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## Fluvoxamine for the treatment of COVID-19

We congratulate Gilmar Reis and colleagues (January, 2022)<sup>1</sup> on their randomised, platform clinical trial (TOGETHER trial) investigating the effects of early treatment with fluvoxamine for patients with COVID-19. In the study, the impressive 5% absolute risk reduction in hospitalisation or prolonged emergency setting observation equates to a number needed to treat of 20, meaning for every 20 individuals treated, one will have this benefit from the treatment.<sup>1</sup> At a US wholesale pharmacy cost of US\$4.66, which equates to \$93 (95%CI 56–285) to prevent one emergency setting visit or hospitalisation among all participants.

The overall objective of early therapy is to prevent clinical deterioration or reduce symptom severity or duration. In this respect, fluvoxamine seems an effective low-cost therapy that provides substantial benefit, particularly in low-income and middle-income countries worldwide where vaccine roll-out and other therapeutics are unavailable.

Yet, the authors should explain more regarding the COVID-19 severity and activities occurring during prolonged emergency setting observation. When the authors did their study,<sup>1</sup> it was likely that the COVID-19 acuity was quite high, and in a fully resourced health-care system absent a pandemic, such individuals would have likely been hospitalised. To enable external comparison, the authors should also present the primary endpoint data per the US Food and Drug Administration categorisation of severe COVID-19, which is defined as hospitalisation or emergency setting observation with SpO<sub>2</sub> less than 93% or PaO<sub>2</sub>/FIO<sub>2</sub> ratio less than 300.<sup>2</sup> The authors should state what proportion of participants in the fluvoxamine and placebo groups progressed to severe COVID-19 and whether fluvoxamine prevented progression to severe COVID-19.

Yet, one question remains as to what is the optimal fluvoxamine dose. This trial result builds off a smaller randomised controlled trial and prospective cohort.<sup>3,4</sup> In the per-protocol analysis of those more than 80% adherent to fluvoxamine or placebo before any clinical deterioration, emergency room visits or hospitalisations were reduced by two-thirds and mortality by 91% (one vs 12 deaths).<sup>1</sup> Lenze and colleagues used 300 mg per day,<sup>3</sup> Reis and colleagues used 200 mg per day,<sup>1</sup> and Seftel and colleagues used 100 mg per day,<sup>4</sup> all in twice per day divided dosing; however, what dose schedule is optimal for effect and tolerability is unclear. University of Minnesota (CovidOut.com; NCT04510194) and NIH ACTIV-6 trials (NCT04885530) are testing 50 mg twice daily. This lower dose will probably be more tolerable, but whether the clinical benefit will be similar is unknown yet.

Lastly, strategies of supportive care should be investigated. In the TOGETHER trial, individuals who were not adherent to fluvoxamine or placebo<sup>1</sup> had an eight-times higher mortality than did those adherent to fluvoxamine or placebo (29 of [9%] of 331 vs 13 [1%] of 1166; p<0.001). Ill COVID-19 patients who cannot tolerate any oral medicine appear to be at substantially higher risk for clinical deterioration. Earlier provision of anti-nausea or anti-motility medication (eg, ondansetron or loperamide) should be investigated both as supportive care to improve the tolerability of fluvoxamine and perhaps for patients with COVID-19 in general.<sup>5</sup>

We declare no competing interests.

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- 1 Reis G, Dos Santos Moreira-Silva EA, Silva DCM, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health* 2022; **10**: e42–51.
- 2 Food and Drug Administration. COVID-19: developing drugs and biological products for treatment or prevention guidance for industry. 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention> (accessed Nov 1, 2021).
- 3 Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA* 2020; **324**: 2292–300.
- 4 Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of coronavirus disease 19. *Open Forum Infect Dis* 2021; **8**: ofab050.
- 5 Dong ZY, Xiang BJ, Jiang M, Sun MJ, Dai C. The prevalence of gastrointestinal symptoms, abnormal liver function, digestive system disease and liver disease in COVID-19 Infection: A systematic review and meta-analysis. *J Clin Gastroenterol* 2021; **55**: 67–76.

