Fluvoxamine

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Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is approved by the Food and Drug Administration (FDA) for the treatment of obsessive-compulsive disorder and is used for other conditions, including depression. Fluvoxamine is not FDA-approved for the treatment of any infection.

Anti-Inflammatory Effect of Fluvoxamine and Rationale for Use in COVID-19

In a murine sepsis model, fluvoxamine was found to bind to the sigma-1 receptor on immune cells, resulting in reduced production of inflammatory cytokines.1 In an in vitro study of human endothelial cells and macrophages, fluvoxamine reduced the expression of inflammatory genes.2 Ongoing studies are establishing whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans and are clinically relevant in the setting of COVID-19.

Recommendation

• There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of fluvoxamine for the treatment of COVID-19.

Rationale

Three randomized trials have studied the use of fluvoxamine for the treatment of nonhospitalized patients with COVID-19. In STOP COVID, a contactless, double-blind randomized placebo-controlled trial conducted in the United States among nonhospitalized adults with mild COVID-19 diagnosed within 7 days of symptom onset, fluvoxamine (100 mg up to 3 times daily for 15 days) reduced clinical deterioration at Day 15.3 Clinical deterioration was defined as shortness of breath plus oxygen saturation (SpO₂) <92% or hospitalization plus SpO₂ <92%. This was a small study (≤80 participants per arm) with limited cases of clinical deterioration and a short follow-up period. In addition, 24% of participants stopped responding to surveys prior to Day 15.

The subsequent STOP COVID 2, a Phase 3 randomized controlled trial (ClinicalTrials.gov Identifier NCT04668950) that enrolled >700 participants in the United States and Canada, was stopped for futility by a data safety monitoring board after lower than expected case rates and treatment effect were observed.4

TOGETHER is an adaptive platform, double-blind randomized placebo-controlled trial conducted in Brazil.5 Nonhospitalized adults with COVID-19 and a known risk factor for progression to severe disease were randomized to fluvoxamine 100 mg twice daily (n = 741) or placebo (n = 756) for 10 days. Fluvoxamine use was associated with a lower risk of the primary composite outcome of retention in the emergency department for >6 hours or admission to a tertiary hospital (79 of 741 participants [11%] in the fluvoxamine arm vs. 119 of 756 participants [16%] in the placebo arm [relative risk 0.68; 95% CrI, 0.52–0.88]). Of note, 87% of the primary outcome events were hospitalizations. There was no statistically significant difference between study arms for the secondary outcomes of need for hospitalization or time to symptom resolution. There was no significant difference in mortality between study arms in the intention-to-treat (ITT) population (17 of 741 participants [2%] in the fluvoxamine arm vs. 25 of 756 participants [3%] in the placebo arm [OR 0.69; 95% CI, 0.36–1.27]). In a secondary, per-protocol analysis of participants who received >80% of possible doses, death was the outcome for 1 of 548 participants (<1%) in the fluvoxamine arm versus 12 of 618 participants (2%) in the placebo arm (OR 0.09; 95% CI, 0.01–0.47). Participants in the fluvoxamine arm were less likely to present to an emergency setting for COVID-19 for any duration, although this analysis was not prespecified.
Compared with those in the placebo arm, participants who received fluvoxamine were less adherent to therapy and discontinued therapy due to intolerance more often.

While fluvoxamine treatment significantly reduced the primary composite outcome in the TOGETHER trial (i.e., retention in the emergency department for >6 hours or admission to a tertiary hospital), the difference in hospitalizations between arms was not significant. Defining the clinical relevance of the >6 hour emergency department observation time endpoint is difficult, especially its applicability to practice settings in different countries. Moreover, the endpoint has not been used in other studies of interventions for nonhospitalized patients at high risk for hospitalization and death. While a per-protocol analysis found a significant treatment effect for mortality in patients taking ≥80% of possible doses (assessed by patient self-report), no such benefit was found in the primary ITT analysis. The 80% threshold has no clear justification, and only 74% of participants in the fluvoxamine arm reached this level of adherence. Since per-protocol analyses are not randomized comparisons, they can introduce bias when adherence is associated with factors that influence the outcome; this bias cannot be excluded in this study. Notably, mortality in the placebo arm was substantially higher in those with ≤80% adherence than in those with >80% adherence, suggesting that factors other than adherence differed in the per-protocol population. Finally, including only participants who could tolerate fluvoxamine does not reflect the actual effectiveness of the drug, since intolerance and adherence appeared to be related.

Additional studies are needed to provide more specific, evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19. Further details of the studies discussed are provided in Table 4c.

Adverse Effects, Monitoring, and Drug-Drug Interactions

When fluvoxamine is used to treat psychiatric conditions, the most common adverse effect is nausea, but adverse effects can include other gastrointestinal effects (e.g., diarrhea, indigestion), neurologic effects (e.g., asthenia, insomnia, somnolence, anxiety, headache), and rarely suicidal ideation.

Fluvoxamine is a cytochrome P450 (CYP) 2D6 substrate and a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9, CYP2D6, and CYP3A4. Fluvoxamine can enhance the serotonergic effects of other SSRIs or monoamine oxidase inhibitors (MAOIs), resulting in serotonin syndrome; therefore, it should not be used within 2 weeks of receipt of other SSRIs or MAOIs. Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants; therefore, patients receiving these drugs should be closely monitored.

Considerations in Pregnancy

Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnancy are limited. The association of SSRI use in the late third trimester with a small, increased risk of primary persistent pulmonary hypertension in newborns has not been excluded, although the absolute risk is likely low. The risk of fluvoxamine use in pregnancy for the treatment of COVID-19 should be balanced with the potential benefit.

Considerations in Children

Fluvoxamine is approved by the FDA for the treatment of obsessive-compulsive disorder in children aged ≥8 years. Adverse effects due to SSRI use seen in children are similar to those seen in adults, although children and adolescents appear to have higher rates of behavioral activation and vomiting than adults. There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in children.
Clinical Trials

See ClinicalTrials.gov for the latest information on studies of fluvoxamine and COVID-19.

References


