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RESEARCH LETTER

# Could Fluvoxamine Dose De-escalation Increase Treatment Compliance Without Sacrificing Efficacy in COVID-19 Patients?

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Multiple studies, including the TOGETHER trial [1], demonstrated the efficacy of fluvoxamine in preventing clinical deterioration in COVID-19 outpatients. A recently published meta-analysis in the *JAMA Network Open* concluded that fluvoxamine use was associated with lower hospitalisation rates in COVID-19 outpatients [2]. While the exact mechanism of action remains unknown, it is thought to be mediated by fluvoxamine's immunomodulatory activity through the sigma-1 receptor (S1R) agonism. The repurposing of fluvoxamine against COVID-19 was inspired by the results of a study conducted in 2019 which found that fluvoxamine had anti-inflammatory and immunomodulatory properties mediated by S1R agonism. The study found that fluvoxamine acted protectively against hypercytokinemia in an animal model of lipopolysaccharide (LPS) sepsis and significantly reduced production of interleukin (IL)-1β, IL-6, IL-8 and IL-12 induced by LPS in peripheral human heparinized blood samples [3]. Although, currently, the most likely mechanism of action of fluvoxamine is S1R-mediated immunomodulation of cytokine production, other potential mechanisms such as interference in endolysosomal trafficking of viral particles, reduction of platelet serotonin and inhibition of melatonin degradation have also been suggested and potentially have a synergist effect alongside S1R agonism. Further information and considerations regarding fluvoxamine's mechanism of action can be found in a review paper on the topic [4] or in one of our previous articles [5].

Although the results of several recent studies and the aforementioned meta-analysis suggested that a safe, inexpensive, and widely available oral anti-COVID-19 drug has been found, some issues regarding the tolerability of fluvoxamine still linger. In the TOGETHER trial [1], only 74% ($n = 548/741$) of participants had compliance > 80%, while 11% ($n = 84/741$) stopped fluvoxamine due to poor tolerability. The intolerability of fluvoxamine was linked to the relatively high targeted dose used in all three trials included in the meta-analysis—100 mg two times daily [2]—while typically, in non-COVID-19 indications, fluvoxamine is started at lower doses which are increased over time to maximise drug tolerability and consequently patient adherence.

Physicians who are already prescribing fluvoxamine off-label to their COVID-19 patients in relatively high starting doses, as suggested in reported clinical trials, will certainly be faced with a dilemma in approximately 10% of their patients with poor tolerance to fluvoxamine 100 mg two times per day, for whom they will need to decide whether to stop the treatment altogether or to attempt a dose reduction. As there are no conducted clinical trials that provided a direct answer to this question, we used pharmacokinetic modelling to try and estimate if fluvoxamine dose de-escalation might attain adequate plasma concentrations to still preserve fluvoxamine's efficacy in COVID-19 patients in the context of the compound's S1R affinity.

Fluvoxamine free plasma concentrations were modelled in PK-Sim® using an extensively validated and published [6] physiology-based pharmacokinetic model freely available on GitHub [7]; data visualisation was done in R (v.4.1.3). Fluvoxamine plasma concentrations were modelled over 10 days of treatment starting with two doses of 100 mg on the first day and a de-escalation to 50 mg every 8 hours (q8h), q12h or q24h for the following 9 days. The model predicted realistic total plasma fluvoxamine concentrations when compared with pharmacokinetic data from the FDA's Full Prescribing Information regarding fluvoxamine. The ratio of fluvoxamine-free plasma concentration (23% free) to its S1R Ki constant (Ki = 36 nM [8]) can be seen in Fig. 1A. According to our simulation, fluvoxamine at 100 mg q12h quickly reaches

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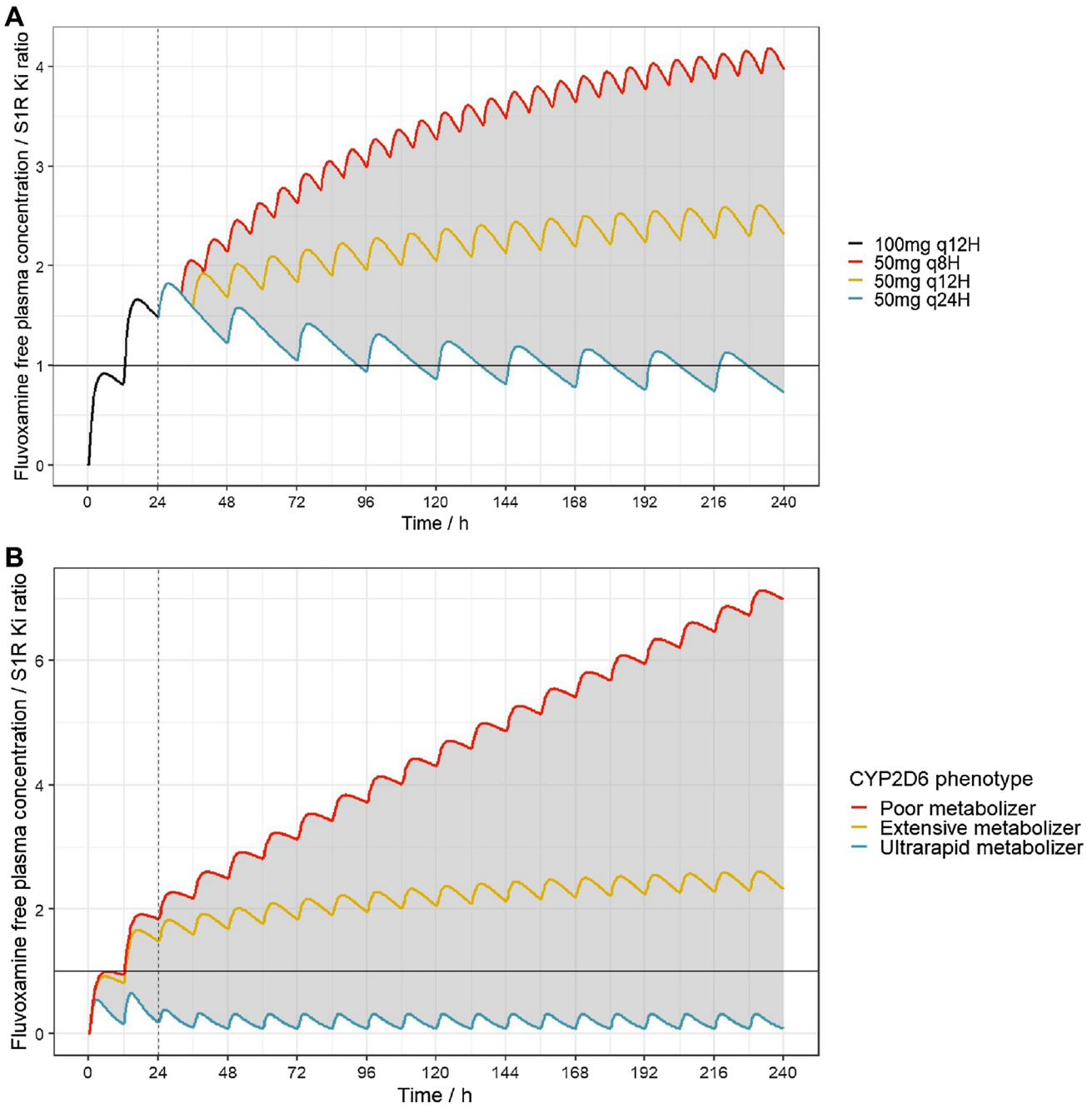


**Fig. 1** **A** Pharmacokinetic simulation of fluvoxamine free plasma concentration to its sigma-1 receptor (S1R) $K_i$ constant ratio over 10 days of treatment starting with two doses of 100 mg on the first day and de-escalating to 50 mg every 8 hours (q8h), q12h or q24h in the following 9 days. **B** Impact of CYP2D6 activity variability on the fluvoxamine free plasma concentration/S1R ratio in the proposed de-escalated dosing regimen of 50 mg q12h after two doses of 100 mg on the first day.

concentrations approximately 1.5 times over the S1R Ki constant and at further de-escalation to doses of 50 mg q8h and q12h remains at satisfactory levels, while at doses of 50 mg q24h plasma concentrations start to decrease and reach a relatively stable ratio $\leq 1$. Therefore, it seems that de-escalating fluvoxamine dosing to 50 mg q12h, after at least two doses of 100 mg, in patients not tolerating higher doses should provide adequate fluvoxamine-free plasma levels.

Additionally, as fluvoxamine has predetermined pharmacokinetic variability due to phenotypic differences in CYP2D6 metabolizing activity, we also attempted to model the impact of a wide range of CYP2D6 activity on fluvoxamine plasma concentrations, Fig. 1B. The CYP2D6 extensive

metaboliser phenotype, also used on simulations in Fig. 1A, is validated with the following pharmacokinetic parameters: $V_{max} = 0.69$ pmol/min/pmol enzyme, $K_m = 76.3$ µmol/L, $k_{cat} = 110.56$ min$^{-1}$ [7]. To simulate the poor metaboliser phenotype, CYP2D6 enzymatic metabolism was completely removed from the model. The ultra-rapid metaboliser phenotype was approximated with data from an in vitro study exploring the pharmacokinetics of 50 CYP2D6 allelic variants in regard to *N*-desmethyltamoxifen metabolism [9]. The lowest CYP2D6 $K_m$ value (4.75 µmol/L) and the highest $V_{max}$ (1.66 pmol/min/pmol enzyme) value from the study were used to approximate an ultra-rapid metaboliser. As can be seen in Fig. 1B, individuals whose CYP2D6 activity ranges from the poor to the extensive metaboliser phenotype (most of the population [10, 11]) should still attain adequately high fluvoxamine plasma concentrations at a de-escalated dose of 50 mg q12h following at least two 100-mg doses. The only patient group in which fluvoxamine plasma concentrations in the de-escalated (and potentially higher) doses would not reach satisfactory plasma levels are CYP2D6 ultrarapid metabolisers. The percentage of ultrarapid metabolisers varies across different major ethnic populations and geographic regions. A study conducted on a large multi-ethnic population of 104,509 patient samples across all regions of the United States found than only 2.2% of patients were ultrarapid CYP2D6 metabolisers [10]; however, the results from other studies looking at global rates indicated that the proportion of ultrarapid metabolisers varied significantly across the world, with estimates ranging from 1.4% in East Asia up to 21.2% in Oceanian, 11.5% in Ashkenazi Jewish, and 11.2% in Middle Eastern populations [11].

Based on our simulated pharmacokinetic data, fluvoxamine dose de-escalation in patients intolerant to doses evaluated in clinical trials conducted thus far might still result in satisfactory plasma concentrations with regards to the compound's S1R affinity. Although the efficacy of lower doses in COVID-19 patients should first be confirmed in randomised clinical trials (testing either lower fluvoxamine doses or a down titration protocol), our pharmacokinetic simulation results indicate that a dose reduction (e.g. fluvoxamine 50 mg two times daily) might be worth trying before the complete treatment cessation.

## Declarations

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**Conflict of interest** No conflicts of interest to declare.

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**Consent to participate** Not applicable.

**Consent for publication** The authors jointly and independently give the publisher the permission to publish their work.

**Availability of Data and Material** R code, Data and Materials are available in the public domain.

**Code Availability** Code is available upon reasonable request from the authors.

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