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 in 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] Further studies are needed to establish whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans beings and are clinically relevant in the setting of COVID-19.

Recommendation

There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of fluvoxamine for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19.

Clinical Trial Data

Placebo-Controlled Randomized Trial in Non-hospitalized Adults With Mild COVID-19

In this contactless, double-blind, placebo-controlled randomized trial, non-hospitalized adults with mild COVID-19 confirmed by SARS-CoV-2 polymerase chain reaction (PCR) assay within 7 days of symptom onset were randomized to receive fluvoxamine up to 100 mg three times daily or matching placebo for 15 days. The primary endpoint was clinical deterioration (defined as having dyspnea or hospitalization for dyspnea or pneumonia and oxygen saturation [SpO_2] <92% on room air or requiring supplemental oxygen to attain SpO_2 ≥92%) within 15 days of randomization. Participants self-assessed their blood pressure, temperature, oxygen saturation, and COVID-19 symptoms and reported the information by email twice daily.[3]

Participant Characteristics

- A total of 152 participants were randomized to receive fluvoxamine (n = 80) or placebo (n = 72).
- The mean age of the participants was 46 years; 72% were women, 25% were Black, and 56% had obesity.

Results

- None of 80 participants (0%) who received fluvoxamine and six of 72 participants (8.3%) who received placebo reached the primary endpoint (absolute difference 8.7%; 95% CI, 1.8% to 16.5%; *P* = 0.009).
- Five participants in the placebo arm and one in the fluvoxamine arm required hospitalization.

- Only 76% of the participants completed the study, and 20% of the participants stopped responding to the electronic survey during the study period but were included in the final analysis.

Limitations

- The study had a small sample size.
- A limited number of events occurred.
- Ascertaining clinical deterioration was challenging because all assessments were done remotely.

Interpretation

In this small placebo-controlled trial, none of the participants who received fluvoxamine and six (8.3%) of those who received placebo reached the primary endpoint. However, due to the study's reliance on participant self-reports and missing data, it is difficult to draw definitive conclusions about the efficacy of fluvoxamine for the treatment of

COVID-19.

Prospective Observational Study During an Outbreak of SARS-CoV-2 Infections

A prospective, nonrandomized observational cohort study evaluated fluvoxamine for the treatment of COVID-19 in 113 outpatients who tested positive for SARS-CoV-2 antigen with the result confirmed by a PCR test. The trial was conducted in an occupational setting during an outbreak of COVID-19. Patients were offered the option of receiving fluvoxamine 50 mg twice daily for 14 days or no therapy.[4]

Patient Characteristics

- Of the 113 participants with positive SARS-CoV-2 antigen, 65 opted to take fluvoxamine and 48 did not.
- More of the patients who did not take fluvoxamine had hypertension. In addition, more of those who were Latinx and more of those who were initially symptomatic opted to take fluvoxamine.

Results

- At Day 14, none of the patients who received fluvoxamine versus 60% of those who did not had persistent symptoms (e.g., anxiety, difficulty concentrating, fatigue) ($P < 0.001$).
- By Day 14, none of the fluvoxamine-treated patients were hospitalized; six patients who did not receive fluvoxamine were hospitalized, including two patients who required care in the intensive care unit.
- No serious adverse events were reported following receipt of fluvoxamine.

Limitations

- The study was a nonrandomized trial.
- The study had a small sample size.
- Limited data were collected during the study.

Limitations (e.g., small sample size) and differences in study populations and fluvoxamine doses make it difficult to interpret and generalize the findings of these trials. Additional studies, including a Phase 3 randomized controlled trial (*ClinicalTrials.gov*Identifier NCT04668950), are ongoing to provide more specific evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19.
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), dermatologic reactions (sweating), and rarely suicidal ideation.

Fluvoxamine is a cytochrome P450 (CYP) D6 substrate and a potent inhibitor of CYP1A2 and 2C19 and a moderate inhibitor of CYP2C9, 2D6, and 3A4.[5] Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants. In addition, it can enhance the serotonergic effects of other SSRIs or monoamine oxidase inhibitors (MAOIs) resulting in serotonin syndrome. Fluvoxamine **should not be used** within 2 weeks of receipt of other SSRIs or MAOIs and should be used with caution with other QT-interval prolonging medications.

Considerations in Pregnancy
Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnancy are limited.[6,7] A small, increased risk of primary persistent pulmonary hypertension in the newborn associated with SSRI use in the late third trimester has not been excluded, although the absolute risk is likely low.[8]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.[9] 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.[10] There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in children.

References

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