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Fluvoxamine

What Prescribers and Pharmacists Need to Know

SCIENCE TABLE
COVID-19 ADVISORY FOR ONTARIO

UNIVERSITY OF WATERLOO | SCHOOL OF PHARMACY

Why is fluvoxamine used to treat COVID-19?

The consequences of COVID-19 that lead to poor outcomes, including hospitalization, invasive ventilation, and death, are in large part due to inflammation.

Fluvoxamine is an SSRI (selective serotonin reuptake inhibitor) typically used to treat depression and anxiety. It affects the sigma-1 receptor that controls inflammation and may reduce inflammation in COVID-19. Fluvoxamine is more anti-inflammatory than other SSRIs (i.e., this is not expected to be a class effect).

Fluvoxamine should not replace outpatient therapies with a higher likelihood of effect, such as sotrovimab and remdesivir. If patients are eligible for and can access these agents, they should be used preferentially.

What is the benefit of fluvoxamine for COVID-19?

Two studies (STOP-COVID 1[1] and the TOGETHER[2] trials) have shown a benefit from treatment with fluvoxamine in adult outpatients with PCR-proven COVID-19 who were less than 7 days from onset of symptoms. The studies suggest **fluvoxamine may reduce ER visit length, hospitalization, and disease progression**.

Research on fluvoxamine was done before widespread immunization and before the Delta and Omicron variants were circulating. However, with the anticipated impact of surging Omicron cases on the healthcare system, the Ontario Science Advisory Table has made a conditional recommendation for the use of fluvoxamine in patients with COVID-19 who are not on supplemental oxygen.[3]

What are other recommended outpatient treatments for COVID-19?

Sotrovimab

Anti-SARS-CoV-2 neutralizing monoclonal antibodies such as sotrovimab have been shown to benefit patients without immunity to COVID-19 (vaccine or disease-induced) who are within 7 days of symptom onset.[4] The evidence of benefit for sotrovimab in patients with COVID-19 not on supplemental oxygen is more certain than the evidence for fluvoxamine.

Remdesivir

Remdesivir is a direct-acting antiviral agent that has been shown to reduce the risk of COVID-19-related hospitalization and death in patients who are within 7 days of symptom onset and have risk factors for disease progression.[5] Remdesivir impacts outcomes that are likely more important to more patients than fluvoxamine (e.g., shorter time to recovery).

Budesonide

The inhaled corticosteroid budesonide has been shown to shorten duration of symptoms for high risk outpatients with COVID-19.[6] It has not been shown to reduce the risk of hospitalization or other serious outcomes.

How do I dose fluvoxamine for treatment of COVID-19?

1. Start with 50 mg PO once daily, preferably at bedtime.
2. If the drug is well tolerated, increase the dose to 100 mg PO BID on day 2.
   If the drug is less well tolerated, consider a dose of 50 mg PO BID on day 2, and increase the dose to 100 mg PO BID on day 3.
3. If the patient was on another SSRI/SNRI* before switching to fluvoxamine, and they were at or near the maximum dose, increase the dose to 150 mg PO BID.
   *Selective serotonin reuptake inhibitor / serotonin-norepinephrine reuptake inhibitor
4. Continue therapy for a total of 10 to 15 days.

Fluvoxamine has many drug interactions.
Refer to page 2 →

[1] https://pubmed.ncbi.nlm.nih.gov/33180097/
[2] https://www.thelancet.com/action/showPdf?pii=S2214-109X%2821%2900448-4
[3] Clinical practice guideline summary: recommended drugs and biologics in adult patients with COVID-19. Ontario COVID-19 Science Advisory Table. 2021; Version 7.0. https://doi.org/10.47326/ocsat.cpg.2022.7.0
[4] https://www.nejm.org/doi/full/10.1056/NEJMoa2107934
[5] https://www.nejm.org/doi/full/10.1056/nejmoa2007764
[6] https://www.thelancet.com/article/S2213-2600(21)00160-0/fulltext

Who should receive fluvoxamine?

Fluvoxamine should be offered preferentially to patients at higher risk of severe disease or complications from COVID-19, including those:

- *Not yet immunized*
- *Immunocompromised*
- *At least 6 months from last dose of vaccine*
- *Age 60+*
- *Age 50+ with at least one comorbidity (e.g., diabetes, cardiovascular disease, obesity, lung disease, kidney disease)*
- *Of Indigenous background*
- *With developmental disabilities*

Fluvoxamine should only be offered to patients with COVID-19* who are not yet on supplemental oxygen, and who are within 7 days of symptom onset.

*Ideally COVID-19 is proven by PCR or a provider-administered rapid test.

What side effects should I be aware of?

Common side effects of fluvoxamine are generally mild and can include nausea, constipation, diarrhea, dry mouth, insomnia, agitation, somnolence, nervousness, headache, and dizziness. Rare, but serious side effects include serotonin syndrome/toxicity and QT prolongation.

Serotonin syndrome is a rare, but serious complication of SSRIs, particularly when the maximum dose is exceeded or when used with other serotonergic drugs.

The risk of QT prolongation is rare and a baseline ECG is not recommended in otherwise healthy patients with no risk factors. Fluvoxamine should be avoided in patients with a history of congenital long QT syndrome or who take medications with significant potential for QT prolongation.

What drug interactions should I consider before prescribing fluvoxamine?

- Fluvoxamine is contraindicated in patients taking:
  - MAO (monoamine oxidase) inhibitors
  - Thioridazine and mesoridazine
  - Pimozide
  - Terfenadine, astemizole, and cisapride
  - Tizadine
- Fluvoxamine should not be used in combination with clopidogrel as it may reduce the anti-platelet effect of clopidogrel (CYP2C19 interaction).
- Fluvoxamine should be used with caution in patients taking any of the following drugs:[†]
  - **Caffeine:** Fluvoxamine raises serum concentrations of caffeine up to 5-fold. Patients should avoid caffeine as much as possible while taking fluvoxamine.
  - **Drugs affecting bleeding risk:** ASA, warfarin, and NSAIDs[‡].
  - **Specific benzodiazepines:** triazolam, midazolam, alprazolam, and diazepam.
  - **Drugs affecting seizure threshold:** e.g., select antidepressants, mefloquin, and tramadol.
  - **CYP 1A2 Substrates:** e.g., amitriptyline, clomipramine, clozapine, quetiapine, and olanzapine.
  - **CYP 2C19 Substrates:** e.g., diazepam, phenytoin, warfarin, lansoprazole, and omeprazole.
  - **CYP 2C9 Substrates:** e.g., valproate.
  - **CYP 3A4 Substrates:** e.g., alprazolam, diltiazem, carbamazepine, methadone, cyclosporine, and sildenafil.
  - **Others:** propranolol and ropinirole.

[‡]Non-steroidal anti-inflammatory drugs

What if my patient is already taking psychiatric drugs?

- If patient is taking **MAO inhibitors**: Do NOT give fluvoxamine due to risk of serotonin syndrome.
- If patient is taking **non-sertraline SSRI/SNRI**: Switch to fluvoxamine for 10 to 15 days, then switch back OR if there are concerns that switching could be detrimental due to discontinuation side effects or negative impact on psychiatric condition, fluvoxamine can be added if the original drug is at low dose (i.e., half of maximum recommended dose).
- If patient is taking **sertraline**: Switch to fluvoxamine. Do NOT add it on, as sertraline can counteract some of fluvoxamine's anti-inflammatory actions.
- Use caution if prescribing fluvoxamine to patients with a history of **bipolar disorder** or **mania**, as it can trigger a manic or hypomanic episode.
- At this time, there is no evidence to support the use of **other SSRI/SNRIs** for the treatment of COVID-19 because they do not have the same degree of anti-inflammatory activity.

[†]For a full list of drug interactions, visit: https://www.mylan.ca/-/media/mylanca/documents/english/product-pdf/luvox-pm-2017-06-15.pdf?la=en-ca

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