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

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To the Editor,

A rather elaborate pharmacodynmics rationale [1] and sound pharmacokinetic reasoning [2] support the use of fluvoxamin in early phases of the COVID-19 disease. Two recent meta-analyses, [3, 4] both based on the same three randomized placebo-controlled trials, emphasized the benefit of early fluvoxamine treatment in non-vaccinated adult symptomatic mild COVID-19 outpatients in terms of a reduced risk of disease deterioration over subsequent days. In the first of the meta-analyzed trials, Stop COVID 1[5], primary outcome was hospitalization or incident hypoxemia needing oxygen treatment within 15 days. The trial was rather small, particularly for a binary outcome (fluvoxamine 2x100 to 3x100 mg/day over 15 days, n=80; placebo n=72) and recorded only 6 events (all with placebo) [5]. Stop COVID 2 [6]followed the same design/outcome, and was stopped at an advanced stage for operational reasons but did not indicate any benefit [incidence 11/272 (4.0%) fluvoxamin vs. 12/275 (4.4%) placebo)]. The meta-analytical pooled estimates [3, 4] were dominated by the results of the TOGETHER trial [7] (fluvoxamine 2x100 mg/day, 10 days) that reported a marked relative reduction in the risk of the primary outcome (emergency room stay of at least 6 hours or hospitalization; over 28 days): 79/741 (11.0%) vs. 119/756 (16.0%), RR=0.69 (95% CrI 0.53-0.90) [7]. By far the most events were hospitalizations, but no clear-cut benefit was obvious in this respect [75/741 (10.0%) vs. 97/756 (13.0%), OR=0.77 (0.55-1.05)[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%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 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 pubslihed of a randomized placebo-controlled trial conducted in 2020 in Korean outpatients (10 days of fluvoxamine 2x100 mg/day)[8]. It was stopped early for operational reasons[8], and the primary outcome (as in 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 (i) it includes the Korean data[8] and (ii) employs Hartung-Knapp-Sidik-Jonkman correction shown to yield the least biased confidence interval coverage with small number of trials considerably varying in size[9]: (a) uncertainty about the benefit regarding "study-defined outcomes" (Figure 1A) is indicated by both the frequentist and Bayesian intervals extending to >1.0 and prediction intervals extending well >1.0. Probability of at least 10% relative risk reduction is 90.0%; (b) uncertainty about the benefit regarding "hospitalizations" (Figure 1B) is even more obvious, with estimate intervals exceding >1.10 (and further extended predictions intervals), with only 73.8% probability of at least 10% relative risk reduction. If one were to disregard two small trials with a few events (and, hence, fragile estimates that could have been by chance, at least in part) [5, 8], for the time being one would be looking at Stop COVID 2 and TOGETHER trial. This means 86/1013 hospitalization events with fluvoxamine vs. 109/1031 events with placebo, and a considerable uncertainty about any practically relevant effect: (i) frequentist RR=0.803 (95%CI 0.422-1.530); (ii) Bayesian RR=0.840 (95%CrI 0.613-1.170) and only 67.4% probablity of at least 10% relative risk reduction. Hopefully, the on-going trials (depicted in ref. 3) will resolve this uncertainty, but presently we might prefer to be cautios rather than overtly optimistic about the actual extent of benefit conveyed by early fluvoxamine treatment in COVID-19 outpatients.

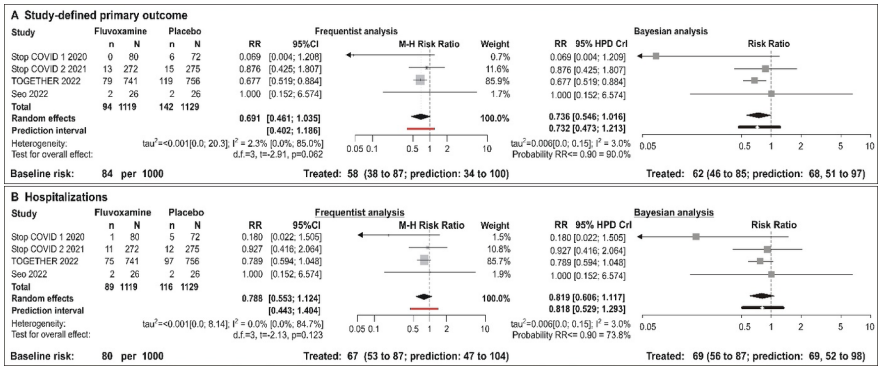

Figure 1 . Meta-analysis of placebo-controlled randomized trials of fluvoxamine (2x100 or 3x100 mg/day over 10 to 15 days) in adult, non-vaccinated symptomatic mild COVID-19 outpatients evaluating the effects on disease progression. Implemented are frequentist and Bayesian random-effects pooling methods 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 calculated 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 one of the co-authors, hence data should be considered accurrate.

Bayesian analysis was performed using package *bayesmeta*[10] in R (as in the published meta-analysis[3]), frequentist analysis was performed using package*meta* (11) in R.

Conflict of interest statement

The author has no conflict of interest to declare.

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