Fluvoxamine for SARS-CoV2 infection and Older Adults: Pharmacology

Thank you for your question regarding the use of fluvoxamine for COVID-19 in older adults in long term care. We agree with your concerns, particularly in patients with polypharmacy, as well as with prolonged QT.

The Ontario COVID-19 Science Advisory Table has created a summary that provides an excellent overview of the potential adverse effects and drug-drug interactions (Fluvoxamine - What Prescribers and Pharmacists Need to Know 2 (covid19-sciencetable.ca)), and we suggest consulting this document for general information about the drug. Another excellent accessible resource for identifying drug-drug interactions is the Indiana University Drug Interaction Flockhart Table (https://drug-interactions.medicine.iu.edu/MainTable.aspx).

However, we suggest exercising caution in implementing those recommendations pertaining to management of drug interactions when prescribing fluvoxamine to older adults. For example, one recommendation is to add fluvoxamine to existing SSRI/SNRI therapy if it is a low dose (or alternatively, switch to fluvoxamine). We argue that fluvoxamine's potential to interact with the existing SSRI/SNRI may be of concern. For example, concomitant fluvoxamine can increase serum concentrations of S-citalopram and R-citalopram by 3.1- and 1.8- fold, respectively.[1]

We therefore recommend that each patient's management should be individualized.

Other considerations in older adults should also be weighed against the evidence of benefit before initiation:

- **Fluvoxamine has been shown to have altered pharmacokinetics with age**. In one single-dose pharmacokinetic study, exposure was almost 3-fold higher (885±560 vs.304±84 ng h ml-1) and maximum concentrations were 2-fold higher (31±19 vs.15±9 ng ml-1) in older adults (mean age 73 years) compared to younger individuals (mean age 35 years).[2]
    - Fluvoxamine also exhibits non-linear kinetics, and exposure can be greater than the expected proportional increase with changes in dose.[3,4] These nonlinear increases in exposure to fluvoxamine may be greater among male patients compared to female patients.[3]
- **Interindividual serum concentrations of fluvoxamine vary** 6- and 4-fold on day 14 and day 28, respectively irrespective of age and comorbidity.[3]
- **Increased risk of falls in older adults with SSRIs.** A population-based retrospective cohort study of LTC residents in Ontario found that new users of an SSRI had a significantly increased risk of ED visits or hospitalizations for falls within 90 days compared to non-users, NNH = 36 (OR 2.0; 95% CI 1.7-2.5).[5]
- **Increased risk of hyponatremia with SSRIs.** Although the absolute risk is low, initiation of antidepressants (including fluvoxamine) in older adults in Ontario, has been associated with a 5-fold increase in the risk of hospitalization with hyponatremia within 30 days (0.33% vs 0.06% in nonusers).[6]

January 26, 2022

Based on the interindividual variability, evidence for higher exposure among older adults, nonlinear pharmacokinetics, longer elimination half-life (and time to steady state) and sex-based differences, one would expect higher serum fluvoxamine levels among older patients, particularly those living in LTC. The risk of fluvoxamine-associated adverse effects and clinically relevant drug-drug interactions would also be higher, particularly as levels of fluvoxamine and related interacting medications accumulated towards the second week of therapy. Among fluvoxamine-COVID trials, the doses ranged and the proportion of older adults included in the studies was low. Based on the potential increased exposure, if fluvoxamine were to be initiated in an older adult with no concerning drug interactions or comorbidities, we would suggest trialing the Ontario COVID-19 Science Advisory Table "if drug is less well tolerated" titration schedule (50 mg qhs day 1, 50 mg BID day 2 and 100 mg BID day 3) first. This would allow for fluvoxamine levels to reach levels required for the hypothesized sigma1 receptor agonism. Starting at the lowest available dose 25 mg (half of the 50 mg tablet) qhs to assess for tolerability before titrating on day 2 to 50 mg BID, then 100 mg po BID in an older adult (>=65 years of age) would likely reach similar levels (overall exposure >3-fold, 40% higher Cmax, half-life increased by 63%), however this dosing has not been evaluated and it may risk a prolonged time to therapeutic range and therefore treatment failure. In addition the Ontario COVID-19 Science Advisory Table recommendations for QT interval, we also suggest monitoring for hyponatremia at baseline and in a week's time after initiation. Please note that other SSRIs (except sertraline) and donepezil may have sigma 1 receptor agonism.

	Dose	Age
Ontario COVID-19 Science Advisory Table	Day 1, 50 mg qhs, then 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 Treatment duration: 10-15 days	n/a
TOGETHER (Reis Lancet Global Health 2022)[7]	Fluvoxamine 100 mg twice a day for 10 days or corresponding placebo starting directly after randomisation (day 1)	Fluvoxamine group: Median 50 years (IQR 39-56)
STOP COVID 1 (Lenze JAMA 2020)[8]	50 mg of fluvoxamine (or matching placebo) in the evening immediately after the baseline assessment and confirmation of eligibility, then for 2 days at a dose of 100 mg twice daily as tolerated, and then increasing to a dose of 100 mg 3 times daily as tolerated through day 15 then stopped	Fluvoxamine group: Median 46 years (interquartile range (IQR) 35-58 years; range 20-75 years)
Prospective cohort open label study associated with a mass outbreak in California, USA (Seftel and Boulware)[9]	fluvoxamine 50- to 100-mg loading dose, then 50 mg twice daily for 14 days vs no therapy.	Fluvoxamine group: mean 44 years, Standard deviation 15 years.
STOP COVID 2 (clinical trials.gov)[10]	Start fluvoxamine 50mg capsule once, then 100mg twice daily. May reduce dose for tolerability reasons. Will be followed in the RCT for approximately 15 days.	Please note that patients on donepezil were excluded due to its potential sigma 1 receptor agonist activity.

References

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