Antiviral efficacy of fluoxetine in early symptomatic COVID-19: an open-label, randomised, controlled, adaptive platform trial (PLATCOV)

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eClinicalMedicine 2025;80: 103036
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.103036

Summary

Background The selective serotonin reuptake inhibitors (SSRIs) fluoxetine and fluvoxamine were repurposed for the treatment of early COVID-19 based on their antiviral activity *in vitro*, and observational and clinical trial evidence suggesting they prevented progression to severe disease. However, these SSRIs have not been recommended in therapeutic guidelines and their antiviral activity *in vivo* has not been characterised.

Methods PLATCOV is an open-label, multicentre, phase 2, randomised, controlled, adaptive pharmacometric platform trial running in Thailand, Brazil, Pakistan, and Laos. We recruited low-risk adult outpatients aged 18–50 with early symptomatic COVID-19 (symptoms <4 days) between 5 April 2022 and 8 May 2023. Patients were assigned using block randomisation to one of eleven treatment arms including oral fluoxetine (40 mg/day for 7 days), or no study drug. Uniform randomisation ratios were applied across the active treatment groups while the no study drug group comprised ≥20% of patients at all times. The primary endpoint was the rate of oropharyngeal viral clearance assessed until day 7. Measurements were taken daily between days 0 and 7 and analysed in a modified intention-to-treat population (>2 days follow-up).
The viral clearance rate was estimated under a Bayesian hierarchical linear model fitted to the $\log_{10}$ viral densities measured in standardised duplicate oropharyngeal swab eluates taken daily over one week (18 measurements per patient). Secondary endpoints were all-cause hospital admission at 28 days, and time to resolution of fever and symptoms. This ongoing trial is registered at ClinicalTrials.gov (NCT05041907).

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Findings 271 patients were concurrently randomised to either fluoxetine (n = 120) or no study drug (n = 151). All patients had received at least one COVID-19 vaccine dose and 67% were female (182/271). In the primary analysis, viral clearance rates following fluoxetine were compatible with a small or no increase relative to the no study drug arm (15% increase; 95% credible interval (CrI): −2 to 34%). There were no deaths or hospitalisations in either arm. There were no significant differences in times to symptom resolution or fever clearance between the fluoxetine and the no study drug arms (although only a quarter of patients were febrile at baseline). Fluoxetine was well tolerated, there were no serious adverse events and only one grade 3 adverse event in the intervention arm.

Interpretation Overall, the evidence from this study is compatible with fluoxetine having a weak *in vivo* antiviral activity against SARS-CoV-2, although the primary endpoint is also compatible with no effect. This level of antiviral efficacy is substantially less than with other currently available antiviral drugs.

Funding Wellcome Trust Grant ref: 223195/Z/21/Z through the COVID-19 Therapeutics Accelerator.

Keywords: SARS-CoV-2; Antivirals; COVID-19; Viral clearance

Research in context

Evidence before this study

The antidepressant SSRIs fluoxetine and fluvoxamine have been proposed as COVID-19 therapeutics based on observational, randomised trial, and *in vitro* evidence. We searched PubMed and EMBASE for studies in English up until the 30th November 2023 using the search terms "fluoxetine", "fluvoxamine", and "COVID-19" with the search restricted to randomised controlled trials (RCTs).

Added value of this study

We provide evidence that in early COVID-19 illness the SSRI fluoxetine may have antiviral activity *in vivo*. This activity is substantially less than other available specific antivirals such as ritonavir-boosted nirmatrelvir and molnupiravir. The pharmacometric approach described here provides a quantitative measure of *in vivo* antiviral effects with tractable sample sizes.

Implications of all the available evidence

Fluoxetine may have weak *in vivo* antiviral activity in early COVID-19, although uncertainty remains. This degree of activity is likely insufficient for it to be recommended for treatment currently.

Introduction

When disease specific medicines are unavailable, repurposing of existing small molecule drugs can provide affordable and widely available treatment or prevention options. At the beginning of the COVID-19 pandemic there was considerable interest in drug repurposing, but there was little success in demonstrating clinical efficacy apart from the use of immunomodulatory drugs for severe and hospitalised patients (e.g., dexamethasone).[1] No clear benefits were demonstrated for any of the initial antiviral candidates. Now, four years later, there are several approved efficacious antiviral drugs to treat early symptomatic COVID-19, but these are expensive, and they are not widely available.[2] Ritonavir-boosted nirmatrelvir is currently the most effective small molecule antiviral drug but, in addition to its very high cost (up to $1600 USD/course), it has major drawbacks including drug interactions, dysgeusia, and it has been associated with viral rebound.[3] The only other widely available efficacious oral drug, molnupiravir, has concerns over generation of mutant viruses.[4,5] There remains a need for effective, reliable, accessible, and affordable antiviral treatments for early COVID-19.

Selective serotonin reuptake inhibitors (SSRIs) are the most widely used class of antidepressants. They are readily available and affordable globally. In some countries over 10% of the adult population are prescribed SSRIs. Observational studies early in the pandemic suggested that patients taking fluoxetine had reduced mortality when admitted to hospital with COVID-19.[6,7] Subsequent studies supported this observation,[8,9] and also suggested that SSRIs may confer a prophylactic benefit.[10] Another SSRI, fluvoxamine, was assessed in a meta-analysis which pooled eight randomised trials.[11–18] One of the trials evaluated two independent groups; patients with mild and moderate disease.[18] Treatment with fluvoxamine was compatible with a moderate reduction in hospitalisation or death in COVID-19 outpatients, with an estimated risk-ratio of 0.80 (95% CI: 0.62–1.01, Supplementary Appendix Figure S2). There were no outpatient randomised controlled trials for fluoxetine (Supplementary Appendix Subsection S12).

The proposed mechanism of antiviral action of SSRIs is through functional inhibition of acid sphingomyelinase (so-called FIASMAs). This may result in

interference with SARS-CoV-2 viral entry or endolysosomal acidification.[19,20] Although most of the earlier research focussed on the closely related compound fluvoxamine, fluoxetine was found to have the greatest *in vitro* FIASMA activity, the best tolerability profile, and the most favourable pharmacokinetic properties.[21] Fluoxetine is on the WHO's list of Essential Medications for the treatment of depression.[22] *In vitro* anti-SARS-CoV-2 activity has been shown at fluoxetine plasma concentrations approximating those during the treatment of depression (20 mg daily; 0.8 μg/mL, 2.6 μM).[23] *In silico* pharmacokinetic modelling determined that an adult dose of 40 mg per day would provide at least 85% of patients with the trough target plasma concentrations needed to reach the estimated target 90% maximal effective concentration (EC90) within 3 days,[24] although the justification for the extrapolated concentration target is not strong.

It is no longer feasible to conduct randomised trials assessing prevention of hospitalisation and death in outpatients with symptomatic COVID-19, as was done earlier in the pandemic. Even in high-risk patients, the proportion of patients with COVID-19 who progress to severe illness and/or require hospitalisation is now very low (<1%).[25] For drugs with weak or moderate antiviral activity (such as fluoxetine) the sample sizes needed to show a clinical benefit for endpoints such as hospitalisation and death have therefore become prohibitively large. Phase III clinical trials now have to rely on other clinical endpoints, such as symptom resolution. For rational and efficient selection of candidate antiviral drugs to treat early COVID-19, we propose assessing their *in vivo* pharmacodynamic activity defined as their effect on the rate of viral clearance. Acceleration in viral clearance correlates with clinical benefit.[26–28]

PLATCOV is an adaptive platform trial in adults with acute early COVID-19. The PLATCOV trial methodology can evaluate antiviral activity rapidly and compare available treatments quantitatively.[4,29–31] Here we report the results for fluoxetine and contextualise these results by pooling all unblinded data from the platform and comparing fluoxetine with the other assessed antiviral interventions.

Methods

Study design

PLATCOV is an ongoing phase 2, open label, multicentre, randomised, controlled, adaptive platform trial running currently in Thailand, Brazil, Pakistan, and Laos (ClinicalTrials.gov: NCT05041907). The trial provides a standardised quantitative comparative methodology for *in vivo* assessment of potential antiviral treatments in low-risk adults with early symptomatic COVID-19. Potential antiviral treatments are entered into the platform when they become available, and they are removed when the prespecified stopping rules are reached. Enrolled patients were admitted to the study ward or managed as outpatients according to patient preference (none of the admissions were for clinical reasons, but for ease of adherence with the study procedures, or for self-isolation).

Standard symptomatic treatment was provided to all patients. Initially, the following drugs were studied: ivermectin, favipiravir, remdesivir, and casirivimab/imdevimab (monoclonal antibody cocktail). These groups have already reached the prespecified stopping rules for efficacy or lack of efficacy and so have been stopped.[4,29–32] Additional interventions, including ensitrelvir, molnupiravir, ritonavir-boosted nirmatrelvir, and the tixagevimab/cilgavimab monoclonal antibody cocktail, were introduced later. The primary analysis reported here includes the results from patients who were allocated concurrently to fluoxetine or no study drug (negative control). In addition, we present a meta-analysis of all small molecule drugs and monoclonal antibodies with unblinded data to provide a calibration of the effect sizes observed for fluoxetine.

PLATCOV is coordinated and monitored by the Mahidol Oxford Tropical Medicine Research Unit (MORU) in Bangkok, is overseen by a trial steering committee (TSC), conducted according to Good Clinical Practice principles, and approved by the local IRB/ECs (see Supplementary Appendix Subsection S2). The results were reviewed regularly by a data and safety monitoring board (DSMB). The funders had no role in the design, conduct, analysis, or interpretation of the trial.

Participants

Previously healthy non-pregnant adults aged between 18 and 50 years were eligible for enrolment in the trial if they had early symptomatic COVID-19 (i.e., symptoms for <4 days), oxygen saturation ≥96%, were unimpeded in activities of daily living, and gave fully informed written consent. SARS-CoV-2 positivity was defined either as a nasal lateral flow antigen test which became positive within two minutes (STANDARD® Q COVID-19 Ag Test, SD Biosensor, Suwon-si, Korea) or a positive PCR test with a cycle threshold value (Ct) <25 (all viral gene targets) within the previous 24 h. Both tests ensure the majority of recruited patients have high viral loads.

Exclusion criteria included taking any potential antivirals or pre-existing concomitant medications, chronic illness or significant comorbidity, haematological or biochemical abnormalities (haemoglobin <8 g/dL, platelet count <50,000/μL, abnormal liver function tests, and estimated glomerular filtration rate <70 mL/min per 1.73 m^2), pregnancy (a urinary pregnancy test was performed in females), breastfeeding, or contraindication or known hypersensitivity to any of the study drugs.

Randomisation and interventions

Block randomisation was performed via a centralised web-app designed by MORU software engineers using

RShiny® hosted on a MORU webserver (Supplementary Appendix Subsection S8). At enrolment, after obtaining fully informed consent and entering the patient details, the app provided the study drug allocation. The "no study drug" arm was allocated to a minimum proportion of 20% of patients, with uniform randomisation ratios applied across the other active treatment arms. The trial was open label as it was impractical to conceal the different interventions. The viral densities were measured blinded to treatment allocation. Fluoxetine was added to the platform on 5th April 2022 in Thailand, 21st June 2022 in Brazil, 20th December 2022 in Laos, and 20th February 2023 in Pakistan. Fluoxetine was removed on the 8th May 2023. During this period, patients were also randomised to remdesivir (until 10th June 2022), casirivimab/imdevimab (Thailand only, until 20th October 2022), favipiravir (until 30th October 2022), molnupiravir (until 22nd February 2023), tixagevimab/cilgavimab (until 4th July 2023), nitazoxanide (Brazil, Laos, and Pakistan, from 18th January 2022 ongoing), ensitrelvir (Thailand and Laos only until 21st of April 2024), and ritonavir-boosted nirmatrelvir (from 6th June 2022, ongoing as positive control).

Procedures

All study drugs were stored under the appropriate conditions. Fluoxetine (Anzac®: Bangkok Lab Cosmetic Co., in Thailand and Laos, Prozac®: Eli Lilly in Brazil, and Flux, Hilton Pharma in Pakistan) was given at an oral dose of 40 mg per day for a total of seven days starting at baseline. This dose was chosen based on previous pharmacokinetic modelling, and was felt to be the highest safe dose which could be administered for this duration.[24] The administration of all drugs was observed directly or via video. After randomisation and baseline procedures (see Supplementary Appendix Page 9) oropharyngeal swabs (two swabs taken from each tonsil) were taken as follows. A flocked swab (Thermo Fisher MicroTest [Thermo Fisher, Waltham, MA, USA] and later COPAN FLOQSwabs® [COPAN Diagnostics, Murrieta, CA, USA]), was rotated against the tonsil through 360° four times and placed in Thermo Fisher M4RT (Thermo Fisher, Waltham, MA, USA) viral transport medium (3 mL). The swabs were transferred at 4–8 °C, aliquoted, and finally frozen at –80 °C within 48 h. Separate swabs from each tonsil were taken once daily from day 0 to day 7, on day 10, and on day 14. Swabs were processed and tested separately. Vital signs were recorded three times daily by the patient (on the first day the initial vital signs were recorded by the study team). Symptoms and any adverse effects were recorded daily.

The TaqCheck® SARS-CoV-2 Fast PCR Assay (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA) quantitated viral loads (RNA copies per mL). This multiplexed real-time PCR method detects the SARS-CoV-2 N and S genes, and human RNase P gene in a single reaction. RNase P was used to adjust for variation in sample human cell content (see SupplementaryAppendix Page 20). Viral loads were quantified against ATCC (Manassas, VA, USA) heat-inactivated SARS-CoV-2 (VR-1986HK strain 2019-nCoV/USA-WA1/2020) standards. Whole genome sequencing was performed to genotype strains and classify the viral variants (see Supplementary Appendix Subsection S7).

Outcomes

The primary outcome measure was the rate of viral clearance estimated from viral genome densities in serial duplicate oropharyngeal viral swab eluates taken daily between days 0 and 7 (see Statistics below and Supplementary Appendix S9 for the method of estimation).

Secondary endpoints were:

(i) All-cause admission to hospital for clinical deterioration (until day 28);
(ii) Time-to-resolution of fever in patients febrile at admission;
(iii) Time-to-resolution of symptoms.

These endpoints were assessed using survival methods because the data at the last visit were right-censored. Patients were defined as febrile at admission if at least one axillary temperature measurement within 24 h of randomisation was ≥37.5 °C. Resolution of fever was defined as an axillary temperature ≤37.0 °C for at least 24 h. Symptom resolution was defined as no reported symptoms. All adverse events were graded as per the Common Terminology Criteria for Adverse Events version 5.0.[33] Summaries were generated if the adverse event was grade 3 or worse, and was new or had increased in intensity. Serious adverse events were recorded separately and reported to the data safety monitoring board, however there were no serious adverse events during this portion of the trial.

Sample size and analysis framework

For each intervention, the sample size was adaptive, based on the prespecified futility and success stopping rules. A maximum sample size of 120 patients was prespecified (this does not include the no study drug arm or the positive control arm—currently ritonavir-boosted nirmatrelvir). Sample size requirements and thresholds for stopping rules, taking into account the effect of multiple interim analyses, were determined by simulation (see statistical analysis plan given in the Supplementary Appendix Subsection S9).

The primary outcome measure, prespecified as the rate of viral clearance between until day 7, was expressed as a slope coefficient and estimated under a Bayesian hierarchical linear model with random effect terms for

the individual patient slope and intercept.[29,33] The model was fitted to the daily $\log_{10}$ oropharyngeal swab eluate viral densities (genomes/mL) between days 0 and 7 (18 measurements per patient), using weakly informative priors and treating non-detectable viral loads (CT value ≥ 40) as left-censored (Supplementary Appendix Subsection S9).[29] The treatment effect was defined as the multiplicative change (%) in the viral clearance rate, either relative to the no study drug arm (when determining if an intervention had an antiviral effect), or relative to the positive control arm (ritonavir-boosted nirmatrelvir).[33] The viral clearance rate (i.e., slope coefficient from the model fit) can also be expressed as a clearance half-life ($t_{1/2} = \log_{10} 0.5/\text{slope}$). A 50% increase in clearance rate equals a 33% reduction in clearance half-life. All models included the time since study commencement, the virus variant, and the study site as covariate terms on the slope coefficient. A sensitivity analysis was performed using a non-linear model fitted to the serial viral densities, which allows for an initial increase followed by a log-linear decrease (Supplementary Appendix Subsection S9).

Because of the changing pattern of evolving viral variants, and the substantial increase in the rate of viral clearance since the beginning of the pandemic, each of the studied interventions was compared only against the concurrent controls, with interim analyses planned every additional ten patients recruited into each group. However, in practice, the interim analyses were less frequent than planned as recruitment occurred quickly. At first, all interim analyses compared the new intervention against the no study drug group. The protocol stipulated dropping the intervention for futility when there was >90% probability that the intervention accelerated viral clearance by less than 20% (this threshold was increased from 12.5% in January 2023; statistical analysis plan version 3.0). If the new intervention reached the success threshold (i.e., >90% probability it accelerated viral clearance >20% relative to no study drug), it was then compared with the positive control. This secondary comparison terminated when the intervention was shown to be inferior, non-inferior, or superior to the positive control group using a 10% non-inferiority margin. If the intervention was superior, it then replaced the positive control group. All stopping decisions were made using data from contemporaneously randomly assigned patients only.

All efficacy analyses were done in a modified intention-to-treat (mITT) population, comprising all patients with >2 days follow-up data. Safety data were analysed in all patients who had received ≥ one dose of the study drug.

Additional post hoc analyses

A recent analysis of all available PLATCOV trial unblinded data (n = 800 patients, not including data from the fluoxetine arm) characterised a substantial increase in natural viral clearance rates since the beginning of the platform trial 28 months ago. The average oropharyngeal viral clearance half-life in the no study drug arm has shortened from ~17 h in late 2021 to ~9 h in October 2023.[34] This analysis also showed that because viral clearance is better approximated as a bi-exponential term as previously reported,[35] restricting the primary endpoint to the clearance rate estimated over the first 5 days, instead of 7 days, resulted in greater power and greater precision in estimating treatment effects (i.e., larger z-scores between effective and ineffective or no drug arms).[34,36] A post-hoc analysis of the fluoxetine data was therefore added in which the estimation of the viral clearance rates was made from the first 5 days only.

Meta-analysis

To calibrate the effect sizes observed for the fluoxetine arm, an individual patient data meta-analysis was conducted of all small molecule drugs and monoclonal antibodies with unblinded data from the PLATCOV trial (molnupiravir,[4] ritonavir-boosted nirmatrelvir,[4] ivermectin,[29] casirivimab/imdevimab,[30] remdesivir,[31] and favipiravir).[32] Not all interventions were randomised concurrently, so the time since study commencement was included as a covariate on the mean slope parameter to control for temporal confounding.

Statistics

All data analysis was done in R version 4.3.2. Posterior distributions were approximated using Hamiltonian Monte Carlo simulation in Stan via the RStan interface, using weakly informative priors (https://github.com/stan-dev/stan/wiki/Prior-Choice-Recommendations).[37] 4000 iterations were run over four independent chains with 2000 iterations for burn-in. Convergence was assessed visually from the trace plots (Supplementary Appendix Figures S4 and S5) and using the R-hat statistic (a value <1.1 was considered acceptable convergence).[38] Goodness of fit was assessed by plotting the residuals over time and comparing the daily median model predictions with the observed values (Supplementary Appendix Figure S5). All point estimates are reported with 95% credible intervals (CrIs), defined by the 2.5% and the 97.5% quantiles of the posterior distribution. Model fits were compared using approximate leave-one-out comparison as implemented in the package loo version 2.6.0.[39]

Ethics

The trial was approved in Thailand by the Faculty of Tropical Medicine Ethics Committee (Mahidol University, FTMEC Ref: TMEC 21-058) and the Central Research Ethics Committee (CREC, Bangkok, Thailand, CREC Ref: CREC048/64BP-MED34), in Brazil by the Research Ethics Committee of the Universidade Federal de Minas Gerais (COEP-UFMG, Minas Gerais, Brazil, COEP-UFMG) and National Research Ethics

Commission- (CONEP, Brazil, COEP-UFMG and CONEP Ref: CAAE:51593421.1.0000.5149), in Laos by the National Ethics Committee for Health Research (NECHR, Lao People's Democratic Republic, Submission ID 2022.48) and the Federal Drug Administration (FDA, Lao People's Democratic Republic, 13066/FDD_12Dec2022), in Pakistan by the National Bioethics Committee (NBC No.4-87/COVID-111/22/842) the Ethics Review Committee (ERC 2022-7496-21924) and the Drug Regulatory Authority (DRAP Ref: No.03-18/2022-CT (PS)) and finally by the Oxford University Tropical Research Ethics Committee (OxTREC, Oxford, UK, OxTREC Ref: 24-21). Informed consent was obtained from all participants.

Role of funding source

The funders had no role in the study design, data collection, data analyses, interpretation, or writing of the report.

Results

The PLATCOV platform trial began recruitment on 30th September 2021. The fluoxetine arm was added in Thailand on 5th April 2022, in Brazil on 21st June 2022, in Laos on 20th December 2022, and in Pakistan on 20th February 2023. It was stopped on 8th May 2023 after 120 patients had been randomised to fluoxetine and the prespecified maximum recruitment had been reached. Of the 675 patients randomised during that period, 120 patients were randomised to fluoxetine, 151 to no study drug, and the remaining 404 were randomised to other interventions (casirivimab/imdevimab, tixagevimab/cilgavimab, nitazoxanide, favipiravir, remdesivir, ivermectin, ensitrelvir, ritonavir-boosted nirmatrelvir, and molnupiravir) (Fig. 1). Four patients from the fluoxetine group withdrew consent. One patient from the no study drug arm withdrew consent.

The majority of patients (89.6%) were enrolled in Bangkok, Thailand (Table 1). The median interval since symptom onset was 2 (IQR: 2–3) days. Most patients had high oropharyngeal eluate viral densities at presentation. The average SARS-CoV-2 eluate density was ~350,000 genomes per mL. Patients were infected with a wide variety of virus variants, the 3 most common being BA.5 (65/266), BA.2.75 (61/266), and BA.2 (51/266).

Tolerability

The oropharyngeal swabbing procedures and all treatments were well-tolerated. Patients allocated to the fluoxetine arm reported increased somnolence compared to the no study drug arm, and so the treatment was given in the evening. Two patients did not complete their courses of fluoxetine. The first had ongoing abdominal pain and elected to skip their last dose. The second patient felt chest pain (see description

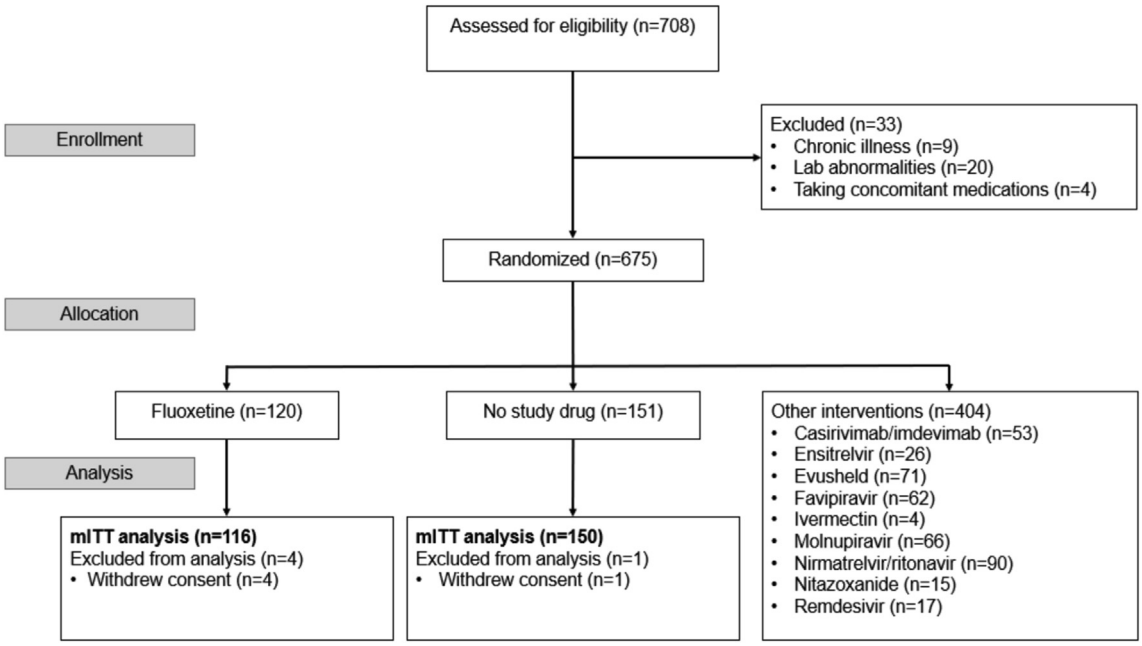

Fig. 1: Study CONSORT diagram for the fluoxetine versus no study drug analysis. In Thailand, pre-screening occurred in the Acute Respiratory Infection (ARI) unit of the Hospital for Tropical Diseases, Bangkok. Potentially eligible patients were selected by the ARI Nurses to be contacted by the study team. Therefore, a high proportion of those assessed for eligibility participated in the study.

	No study drug	Fluoxetine
Patient number: all sites	150	116
Brazil	17 (11.3%)	12 (10.3%)
Thailand	129 (86.0%)	101 (87.1%)
Laos	0 (0%)	1 (0.9%)
Pakistan	4 (2.7%)	2 (1.7%)
Age (years)	30.5 (7.8)	29.5 (7.7)
Female N (%)	98 (65.3%)	82 (70.7%)
Weight (kg)	62.7 (13.4)	59.6 (11.3)
Body mass index (kg/m^2)	23.2 (4.0)	22.3 (3.5)
[a]Baseline viral density (log_{10} copies per mL)	5.6 (4.7–6.3)	5.7 (4.9–6.6)
[a]Symptom onset (days)	2 (2–3)	2 (2–3)
Drug adherence	N/A	114 (98.0%)
Vaccinated (%)	150 (100.0%)	116 (100.0%)
SARS-CoV-2 variants		
BA.2 (%)	30 (20.0%)	24 (20.7%)
BA.2.3.20 (%)	0 (0.0%)	1 (0.9%)
BA.2.75 (%)	41 (27.3)	34 (29.3%)
BA.4 (%)	2 (1.3%)	0 (0.0%)
BA.5 (%)	42 (28.0%)	31 (26.7%)
BN.1.9 (%)	2 (1.3%)	0 (0.0%)
XBB (%)	10 (6.7%)	9 (7.8%)
XBB.1.5-like (%)	23 (15.3%)	15 (12.9%)
Others (%)	0 (0.0)	2 (1.7)

For categorical variables, the number (%) is shown. For continuous variables, the mean (standard deviation) is shown, unless noted with,[a] in which case the median (interquartile range) is shown.

Table 1: **Admission patient characteristics in the mITT population.**

in of the grade 3 adverse event in clinical responses below) (Table 1).

Clinical responses

There were no serious adverse events (SAEs), hospitalisations or deaths in either arms, and no patients developed severe disease. There was one grade three adverse event in the fluoxetine arm (acute onset chest pain, normal electrocardiogram, acute coronary syndrome ruled out by physician and discharged with no concerns, considered as likely caused by COVID-19). There were no significant differences in times to symptom resolution or fever clearance between the fluoxetine and the no study drug arms, however only a quarter of patients were febrile at baseline (Supplementary Appendix Figures S6 and S7).

Virological responses

Rates of viral clearance were estimated in the mITT population (4772 measurements in 266 patients, of which 3983 (83%) were above the lower limit of quantification). Under the linear model, patients assigned to fluoxetine had a 15% (95% CrI: −2 to 34%) faster average rate of viral clearance over 7 days relative to no study drug (Fig. 2). The posterior probability that the effect of fluoxetine was less than the pre-specified futility margin of 20% was 0.70. The non-linear model gave very similar estimates: an acceleration in viral clearance rate of 11% (95% CrI: −3 to 29%) relative to the no study drug. Under the linear model, the median estimated viral clearance half-lives were 14.0 h (9.3–18.0) with fluoxetine and 14.9 h (11.5–20.8) in the concurrent no study drug group (Fig. 3).

A *post hoc* sensitivity analysis was performed, in which the treatment effect of fluoxetine was estimated using data only from the first 5 days after randomisation. Under the linear and non-linear models, the estimated fluoxetine treatment effects were substantially larger: 26% (95% CrI: 5–50%) under the linear model; and 18% (95% CrI: 2–39%) under the non-linear model (Fig. 2B). Viral rebound occurred in 1/150 patients in the no study drug arm and 3/116 in the fluoxetine arm (p-value 0.27) (See Statistical Analysis plan for definition).

Meta-analysis

Under the linear model analysing viral clearance rates over 7 days, the meta-analysis including all unblinded drugs (not concurrently randomised) and adjusting for calendar time and viral variants, estimated that fluoxetine increased viral clearance by 16% (95% CrI: 3–32%) compared to the no study drug group (Fig. 4). Fluoxetine treatment resulted in a higher viral clearance rate than two interventions previously reported in the PLATCOV study to have no clinical antiviral effect; ivermectin and favipiravir. The treatment effect of fluoxetine was lower than that of casirivimab/imdevimab, remdesivir, molnupiravir, and substantially lower than ritonavir-boosted nirmatrelvir, with the probabilities of 0.88, 0.94, 0.98, and 1.00, respectively. These four active antivirals/monoclonal antibodies increased the rates of viral clearance by 29% (95% CrI: 10–48%), 35% (95% CrI: 14–59%), 37% (95% CrI: 18–60%), and 85% (95% CrI: 61–112%), respectively. Additionally, consistent with the main analysis, a post-hoc meta-analysis of viral clearance assessed over 5 days demonstrated a larger effect size of fluoxetine (Fig. 4) and this indicated that fluoxetine increased the viral clearance rate by 28% (95% CrI: 11–49%).

Discussion

Overall, this clinical pharmacodynamic evaluation suggests that the widely used SSRI fluoxetine, which has the same proposed FIASMA mechanism of action as fluvoxamine,[40] may have weak antiviral activity against SARS-CoV-2 *in vivo* (albeit with a high degree of uncertainty, although the primary analysis taken alone is compatible with no antiviral effect). There were no significant differences in time to symptom resolution or time to fever clearance between the fluoxetine and the no study drug arms, although only a quarter of patients were febrile at baseline.

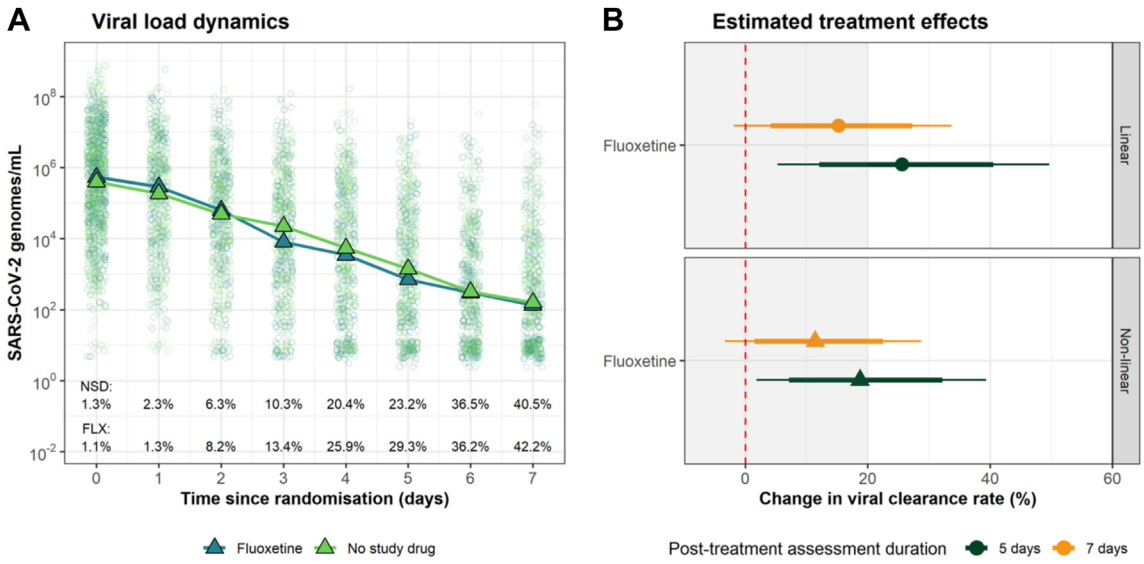

Fig. 2: Antiviral effect of fluoxetine in early COVID-19. Panel A: individual viral densities data (fluoxetine: dark green; no study drug: light green). Triangles show the daily median oropharyngeal eluate viral densities by arm. Text annotations indicate the proportions of samples with viral densities below the limit of quantification (NSD: No study drug; FLX: Fluoxetine). Panel B: posterior estimates of the treatment effects of fluoxetine relative to no study drug, under the linear and non-linear models (orange: viral clearance assessed over 7 days; green: viral clearance assessed over 5 days). Thick and thin error bars represent the 80% and 95% CrIs, respectively.

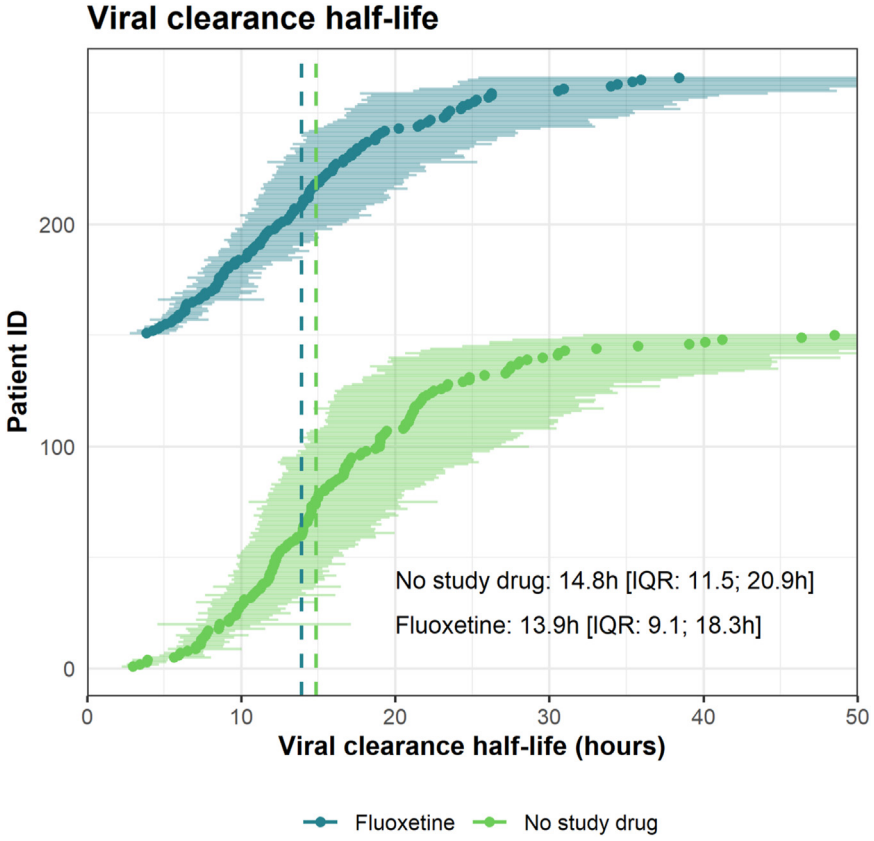

Fig. 3: Estimated SARS-CoV-2 clearance half-lives (in hours) estimated over 7 days for individual patients in the fluoxetine arm (dark green), and the no-study-drug arm (light green). The median estimates (circles) and 80% credible intervals (error bars) are displayed. Vertical dashed lines indicate the median half-lives of each group.

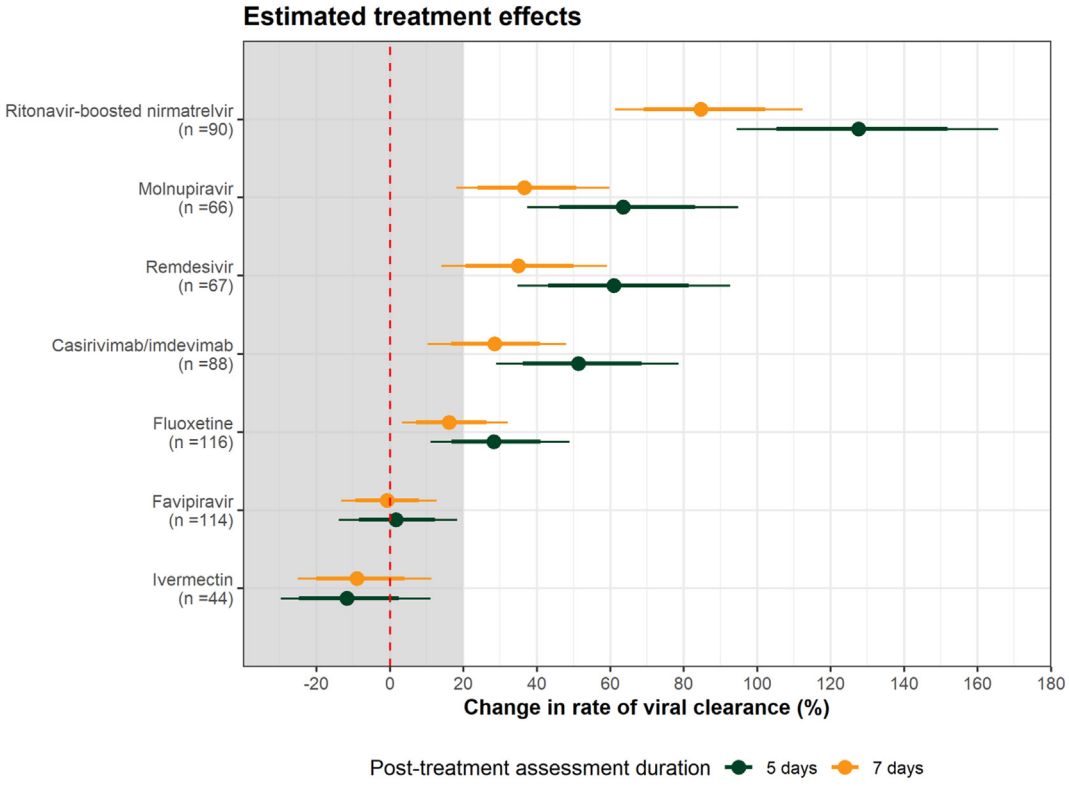

Fig. 4: Individual patient data meta-analysis of antiviral interventions relative to the no study drug arm (n = 783 patients enrolled into the trial between the 30th September 2021 and the 23rd May 2023, not all concurrently). Circles show the median posterior estimates of the change in viral clearance rate under the linear model, adjusting for calendar time and virus variant (orange: viral clearance assessed over 7 days; green: viral clearance assessed over 5 days). Thick and thin error bars represent 80% and 95% centred credible intervals, respectively. The shaded area indicates the futility zone (<20% increase in viral clearance rate). Ivermectin was evaluated in the study between 30th September 2021 and 18th of April 2022; 95% had received at least one COVID-19 vaccine. Favipiravir was evaluated between 30th September 2021 and 31st October 2022; 97.5% had been vaccinated. Casirivimab/imdevimab was evaluated between 30th September 2021 and 24th August 2022. Remdesivir was evaluated between 30th September 2021 and 10th June 2022. Molnupiravir and ritonavir-boosted nirmatrelvir were both evaluated in the study from 6th June 2022. Molnupiravir was stopped on 23rd February 2023 and ritonavir -boosted nirmatrelvir remains as the positive control. The proportions vaccinated were 100% and 99% respectively.

Earlier in the pandemic, before effective antivirals and before vaccines were deployed, any available drug with anti-SARS-CoV-2 activity could have played a role in the management of COVID-19. Several observational studies reported lower mortalities in patients receiving certain SSRIs,[6–9] and also provided some evidence for prophylactic activity.[10] Based on these, the SSRIs fluoxetine and fluvoxamine were proposed as treatments for early COVID-19. Both drugs are interesting choices as they are inexpensive, widely available, very widely used, and have excellent safety profiles. A meta-analysis of randomised controlled trials of fluvoxamine showed a slight, but non-significant reduction in hospitalisation ± mortality (Supplementary Appendix Subsection S1). These results were not sufficient to change treatment policies and practices. In May 2022, the US FDA rejected an emergency use authorisation (EUA) for fluvoxamine maleate in outpatients with COVID-19, on the basis that there was insufficient evidence that fluvoxamine can prevent progression to severe disease or hospitalisation. The US FDA noted that "it is unlikely that fluvoxamine possesses a high degree of activity against SARS-CoV-2".[41] There have been no randomised controlled trials in outpatients assessing fluoxetine.

In this comparative *in vivo* pharmacodynamic platform trial, carried out in low-risk adults with early symptomatic COVID-19 infection, fluoxetine demonstrated weak antiviral activity. This was not sufficient for it to reach the prespecified success threshold of a 20% acceleration of viral clearance (assessed over 7 days) compared to the contemporaneous control group. This high threshold was set because there are now highly effective antiviral drugs for early symptomatic COVID-19,[4,31] and so it is unlikely that drugs with a substantially lower potency would be used in treatment. The main

protease inhibitor nirmatrelvir, in combination with ritonavir, is currently the most effective antiviral treatment assessed in this platform trial. In the 7-day assessment its acceleration of viral clearance was over five times greater than that of fluoxetine.[4] But it has several disadvantages and is not readily available worldwide.

The methodology used in this platform trial is an effective way to measure antiviral effects in COVID-19. Acceleration of viral clearance reflects the *in vivo* antiviral effect and correlates with prevention of hospitalisation and death.[42] It has become increasingly difficult to carry out large trials with clinical endpoints. This is because the low rates of hospitalisation and death in COVID-19 infections with current viral variants in an increasingly immune population mean that sample sizes using these endpoints must be prohibitively large.[25] Virological pharmacodynamic endpoints can be used to measure antiviral effects with substantially smaller sample sizes. The pharmacodynamic assessment has also become simpler. Increased rates of viral clearance since the pandemic started now mean that viral clearance can be measured more accurately over 5 rather than 7 days.[34,36]

The study has several limitations. It is open-label, which may have influenced the symptom reporting in each arm. There is substantial variability in estimated serial viral densities and much of the inter-subject variance in viral clearance rates is unexplained. There still remains some uncertainty about the antiviral potency of fluoxetine (at the doses evaluated) and the optimal duration. Whether larger doses, or a loading dose to achieve therapeutic concentrations earlier,[24] would have provided greater activity is not known, although tolerability would have been reduced. Drug measurements in blood would have clarified exposure–response relationships. Pharmacogenetic characterisation of cytochrome P450 genetic polymorphisms (2D6 and 2C9) which affect fluoxetine metabolism may have been relevant. 86% of the participants were from the Thailand site. A systematic review found that the most common CYP2D6 allele (present in 39% of Thais assessed) caused decreased enzymic activity which would lead to an increase in drug concentrations. This may have given increased exposures, leading to greater effects.[43] The applicability of this result to other SSRIs or other FIASMAs was not determined. Finally, serum antibody levels were not available in this analysis. There is evidence that effective antivirals such as molnupiravir may result in lower antibody levels post treatment, although the reported effect sizes are small and the impact on subsequent clinical outcomes is unknown.[44]

In summary, these data suggest that fluoxetine may have weak *in vivo* antiviral activity in early COVID-19, although some uncertainty remains. The acceleration in viral clearance was considerably less than with currently available effective antivirals. Given that there are more effective, albeit much more expensive drugs, fluoxetine is unlikely to be used in the treatment of COVID-19 at this stage of the pandemic, but whether it could have had a useful role earlier is unclear. Fluoxetine might still have a role in high-risk patients unable to access or take other treatments, or in future pandemics, and it might have prophylactic value, but further evidence would be needed before such recommendations can be made. *In vivo* pharmacodynamic assessments of drugs should be more widely adopted.

Contributors

PJ-investigation, methodology, project administration, supervision, validation, and writing-original draft. SB-investigation, methodology, project administration, writing-original draft. PJ and SB contributed equally. WHKS-funding acquisition, investigation, methodology, project administration, supervision, validation, and writing-original draft. JAW-conceptualisation, data curation, formal analysis, funding acquisition, methodology, visualisation, and writing-original draft. TN, TS, and VL-Investigation, methodology, supervision. EMB-data curation, formal analysis, visualisation. PW-data curation, formal analysis, visualisation, and writing-original draft. RSA, FRA, and NKG-formal analysis, investigation. LME, PJA, CC, JJC, SS, VK, TN, JT, FQ, and AMK-methodology, investigation, project administration. WM, KS, and AP-investigation, methodology. BH and KP-methodology, investigation, supervision. MP, AS, and BL-resources. WRJT-methodology, supervision. KC and MI-formal analysis, investigation, resources, supervision. SP, AMD, MAB, MMT, WaP, WeP, DC, and SV-methodology, investigation, resources, supervision. NPJD-funding acquisition, methodology, investigation, resources, supervision. NJW-conceptualisation, funding acquisition, methodology, supervision, validation, and writing-original draft.

All Authors were involved in writing, reviewing & editing the final manuscript.

JAW, WHKS, EMB, TN, MI, and NJW have directly accessed and verified the underlying data reported in the manuscript.

Data sharing statement

All code and de-identified patient data required for replication of the study's endpoints are openly accessible via GitHub, as well as the study protocol and statistical analysis plan, from publication date onwards: https://github.com/jwatowatson/PLATCOV-Fluoxetine Individual Patient Data can be requested and may be shared according to the terms defined in the MORU data sharing policy with other researchers to use in the future from the date of publication. Further information on how to apply is found here: https://www.tropmedres.ac/units/moru-bangkok/bioethics-engagement/data-sharing.

Declaration of interests

All authors declare no competing interests.

Acknowledgements

The trial was supported by the Wellcome Trust Grant ref: 223195/Z/21/Z through the COVID-19 Therapeutics Accelerator.

We thank all the patients with COVID-19 who volunteered to be part of the study. We thank the data safety and monitoring board (DSMB) (Tim Peto, André Siqueira, and Panisadee Avirutnan); the trial steering committee (TSC) (Nathalie Strub-Wourgaft, Martin Llewelyn, Deborah Waller, and Attavit Asavisanu); Sompob Saralamba and Tanaphum Wichaita for developing the RShiny randomisation app; and Mavuto Mukaka for invaluable statistical support. We also thank all the staff of the Clinical Trials Unit (CTU) at MORU, PCR Expert group (Janjira Thaipadungpanit, Audrey Dubot-Pérès, and Clare Ling), Thermo Fisher for their excellent support with this project, and all the hospital staff at the Hospital for Tropical Diseases, Faculty of Tropical Medicine, as well as those involved in sample processing in MORU and the processing and analysis at the Faculty of Tropical Medicine (FTM), molecular

genetics laboratory. We thank the MORU Clinical Trials Support Group (CTSG) for data management, monitoring, ethics and regulatory submissions and logistics, and the purchasing, administration, and support staff at MORU, and those at the Brazil site who provided expert help in managing patients (Joseane Fratari, Josiane Vaz, and Fátima Brant). We would also like to thank everyone who supported the Laos and Pakistan sites. We thank Lorenz von Seidlein for reviewing the study protocol. Finally, we would like to thank Nicolas Hoertel and Céline Cougoule for their invaluable prior work on fluoxetine in COVID-19.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103036.

References

1 RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384:693–704.
2 Usher AD. The global COVID-19 treatment divide. *Lancet*. 2022;10327:779–782.
3 Zhuang W, Xu J, Wu Y. Post-marketing safety concerns with nirmatrelvir: a disproportionality analysis of spontaneous reports submitted to the FDA Adverse Event Reporting System. *Br J Clin Pharmacol*. 2023;9:2830–2842.
4 Schilling WH, Jittamala P, Watson JA, et al. Antiviral efficacy of molnupiravir versus ritonavir-boosted nirmatrelvir in patients with early symptomatic COVID-19 (PLATCOV): an open-label, phase 2, randomised, controlled, adaptive trial. *Lancet Infect Dis*. 2023;24:36–45.
5 Sanderson T, Hisner R, Donovan-Banfield IA, et al. A molnupiravir-associated mutational signature in global SARS-CoV-2 genomes. *Nature*. 2023;623:594–600.
6 Hoertel N, Sánchez-Rico M, Vernet R, et al. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: results from an observational study. *Mol Psychiatry*. 2021;26:5199–5212.
7 Oskotsky T, Marić I, Tang A, et al. Mortality risk among patients with COVID-19 prescribed selective serotonin reuptake inhibitor antidepressants. *JAMA Netw Open*. 2021;4:e2133090.
8 Hoertel N, Sánchez-Rico M, Kornhuber J, et al. Antidepressant use and its association with 28-day mortality in inpatients with SARS-CoV-2: support for the FIASMA model against COVID-19. *J Clin Med*. 2022;11:5882.
9 Hoertel N, Sánchez-Rico M, Gulbins E, et al. Association between FIASMA psychotropic medications and reduced risk of intubation or death in individuals with psychiatric disorders hospitalized for severe COVID-19: an observational multicenter study. *Transl Psychiatry*. 2022;12:90.
10 Clelland CL, Ramiah K, Steinberg L, Clelland JD. Analysis of the impact of antidepressants and other medications on COVID-19 infection risk in a chronic psychiatric in-patient cohort. *BJPsych Open*. 2022;8:e6.
11 Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. 2020;324:2292–2300.
12 Reis G, dos Santos Moreira-Silva EA, Silva DC, 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;1:e42–e51.
13 Reis G, dos Santos Moreira Silva EA, Medeiros Silva DC, et al. Oral fluvoxamine with inhaled budesonide for treatment of early-onset COVID-19: a randomized platform trial. *Ann Intern Med*. 2023;176:667–675.
14 Reiersen AM, Mattar C, Bender Ignacio RA, et al. The STOP COVID 2 study: fluvoxamine vs placebo for outpatients with symptomatic COVID-19, a fully remote randomized controlled trial. *Open Forum Infect Dis*. 2023;10:ofad419.
15 Stewart TG, Rebolledo PA, Mourad A, et al. Higher-dose fluvoxamine and time to sustained recovery in outpatients with COVID-19: the ACTIV-6 randomized clinical trial. *JAMA*. 2023;24:2354–2363.
16 Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized trial of metformin, ivermectin, and fluvoxamine for Covid-19. *N Engl J Med*. 2022;387:599–610.
17 McCarthy MW, Naggie S, Boulware DR, et al. Effect of fluvoxamine vs placebo on time to sustained recovery in outpatients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. 2023;329:296–305.
18 Siripongboonsitti T, Ungtrakul T, Tawinprai K, et al. Efficacy of combination therapy of fluvoxamine and favipiravir vs favipiravir monotherapy to prevent severe COVID-19 among mild to moderate COVID-19 patients: open-label randomized controlled trial (EFFaCo study). *Int J Infect Dis*. 2023;134:211–219.
19 Kornhuber J, Hoertel N, Gulbins E. The acid sphingomyelinase/ceramide system in COVID-19. *Mol Psychiatry*. 2022;27:307–314.
20 Pauletto PJ, Delgado CP, da Rocha JB. Acid sphingomyelinase (ASM) and COVID-19: a review of the potential use of ASM inhibitors against SARS-CoV-2. *Cell Biochem Funct*. 2023;41:284–295.
21 Fred SM, Kuivanen S, Ugurlu H, et al. Antidepressant and antipsychotic drugs reduce viral infection by SARS-CoV-2 and fluoxetine shows antiviral activity against the novel variants in vitro. *Front Pharmacol*. 2022;12:755600.
22 World Health Organization. *WHO Model List of Essential Medicines - 23rd List*. WHO; 2023. https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists.
23 Zimniak M, Kirschner L, Hilpert H, et al. The serotonin reuptake inhibitor Fluoxetine inhibits SARS-CoV-2 in human lung tissue. *Sci Rep*. 2021;11:5890.
24 Eugene AR. Fluoxetine pharmacokinetics and tissue distribution suggest a possible role in reducing SARS-CoV-2 titers. *F1000 Research*. 2021;10:477.
25 Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet*. 2023;401:281–293.
26 de Grooth HJ, Parienti JJ. Surrogate endpoints in pandemic preparedness. *J Infect Dis*. 2024;229:1244–1245.
27 Elias KM, Khan SR, Stadler E, et al. Viral clearance as a surrogate of clinical efficacy for COVID-19 therapies in outpatients: a systematic review and meta-analysis. *Lancet Microbe*. 2024;5:e459–e467.
28 Singh S, Boyd S, Schilling WH, et al. The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis. *J Antimicrob Chemother*. 2024;79:935–945.
29 Schilling WH, Jittamala P, Watson JA, et al. Pharmacometric assessment of the in vivo antiviral activity of ivermectin in early symptomatic COVID-19. *Elife*. 2023;12:e83201.
30 Jittamala P, Schilling WH, Watson JA, et al. Clinical antiviral efficacy of remdesivir and casirivimab/imdevimab against the SARS-CoV-2 Delta and Omicron variants. *medRxiv*. 2022. https://doi.org/10.1101/2022.10.17.22281161.
31 Jittamala P, Schilling WHK, Watson JA, et al. Clinical antiviral efficacy of remdesivir in coronavirus disease 2019: an open-label, randomized controlled adaptive platform trial (PLATCOV). *J Infect Dis*. 2023;228:1318–1325. https://doi.org/10.1093/infdis/jiad275. PMID: 37470445; PMCID: PMC10640773.
32 Luvira V, Schilling WHK, Jittamala P, et al. Clinical antiviral efficacy of favipiravir in early COVID-19 (PLATCOV): an open-label, randomised, controlled, adaptive platform trial. *BMC Infect Dis*. 2024;24:89. https://doi.org/10.1186/s12879-023-08835-3.
33 NIH National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed November 27, 2017.
34 Wongnak P, Schilling WHK, Jittamala P, et al. Temporal changes in SARS-CoV-2 clearance kinetics and the optimal design of antiviral pharmacodynamic studies: an individual patient data meta-analysis of a randomised, controlled, adaptive platform study (PLATCOV). *Lancet Infect Dis*. 2024;24:953–963.
35 Watson JA, Kissler SM, Day NPJ, et al. Characterizing SARS-CoV-2 viral clearance kinetics to improve the design of antiviral pharmacometric studies. *Antimicrob Agents Chemother*. 2022;66:e00192-22. https://doi.org/10.1128/aac.00192-22.
36 Visser LG. Identifying efficacious SARS-CoV-2 antivirals in a changing immune landscape. *Lancet Infect Dis*. 2024;24:936.
37 Stan Development Team. "RStan: the R interface to Stan." R package version 2.32.3. https://mc-stan.org/; 2023. Accessed October 15, 2023.
38 Vehtari A, Gelman A, Simpson D, Carpenter B, Bürkner P-C. Rank-normalization, folding, and localization: an improved rhat for assessing convergence of MCMC (with discussion). *Bayesian Anal*. 2021;16:667–718.

39 Vehtari A, Gelman A, Gabry J. Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. *Stat Comput*. 2017;27:1413–1432.

40 Hoertel N. Do the selective serotonin reuptake inhibitor antidepressants fluoxetine and fluvoxamine reduce mortality among patients with COVID-19? *JAMA Netw Open*. 2021;11:e2136510.

41 Memorandum explaining basis for declining request for emergency use authorization of fluvoxamine maleate. News release. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/EUA%20110%20Fluvoxamine%20Decisional%20Memo_Redacted.pdf. Accessed December 15, 2023.

42 Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med*. 2022;15:1397–1408.

43 Dorji PW, Tshering G, Na-Bangchang K. CYP2C9, CYP2C19, CYP2D6 and CYP3A5 polymorphisms in South-East and East Asian populations: a systematic review. *J Clin Pharm Therapeut*. 2019;44:508–524.

44 Standing JF, Buggiotti L, Guerra-Assuncao JA, et al. Randomized controlled trial of molnupiravir SARS-CoV-2 viral and antibody response in at-risk adult outpatients. *Nat Commun*. 2024;15:1652.