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Fluvoxamine for the treatment of COVID-19

We read with interest the investigation by Gilmar Reis and colleagues¹ who studied the repurposing of fluvoxamine for the mitigation of hospitalisation risk among acutely symptomatic patients with COVID-19 in Brazil. Although impressive, their observation that a 10-day course of fluvoxamine resulted in an absolute risk reduction of 5% and a relative risk reduction of 32% for hospitalisations might be an underestimate of its potential efficacy.

It is reasonable to believe that in order for fluvoxamine to exert a therapeutic benefit, it must reach a therapeutic systemic concentration, which is dependent on variables such as gastrointestinal absorption, hepatic function, renal function, and concomitant medications. However, one important variable that is not addressed in the paper is pharmacogenomic differences in CYP2D6, the enzyme primarily responsible for metabolic degradation of fluvoxamine. CYP2D6 is an important metabolic pathway for many pharmacologically significant substrates, including selective serotonin reuptake inhibitors such as fluvoxamine. Unlike other related genes, CYP2D6 exhibits clinically significant copy number variation resulting in some cases with an increased number of functional copies contributing to ultrarapid metabolic activity. Consequently, this directly affects bioavailability to such a degree that it is part of the determination for certain drug prescribing, as shown by guidelines from the Clinical Pharmacogenetics Implementation Consortium.² However, there are no clear fluvoxamine dosing recommendations for CYP2D6 ultrarapid metabolisers.

In a genetically heterogeneous population such as Brazilians, genetic contributions from Native American, European, and African ancestries,

could affect patients' responses to medications. It has been noted that the proportion of Brazilians with CYP2D6 duplications can be as high as 8.5%.³ Therefore, it is likely that of the 741 patients who received fluvoxamine in this study, approximately 63 patients might have had more than two functional copies of the gene, which could increase the likelihood of their being ultrarapid metabolisers. As a result, these patients might not have experienced therapeutic benefit due to faster metabolism of the drug, rendering their observed therapeutic responses closer to that of the placebo group. Because genetic variants in CYP2D6 would only be relevant in the active drug cohort, the net effect of not controlling for this variable would be to diminish the observed potential role of fluvoxamine.

This study highlighted the prospect of repurposing of existing drugs in the battle against COVID-19. We believe that studying the contribution of pharmacogenomic variants in affecting therapeutic response to fluvoxamine may enhance the findings of this study.

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.
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