Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Fluvoxamine for the treatment of COVID-19

Author's reply

We are grateful for the communications pertaining to our trial.[1] After publication, we noticed that some decision-making groups might not have the correct understanding of composite endpoints. Composite endpoint guidance is well-established. Strictly speaking, all clinical endpoints are a form of composite (eg, death can be from different reasons).[2] If we apply the same composite endpoint (hospitalisation or emergency care >24 h) used in the paxlovid trial[3] and molnupiravir trial,[4] our effect size does not change importantly (relative risk [RR] 0·74 [95% CI 0·56–0·98]).

David Boulware and Mahsa Abasi raise important points and we agree with them all. The emergency settings we describe in our trial are temporary hospitals capable of providing advanced medical care including intensive care, except for extracorporeal membrane oxygenation. In our trial, all but one patient who met our primary endpoint had at least one US Food and Drug Administration criterion for severe COVID-19, defined as (1) SpO_2 93% or less on room air; (2) PaO_2/FiO_2 less than 300 mm Hg; (3) a respiratory rate more than 30 breaths per min or lung infiltrates more than 50% by chest CT scan. The further one control patient was hospitalised due to proximal deep vein thrombosis. Updating our results using the US Food and Drug Administration definition concludes with a similar RR as the definition we had used (RR 0·67 [95% CI 0·52–0·86], number needed to treat 18 (86/741 *vs* 130/756).

Hyun Kim and colleagues raise an interesting pharmacogenomic issue that we did not examine. However, considering the randomised and blinded trial design, this should affect both groups equally, as a relative effect.

Catia Marzolini and colleagues address an important concern about drug–drug interactions. We measured QTc intervals from all patients and did not identify important changes. We carefully avoided known associations that would elicit QTc prolongation and also potential medications that interact with fluvoxamine. We excluded patients on previous selective serotonin reuptake inhibitors. We understand the risks for a patient already on other neuroleptics, and we carefully followed up all patients for drug-induced toxicity or interactions. We have not identified any clinically relevant drug–drug interactions so far in the 1497 enrolled patients.

Finally, we are grateful to Michael Dodds and colleagues for their pharmacokinetic modelling. We too are interested in whether fluoxetine might offer benefits over fluvoxamine and are now beginning an evaluation of fluoxetine in our trial. We are also examining fluvoxamine plus inhaled budesonide as a combination. We are intending to evaluate fluvoxamine plus molnupiravir once we can access the antiviral.

We declare no competing interests.

*Gilmar Reis, *Edward Mills*
millsej@mcmaster.ca

Gilmar Reis, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil (GR); Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON L8S 4K1, Canada (EM)

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 Montori V, Permanyer-Miralda G, Ferreira-Gonzales I, et al. Validity of composite endpoints in clinical trials. *BMJ* 2005; **330:** 5945–96.

3 US Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. https://www.fda.gov/media/155050/download (accessed Jan 10, 2022).

4 Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med* 2021; published online Dec 16. https://doi.org/10.1056/NEJMoa2116044.