



RESEARCH ARTICLE

REVISED Fluoxetine pharmacokinetics and tissue distribution quantitatively supports a therapeutic role in COVID-19 at a minimum dose of 20 mg per day [version 3; peer review: 2 approved]

Previously titled: Fluoxetine pharmacokinetics and tissue distribution suggest a possible role in reducing SARS-CoV-2 titers

Andy R. Eugene ^{1,2}

¹Independent Neurophysiology Laboratory, Department of Psychiatry, Medical University of Lublin, Lublin Voivodship, 20-059, Poland

²Institute for the Study of Child Development, Department of Pediatrics, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, New Jersey, 08901, USA

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Abstract

Background. Various *in vitro* studies have shown fluoxetine inhibits multiple variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogen causing the coronavirus disease 2019 (COVID-19) worldwide pandemic and multiple observational clinical studies have shown that patients receiving fluoxetine experienced clinical benefit by lowering the risk of intubation and death. The aim of this study is to conduct population pharmacokinetic dosing simulations to quantify the percentage of patients achieving a *trough* level for the effective concentration resulting in 50% (EC50) and 90% (EC90) inhibition of SARS-CoV-2 as reported in Calu-3 human lung cells.

Methods. Pharmacometric parameter estimates used in this study were obtained from the U.S. FDA website from a new drug application for fluoxetine hydrochloride. A population of 1,000 individuals were simulated at standard fluoxetine antidepressant doses (20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, and 60 mg/day) to estimate the percentage of the patients achieving a *trough* plasma level for the EC50 and EC90 SARS-CoV-2 inhibition. All analyses were conducted in R.

Results. By day-10 at 20 mg/day, 93.2% and 47% of the population will achieve the *trough* target plasma EC50 and EC90 concentrations,

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1. **Nicolas Hoertel** , Assistance Publique-Hôpitaux de Paris (AP-HP), Issy-les-Moulineaux, France
Paris University, Paris, France
2. **Eero Castren** , University of Helsinki, Helsinki, Finland

Any reports and responses or comments on the

respectively, which translates to a lung tissue distribution coefficient of 60-times higher EC50 (283.6 ng/ml [0.82 mM]) and EC90 (1390.1 ng/ml [4.02 mM]). Further, by day-10 at an ideal dose of 40 mg/day, 99% and 93% of patients will reach the *trough* EC50 and EC90 concentrations, respectfully. Lastly, only a dose of 60 mg/day will reach the SARS-CoV-2 EC90 inhibitory concentration in the brain at pharmacokinetic steady-state.

Conclusion. Overall, with a minimum treatment period of 10-days and a minimum dose of 20 mg/day, this study corroborates *in vitro* studies reporting fluoxetine inhibiting SARS-CoV-2 titers and also multiple *observational* clinical studies showing therapeutic benefit of fluoxetine in COVID-19 patients.

Keywords

SARS-CoV-2, COVID-19, SSRI, psychopharmacology, coronavirus, fluoxetine vs fluvoxamine, titers, repurposing

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Corresponding author: Andy R. Eugene (andyeugene.md@gmail.com)

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REVISED Amendments from Version 2

In this revised version of this manuscript the following were made:

- 1) For all graphs, there is an additional y-axis scaled showing concentrations in micromolar.
- 2) In the Limitations subsection of the discussion, references are added to provide clarity the time to achieving the simulated concentrations in the organs will likely be more accurate at pharmacokinetic steady-state; more specifically at 10-days to 21-days.
- 3) An extra figure was added to show the fluoxetine organ tissue distribution results in micromolar concentrations with horizontal dashed lines depicting the EC50 and EC90 thresholds inhibiting SARS-CoV-2 in human lung cells.
- 4) In the discussion section, sub-headings are added for clarity for the reader.

Any further responses from the reviewers can be found at the end of the article

Introduction

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that is a racemic mixture of two stereoisomers, *R*-fluoxetine and *S*-fluoxetine, and maintains regulatory approvals for a wide-array of clinical indications in the medical specialty of psychiatry. Several recent *in vitro* studies have shown that fluoxetine inhibits replication of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pathogen causing the worldwide novel coronavirus disease 2019 (COVID-19) pandemic (Schloer *et al.*, 2020; Zimniak *et al.*, 2020, 2021; Dechaumes *et al.*, 2021; Fred *et al.*, 2021). The potential underlying mechanisms showing clinically protective factors in the SARS-CoV-2 infection is at least in-part due to fluoxetine being a functional inhibitor of acid sphingomyelinase (FIASMA) – the ceramide system – which is reported to play a critical central role in COVID-19, as shown in both preclinical (Carpinteiro *et al.*, 2020a, 2021) and observational clinical studies (Darquennes *et al.*, 2021; Hoertel *et al.*, 2021a,c). Further, another important mechanism is that fluoxetine (sigma-1 receptor, $K_i=191.2$ nM) and as fluvoxamine (sigma-1 receptor, $K_i=17.0$ nM), are endoplasmic reticulum-derived sigma-1 receptor agonists, which is known to inhibit cytokine production; thereby mitigating inflammation by decreasing tumor necrosis factor (TNF- α) and is protective against clinical deterioration in sepsis (Roumestan *et al.*, 2007; Hashimoto, 2015; Köhler *et al.*, 2018; Rosen *et al.*, 2019; Sukhatme *et al.*, 2021). Similarly, Marín-Corral *et al.* evaluated 22 metabolomics biomarkers from plasma samples in hospitalized COVID-19 patients (n=49) in an effort to guide COVID-19 clinical decisions by disease severity and found that ceramide metabolism, tryptophan degradation, as well as reduction in nicotinamide adenine nucleotide reactions were significantly associated with respiratory severity and inflammation patients in COVID-19 patients (Marín-Corral *et al.*, 2021). These known facts not only point to further understanding of the pathogenesis and efficacy of fluoxetine in depression, but also is suggestive of the compound being repurposed in infectious diseases.

In preclinical studies, Zimniak *et al.* reported that following a three day incubation period of fluoxetine in Vero cells, inoculated at a multiplicity of infection (MOI) of 0.5, resulted in the median maximal effective concentration (EC50) of 387 ng/ml (1.1 μ M) and further found a concentration of 800 ng/ml (2.3 μ M) significantly inhibited SARS-CoV-2 replication (Zimniak *et al.*, 2020, 2021). Similarly, Schloer *et al.* found that fluoxetine significantly decreases SARS-Cov-2 titers, after a 48-hour incubation period, in both African green monkey kidney epithelial Vero E6 cells (EC50=0.69 μ M and 90% maximal effective concentration [EC90]=1.81 μ M, MOI=0.01) and human-lung Calu-3 cells (EC50=0.82 μ M and EC90=4.02 μ M, MOI=0.1) (Schloer *et al.*, 2020). Further, Dechaumes *et al.* reported that fluoxetine can inhibit SARS-CoV-2 replication in Vero E6 cells at a MOI of 0.01 reducing infectious titers below the limit of quantification after 48-hours at 10 μ M (Dechaumes *et al.*, 2021). Lastly, Fred *et al.*, from the University of Helsinki, reported fluoxetine inhibits SARS-CoV-2 variants (B.1.1.7 and B.1.351) and the spike mutations (E484K, K417N, N501Y) in Calu-1 human lung epithelial cells at a median inhibitory concentration (IC50) of 5.992 μ M (Fred *et al.*, 2021). Taken together these *in vitro* studies prove in a dose-dependent manner that the SSRI fluoxetine inhibits the SARS-CoV-2 pathogen known to cause the worldwide pandemic, the novel coronavirus disease 2019 (COVID-19).

Clinically, the fluoxetine SARS-CoV-2 *in vitro* findings were corroborated by Hoertel *et al.* who showed in a multicenter observational retrospective cohort study of patients treated with fluoxetine and diagnosed with COVID-19, experienced a lower risk of intubation and death (hazard ratio [HR]=0.32; 95% confidence interval [CI], 0.14–0.73, p=0.007) at a median fluoxetine dose of 20 mg (standard deviation [SD]=4.82) (Hoertel *et al.*, 2020, 2021b). In addition, the association and/or effect of antidepressants improving clinical outcomes in COVID-19 have been confirmed in several recent observational clinical studies. Diez-Quevedo *et al.* aimed to identify how psychiatric disorders and psychopharmacological therapeutics prior to and throughout COVID-19 hospital admissions were related to mortality and found that out of 2,150 cases (between March 1, 2020 and November 17, 2020), 1,011 received psychotropics during admission (767 *de novo*, without history of psychotropics), and antidepressants (SSRI=220 [18.1%], mirtazapine=284 [59%]) were associated with a lower risk of mortality (HR=0.34, 95% CI, 0.17-0.67, p=0.002) (Diez-Quevedo *et al.*, 2021).

Hoertel *et al.* investigated compounds classified as FIASMAs, due to the ceramide/acid sphingomyelinase system being related to SARS-CoV-2 infection, found that out of a total of 2,846 hospitalized cases (277, 9.7% taking a FIASMA-based compounds), patients with FIASMA medications were significantly associated with lower likelihood of intubation or death (HR=0.71; 95% CI=0.58-0.87, $p<0.001$) (Hoertel *et al.*, 2021c). Another study ($n=545$) by Hoertel *et al.* which also investigated FIASMA psychotropics against COVID-19, reported that in 164 (30.1%) patients who were treated with FIASMA-based compounds at baseline, had a significant lower risk of intubation or death (HR=0.42; 95%CI=0.31-0.57; $p<0.01$) (Hoertel *et al.*, 2021a). Recently, Oskotsky and colleagues reported that among SSRIs, fluoxetine alone had a statistically significant lower relative risk of mortality in comparison to COVID-19 patients who were not prescribed the SSRI (Oskotsky *et al.*, 2021). Nemeth *et al.* reported in a retrospective case-control study conducted at the Uzsoki Street Teaching Hospital at the Semmelweis University found that, when compared to patients not taking fluoxetine, patients taking fluoxetine (20 mg/day) and diagnosed with COVID-19 pneumonia was associated with a 70% decrease of mortality (odds-ratio = 0.33 [95% CI, 0.16–0.68, $p=0.002$]) (Németh *et al.*, 2021). Most recently, in a large state psychiatric hospital operated by the New York State Office of Mental Health, Clelland *et al.* showed patients treated with fluoxetine ($p=0.023$) or trazodone ($p=0.001$) had statistically significant lower risk of infection with COVID-19, while there was a trend of higher risk of infections with patients treated with the atypical antipsychotic olanzapine ($p=0.084$) (Clelland *et al.*, 2022).

Two clinical trials showed another SSRI antidepressant fluvoxamine – also a FIASMA-based compound with sigma-1 receptor agonist properties – had clinical benefit against COVID-19 (Lenze *et al.*, 2020; Seftel & Boulware, 2021). Lenze *et al.* reported in a double-blind randomized clinical trial ($n=152$) between April 10, 2020 and August 5, 2020, that none (0 of 80) of the patients who received fluvoxamine ($n=80$) at 100 mg/day compared to 8.3% (6 of 72) of patients receiving placebo ($n=72$) three-times per day for 15 days experienced clinical deterioration (absolute difference=8.7%, 95% CI, 1.8%-16.4%, $p=0.009$) (Lenze *et al.*, 2020). Seftel *et al.* found in a prospective cohort study, none (0 of 65) of the patients who received fluvoxamine 50 mg twice daily (100 mg/day) versus 12.5% (6 of 48) of patients who were observed alone were hospitalized and by day-14, residual COVID-19 symptoms were evident in none (0 of 65) of patients treated with fluvoxamine versus 60% (29 of 48) of patients who observed alone (Seftel & Boulware, 2021).

Considering the COVID-19 clinical symptoms affecting the lungs, fluoxetine lung concentrations is a critically important factor to consider when interpreting study results of SARS-CoV-2 inhibition. Johnson *et al.* reported human-tissue concentrations of fluoxetine in airline pilots in whole-blood ranged from 0.021–1.4 µg/ml and lung concentrations ranged from 1.56 µg/ml to 51.9 µg/ml, leading to a fluoxetine distribution coefficient of 60, and is clinically relevant when investigating the pharmacokinetics of fluoxetine (Johnson, Lewis & Angier, 2007). In this context, the aim of this study is to conduct *in silico* population pharmacokinetic dosing simulations, which serve as the pharmacometrics standard in clinical trials and regulatory drug application submissions, to quantify the percentage of patients expected to achieve the *trough* effective concentration resulting in 90% inhibition of SARS-CoV-2 as found in Calu-3 human lung cells.

Methods

Pharmacokinetic model

The pharmacometrics model that incorporates differential equation variables and the respective variances for a structural one-compartment pharmacokinetic model with first-order absorption was referenced from the United State Food and Drug Administration's (FDA) Center for Drug Evaluation and Research Clinical Pharmacology and Biopharmaceutics Review(s) for a New Drug Application (NDA) 19-936 SE5-064 for Prozac (Fluoxetine Hydrochloride) that was submitted by Eli Lilly (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/18936S064_Prozac%20Pulvules_biopharmr.pdf) (Center for Drug Evaluation and Research, 2002). For this study, the pharmacokinetic parameters referenced from the NDA were calculated by the FDA after combining 3 pharmacokinetic study datasets resulting in the following pharmacometric parameters: volume of distribution (Vd) value of 1,480 liters (variance [ω], 0.22), clearance rate (CL) value of 29.1 liters/hour ($\omega=0.376$), and fixed absorption rate (Ka) of 0.67 (1/hour) (ω =not applicable as value was fixed) (Center for Drug Evaluation and Research, 2002). As noted in the fluoxetine NDA, the influence of age was neither relevant for clearance nor volume of distribution (Center for Drug Evaluation and Research, 2002).

Target fluoxetine plasma concentration to achieve the EC50 and EC90 lung concentrations

The molecular weight of fluoxetine hydrochloride is 345.8 g/mol and the reported EC50 (0.82 µM) and EC90 (4.02 µM) values from the Schloer *et al.* study are equivalent to EC50=283.6 ng/ml and EC90=1390.1 ng/ml, respectively. For all calculations, the *trough* target plasma concentrations will be referenced from the Schloer *et al.* study who reported after a 48-hour incubation period in Calu-3 lung cells (Schloer *et al.*, 2020) which are significantly higher than the EC90 in Vero E6 cell results from Zimniak *et al.* study (Schloer *et al.*, 2020; Zimniak *et al.*, 2020, 2021).

Dosing simulations

To estimate the percentage of patients from a population of one thousand simulated patients who would achieve the *trough* target EC90 concentration, pharmacokinetic dosing of fluoxetine consisted of three dosing trials of fluoxetine: 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, and lastly 60 mg/day.

Software and statistics

All pharmacokinetic dosing simulations are conducted with a population of 1,000 patients using *mrgsolve* and pharmacokinetic parameter estimates using *PKNCA* in R version 3.6.3 (R Core Team, 2015). The overall R script has been adapted from a study published in Clinical Pharmacology and Therapeutics using hydroxychloroquine (Al-Kofahi *et al.*, 2020). Statistical results providing percentage estimates are calculated from *trough* concentrations of patients achieving the effective concentrations and is referenced from the Schloer *et al.* study reporting the EC50 and EC90 values in human-lung Calu-3 cells (Schloer *et al.*, 2020).

Results

The fraction of fluoxetine bound in human plasma is 94%, which leaves only 6% of the compound being unbound in human plasma (Sommi, Crismon & Bowden, 1987). Despite fluoxetine being highly protein bound, a study by Mantinieks *et al.* reported in paired antemortem and postmortem cases (n=18), fluoxetine concentrations had a human whole-blood to plasma ratio of 0.8-1.0, meaning that the *fluoxetine whole-blood concentrations are actually less than plasma or, at most, up to a 1:1 ratio* and would not require to be scaled from plasma to whole-blood (Mantinieks *et al.*, 2020). Moreover, Mantinieks *et al.* found the postmortem (range: 0.031–1.4 mg/L) to antemortem (range: 0.018–0.51 mg/L) fluoxetine drug concentration ratio as 1.8, but was not statistically significant as the p-value > 0.05 and thus the 1.8 ratio is not applicable to this study (Mantinieks *et al.*, 2020). Therefore, this study directly translates the simulated fluoxetine plasma concentrations and directly applied the tissue distribution coefficients (60 for lung, 15 for brain, 10 for heart, 38 for liver, 20 for spleen, and 9 for kidneys) from the Johnson *et al.* study and the original preprint version of this manuscript is updated to account for the findings from Mantinieks *et al.* (Johnson, Lewis & Angier, 2007; Eugene, 2020, 2021; Mantinieks *et al.*, 2020).

The target EC90 endpoint lung concentration for fluoxetine is 1390.1 ng/ml [4.02 µM] and 1/60 of this concentration is the new EC90-plasma concentration of 23.2 ng/ml [0.067 µM]. Similarly, the fluoxetine SARS-CoV-2 lung EC50 is 283.6 ng/ml [0.82 µM] and 1/60 of the EC50 at the target lung concentration in the plasma results in 4.7 ng/mL. The percentage of the 1,000 simulated patients are illustrated in the following figures: Figure 1 (20 mg/day), Figure 2 (30 mg/day), Figure 3 (40 mg/day), Figure 4 (50 mg/day), and Figure 5 (60 mg/day) with a horizontal dashed-line throughout the pharmacokinetic dosing figures showing the required *trough* EC50 and EC90-plasma levels that translates to the 60-times higher lung concentrations.

At the peak fluoxetine concentration (C_{max}), the corresponding median time T_{max} is 220 hours (range, 49–220) and has a half-life (t_{1/2}) – expressed as arithmetic mean (standard deviation, SD) – of 46.6 hours (SD=40.8) for the study population. Further, in a population of 1,000 patients during a fluoxetine treatment period of once daily dosing for 10-days, the following are the maximum lung concentrations (C_{max}-lungs): 20 mg/day (C_{max}-lungs = 1950 ng/mL [5.6 µM]), 30 mg/day (C_{max}-lungs=2922 ng/mL [8.4 µM]), 40 mg/day (C_{max}-lungs=3900 ng/mL [11.3 µM]), 50 mg/day (C_{max}-lungs=4872 ng/mL [14.1 µM]), 60 mg/day (C_{max}=5844 ng/mL [16.9 µM]). At all doses ranging from 20 mg/day to 60 mg/day, oral fluoxetine doses were able to exceed the target SARS-CoV-2 EC50 [0.82 µM] and EC90 [4.02 µM] inhibitory values. Detailed results of all of the maximum concentrations in the plasma, whole-blood, lungs, heart, liver, spleen, and kidney are found in Table 1.

Table 2 provides all of the pharmacodynamic population outcomes of the percentage of the patient population achieving the EC50 and EC90 *trough* target lung concentrations. Using the mean fluoxetine pharmacokinetic dosing parameters, dosing simulations are graphically depicted in Figure 6 and Figure 7. The *trough* plasma (C_{min}) and lung concentrations, prior to the morning dose on Day-10, are identified to be: C_{min}_{20mg}=22.8 ng/ml (lung=1368 ng/ml [4.0 µM]), C_{min}_{30mg}=34.1 ng/ml (lung=2046 ng/ml [5.9 µM]), C_{min}_{40mg}=45.5 ng/ml (lung= 2730 ng/ml [7.9 µM]), C_{min}_{50mg}=56.9 ng/ml (lung=3414 ng/ml [9.9 µM]), and C_{min}_{60mg}=68.3 ng/ml (lung= 4098 ng/ml [11.9 µM]).

The difference between the C_{max} and C_{min} in this study is approximately 20 ng/ml and to calculate the equivalent micromolar concentration, the ng/ml value is divided by the molecular weight of 345.8 g/mol. With a t_{1/2} of 46.6 hours and summing the t_{1/2} with the standard deviation of 40.8 hours, a portion of the population will take 21-days to reach steady-state. Further, assuming all patients are treated with fluoxetine for either 10-days or 21-days and with the last dose being on the morning of either day-10 or day-21, the amount of time it would take for the plasma concentration to fall beneath the threshold plasma EC50 (4.7 ng/ml [0.014 µM]) and EC90 (23.2 ng/ml [0.067 µM]) values that results in

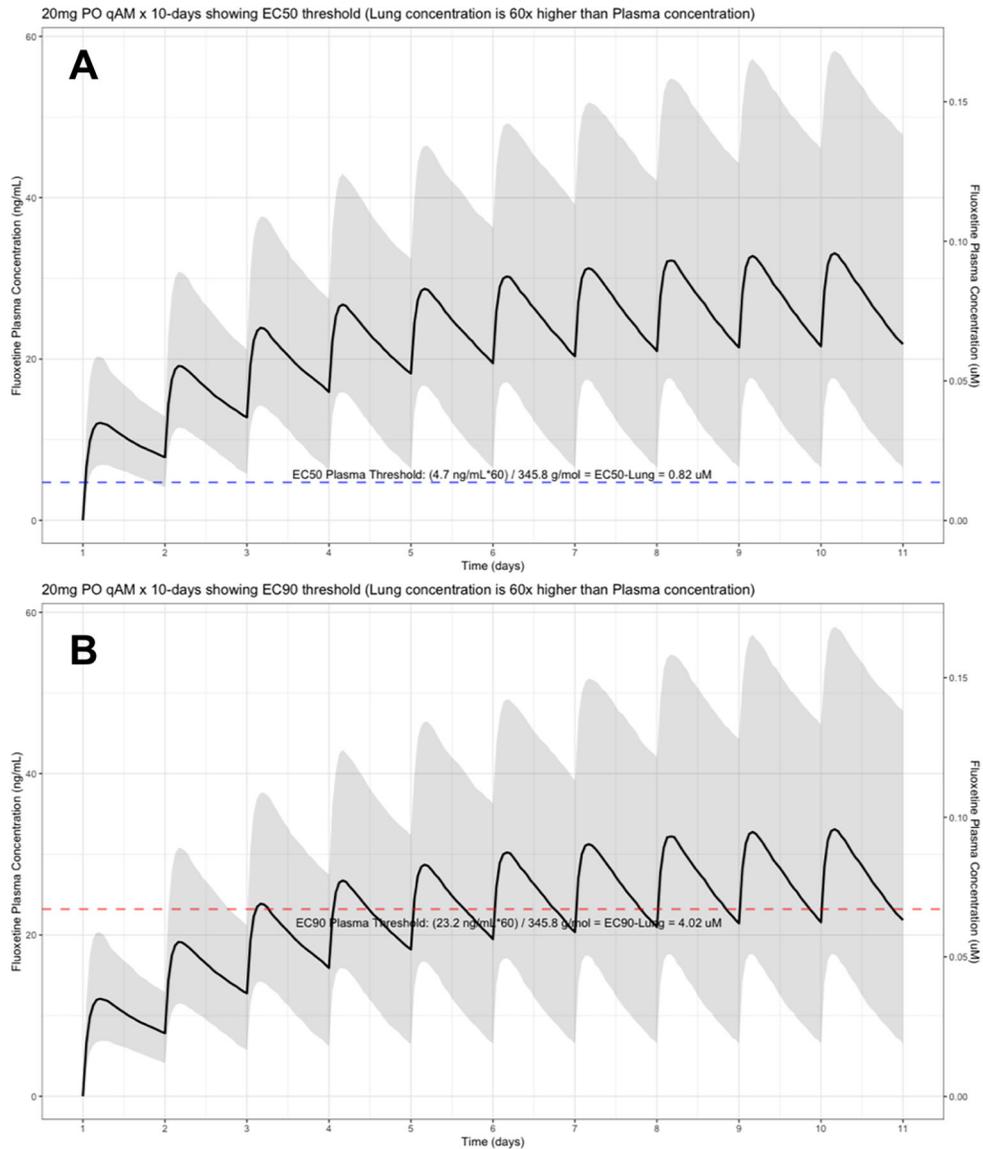


Figure 1. Fluoxetine population (n=1,000) dosing simulation results for an oral dose of 20 mg/day for 10 days. The shaded regions illustrate the 10th (lower) and 90th (upper) percentiles with the solid line within the shaded region representing the median fluoxetine concentration. The dashed horizontal line depicts the effective concentration resulting (A) 50% and (B) 90% inhibition (EC90) of SARS-Cov-2 that will result in 60-times higher level in the lungs.

60-times higher lungs (EC50=283.6 ng/ml [0.82 μM]) and EC90=1390.1 ng/ml [4.02 μM], are as follows: 20 mg/day (3.4 days to EC50; 0 days to EC90), 30 mg/day (4.2 days to EC50; 0.8 days to EC90), 40 mg/day (4.8 days to EC50; 1.5 days to EC90), 50 mg/day (5.3 days to EC50; 1.9 days to EC90), and 60 mg/day (5.7 days to EC50; 2.3 days to EC90). **Figure 6** illustrates the fluoxetine pharmacokinetics over 10-days and **Figure 7** shows fluoxetine pharmacokinetics throughout 21-days for once daily dosing in the morning with EC50 and EC90 threshold values. **Figure 8** shows fluoxetine median organ concentrations (μM) at pharmacokinetic steady-state with EC50 (0.82 μM) and EC90 (4.02 μM) thresholds known to inhibit SARS-CoV-2.

Discussion

Brain EC50 and EC90 concentrations

Extrapolating from *in vitro* to *in vivo* concentrations are dependent on intracellular versus extracellular concentrations, as well as the methodology of quantifying either whole-blood versus plasma concentrations in human pharmacokinetic studies. The EC50 and EC90 target concentrations represent the extracellular fluoxetine concentrations in the

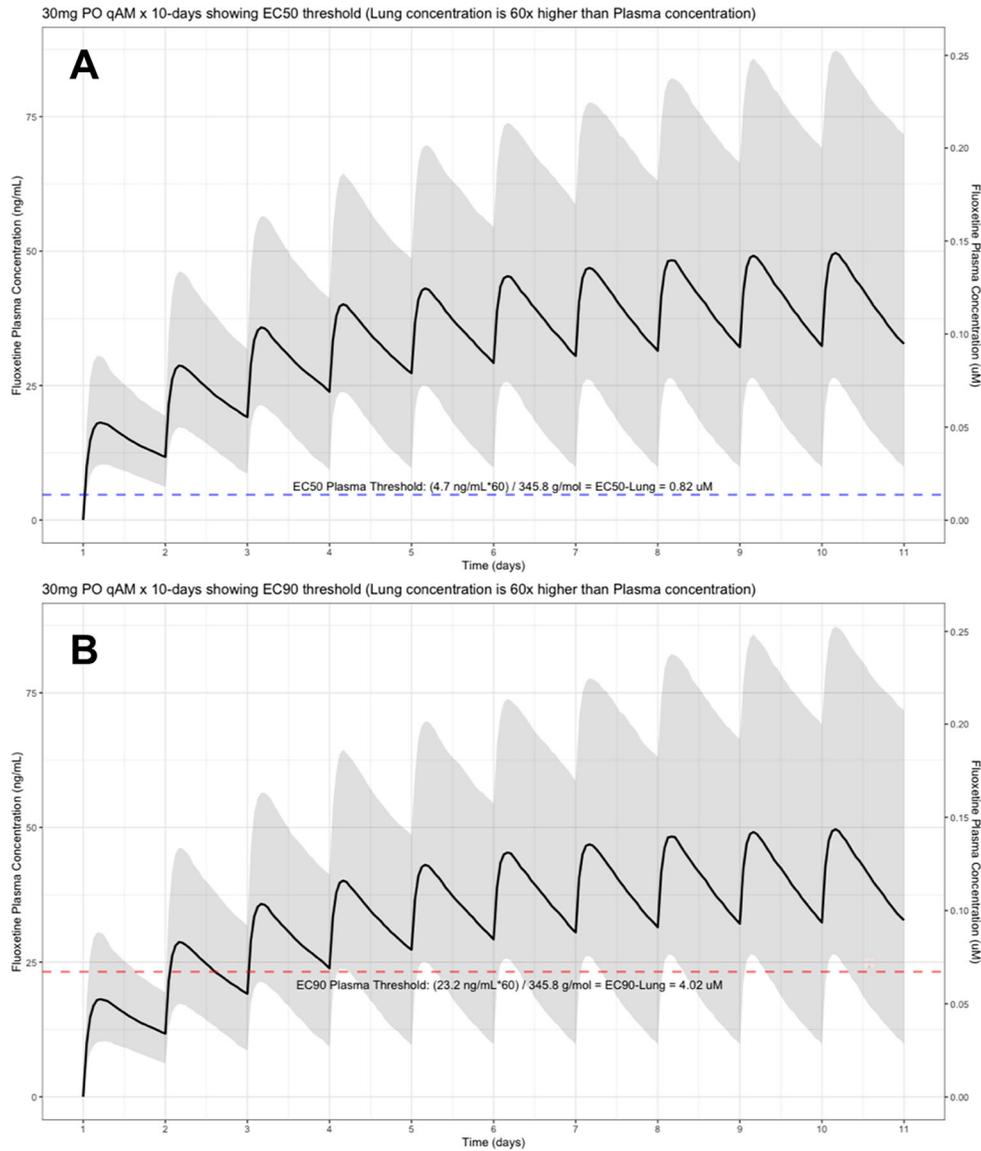


Figure 2. Fluoxetine population (n=1,000) dosing simulation results for an oral dose of 30 mg/day for 10 days. The shaded regions illustrate the 10th (lower) and 90th (upper) percentiles with the solid line within the shaded region representing the median fluoxetine concentration. The dashed horizontal line depicts the effective concentration resulting (A) 50% and (B) 90% inhibition (EC90) of SARS-CoV-2 that will result in 60-times higher level in the lungs.

SARS-CoV-2 cell culture media. As COVID-19 is known to affect the brain during active infection and in post-COVID-19, adequate brain concentrations would be clinically important in patients who may experience depression. Bolo *et al.* reported fluoxetine brain concentrations, at steady-state, using fluorine magnetic spectroscopy and showed fluoxetine concentrations were 10-times higher in the brain than in human plasma (Bolo *et al.*, 2000). Specifically, Bolo *et al.* found in study participants taking oral doses (10 mg, n=1; 20 mg, n=1; 40 mg, n=2) with a treatment period ranging from three months to 12-months that fluoxetine human brain concentrations were 13 μM (SD=7) versus 1.73 μM (SD=1.00) in human plasma fluoxetine (Bolo *et al.*, 2000). In comparison, Johnson *et al.* found the coefficients for tissue distribution of fluoxetine relative to whole-blood was: 60 \times higher for the lung, 15 \times for brain, 10 \times for heart, 38 \times for liver, 20 \times for spleen, and 9 \times higher for the kidneys (Johnson, Lewis & Angier, 2007). Of note, all fluoxetine doses of at least 20 mg/day exceeds the EC50 in the brain; however, only a fluoxetine dose of 60 mg/day exceeds the EC90 in the brain resulting in 90% inhibition of the SARS-CoV-2 titers and likely most beneficial for long COVID-19 and likely treatment-resistant depression associated with inflammatory biological markers.

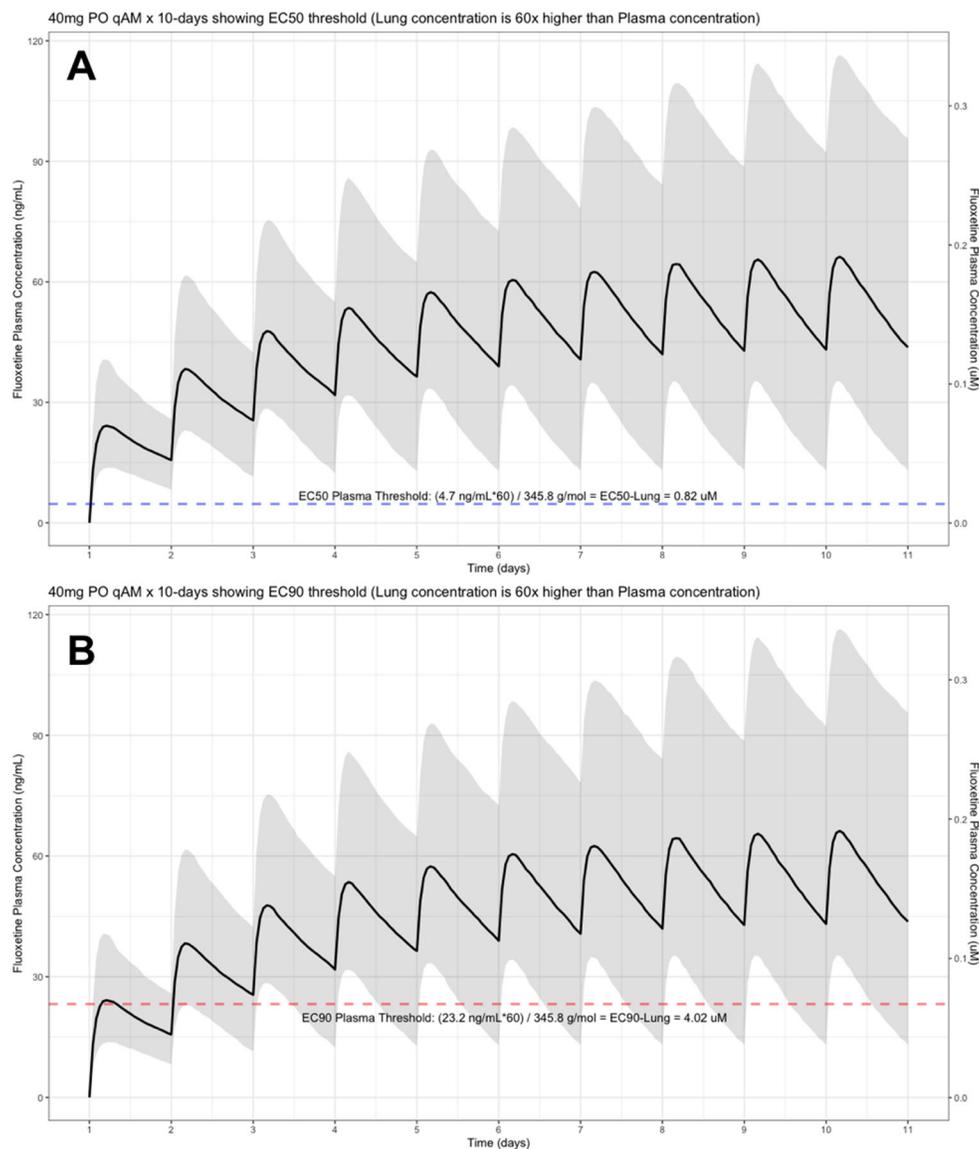


Figure 3. Fluoxetine population (n=1,000) dosing simulation results for an oral dose of 40 mg/day for 10 days. The shaded regions illustrate the 10th (lower) and 90th (upper) percentiles with the solid line within the shaded region representing the median fluoxetine concentration. The dashed horizontal line depicts the effective concentration resulting (A) 50% and (B) 90% inhibition (EC90) of SARS-CoV-2 that will result in 60-times higher level in the lungs.

Fluoxetine adverse drug reactions and drug-drug-interactions

According to the United States Food and Drug Administration Adverse Events Reporting System (FAERS) during the window period of 1982 to June 30, 2022, fluoxetine was reported to have a total of 85,407 cases, 67,924 serious cases, and 11,046 end of life cases (<https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard>). Females (n=49,467) represented 58% of the adverse drug reaction (ADR) cases, males (n=23,240) represented 27% of the ADRs cases, and 15% of the ADR cases did not specify (n=12,700) a gender. The most common adverse drug event reported for fluoxetine is Drug Interaction and amounts to 4,347 cases (5.1% of total). Given this information, drug interactions associated with fluoxetine are due to inhibition of the cytochrome P450 (CYP) system. Specifically, CYP2C19 and CYP2D6 may have interactions such as in patients taking tamoxifen for breast cancer by inhibiting conversion to the active endoxifen metabolite via CYP2D6 or in cases of clopidogrel in cardiology by inhibiting the conversion of clopidogrel to the active 2-oxo-clopidogrel metabolite (Spina, Trifirò & Caraci, 2012; Eugene, 2019).

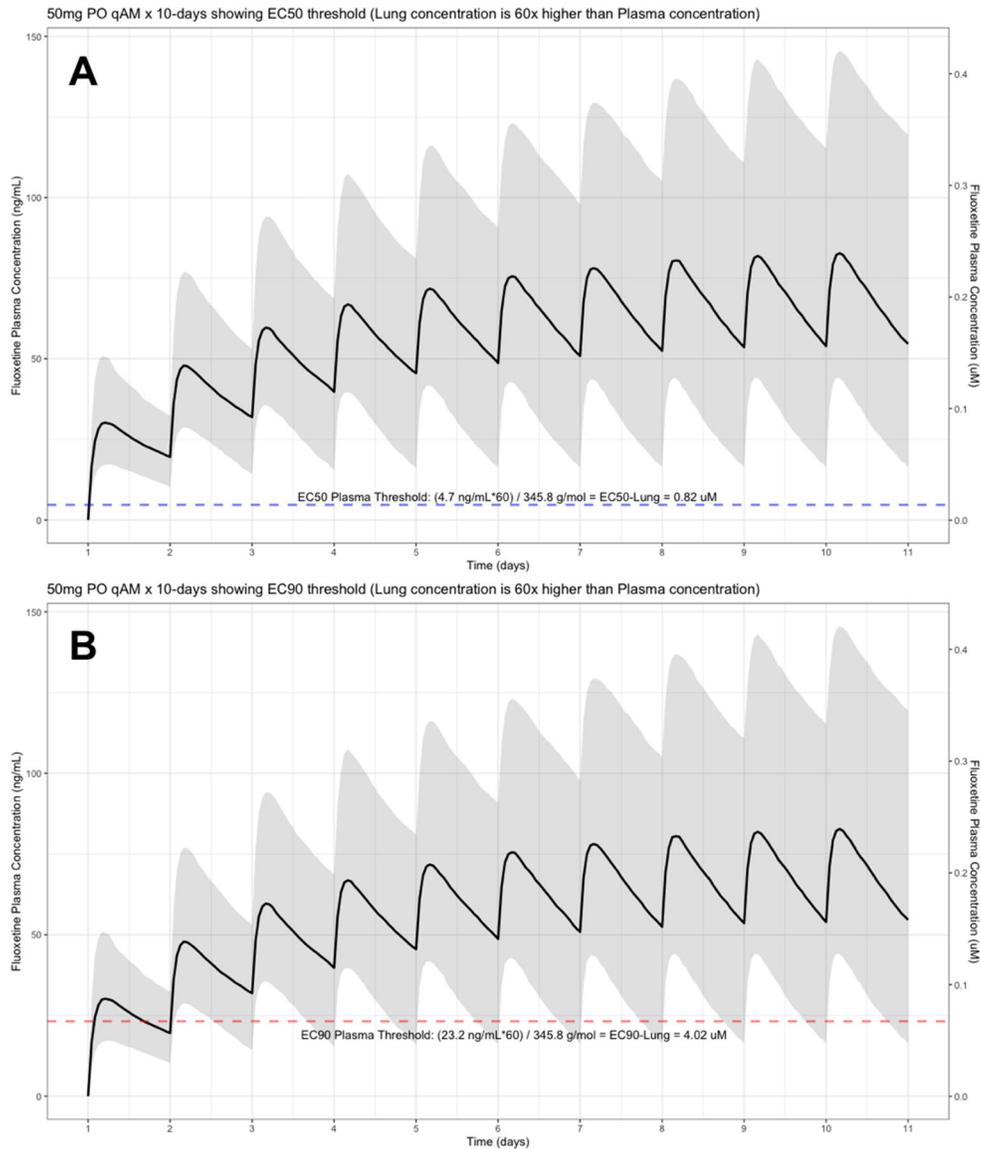


Figure 4. Fluoxetine population (n=1,000) dosing simulation results for an oral dose of 50 mg/day for 10 days. The shaded regions illustrate the 10th (lower) and 90th (upper) percentiles with the solid line within the shaded region representing the median fluoxetine concentration. The dashed horizontal line depicts the effective concentration resulting (A) 50% and (B) 90% inhibition (EC90) of SARS-CoV-2 that will result in 60-times higher level in the lungs.

Overall, from a drug-safety perspective, prior to administering fluoxetine, a careful review of all current medications and clinical status by a physician clinical pharmacologist to avoid drug interactions due to fluoxetine’s ability to strongly inhibit CYP2C19 and CYP2D6 (Hefner, 2018). Compounds that are sensitive and moderate CYP2C19 substrates (e.g. omeprazole, diazepam, lansoprazole, rabeprazole, voriconazole) and CYP2D6 substrates (e.g. dextromethorphan, eliglustat, nebivolol, tolterodine, encainide, metoprolol, propranolol, tramadol) will have an increased total area under the concentration-time curve of ≥ 5 -fold drug exposure when treated with fluoxetine (<https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>). Lastly, patients who have a pharmacogenomic profile of being a CYP2D6 Ultra-rapid Metabolizers may have sub-therapeutic fluoxetine concentrations; while, CYP2D6 Poor Metabolizer or Intermediate Metabolizers may have supratherapeutic concentrations and should be monitored for potential fluoxetine side-effects; but may also have a higher rate of achieving the target trough EC90 concentration at a 20 mg/day fluoxetine dose relative to CYP2D6 Normal (Extensive) Metabolizers.

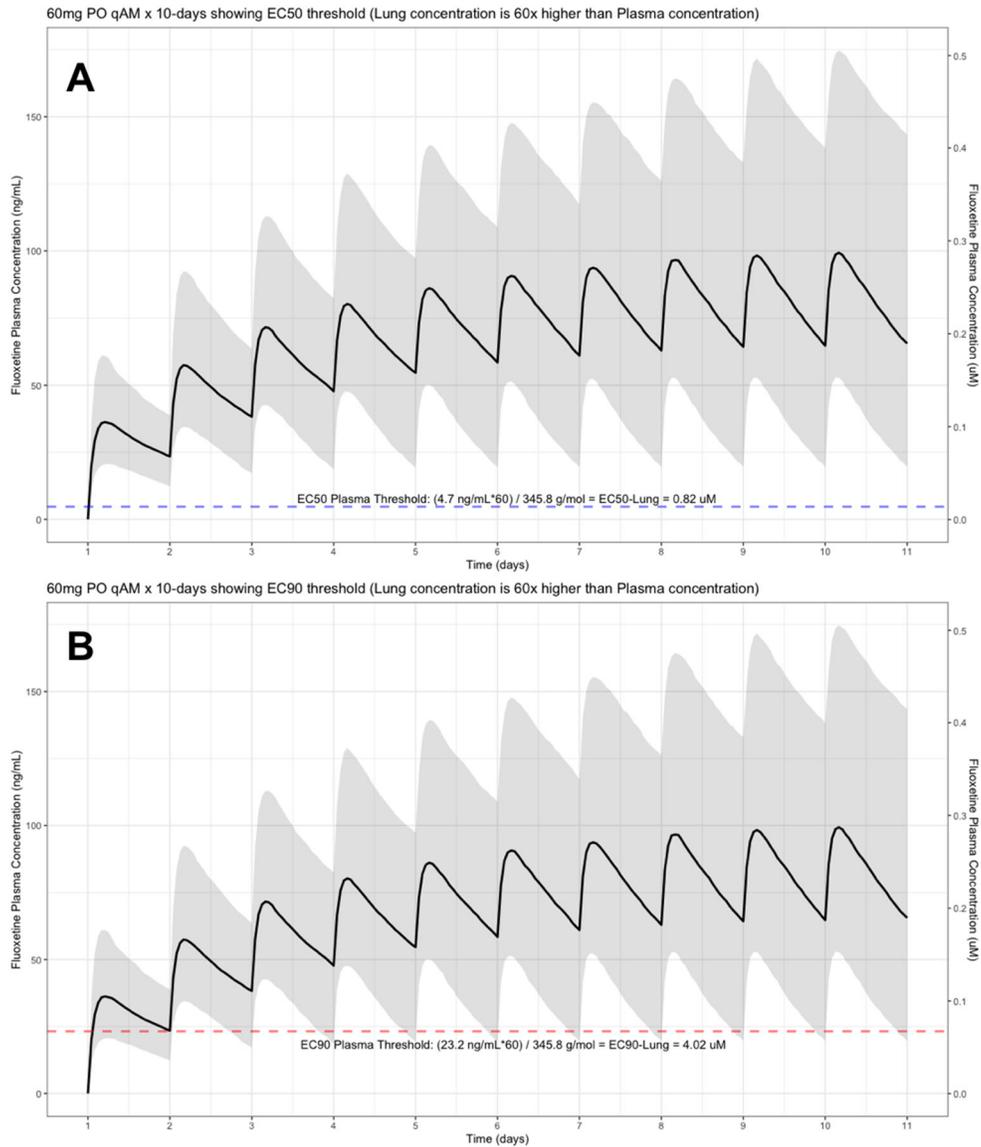


Figure 5. Fluoxetine population (n=1,000) dosing simulation results for an oral dose of 60 mg/day for 10 days. The shaded regions illustrate the 10th (lower) and 90th (upper) percentiles with the solid line within the shaded region representing the median fluoxetine concentration. The dashed horizontal line depicts the effective concentration resulting (A) 50% and (B) 90% inhibition (EC90) of SARS-CoV-2 that will result in 60-times higher level in the lungs.

Long COVID-19 and fluoxetine

As patients recover from the acute COVID-19 symptoms, long-term sequelae are being documented and in one of the long COVID-19 study in young patients reported that 92% were found to have ongoing cardiorespiratory symptoms with organ dysfunction and impairment in the lungs (33%), heart (32%), kidneys (12%) (Dennis *et al.*, 2020). In another long COVID-19 syndrome study, 96% of the patients were female and experienced statistically significant exercise intolerance, dyspnea, and chest pain when compared to those not diagnosed with COVID-19 (Walsh-Messinger *et al.*, 2020). Moreover, Walsh-Messinger *et al.* found patients with long COVID-19 syndrome had higher ratings of depression subscale markers of altered sleep and thinking, but depression severity was not significantly different with patients not diagnosed with COVID-19 (Walsh-Messinger *et al.*, 2020). As shown in Table 1, a fluoxetine dose of 60 mg/day achieves the EC90 concentration in the brain and would likely benefit patients with neuropsychiatric symptoms of COVID-19 at pharmacokinetic steady-state.

Table 1. Fluoxetine pharmacokinetics showing median organ concentrations (ng/mL and μM) aiming to achieve the target SARS-CoV-2 EC50 (283.6 ng/ml [0.82 μM]) and EC90 (1390.1 ng/ml [4.02 μM]) during by day-10 of treatment in humans.

Organ	Fluoxetine organ distribution concentrations at standard antidepressant doses				
	20 mg/day	30 mg/day	40 mg/day	50 mg/day	60 mg/day
	Cmax ng/ml [μM]	Cmax ng/ml [μM]	Cmax ng/ml [μM]	Cmax ng/ml [μM]	Cmax ng/ml [μM]
Plasma	32.5 [0.09]	48.7 [0.14]	65 [0.19]	81.2 [0.23]	97.4 [0.28]
Whole-Blood	32.5 [0.09]	48.7 [0.14]	65 [0.19]	81.2 [0.23]	97.4 [0.28]
Lung	1950 [5.6]	2922 [8.4]	3900 [11.3]	4872 [14.1]	5844 [16.9]
Brain	487.5 [1.4]	730.5 [2.1]	975 [2.8]	1218 [3.5]	1461 [4.2]
Heart	325 [0.9]	487 [1.4]	650 [1.9]	812 [2.3]	974 [2.8]
Liver	1235 [3.6]	1850.6 [5.4]	2470 [7.1]	3085.6 [8.9]	3701.2 [10.7]
Spleen	650 [1.9]	974 [2.8]	1300 [3.8]	1624 [4.7]	1948 [5.6]
Kidney	292.5 [0.8]	438.3 [1.3]	585 [1.7]	730.8 [2.1]	876.6 [2.5]

Maximum plasma concentration (Cmax) are expressed as geometric mean (geometric coefficient of variation, CV%). Fluoxetine tissue distribution coefficients (60 for lung, 15 for brain, 10 for heart, 38 for liver, 20 for spleen, and 9 for kidneys) as reported (Johnson, Lewis & Angier, 2007).

Table 2. Predicted SARS-CoV-2 pharmacodynamics showing the daily fluoxetine dose and corresponding percent of the population (n=1,000) achieving a trough plasma concentration of 4.7 ng/ml (EC50-plasma) and 23.2 ng/ml (EC90-plasma), which leads to 60-times higher lungs based on the target EC50 (283.6 ng/ml [0.82 μM]) and EC90 (1390.1 ng/ml [4.02 μM]) concentrations, during a treatment period of 10-days.

Time point	20 mg/day		30 mg/day		40 mg/day		50 mg/day		60 mg/day	
	% EC50	% EC90								
Day 1	85.7	0.3	94.9	4.2	97	14.7	98.2	34	98.7	51.6
Day 2	93	6.7	96.4	33.3	97.6	56.9	98.6	72.4	98.7	82.1
Day 3	93.2	19.4	96.5	52.6	97.6	71.2	98.6	81.5	98.7	85.9
Day 4	93.2	30.8	96.6	59.7	97.7	75.4	98.6	83	98.7	87.1
Day 5	93.2	37.9	96.6	64.2	97.7	77.6	98.6	83.7	98.7	87.4
Day 6	93.2	42.3	96.6	66.1	97.8	78.1	98.6	83.9	98.7	87.4
Day 7	93.2	44.5	96.6	67.1	97.8	78.5	98.6	83.9	98.7	87.6
Day 8	93.2	45.8	96.6	67.6	97.8	78.5	98.6	83.9	98.7	87.6
Day 9	93.2	46.6	96.6	67.8	97.8	78.5	98.6	83.9	98.7	87.6
Day 10	93.2	47	96.6	68	97.8	78.6	98.6	83.9	98.7	87.6

Opportunities for repurposing compounds in COVID-19

In addition to *fluoxetine*, other psychotropics (*fluvoxamine*, *hydroxyzine*, and *trazodone*) and one antihypertensive (*amlodipine*) are reported to be associated with reducing risk of death in patients with COVID-19 (Zhang *et al.*, 2020; Darquennes *et al.*, 2021; Sánchez-Rico *et al.*, 2021; Clelland *et al.*, 2022; Reis *et al.*, 2022). Further, Reznikov *et al.* showed three antihistamines (*azelastine*, *diphenhydramine*, and *hydroxyzine*) have direct inhibitory activity against SARS-CoV-2 *in vitro*; while clinically, Reznikov *et al.* showed *azelastine*, *cetirizine*, *diphenhydramine*, *hydroxyzine*, and *loratadine* was significantly associated with a lower incidence of testing positive for COVID-19 in patients 61-years-old and older, but only *cetirizine* had the same association in patients 31-years-old and older (Reznikov *et al.*, 2020).

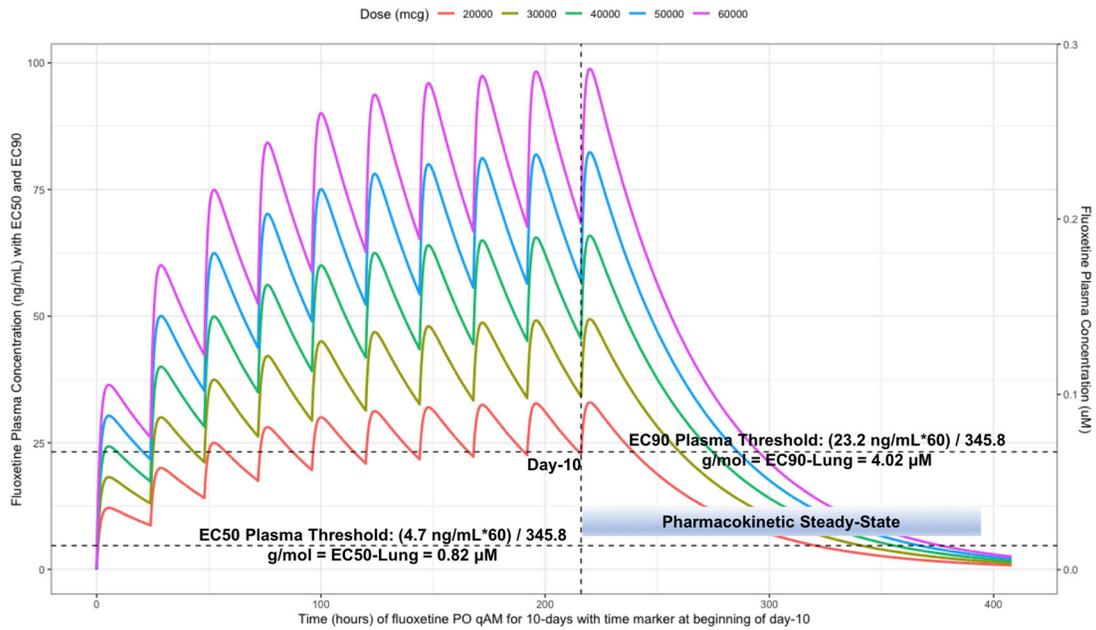


Figure 6. Fluxetine concentration-time profile in human plasma at standard daily antidepressant doses (20 mg/day, 30 mg/day, 40mg/day, 50 mg/day, 60 mg/day) throughout 10 days. The vertical line illustrates the morning dose on day-10, the highest (EC90) and lowest (EC50) horizontal lines illustrates the threshold for the plasma effective concentrations inhibiting 50% and 90% of SARS-CoV-2 titers that distributes to 60-times higher concentrations within the lungs, respectively.

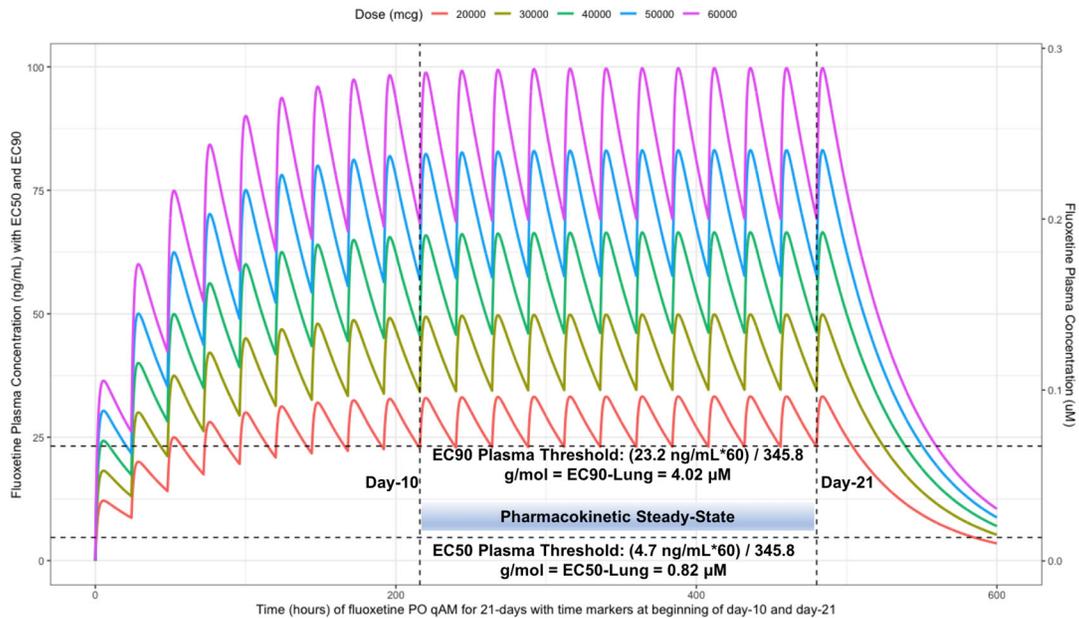


Figure 7. Fluxetine concentration-time profile in human plasma at standard daily antidepressant doses (20 mg/day, 30 mg/day, 40mg/day, 50 mg/day, 60 mg/day) throughout 21 days. The two vertical line illustrates the morning doses on day-10 and on day-21. The highest (EC90) and lowest (EC50) horizontal lines illustrates the threshold for the plasma effective concentrations inhibiting 50% and 90% of SARS-CoV-2 titers that distributes to 60-times higher concentrations within the lungs, respectively.

Further, of note, the over-the-counter compound famotidine (PEPCID®), a histamine type 2 H₂ receptor antagonists, which has been shown to inhibit the human immunodeficiency virus (HIV) (Bourinbaiair & Fruhstorfer, 1996), has also been shown to provide clinical benefit in patients with COVID-19 – particularly COVID-19 pneumonia – and future

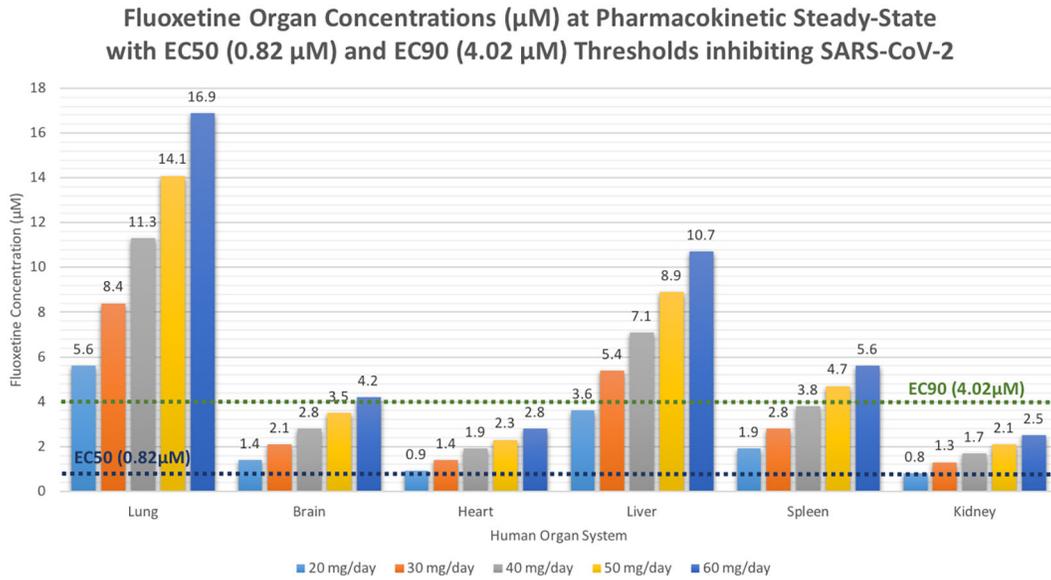


Figure 8. Fluoxetine median organ concentrations (µM) at pharmacokinetic steady-state with EC50 (0.82 µM) and EC90 (4.02 µM) thresholds known to inhibit SARS-CoV-2.

retrospective studies should evaluate potential synergistic benefit as famotidine is available in both oral and intravenous formulations (Freedberg *et al.*, 2020; Janowitz *et al.*, 2020; Mather, Seip & McKay, 2020). Lastly, doxycycline has also been shown to provide benefit in patients with COVID-19 pneumonia even in high-risk elderly nursing home patients and achieves therapeutic levels in lungs as found *in vitro* (Alam *et al.*, 2020; Gendrot *et al.*, 2020; Stricker & Fesler, 2020; Yates *et al.*, 2020; Alexpandi *et al.*, 2022).

Previously known antimicrobial properties of fluoxetine

Antimicrobial properties of fluoxetine are well reported in the biomedical literature. Carpinteiro *et al.* reported that fluoxetine inhibits acid sphingomyelinase preventing infection of both cultured cells and human nasal epithelial cells in SARS-CoV-2, as well as in vesicular stomatitis virus pseudoviral particles presenting the SARS-CoV-2 spike protein (Carpinteiro *et al.*, 2020b). A study by Zuo *et al.* showed fluoxetine resulted in potent inhibition of the coxsackievirus by reducing both synthesis of viral RNA and protein (EC50 of 2.3 µM or 795.34 ng/ml) exhibiting peak antiviral properties at 6.25 µM (2161.25 ng/ml) (Zuo *et al.*, 2012). Bauer *et al.* showed, in a broad-spectrum manner, fluoxetine inhibited enterovirus (picornaviridae family) replication with the *S*-fluoxetine enantiomer exhibiting a 5-fold lower EC50 than the racemic mixture of *R*- and *S*-fluoxetine (Bauer *et al.*, 2019). Further, Bauer *et al.* found the following fluoxetine EC50 values for the following pathogens: coxsackievirus B3 (racemate-EC50=2.02 µM or 698.5 ng/ml, *S*-fluoxetine-EC50=0.42 µM or 145.2 ng/ml), enterovirus EV-D68 (racemate-EC50=1.85 µM or 639.7 ng/ml, *S*-fluoxetine-EC50=0.67 µM or 231.7 ng/ml), and *S*-fluoxetine values alone for rhinovirus HRV-A2 (EC50=7.95 µM or 2749.1 mg/ml) and HRV-B14 (EC50=6.34 µM or 2192.4 ng/ml) (Bauer *et al.*, 2019). Notably, Zimniak *et al.* found that individual stereoisomers, *R*-fluoxetine and *S*-fluoxetine, inhibited the SARS-CoV-2 viral load; however, in contrast, fluoxetine could not inhibit gene expression of the herpes simplex-1 virus, human herpes virus-8, rabies virus, nor the respiratory syncytial virus (Zimniak *et al.*, 2020, 2021). As shown in Table 1, standard fluoxetine doses are capable of achieving the aforementioned EC50s for all of the aforementioned microbes and fluoxetine may be combined with antipsychotics (e.g. olanzapine) to treat bipolar depression, treatment-resistant depression, schizophrenia in general and these antipsychotics may have notable associations with sedation and somnolence (Eugene *et al.*, 2021).

Direct clinical translation of this current pharmacokinetic study supports the findings from a retrospective multicenter observational study by Hoertel *et al.*, who found a median fluoxetine dose of 20 mg/day resulted in a significantly lower risk of intubation and death in a population composed of 63% women and 37% men (Hoertel *et al.*, 2020, 2021b). Comparing the Hoertel *et al.* and Zimniak *et al.* publications, Hoertel *et al.* found that in addition to fluoxetine, venlafaxine (median dose of 75 mg/day) and escitalopram (median dose of 10 mg) were also associated with a lower risk of intubation and death; however, Zimniak *et al.* showed that neither escitalopram nor paroxetine inhibited SARS-CoV-2 *in vitro* (Hoertel *et al.*, 2020, 2021b; Zimniak *et al.*, 2020, 2021). There have been authors who have suggested that the effect of fluoxetine in treating depression is due to a placebo effect; however, with all due respect, it

suggests of the lack of knowledge of the etiologies of depression and clinical pharmacology of fluoxetine beyond serotonin transporters to inhibiting inflammatory cytokines and more that will be identified (Kirsch & Sapirstein, 2004).

Fluoxetine dose for COVID-19 clinical trials

Optimal dose selection for clinical trials are of importance to ensure the maximum number of patients achieve the effective concentration resulting in 90% inhibition of the SARS-CoV-2 pathogen similarly to that reported in Calu-3 human lung cells. Based on the study findings showing the percentage of the population achieving the EC50 and EC90 inhibitory concentrations in the lungs, a dose of 40 mg/day would be recommended to achieve therapeutic potential inhibiting SARS-CoV-2 titers. Overall, given the abundance of clinical trial data and published clinical studies investigating various dosing approaches (e.g. loading dose) for fluoxetine, this author defers all final dosing recommendations for fluoxetine to the FDA approved package-insert for adults and for the pediatrics population (Eli Lilly / Dista Products Company, 2021). For an application in pediatrics, fluoxetine doses in children are recommended to start at 10 mg/day and then titrate to 20 mg/day, whereas in adults with depression, a 20 mg/day is recommended as a starting dose (Eli Lilly/Dista Products Company, 2021). Lastly, given pharmacogenomic (drug-gene), DDIs, and drug-drug-gene interactions that are likely in patients taking multiple medications, therapeutic drug monitoring of fluoxetine and other co-administered medications are recommended.

Study limitations

A limitation of this study is in respect to how fast the trough concentrations are achieved which assumes that fluoxetine immediately distributes to lung tissue at the estimated 60-fold concentration compared to plasma levels. There is some evidence that suggests fluoxetine may accumulate into tissues over time as is reported by Erb *et al.* who found that certain antidepressants accumulate in lipid rafts *in vitro* over several days of exposure (Erb, Schappi & Rasenick, 2016). In reference to human brain fluoxetine concentrations, Karson *et al.* used spectroscopy and determined that fluoxetine and the norfluoxetine metabolite are not detectable in human brain at about 1 week, but actually detectable at about 2- to 3-weeks of treatment the concentrations were able to be assayed indicating that fluoxetine accumulates in brain over time (Karson *et al.*, 1993). Therefore, with this evidence, it is likely that the fluoxetine lung concentrations would not be evident as quickly as reported in the simulations and the data should be interpreted assuming the target EC50 and EC90 concentrations inhibiting SARS-CoV-2 at fluoxetine's pharmacokinetic steady-state concentrations – that is between 10-days and 21-days of treatment – and patients should in-turn be treated for 21-days with fluoxetine in order to have a valid clinical trial with a dose of at least 20 mg/day and ideally at 40 mg/day.

Another limitation of this study is that the results are purely quantitative using pharmacometrics simulations based on differential equations and not a randomized controlled clinical trial. Despite this limitation, it is important for the reader to note that the methodology used in this study is standard practice for all drugs undergoing Phase-1 Clinical Trials in drug development by clinical pharmacologists for later regulatory approval for human use. Moreover, the pharmacometric parameters used were estimated from an NDA submitted to the United States Food and Drug Administration with parameter estimates actually calculated by the FDA clinical pharmacologists as reported in the Clinical Pharmacology and Biopharmaceutics Review after combining three human study datasets provided by the study sponsor (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/18936S064_Prozac%20Pulvules_biopharmr.pdf).

Conclusions

This study investigated fluoxetine pharmacokinetics and human organ distribution which confirmed that previously published median effective concentrations and specifically, the EC90 fluoxetine value inhibiting SARS-CoV-2 in Calu-3 human lung cells are achievable using standard fluoxetine antidepressant doses (20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, and 60 mg/day) and also corroborates findings from multiple retrospective clinical studies showing patients who were exposed to fluoxetine during COVID-19 were associated with reduced risk of clinical deterioration and death. Overall, assuming patients are not treated with medications that result in significant DDIs or have the clinically relevant pharmacogenomic concerns, a minimum dose of 20 mg/day for at least 10-days inhibits SARS-CoV-2 viral titers, but a dose of 40 mg/day would be ideal for clinical trials evaluating fluoxetine in COVID-19 due to efficient lung distribution at a 60-times higher concentration.

Data availability

Underlying data

Open Science Framework: All pharmacokinetic data presented in this study are available for download at the following link: <https://doi.org/10.17605/OSF.IO/RVYPZ>.

This project contains the following underlying data:

- Data File 1: v2_fluoxetine_20mg_PO_QAM.csv
- Data File 2: v2_fluoxetine_30mg_PO_QAM.csv
- Data File 3: v2_fluoxetine_40mg_PO_QAM.csv
- Data File 4: v2_fluoxetine_50mg_PO_QAM.csv
- Data File 5: v2_fluoxetine_60mg_PO_QAM.csv
- Data File 6: v2_fluoxetine_all_doses_10days.csv
- Data File 7: v2_fluoxetine_all_doses_21days.csv

Software availability

Open Science Framework: The R programming language pharmacokinetic script that produces the general results of this study are available for download at: <https://doi.org/10.17605/OSF.IO/RVYPZ> (Eugene, 2021).

This project contains the following software:

- v3_Fluoxetine_pharmacokinetic_sars_cov2_simulation_script - publication - DrAndy_R_EugeneMDPhD.R

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Eero Castren 

Neuroscience Center, Helsinki Institute of Life Science HiLIFE, University of Helsinki, Helsinki, Finland

The revised article is fine.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuropharmacology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 25 February 2022

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Eero Castren 

Neuroscience Center, Helsinki Institute of Life Science HiLIFE, University of Helsinki, Helsinki, Finland

The author has only partially responded to the comments I gave to the previous version. It is also very difficult to see what changes have actually been made to the version 1.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuropharmacology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 09 February 2022

<https://doi.org/10.5256/f1000research.119937.r121955>

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Nicolas Hoertel 

¹ Hôpital Corentin-Celton, Service de Psychiatrie, Assistance Publique-Hôpitaux de Paris (AP-HP), Issy-les-Moulineaux, France

² Paris University, Paris, France

All my comments have been well addressed. I thank and congratulate the author for this very important PK modelling study.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psychiatry; antidepressants; methodology; biostatistics; epidemiology; sphingomyelinase; COVID-19.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 23 June 2021

<https://doi.org/10.5256/f1000research.56641.r87690>

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Eero Castren 

Neuroscience Center, Helsinki Institute of Life Science HiLIFE, University of Helsinki, Helsinki, Finland

Andy Eugene has written an interesting paper on a very timely topic. Preclinical as well as limited clinical data support the idea that some antidepressants and related compounds may protect cells from SARS-CoV2 infection, but it has been unclear whether concentrations that are found in cell culture studies to be inhibitory are really achieved in clinical treatments. It is unfortunate that there is only limited amount of high-quality data on the tissue concentrations and distribution of fluoxetine in human tissues, but Eugene has taken advantage of the data that is available to model fluoxetine pharmacokinetics in human lung tissue. His results suggest that sufficiently high lung tissue concentrations are achieved within a 10 day treatment period in majority of patients with a standard 20 mg/day dosing, and with higher doses, the trough concentration is achieved within the first days of treatment. The simulations appear properly conducted and the manuscript is well written. I have a few issues that might improve the manuscript further.

1. The conclusions about how fast trough concentrations are achieved is based on the assumption that fluoxetine immediately distributes to lung tissue at the estimated 60 fold concentration compared to plasma levels. However, there is some (although clearly incomplete) information that fluoxetine may accumulate into tissues over time. Rasenick and colleagues have found that certain antidepressants accumulate in lipid rafts in vitro over several days of exposure (Erb *et al.* 2016¹) For human brain, Karson *et al.* have found that, using spectroscopy, fluoxetine/norfluoxetine is not detectable in human brain at about 1 week, but at about 2-3 weeks of treatment, concentrations of several micromolar can be assayed (Karson *et al.* (1993²)) indicating that fluoxetine accumulates in brain over time. If the same is true for lung tissue, the 60-fold concentrations may not be reached in lung tissues as quickly as estimated here. Although paucity of information prevents any proper estimations, I think it would be important to discuss this issue in the discussion section.
2. The author should be complemented for indicating in many places in the manuscript fluoxetine concentrations in both ng/ml and in molar units, however, this is not done systematically. It would be very helpful to, wherever possible, indicate both units. In the figures, it may not be feasible to have double set of units in the Y-axis, I would prefer molar units, but if the author prefers ng/ml, that is not a major problem.
3. The author may want to mention that a **clinical phase 3 trial** evaluating the effect of fluvoxamine vs. placebo is ongoing and should be completed by September this year.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuropharmacology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 21 June 2021

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Nicolas Hoertel

¹ Hôpital Coirentin-Celton, Service de Psychiatrie, Assistance Publique-Hôpitaux de Paris (AP-HP), Issy-les-Moulineaux, France

² Paris University, Paris, France

This is a review of the manuscript "Fluoxetine pharmacokinetics and tissue distribution suggest a possible role in reducing SARS-CoV-2 titers" submitted for publication in *F1000Research*. This is a very interesting and important study, which addresses a timely and important question – in a context of a growing number of preclinical and clinical studies showing a potential efficacy of certain antidepressants, and particularly fluoxetine, in COVID-19, what dose of fluoxetine should be optimally prescribed in clinical trials to ensure a maximum of patients achieve the effective concentration resulting in 90% inhibition (EC90) of SARS-CoV-2 as reported in Calu-3 human lung cells. On a more general, and potentially more innovative front, it is one of a small (but quickly

increasing) number of studies contributing to this topic and the first study to the reviewer's knowledge addressing this specific pharmacokinetic issue, which is an important area of inquiry with major implications in this context of pandemic. There is much to like about this manuscript. The results are presented clearly, the methods are sound, the discussion follows well from it, and the manuscript is very well written. Below are several points that would strengthen the submission:

Title:

- A minor suggestion would be a modification of the title to increase the interest to this important study, such as "Fluoxetine pharmacokinetics and tissue distribution suggest a possible therapeutic role in COVID-19 at usual antidepressant dose".

Introduction:

- The introduction section should be updated and include a description of results from recent studies focused on the association between antidepressant use and the course of COVID-19, which would be very helpful to readers to understand the clinical context of this study and why this study (and its results) are important. In addition to the medRxiv one, the reference to the published article of Hoertel N *et al.* should be cited (Hoertel N *et al.* (2021¹)). This association/potential effect of certain antidepressants in COVID-19 has been confirmed in several other observational studies (Diez-Quevedo *et al.* (2021²), Hoertel *et al.* (2021³), Hoertel *et al.* (2021⁴)), two clinical trials (1 RCT and 1 open-label study) with the antidepressant fluvoxamine (which is, like fluoxetine, a functional inhibitor of sphingomyelinase acid and a 51R agonist) (Lenze *et al.* (2020⁵), Seftel & Boulware (2021⁶)), and other preclinical studies (Dechaumes *et al.* (2021⁷), Fred *et al.* (2021⁸)). Results from all those studies, increasing the interest in the present submission, should be recognized and briefly summarized in the Introduction.
- As evoked in the discussion, potential underlying mechanisms include antiviral effect of certain antidepressants, and particularly fluoxetine, through the inhibition of the acid sphingomyelinase/ceramide system, which may play a central role in COVID-19, as suggested by preclinical studies (Carpinteiro *et al.* (2020⁹), and Carpinteiro *et al.* (2021¹⁰)) and observational studies (Hoertel N *et al.* (2021³), Darquennes G *et al.* (2021¹¹), Hoertel *et al.* (2021⁴)), as well as anti-inflammatory properties through sigma-1-receptor agonist effect of certain antidepressants, and particularly fluoxetine and fluvoxamine (Köhler CA *et al.* (2018¹²), Rosen D *et al.* (2019¹³), Sukhatme VP *et al.* (2021¹⁴), Roumestan C *et al.* (2007¹⁵)). Moreover, a recent study (Marín-Corral *et al.* (2021¹⁶)) showed that ceramide plasma concentration is associated with inflammatory markers and clinical outcomes in COVID-19 patients. I think that results from all those studies should also be recognized and shortly summarized in the Introduction.
- The abstract might include some of these points listed above.

Results:

- Importantly, results from that study can help guide the choice of the right dose to use in COVID-19 clinical trials. I would strongly recommend the author to present in the result section as well as in the abstract (for main findings) for each following dose: 20 mg/d, 30mg/d (which is also interesting for clinical tolerability purpose), 40 mg/d and 60 mg/d the percentage of patients reaching a) EC90 and b) EC50 at (i) 1 day, (ii) 2 days, and (ii) 3 days. In

addition, given that 40 mg/d might lead to increased risk of mild side effects among older adults and that at the same time reaching the efficient dose as fast as possible is desirable given the potential antiviral properties of fluoxetine, would a loading dose of 30 mg or 40 mg the first or two first days, followed by a dose of 20 mg/day, perform better than only taking 20 mg/d?

- Finally, is there a way to ensure that at no point of the 10 day treatment course, no patient (typically older adults) will reach a toxic plasma dose with the different scenarios, as I think 40 mg/d is the maximum recommended dose in the elderly population? Even if the reviewer recognizes that it may represent a substantial additional amount of work, these detailed results will certainly be of great help to clinicians to balance the risks associated for each dose and the potential benefits, and help them design ideal clinical trial.
- With the different scenarios, at the end of the 10-day treatment, how long would it take to have a substantial decrease in the fluoxetine plasma concentration (and its metabolite norfluoxetine)? This information would give an idea of the duration of potential protection of the treatment against SARS-CoV-2 once stopped and of the required duration of medical follow-up.

Conclusion:

- Finally, with these different dose scenarios, what recommendation(s) of dose would do the author for a clinical trial including fluoxetine for COVID-19? Would it be desirable to do a loading dose then decrease to the standard 20 mg/d dose which is known to be very well tolerated in older adults? Or keeping 30 mg/d or 40 mg/d throughout the trial would be the best choice?

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

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Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psychiatry; antidepressants; methodology; biostatistics; epidemiology; sphingomyelinase; COVID-19.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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