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Source / Izvornik: **British Journal of Clinical Pharmacology**, 2022, 88, 4654 - 4656

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1111/bcp.15451>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:220170>

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## LETTER TO THE EDITOR

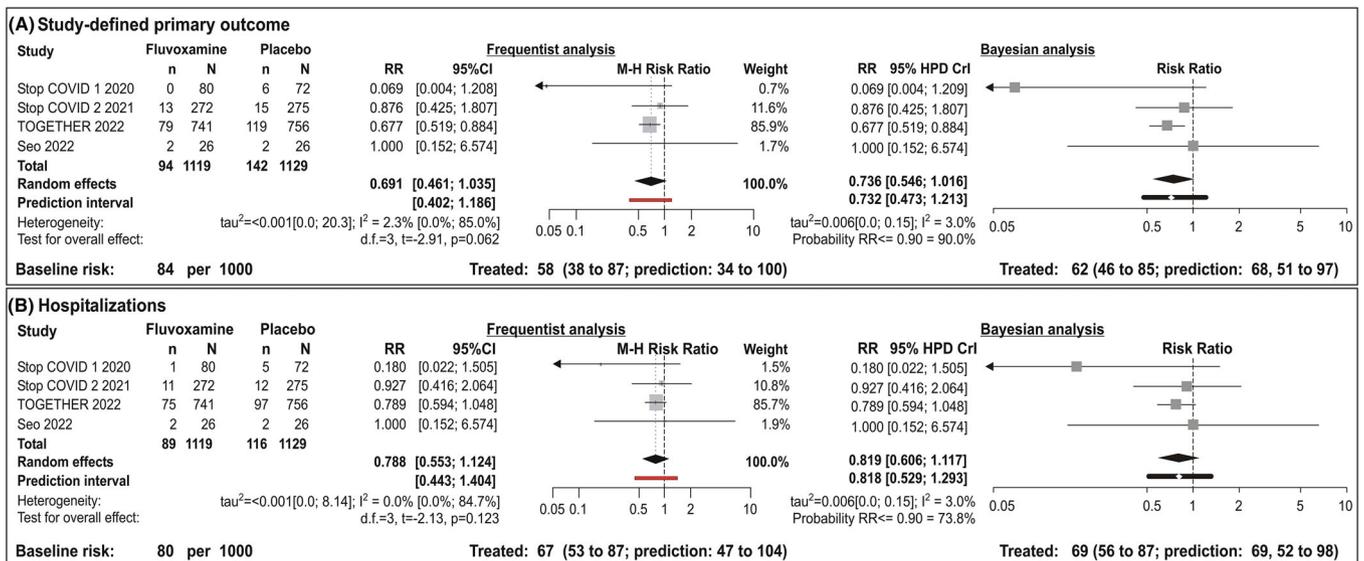
# Fluvoxamine for COVID-19 outpatients: For the time being, we might prefer to curb our optimism

To the Editor,

A rather elaborate pharmacodynamics rationale<sup>1</sup> and sound pharmacokinetic reasoning<sup>2</sup> support the use of fluvoxamine in early phases of the COVID-19 disease. Two recent meta-analyses,<sup>3,4</sup> 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,<sup>5</sup> 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).<sup>5</sup> Stop COVID 2<sup>6</sup> 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<sup>3,4</sup> were dominated by the TOGETHER trial<sup>7</sup> (fluvoxamine 2×100 mg/d, 10 d) that reported a marked relative risk reduction for the primary outcome (emergency room stay of  $\geq 6$  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).<sup>7</sup> 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]<sup>7</sup>). The meta-analysis by Lee *et al.*<sup>3</sup> 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  $\leq$  0.90).<sup>3</sup> Guo *et al.*<sup>4</sup> 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).<sup>4</sup> 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).<sup>8</sup> It was stopped early for operational reasons,<sup>8</sup> and the primary outcome (defined as in the Stop COVID trials) was observed in 2/26 treated and 2/26 placebo patients.<sup>8</sup> 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.*<sup>3</sup> except that it includes the Korean data<sup>8</sup> and employs Hartung–Knapp–Sidik–Jonkman correction shown to improve confidence interval coverage with small number of trials differing in size<sup>9</sup>: (i) for both outcomes, frequentist point-estimates are closely similar to those published,<sup>3,4</sup> 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<sup>3</sup> (RR = 0.78) and CIs and (wide) prediction intervals are shifted to the right (imprecision, heterogeneity). In agreement, estimated probability of  $\geq 10\%$  relative risk reduction is reduced (73.8%, Figure 1B vs. 81.6%<sup>3</sup>), and there is 50% probability that relative risk reduction is  $\geq 18\%$  (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,<sup>5</sup> signalling a potentially large benefit and the Korean trial<sup>8</sup> 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.<sup>10</sup> 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  $\tau^2$  (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<sup>3</sup>) 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.*<sup>3</sup> (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<sup>3,4</sup> are in that: (i) it includes data from the Korean trial (Seo *et al.*<sup>8</sup>) and (ii) uses Hartung–Knapp–Sidik–Jonkman correction to calculate frequentist confidence intervals, as recommended.<sup>9</sup> (A) Meta-analysis of study-defined primary outcomes (explained in the text). Data for Stop COVID 1,<sup>5</sup> TOGETHER<sup>7</sup> and the Korean trial (Seo *et al.*<sup>8</sup>) 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.*<sup>3</sup> (B) Meta-analysis of hospitalizations. Data for TOGETHER trial<sup>7</sup> and the Korean trial<sup>8</sup> are taken from the respective publications. Data for Stop COVID 1 and 2 trials are taken from the meta-analysis by Lee *et al.*<sup>3</sup>; 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*<sup>11</sup> in R (as in the published meta-analysis<sup>3</sup>), frequentist analysis was performed using package *meta*<sup>12</sup> in R

## KEYWORDS

COVID-19, fluvoxamine, hospitalizations, outpatients

## COMPETING INTERESTS

The author has no conflict of interest to declare.

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