



Fluvoxamine for the treatment of COVID-19

The clinical efficacy of fluvoxamine observed in the TOGETHER trial¹ (although no change in virological outcomes was observed) might be related to anti-inflammatory effects via sigma-1 receptor agonism,² but several other possible mechanisms warrant further investigation.³

After the clinical success of fluvoxamine, extrapolation of other therapeutics is inevitable. A logical candidate is fluoxetine, another selective serotonin reuptake inhibitor.

To translate in-vitro findings to the clinic, we apply pharmacokinetic modelling to compare free-drug concentration (unbound to plasma proteins) to in-vitro potency.^{2,4} Pharmacokinetic parameter estimates for fluvoxamine and fluoxetine were obtained from US prescribing information (Luvox, Solvay pharmaceuticals, US Food and Drug Administration, 1994; and Prozac, Eli Lilly and Company, US Food and Drug Administration, 1987), with additional fluoxetine parameter estimates from a study by Panchaud and colleagues.⁵

One-compartment models with first-order absorption were built and used to simulate fluvoxamine (association constant $[K_a]=0.356$ 1/h, oral clearance $[CL/F]=30.2$ L/h, volume of distribution $[V/F]=928$ L) and fluoxetine ($K_a=0.3$ 1/h, $CL/F=8.42$ L/h, $V/F=690$ L) plasma concentrations. The models were used to simulate dosing over 10 days. Free plasma concentrations were calculated for fluvoxamine (20% free) and fluoxetine (5.5% free). Ratio of plasma concentrations to sigma-1 receptor inhibitor constant⁴ and the half-maximal inhibitory concentration² of HEK293T cell lines expressing ACE2 and TMPRSS2 are reported (appendix).

Unbound fluvoxamine concentration is predicted to be three times greater than sigma-1 receptor binding affinity, suggesting anti-inflammatory fluvoxamine concentrations can be

reached clinically, in alignment with outcomes from the TOGETHER trial.¹ By contrast, predicted fluoxetine concentrations were ten times lower than sigma-1 receptor inhibitory constant, suggesting fluoxetine treatment at clinically approved doses might not be successful (appendix). Comparing plasma concentrations to half-maximal inhibitory concentrations of pseudotyped virus, neither fluvoxamine nor fluoxetine appeared promising (concentration or half-maximal inhibitory concentration ratios <1 ; appendix), which reflects primarily on the relevance of the potential mechanism of action assessed in these experiments.

These observations underscore the challenge of translation of in-vitro experience to clinic. It is important to use non-clinical data that inform the hypothesised primary pharmacology and use pharmacokinetic modelling of anticipated unbound concentrations relative to the non-clinical evaluations in translational efforts.

In conclusion, although the available pharmacological data do not provide a strong translational rationale for fluoxetine for treatment of SARS-CoV-2, available scientific data are very scarce. As such, further exploration of mechanistic and clinical potential of fluoxetine is warranted. Clinical potential should be established within the context of clinical trials where posology can be properly investigated and appropriate safeguards are in place for patients and off-label use should be discouraged.

MGD, EBD, FB, CRR are employed by Certara. Certara scientific support into the TOGETHER study was funded by the Bill and Melinda Gates Foundation. AMR is a co-applicant on a patent application filed by Washington University for the public use of generic selective serotonin reuptake inhibitors for COVID-19.

Copyright © 2022 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Michael G Dodds, *Eileen B Doyle,
Angela M Reiersen, Fran Brown,
Craig R Rayner
eileen.doyle@certara.com

Certara, Princeton, NJ 08540, USA (MGD, EBD, FB, CRR); Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA (AMR); Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia (CRR)

- 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 Fred SM, Kuivaneen S, Ugurlu H, et al. Antidepressant and antipsychotic drugs reduce viral infection by SARS-CoV-2 and fluoxetine show antiviral activity against the novel variants in vitro. *bioRxiv* 2021; published online March 23. <https://doi.org/10.1101/2021.03.22.436379> (preprint).
- 3 Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV. Fluvoxamine: a review of its mechanism of action and its role in COVID-19. *Front Pharmacol* 2021; **12**: 652688.
- 4 Brimson JM, Prasanth MI, Malar DS, Brimson S, Thitilertdecha P, Tencomnao T. Drugs that offer the potential to reduce hospitalization and mortality from SARS-CoV-2 infection: the possible role of the sigma-1 receptor and autophagy. *Expert Opin Ther Targets* 2021; **25**: 435–49.
- 5 Panchaud A, Garcia-Bournissen F, Csajka C, et al. Prediction of infant drug exposure through breastfeeding: population PK modeling and simulation of fluoxetine exposure. *Clin Pharmacol Ther* 2011; **89**: 830–36.

See Online for appendix