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 approved by the FDA for the treatment of any infection.

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]

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **fluvoxamine** for the treatment of COVID-19 in nonhospitalized patients **(AIIa)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of the combination of inhaled budesonide plus fluvoxamine for the treatment of COVID-19 in nonhospitalized patients.
- Patients with COVID-19 who are receiving **fluvoxamine** for an underlying condition should continue this therapy as directed by their health care provider **(AIII)**.

Rationale

Six randomized trials have studied the use of fluvoxamine for the treatment of nonhospitalized patients with COVID-19.[3-8] The TOGETHER and STOP COVID 2 trials enrolled unvaccinated patients with COVID-19 who had at least 1 risk factor for disease progression.[3,5] These studies did not identify a consistent benefit of using fluvoxamine in these patients, although STOP COVID 2 was stopped early due to low primary outcome rates. Other outpatient therapies (i.e., ritonavir-boosted nirmatrelvir [Paxlovid], remdesivir) have been shown to be effective in preventing hospitalization or death in unvaccinated patients who are at high risk of disease progression. In subsequent trials where the majority of enrolled patients were vaccinated against COVID-19, fluvoxamine did not significantly reduce the risk of hospitalization or death, the time to recovery, or health care utilization.[6-8] In several of these studies, fluvoxamine was associated with decreased adherence and/or an increase in the occurrence of nonserious adverse effects, primarily gastrointestinal symptoms.[3,5,6]

The TOGETHER trial was a large, double-blind, placebo-controlled, adaptive randomized trial in Brazil that evaluated the use of inhaled budesonide plus oral fluvoxamine in patients with COVID-19.[9] Over 90% of the patients had received at least 2 doses of a COVID-19 vaccine. Treatment with this combination significantly reduced the incidence of the primary outcome, which was a composite of hospitalization or retention in an emergency setting for >6 hours. The proportion of patients who were hospitalized was the same in the treatment and placebo arms (0.9% vs. 1.1%), and the treatment did not significantly impact secondary outcomes such as health care attendance or the need for an emergency setting visit. It is unclear how the >6-hour emergency setting outcome translates to other settings. In addition, treatment with budesonide plus fluvoxamine was associated with significantly more adverse events.

Summaries of the studies that informed the Panel's recommendations can be found in Table 7a.

Monitoring, Adverse Effects, 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, a potent inhibitor of CYP1A2 and CYP2C19, and a moderate inhibitor of CYP2C9, CYP2D6, and CYP3A4.[10] Fluvoxamine can enhance the serotonergic effects of other SSRIs or monoamine oxidase inhibitors, resulting in serotonin syndrome; therefore, it should not be used within 2 weeks of receiving other SSRIs or monoamine oxidase inhibitors. Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants. Patients who are receiving these drugs should be closely monitored.

Considerations in Pregnant People

Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnant individuals are limited.[11,12] An association between SSRI use in the late third trimester and a small increase in the risk of primary persistent pulmonary hypertension in newborns has not been excluded, although the absolute risk is likely low.[13]

Considerations in Children

Fluvoxamine is approved by the FDA for the treatment of obsessive-compulsive disorder in children aged ≥8 years.[14] The adverse effects of SSRI use seen in children are similar to those seen in adults, although children and adolescents appear to have higher rates of activation and vomiting than adults.[15] There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in children.

References

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