospective analysis of thousands of adults hospitalized for COVID-19 in France early in the pandemic, those who were taking antidepressants had a 44% lower risk for intubation or death.

And in a study under review, researchers at Stanford University and the University of California, San Francisco, analyzed electronic health records to explore a potential link between fluoxetine use and COVID outcomes among more than 80,000 patients from over 80 institutions across the United States. Other research suggests that antipsychotics could also have protective effects for patients with COVID-19.

Long COVID, Long-term Challenges

On the basis of its potential mechanisms of action, fluvoxamine may be able to prevent or treat long COVID, Reiersen said. That possibility will be assessed among other secondary endpoints in two ongoing studies of repurposed drugs: the NIH's ACTIV-6, and the University of Minnesota's COVID-OUT, an at-home trial of ivermectin, metformin, and fluvoxamine.

Reiersen and Washington University colleagues are also analyzing longer-term outcomes of participants in their own phase 3 trial of fluvoxamine (Stop COVID 2), which was discontinued when enrollment slowed to a trickle during the US vaccine rollout. Logistical hurdles and scant funding have greatly hampered efforts to test the use of off-patent drugs for COVID-19 outpatients during the pandemic.

US efforts face other obstacles as well. Elsewhere in the world — including Brazil, where the TOGETHER trial was run — vaccines are scarce, and there are no monoclonal antibodies.

"People have a great sense of community duty, and they're participating in the trials," Mills said. "You're in a much more political environment in the US on these outpatient trials."

The TOGETHER trial was funded by Fast Grants and the Rainwater Foundation. Reiersen is an inventor on a patent application related to methods of treating COVID-19, which was filed by Washington University in St. Louis. Mills, Domino, and Sax report no relevant financial relationships.

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