Fluvoxamine for COVID-19 outpatients: For the time being, we might prefer to curb our optimism

Trkulja, Vladimir

Received: 27 May 2022 | Revised: 23 June 2022 | Accepted: 26 June 2022

DOI: 10.1111/bcp.15451

LETTER TO THE EDITOR

Fluvoxamine for COVID-19 outpatients: For the time being, we might prefer to curb our optimism

To the Editor,

A rather elaborate pharmacodynamics rationale[1] and sound pharmacokinetic reasoning[2] support the use of fluvoxamine in early phases of the COVID-19 disease. Two recent meta-analyses,[3,4] both based on the same 3 randomized placebo-controlled trials, emphasized the benefit of early fluvoxamine treatment in nonvaccinated adult symptomatic mild COVID-19 outpatients in terms of a reduced risk of disease deterioration over subsequent days. In the first of the trials, Stop COVID 1,[5] primary outcome was hospitalization or hypoxaemia needing oxygen treatment within 15 days. The trial was rather small (fluvoxamine 2×100 to 3×100 mg/d, 15 d, $n = 80$; placebo $n = 72$) and recorded only 6 events (all with placebo).[5] Stop COVID 2[6] followed the same design/primary outcome, and was stopped at an advanced stage for operational reasons but did not indicate a benefit (primary outcome 13/272 [4.8%] fluvoxamine *vs*. 15/275 [5.4%] placebo; hospitalizations 11/272 [4.0%] fluvoxamine *vs*. 12/275 [4.4%] placebo). The meta-analytical estimates[3,4] were dominated by the TOGETHER trial[7] (fluvoxamine 2×100 mg/d, 10 d) that reported a marked relative risk reduction for the primary outcome (emergency room stay of ≥6 h or hospitalization >28 d): 79/741 (11.0%) *vs*. 119/756 (16.0%), risk ratio (RR) = 0.68 (95% credible interval [CrI] 0.52–0.88) in the intent-to-treat analysis (unadjusted Bayesian relative risk).[7] By far the most events were hospitalizations, but benefit was less obvious in this respect (75/741 [10.0%] *vs*. 97/756 [13.0%], odds ratio = 0.77 [0.55–1.05] intent-to-treat [unadjusted frequentist odds ratio][7]). The meta-analysis by Lee *et al*.[3] focused on hospitalizations and reported a 25% relative risk reduction by a frequentist method (RR = 0.75, 95% confidence interval [CI] 0.58–0.97), while the Bayesian analysis (weakly informative neutral prior) indicated somewhat more uncertainty (RR = 0.78, 95%CrI 0.58–1.08; 81.6% probability of RR ≤ 0.90).[3] Guo *et al*.[4] employed only frequentist pooling to indicate a marked benefit regarding "study-defined primary outcomes" (RR = 0.69 95%CI 0.54–0.88) and somewhat more uncertainty regarding "hospitalizations" (RR = 0.79, 95%CI 0.60–1.03).[4] In the meantime, a report was published of a randomized placebo-controlled trial in 2020 in Korean outpatients (~10 d of fluvoxamine 2 × 100 mg/d).[8] It was stopped early for operational reasons,[8] and the primary outcome (defined as in the Stop COVID trials) was observed in 2/26 treated and 2/26 placebo patients.[8] Figure 1 depicts meta-analysis of study-defined primary outcomes and of hospitalizations that uses the same frequentist and Bayesian methodology as used by Lee *et al*.[3] except that it includes the Korean data[8] and employs Hartung–Knapp–Sidik–Jonkman correction shown to improve confidence interval coverage with small number of trials differing in size[9]: (i) for both outcomes, frequentist point-estimates are closely similar to those published,[3,4] but indicators of uncertainty are more obvious—CIs are wider (and embrace unity; imprecision), and prediction intervals are wide (heterogeneity; Figure 1); (ii) Bayes point-estimate for *hospitalizations* (Figure 1B) indicates somewhat less risk reduction (RR = 0.819) than published[3] (RR = 0.78) and CIs and (wide) prediction intervals are shifted *to the right* (imprecision, heterogeneity). In agreement, estimated probability of ≥10% relative risk reduction is reduced (73.8%, Figure 1B *vs*. 81.6%[3]), and there is 50% probability that relative risk reduction is ≥18% (RR = 0.82). Cumulative data (Figure 1B) indicate 8% hospitalization rate with placebo (80/1000), hence 18% relative risk reduction corresponds to an absolute risk reduction of 1.4%; it follows that there is 50% probability of some mild (and questionably relevant) benefit or of no benefit, and 50% probability of a more reasonable benefit. Two further points additionally illustrate current uncertainty about the effect of fluvoxamine. First, the proportions reported in the 2 smaller trials (Stop COVID 1,[5] signalling a potentially large benefit and the Korean trial[8] signalling no potential benefit) are fragile (numerically unstable): it can be shown that even under the assumption of a marked fluvoxamine effect 1 or 2 events more in the fluvoxamine arms and 1 or 2 fewer in the placebo arms would be equally as probable as the observed numbers of events. Next, estimates of heterogeneity across trials that substantially differ in size are problematic.[10] Using metaregression (i.e., meta-analysis with subgroups based on trial size), frequentist estimates in the 2 small trials have extremely wide intervals with a large τ^2 (0.422), while for the larger trials $\tau^2 = 0.000$, and RR = 0.803 (95%CI 0.421–1.530). Bayes estimates are in agreement (larger trials RR = 0.811, 95%CrI 0.538–1.232). Again, point-estimates indicate some benefit, but imprecision (uncertainty) is considerable.

In conclusion, in line with a pharmacological rationale, current trials indicate that fluvoxamine might somewhat reduce the risk of disease progression in mild COVID-19 outpatients, but uncertainty about the size and relevance of the effect is substantial. The on-going trials (depicted in[3]) will hopefully resolve this uncertainty, but presently we might prefer to be cautious rather than overtly optimistic about the extent of benefit conveyed by early fluvoxamine treatment in this setting.

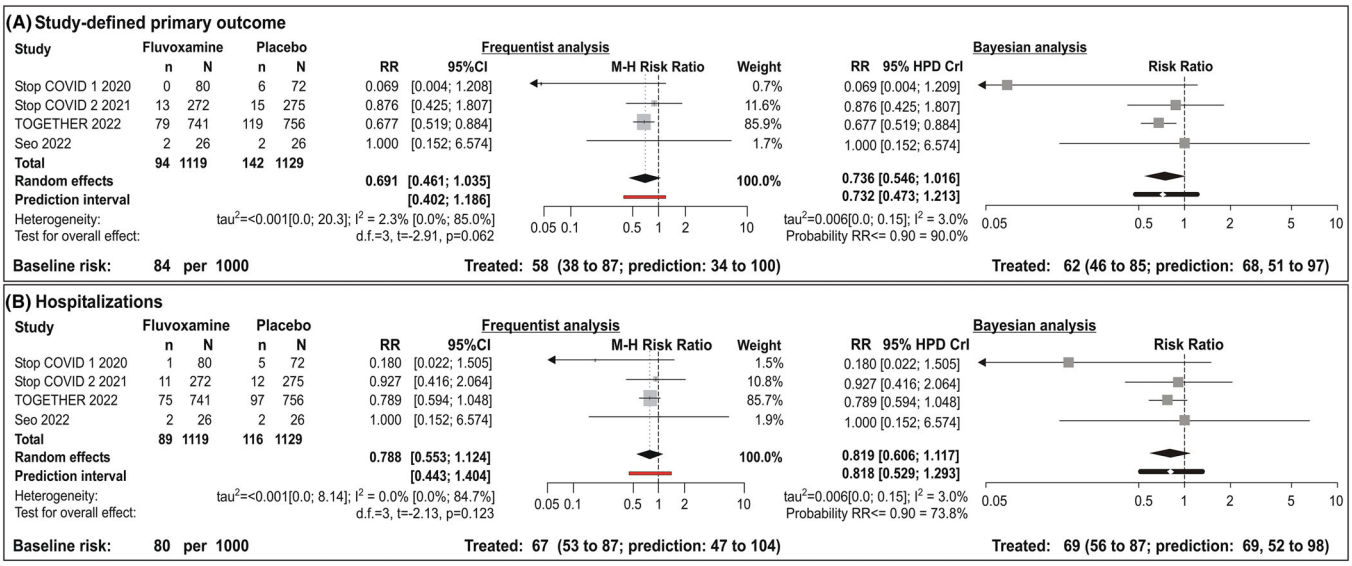

FIGURE 1 Meta-analysis of placebo-controlled randomized trials of fluvoxamine (2×100 or 3×100 mg/d over 10–15 d) in adult, nonvaccinated symptomatic mild COVID-19 outpatients evaluating the effects on disease progression. Implemented are frequentist and Bayesian random-effects pooling methods used also in the meta-analysis by Lee *et al.*[3] (restricted maximum likelihood estimator of across study variance in the frequentist analysis, and weakly informative neutral prior for the effect—0 for ln [RR] and 0.355 for its standard deviation—and half-cauchy with scale 0.10 for the heterogeneity parameter). The differences *vs.* the published meta-analyses[3,4] are in that: (i) it includes data from the Korean trial (Seo *et al.*[8]) and (ii) uses Hartung–Knapp–Sidik–Jonkman correction to calculate frequentist confidence intervals, as recommended.[9] (A) Meta-analysis of study-defined primary outcomes (explained in the text). Data for Stop COVID 1,[5] TOGETHER[7] and the Korean trial (Seo *et al.*[8]) are taken from the respective publications. Data for Stop COVID 2 are not publicly available and were taken from the meta-analysis by Lee *et al.*[3] (B) Meta-analysis of hospitalizations. Data for TOGETHER trial[7] and the Korean trial[8] are taken from the respective publications. Data for Stop COVID 1 and 2 trials are taken from the meta-analysis by Lee *et al.*[3]; the principal investigator of the Stop COVID trials is 1 of the coauthors, hence data should be considered accurate. Bayesian analysis was performed using package *bayesmeta*[11] in R (as in the published meta-analysis[3]), frequentist analysis was performed using package *meta*[12] in R

KEYWORDS

COVID-19, fluvoxamine, hospitalizations, outpatients

COMPETING INTERESTS

The author has no conflict of interest to declare.

Vladimir Trkulja

Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia

Correspondence

Vladimir Trkulja, MD, PhD, Department of Pharmacology, Zagreb University School of Medicine, Šalata 11, 10000 Zagreb, Croatia.

Email: vladimir.trkulja@mef.hr

ORCID

Vladimir Trkulja https://orcid.org/0000-0002-0968-1194

REFERENCES

1. Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV. Fluvoxiamine: a review of its mechanism of action and its role in COVID-19. *Frontiers Pharmacol*. 2021;12:652688. doi:10.3389/fphar.2021.652688
2. Dodds MG, Doyle EB, Reiersen AM, Brown F, Rayner CR. Fluvoxamine for the treatment of COVID-19. *Lancet Glob Health*. 2022;10(3): e332. doi:10.1016/S2214-109X(22)00006-7
3. Lee TC, Vigod S, Bortolussi-Courval E, et al. Fluvoxamine for outpatient management of COVID-19 to prevent hospitalization. A systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(4):e226269. doi:10.1001/jamanetworkopen.2022.6269
4. Guo CM, Harari O, Chernecki C, THorlund K, Forrest JI. Fluvoxamine for the early treatment of COVID-19: a meta-analysis of randomized clinical trials. *Am J Trop Med Hyg*. 2022;106(5):1315-1320. doi:10.4269/ajtmh.21-1310
5. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. *Jama*. 2020;324(22):2292-2300. doi:10.1001/jama.2020.22760
6. Lenze E. Fluvoxamine for early treatment of COVID-19: a fully-remote, randomized placebo controlled trial. *ClinicalTrials.gov*. Accessed May 26, 2022. https://clinicaltrials.gov/ct2/show/NCT04668950
7. Reis G, dos Santos Moreira-Silva EA, Medeiros Silva DC, et al. Effect of early treatment with fluvoxamine on risk of emergeny care and hospitalizations among patients with COVID-19: the TOGETHER randomized platform trial. *Lancet Glob Health*. 2022; 10:e42-e51.
8. Seo H, Kim H, Bae S, 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):102-113. doi:10.3947/ic.2021.0142

9. Langan D, Higgins JPT, Jakson D, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods*. 2019;10(1):83-98. doi:10.1002/jrsm.1316
10. IntHout J, Ionannidis JPA, Borm GF, Goeman JJ. Small studies are more heterogeneous than large ones: a meta-meta-analysis. *J Clin Epidemiol*. 2015;68(8):860-869. doi:10.1016/j.jclinepi.2015.03.017
11. Röver C. Bayesian random-effects meta-analysis using the bayesmeta R Package. *J Stat Softw*. 2020;93(6):1-51. doi:10.18637/jss.v093i06
12. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4):153-160. doi:10.1136/ebmental-2019-300117