Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Efficacy and safety of fluvoxamine for the treatment of COVID-19 patients: A systematic review and meta-analysis

Dear Editor,

We read with great interest the recent article by Qian et al. that reported the efficacy of paxlovid for the treatment of COVID-19 patients.[1] However, the cost of currently approved oral antivirals, paxlovid and molnupiravir, restricts their access in developing countries.[2,3] Therefore, it is crucial to find affordable, widely accessible, and potent treatments for COVID-19. Particularly appealing is the idea of repurposing currently available medications that are widely accessible and have known safety characteristics.[4]

Fluvoxamine, a widely available, inexpensive selective serotonin reuptake inhibitors (SSRIs), has shown potential for treating COVID-19 as an early outpatient treatment, despite many recommended repurposed medicines failing.[5] The underlying mechanism of the effect of fluvoxamine in COVID-19 patients is currently unclear, but it is thought to be multifactorial. In addition to functioning as an SSRI, fluvoxamine has a strong affinity for the σ-1 receptor (S1R), which is believed to be the mechanism by which it achieves its anti-inflammatory and immunomodulatory properties. S1R stimulation is thought to have an immunomodulatory effect by lowering stress in the endoplasmic reticulum brought on by viral replication, which in turn lowers the generation of inflammatory cytokines.[6] In order to combine the existing data and assess the efficiency and safety of fluvoxamine as a treatment for COVID-19, we undertook this updated meta-analysis.

Our pre-registered meta-analysis (PROSPERO CRD42022361850) was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Embase, the Cochrane Library and ClinicalTrials.gov were searched from inception to September 2022 using a search strategy consisting of terms related to “fluvoxamine”, “SSRIs” and “COVID-19”. The reference lists of the relevant records were also checked. All randomized controlled trials (RCTs) and comparative observational studies evaluating fluvoxamine use for the treatment of COVID-19 patients were included in this review. After screening, five RCTs,[7–11] one quasi-randomized trial[12] and two prospective cohort studies[13,14] were found to be eligible for our meta-analysis. Table 1 provides a summary of the features of the included studies. For quality assessments of the RCTs, we used the revised Cochrane Risk of Bias tool (RoB2) (Supplementary Fig. 1) while for the non-randomized studies, we used the New-Castle-Ottawa scale (NOS) (Supplementary Table 1). Our primary outcome was all-cause mortality and the secondary outcomes were the risk of hospitalization and COVID-19 progression, and the incidence of adverse events. The meta-analysis was performed using RevMan 5.4 with risk ratio (RR), with corresponding 95% confidence interval (CI), as the effect measure.

Our findings demonstrated that fluvoxamine was associated with a nonsignificant reduction in the risk of mortality (RR 0.49; 95% CI: 0.21-1.17; I^2=78%; Fig. 1A) and hospitalization (RR 0.46; 95% CI: 0.21-1.02; I^2=54%; Fig. 1B) in COVID-19 patients. Fluvoxamine did not reduce the risk of COVID-19 progression (RR 0.74; 95% CI: 0.21-2.57; I^2=44%; Supplementary Fig. 2). The incidence of adverse events did not differ significantly between the fluvoxamine and the control groups (RR 0.94; 95% CI: 0.79-1.11; I^2=0%; Supplementary Fig. 3). In one study, one patient receiving fluvoxamine reported a serious adverse event as compared to six patients in the control group.[10] In sensitivity analyses by excluding Bramante et al. in which patients in the control group received metformin,[11] a drug known to be beneficial for COVID-19, the results for hospitalization (RR 0.37; 95% CI: 0.14-0.95; I^2=58%) became significant in favor of fluvoxamine but the outcome of COVID-19 progression (RR: 0.33; 95% CI: 0.03-4.35; I^2=57%) remained non-significant.

To the best of our knowledge, this is the largest meta-analysis to date to evaluate the potential effectiveness of fluvoxamine as a COVID-19 treatment. Our findings showed that fluvoxamine use was associated with a large but statistically non-significant reduction in mortality and hospitalization rates in patients with COVID-19 without increasing the incidence of adverse events. Our findings agree with a previous meta-analysis which showed that fluvoxamine did not decrease the risk of mortality or hospitalization.[15] However, this meta-analysis was based on only three studies and therefore, was relatively underpowered. After excluding a trial with an active comparator, we showed that fluvoxamine did reduce the risk of hospitalization in contrast with the previous meta-analyses which did not find any benefits of fluvoxamine use.[15,16] Moreover, the TOGETHER trial found that fluvoxamine decreased the risk of hospitalization in high-risk COVID-19 patients.[9] This suggests that fluvoxamine may not be effective for every patient on a routine basis and that outpatient populations with an elevated risk of comorbidities must be identified to maximize the benefits of fluvoxamine therapy.[9]

Fluvoxamine may be beneficial for treating COVID-19 because of its easy accessibility and affordable price. A 10-day regimen of fluvoxamine costs about $4; hence, in low-income countries, it is a cost-effective treatment for COVID-19 if compared with other approved oral antivirals, including paxlovid and molnupiravir.[2]

Due to the small number of available trials and the inclusion of observational studies, our study has several limitations, including low statistical power and a risk of confounding bias. Additionally, we could not assess long-term outcomes as they were not reported by the studies.

In conclusion, treatment with fluvoxamine did not decrease mortality and hospitalization rates in patients with COVID-19 but due to the imprecise CIs, a large possible benefit cannot be ruled out. The sensitivity analysis showing a statistically significant reduction in risk of hospitalization further reinforces this point and is highly encouraging. To strengthen these findings, further large-scale RCTs, especially for longer-term outcomes, are needed.

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Table 1
Characteristics of included studies.

Sr No	Author, year	Study Design	Country	Sample size	Age	Sex	Population	Intervention	Comparator
1	Lenze 2020	Phase 2, Double-Blind RCT	USA	152	46.0±13.0	Male: 43 (28.3) Female: 109 (71.7)	Adults with SARS-CoV-2 infection confirmed by polymerase chain reaction assay and who were symptomatic within 7 days of the first dose of study medication	Participants received a dose of 50 mg of fluvoxamine immediately after inclusion, then for 2 days at a dose of 100 mg twice daily as tolerated, and then increasing to a dose of 100 mg 3 times daily as tolerated through day 15 then stopped.	Participants received a dose of 50 mg of placebo immediately after inclusion, then for 2 days at a dose of 100 mg twice daily as tolerated, and then increasing to a dose of 100 mg 3 times daily as tolerated through day 15 then stopped.
2	STOP COVID 2, unpublished	Phase 3, triple-blind RCT	USA and Canada	547	47 (IQR 40-55) for Fluvoxamine group, 48 (IQR 41-56) for control	Male: 208 (38) Female: 339 (62)	Patients with age greater than 30 years who are unvaccinated and positive PCR result within 6 days of symptoms onset and a criterion of high risk	100 mg Fluvoxamine twice a day for 15 days	Placebo
3	Calusic 2021	Prospective cohort study	Croatia	102	NA	Male: 68 (66.7) Female: 34 (33.3)	Patients over age 18, with positive SARS-COV2 PCR test and acute COVID-19 infection requiring ICU admission	100 mg Fluvoxamine three times a day for 15 days, then taper off to 50 mg for the next 7 days	Standard care
4	Seftel 2021	Prospective cohort study	USA	113	42 (IQR 33-56)	Male: 85(75) Female: 28 (25)	Patients with positive COVID-19 antigen cards test coupled with PCR confirmation who consented to treatment with fluvoxamine	Fluvoxamine at a 50- to 100-mg loading dose, then 50 mg twice daily for 14 days	Standard care
5	Seo 2022	Phase 2 Single-blind RCT	Korea	52	53 (IQR 43.3-60)	Male: 31 (60) Female: 21 (40)	Patients over 18 with symptoms consistent with COVID-19 with onset less than 7 days after randomization and had positive RT-PCR results within 3 days of randomization	50 mg of fluvoxamine on day 1, then an increased dose of 100 mg twice daily, as tolerated, until discharge from the CTC (about 10 days).	50 mg of placebo (ursodeoxycholate) on day 1, then an increased dose of 100 mg twice daily, as tolerated, until discharge from the CTC (about 10 days).
6	Bramante 2022	Phase 3, Double-Blind RCT	USA	661	46 (IQR 38-53) for the intervention group, 43 (IQR 37-53) for the control group	Male: 273 (41.3) Female: 388 (58.7)	Patients from age 30 to 85 years; with a body-mass index (BMI) associated with overweight or obesity; proof of SARS-CoV-2 infection within the past 3 days; and the onset of symptoms within 7 days before randomization*	Fluvoxamine 50mg twice daily alone for 15 days or fluvoxamine 50 mg twice daily plus metformin up to 1500 mg for 15 days	Placebo or metformin up to 1500 mg for 15 days alone
7	Reis 2021	Phase 3, Double-Blind RCT	Brazil	1497	50 (IQR 18-102)	Male: 635 (42.4) Female: 862 (57.5)	Patients over 18 presenting to the OPD with symptoms consistent with COVID 19 or a positive SARS-COV2 antigen test at screening or 7 days within symptoms onset	Fluvoxamine# 100 mg twice a day	Placebo 100 mg twice a day
8	Pineda 2022	Prospective cohort study	Honduras	657	48.1 (mean)	Male: 330 (50.2) Female: 327 (49.8)	Patients fifteen years of age or older, with mild to moderate COVID-19 with a positive SARS-CoV-2 antigen or RT-PCR	Fluvoxamine 50 mg orally twice daily for three days and titrated up to 100 mg two or three times a day depending on patient tolerance and disease severity to complete a fourteen-day course	Standard care

* The six trial groups were assigned to receive the following drugs or combinations of drugs: group 1, metformin plus fluvoxamine; group 2, metformin plus ivermectin; group 3, metformin plus placebo; group 4, placebo plus fluvoxamine; group 5, placebo plus ivermectin; and group 6, placebo plus placebo.

741 patients received fluvoxamine, 756 were allocated to receive placebo while 1826 were allocated to other treatment groups like hydroxycholorquine, liponavir-ritonavir, previous placebo, metformin, ivermectin, doxazosin or interferon lambda.

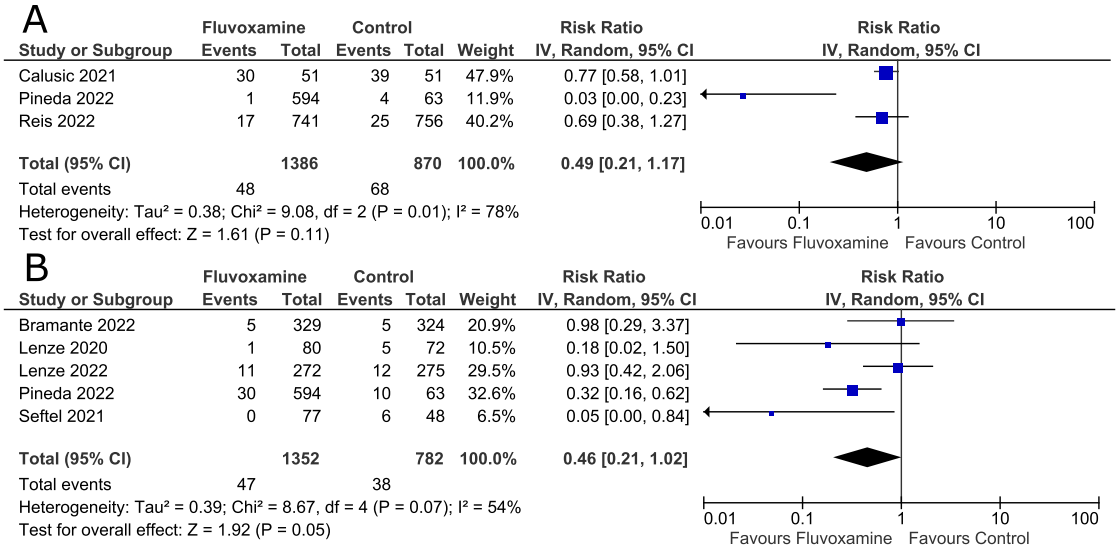

Fig. 1. Effect of fluvoxamine on: (A) all-cause mortality and (B) hospitalization in COVID-19 patients.

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Availability of data

The data that support the findings of this study are available from the corresponding author, HAC, upon reasonable request.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

CRediT authorship contribution statement

Huzaifa Ahmad Cheema: Conceptualization, Visualization, Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Uzair Jafar:** Conceptualization, Visualization, Funding acquisition, Formal analysis, Data curation, Writing – original draft. **Asmaa Ahmed Elrashedy:** Conceptualization, Visualization, Writing – original draft. **Abia Shahid:** Conceptualization, Visualization, Writing – original draft. **Rehmat Ullah Awan:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Muhammad Ehsan:** Funding acquisition, Formal analysis, Data curation, Writing – original draft. **Muhammad Ayyan:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Syeda Sahra:** Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.10.012.

References

1. Qian Z, Pengfei M, Mingwei W, Yongran C, Mengyun Z, Lan Ye, et al. Efficacy and safety of Paxlovid for COVID-19:a meta-analysis. *J Infect* 2022. doi:10.1016/j.jinf.2022.09.027.
2. Junzheng W, Jacob L, Leah E, Andrew H. Minimum manufacturing costs, national prices, and estimated global availability of new repurposed therapies for Coronavirus Disease 2019. *Open Forum Infect Dis* 2022;**9**(1). doi:10.1093/ofid/ofab581.
3. Maurish F, Saleha A, Junaid S, Abia S, Cheema HA. Efficacy and safety of molnupiravir for COVID-19 patients. *Eur J Intern Med* 2022;**102**:118–21. doi:10.1016/j.ejim.2022.05.024.
4. Rayner Craig R, Louis D, Park Jay JH, Decloedt Eric H, Cotton Mark F, Vis N, et al. Accelerating clinical evaluation of repurposed combination therapies for COVID-19. *Am J Trop Med Hyg* 2020;**103**(4):1364–6. doi:10.4269/ajtmh.20-0995.
5. Sukhatme Vikas P, Reiersen Angela M, Vayttaden Sharat J, Sukhatme Vidula V. Fluvoxamine: a review of its mechanism of action and its role in COVID-19. *Front Pharmacol* 2021;**12**:763. doi:10.3389/fphar.2021.652688.
6. Tamaki I, Yuko F, Kenji H. Interaction of new antidepressants with sigma-1 receptor chaperones and their potentiation of neurite outgrowth in PC12 cells. *Eur J Pharmacol* 2014;**727**(1):167–73. doi:10.1016/j.ejphar.2014.01.064.
7. L. Eric, L. St. Fluvoxamine for early treatment of COVID-19: the STOP COVID 2 trial. ClinicalTrials.Gov. Available at https://clinicaltrials.gov/ct2/show/NCT04668950. Accessed October 4, 2022, 2022.
8. Hyeonji S, Haein K, Seongman B, Seonghee P, Hyemin C, Sup SH, et al. Fluvoxamine treatment of patients with symptomatic COVID-19 in a community treatment center: a preliminary result of randomized controlled trial. *Infect Chemother* 2022;**54**(1):102. doi:10.3947/ic.2021.0142.
9. Gilmar R, Augusto SMSE, Medeiros SDC, Lehana T, Cruz MA, Santiago FT, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health* 2022;**10**(1):e42–51. doi:10.1016/S2214-109X(21)00448-4.
10. Lenze EJ, Caline M, Zorumski CF, Angela S, Julie S, Nicol Ginger E, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA* 2020;**324**(22):2292–300. doi:10.1001/jama.2020.22760.
11. Bramante Carolyn T, Huling Jared D, Tignanelli Christopher J, Buse John B, Liebovitz David M, Nicklas Jacinda M, et al. Randomized trial of metformin, ivermectin, and fluvoxamine for Covid-19. *N Engl J Med* 2022;**387**(7):599–610. doi:10.1056/NEJMoa2201662.
12. David S, Boulware DR. Prospective cohort of fluvoxamine for early treatment of Coronavirus Disease 19. *Open Forum Infect Dis* 2021;**8**(2):ofab050. doi:10.1093/ofid/ofab050.
13. Estela P, Jarmanjeet S, Vargas PMF, Garay UJR, Fernando B, Luis B, et al. Impact of fluvoxamine on outpatient treatment of COVID-19 in Honduras. *MedRxiv* 2022. doi:10.1101/2022.09.27.22280428.
14. Martina C, Robert M, Lea L, Ivan J, Natasa K, Slobodan M, et al. Safety and efficacy of fluvoxamine in COVID-19 ICU patients: An open label, prospective cohort trial with matched controls. *Br J Clin Pharmacol* 2022;**88**(5):2065–73. doi:10.1111/bcp.15126.
15. Sapan B, Waleed K, Nithin K, Saffa I, Azizullah B, Mohammed M, et al. Fluvoxamine in nonhospitalized patients with acute COVID-19 infection and the lack of efficacy in reducing rates of hospitalization, mechanical ventilation, and mortality in placebo-controlled trials: a systematic review and meta-analysis. *Am J Ther* 2022;**29**(3):e298–304. doi:10.1097/MJT.0000000000001496.
16. Lz NJ, Mario S, Ingrid T, Agata M, Cornelius L, Ina M, et al. Fluvoxamine for the treatment of COVID-19. *Cochrane Database Syst Rev* 2022;**2022**(9):CD015391. doi:10.1002/14651858.CD015391.

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