

Why we should not recommend or offer fluvoxamine to COVID-19 patients?

Trkulja, Vladimir

Source / Izvornik: **European Journal of Clinical Pharmacology, 2023, 79, 321 - 322**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1007/s00228-022-03447-3>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:779915>

Rights / Prava: [In copyright](#) / [Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-08-30**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine
Digital Repository](#)





Why we should not recommend or offer fluvoxamine to COVID-19 patients?

Vladimir Trkulja¹

Received: 29 October 2022 / Accepted: 18 December 2022 / Published online: 23 December 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

To the Editor,

The answer to the posted question is rather straightforward: not only there is no explicit evidence of a benefit of fluvoxamine in COVID-19 patients, but there is rather explicit evidence of no (relevant) benefit. The apparently reasonable pharmacodynamic/pharmacokinetic rationale [1, 2] and a huge amount of observational data (too extensive to be individually addressed here)—although commonly contradictory—have indicated a possibility that early commenced fluvoxamine in COVID-19 outpatients might prevent disease progression; or that fluvoxamine in hospitalized and even critical (e.g., managed in intensive care units, ICU) COVID-19 patients might reduce mortality. Regarding the former (mildly symptomatic COVID-19 outpatients, fluvoxamine within 7 days since diagnosis), randomized placebo-controlled trials (RCT) are rather consistent in showing no relevant benefit: (i) initially, a small STOP-COVID 1 RCT [3] (fluvoxamine 2×100 to 3×100 mg/day, 15 days $n=80$, placebo $n=72$) indicated a reduced 15-day hospitalization/new onset hypoxemia rate, but only 6 events were recorded (0/80 vs. 6/72); (ii) the trial extension, STOP-COVID 2 (never published) [4], however, found no benefit: 11/272 (4.0%) events vs. 12/275 (4.4%); (iii) the TOGETHER trial [5] (fluvoxamine 2×100 mg/day, 10 days, $n=741$, placebo $n=756$) indicated a mild reduction in 28-day hospitalization rates (10.0% vs. 13.0%); (iv) a small South Korean trial (fluvoxamine 2×100 mg/day, 10 days, $n=26$, placebo $n=26$; outcomes as in STOP-COVID) found no indication of a treatment benefit (2 events vs. 2 events) [6]; (v) the recent COVID-OUT RCT [7] (fluvoxamine 2×50 mg/day, 14 days, $n=334$, placebo $n=327$) found similar 14-day rates of a composite of new onset hypoxemia, hospitalization, emergency room visit or death (24.0% vs. 24.9%) and of

each of its components; (vi) finally, the recent ACTIV-6 trial [8] (fluvoxamine 2×50 mg/day, 10 days, $n=674$, placebo $n=614$) reported similar 28-day hospitalization/emergency room visit rates (3.9% fluvoxamine vs. 3.8% placebo) and similar time to recovery (HR=0.96, 95%CrI 0.86–1.07). Recommending or offering a non-functional treatment is unethical, and “publicizing” its existence might generate a false sense of security in those reluctant to receive vaccination if being viewed as a helpful alternative resource.

Why, then, do many colleagues support (in this or that way) the use of fluvoxamine in this setting? To this question, the answer is a more complex one. Undoubtedly driven by good intentions and facing an unprecedented pandemic of a devastating disease, we might have developed a cognitive bias and are prone to see what we would like to see, rather than the objective “state of the matter,” particularly when resources are limited. However, a large part of the problem is elsewhere [9, 10]: (i) much of the published medical research is methodologically inadequate and misleading; (ii) much of

it is both carried out and published for wrong reasons (the latter might be particularly applicable to COVID-19-related manuscripts [11]); (iii) most healthcare professionals are not aware of this problem and lack the skills needed to evaluate reliability and usefulness of data. This is particularly so with non-randomized/observational data which tend to be perceived and interpreted as if coming from valid experiments although commonly burdened by a range of biases unrecognized by the readers, and seemingly also by journal editors (see, e.g., [12] as a worked-out critique of a published study advocating fluvoxamine benefits, which was so heavily flawed that it should best be completely ignored; see [13] for the elaboration of biases particularly common in observational studies on COVID-19).

If the tendency of publishing research on fluvoxamine in COVID-19 that is of highly questionable validity continues, we might find ourselves in a situation that is almost impossible to rectify—we would not be able to discourage the public in their views of fluvoxamine as a “wonder drug,” just as we are unable to rectify the confusion about ivermectin.]

✉ Vladimir Trkulja
vladimir.trkulja@mef.hr

¹ Department of Pharmacology, Zagreb University School of Medicine, Šalata 11, 10000 Zagreb, Croatia

Author contributions This is a Letter to Editor authored by Vladimir Trkulja

Data availability This Letter to Editor contains no data.

Declarations

Competing interests The author declares no competing interests.

References

1. Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV (2021) Fluvoxamine: a review of its mechanism of action and its role in COVID-19. *Frontiers Pharmacol* 12:652688. <https://doi.org/10.3389/fphar.2021.652688>
2. Dodds MG, Doyle EB, Reiersen AM, Brown F, Rayner CR (2022) Fluvoxamine for the treatment of COVID-19. *Lancet Glob Health* 10(3):e332. [https://doi.org/10.1016/S2214-109X\(22\)00006-7](https://doi.org/10.1016/S2214-109X(22)00006-7)
3. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE et al (2020) Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. *JAMA* 324:2292–2300
4. Lenze E. Fluvoxamine for early treatment of COVID-19: a fully-remote, randomized placebo controlled trial. <https://clinicaltrials.gov/ct2/show/NCT04668950>. Accessed 26 Oct 2022
5. Reis G, dos Santos Moreira-Silva EA, Medeiros Silva DC, Thabane L, Cruz Milagres A, Santiago Ferreira T et al (2022) Effect of early treatment with fluvoxamine on risk of emergency care and hospitalizations among patients with COVID-19: the TOGETHER randomized platform trial. *Lancet Glob Health* 10:e42-51. [https://doi.org/10.1016/S2214-109X\(21\)00448-4](https://doi.org/10.1016/S2214-109X(21)00448-4)
6. Seo H, Kim H, Bae S, Park S, Chung H, Sung H, Jung J et al (2022) Fluvoxamine treatment of patients with symptomatic COVID-19 in a community treatment center: a preliminary result of randomized controlled trial. *Infect Chemother* 54:102–113
7. Bramante CT, Juling JD, Tignanelli CJ, Buse JB, Liebovitz DM, Nicklas JM et al (2022) Randomized trial of metformin, ivermectin and fluvoxamine for COVID-19. *N Engl J Med* 387:599–610
8. McCarthy MW, Naggie S, Boulware DR, Lindsell CJ, Stewart TG, Felker GM et al (2022) Fluvoxamine for outpatient treatment of COVID-19: a decentralized, placebo-controlled, randomized platform clinical trial. *medRxiv*. <https://doi.org/10.1101/2022.10.17.22281178>
9. Ioannidis JPA, Stuart ME, Brownlee S, Strite S (2017) How to survive the medical misinformation mess. *Eur J Clin Invest* 47:795–802
10. Altman DG (1994) The scandal of poor medical research. *BMJ* 29:283–284
11. Kodvanj I, Homolak J, Virag D, Trkulja V (2022) Publishing of COVID-19 preprints in peer-reviewed journals, preprinting trends, public discussion and quality issues. *Scientometrics* 127:1339–1352
12. Trkulja V (2022) Fluvoxamine for COVID-19 ICU patients? *Br J Clin Pharmacol* 88:2454–2455
13. Griffith GJ, Morris TT, Tudball MJ, Herbert A, Mancano G, Pike L et al (2020) Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun* 11:5749. <https://doi.org/10.1038/s41467-020-19478-2>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.