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

The clinical efficacy of fluvoxamine observed in the TOGETHER trial[1] (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 Drud 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 constant[4] and the half-maximal inhibitory concentration[2] 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.

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See **Online** for appendix