— Group of physician-scientists believes data support authorization for treating COVID-19

by Sophie Putka, Enterprise & Investigative Writer, MedPage Today
December 29, 2021

It took about 4 days for David Boulware, MD, MPH, to write the FDA emergency use authorization (EUA) application for fluvoxamine.

Yes, a doctor wrote an EUA application -- a task that has typically been relegated to pharmaceutical companies -- and yes, it was for a generic drug that physicians could technically prescribe off-label.

But Boulware, of the University of Minnesota, who is involved in a trial that's investigating fluvoxamine and other repurposed drugs -- along with a handful of other doctors and researchers -- took it upon themselves to apply because they believe the data substantiate its use in COVID-19.

"The big thing is, the data [are] available," Boulware said in an interview, referring to two published randomized, double-blind, placebo-controlled trials. "There should be enough data that the FDA would approve this under the normal review process to add a new indication for the drug."

He added that doctors may be "reluctant" to prescribe a drug off-label, or that "some health systems may have policies against it."

"I think most providers would feel more comfortable doing it if that therapy were FDA approved for that indication," said Carolyn Bramante, MD, MPH, also of the University of Minnesota.

Supporting Data

Boulware said two randomized controlled trials support the use of fluvoxamine in preventing disease progression. In November 2020, the STOP-COVID study, led by Eric Lenze, MD, of Washington University in St. Louis, was published as a preliminary

group.

The TOGETHER trial, led by Brazilian researchers, included 1,497 COVID-19 positive outpatients with a risk factor for severe disease. Overall, those who took fluvoxamine spent less time in the emergency room and were less likely to transfer to the hospital than those who got placebo (RR 0.68, 95% CI 0.52-0.88).

Boulware also mentioned a study -- though not a randomized controlled trial -- by David Seftel, MD, a doctor and CEO of Enable Biosciences, an antibody diagnostics company. Seftel conducted his own experiment, offering fluvoxamine to patients exposed to COVID-19 at a racetrack, and comparing those who accepted it with those who did not. None of those who took the drug were hospitalized, while 12.5% of those who refused the drug were, they reported in *Open Forum Infectious Diseases.*

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Boulware was interested by the early data and helped Seftel write up the racetrack study, but he knew more data were needed. So the University of Minnesota team, led by Bramante, launched the COVID-OUT trial, with plans to enroll 1,160 COVID-19 outpatients. In addition to fluvoxamine, it will also test metformin and ivermectin for the early treatment of COVID-19.

The NIH also included a fluvoxamine arm in its ACTIV-6 study, Boulware said.

Pros and Cons

One of the main benefits of fluvoxamine is its decades-long safety track record. It's also easy and relatively inexpensive to manufacture, the researchers said.

distributed so far. And molnupiravir had a similarly modest effect on hospitalization and death.

Like the antivirals, fluvoxamine's effects won't be variant-dependent, unlike some of the monoclonal antibodies that have been rendered useless in the face of Omicron.

While the mechanism behind fluvoxamine's effects in COVID-19 isn't clear, one perspective published in *Frontiers in Pharmacology* posits that its sigma-1 receptor agonism has an anti-inflammatory effects. It also may reduce platelet activation, or increase melatonin, or act in other ways to help alleviate the "cytokine storm" brought on by COVID-19.

Also, Boulware said, fluvoxamine "is anti-inflammatory, but it's not necessarily [an] immunosuppressant," compared to using steroids to treat COVID-19, which he calls "kind of a big sledgehammer of an anti-inflammatory."

To be sure, the results of the TOGETHER trial aren't spectacular: "It's a modest benefit," Boulware said, but 30% reduction in ER visits and hospitalization is a pretty good reduction if you think about it on a population scale, particularly if you have no alternative therapies," he said.

The problem, Boulware said, is that fluvoxamine "is a generic medicine and so there's no big pharmaceutical company that's going to take the effort and the time to apply [for an EUA] because it's made by six different companies or so in the U.S., and it's an inexpensive, $5-to-$10-treatment-course, kind of medicine."

Taking Matters Into Their Own Hands

So Boulware decided to file the application himself. He spent about 4 days compiling the data, explaining why there were few alternatives to the drug, and illustrating that the benefits outweighed potential risks of taking an antidepressant.

He said prior experience writing investigational new drug (IND) applications proved helpful, and he followed the agency's EUA submission guidance to a tee. He also had colleagues proofread the application.

for the EUA application. It might also be first in line to make the drug should the EUA come through.

Other caveats, Boulware said, are the lack of clarity on proper dosage of the drug. A number of study participants in the TOGETHER trial couldn't tolerate the dose of 100 mg twice a day, quitting before the treatment was done. Nausea, sexual dysfunction, excess alertness, and sleep changes are among the side effects that might stop someone from taking the fluvoxamine. Researchers still need to pin down an appropriate dose, which will likely fall somewhere in between 100 mg twice a day and 50 mg twice a day -- the dose used in the racetrack study and in COVID-OUT.

There's also a stigma around taking antidepressants and similar drugs. "It's been brought to my attention that people may refuse it because it's an antidepressant, so that is unfortunate -- the concern that it might cause changes in psyche," said Bramante.

Still, "most people who are eligible would not have a bad effect from it," she noted.

Boulware and Bramante said SSRIs take weeks to affect mood, and would be highly unlikely to have a noticeable effect in just 10 days of treatment.

Boulware says he doesn't know when he'll hear back from the FDA about the EUA, but he said he received an emailed response from the agency confirming his submission.

His best guess is that he'll have a response in a matter of weeks: "There will be more trials coming, and so [the COVID-OUT] trial will be done in a month from now," he said. "And so if they say no, we need more data, we'll just reapply a month from now."

Last Updated December 29, 2021

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