Fluvoxamine for COVID-19 ICU patients?

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To the Editor,

I read with interest a recently BJCP-accepted manuscript on the use of fluvoxamine in COVID-19 patients who needed admission to an intensive care unit (ICU) [1]. It was instructive to read about the pre-existing clinical experience and about possible mechanisms of presumed benefits of fluvoxamine in COVID-19. However, attention needs to be drawn to the suggested effect of fluvoxamine quantified as a 40% reduction in instantaneous risk of death. The authors report[1] on a cohort (n=51) of patients who, upon ICU admission, were treated with oral fluvoxamine added to the standard of care (SoC) (3x100 mg/day over 15 days, then 2x50 mg/day over 7 days), and who were compared to a cohort (n=51) of SoC-only patients. The two cohorts were said to be matched [1]. Based on reported data [1], it appears that the patients were matched exactly in respect to gender and COVID-19 vaccination status, and, seemingly, on a rather narrow age-caliper, but the matching method was not reported [1]; not reported was also a measure of matching adequacy – standardized difference (d), a preferred method of balance assessment (adequate if $d <0.1$) since independent of the sample size [2]. Based on the reported data[1], for example, the *fluvoxamine – SoC d* regarding body mass index was -0.30 (-0.31 in women and -0.29 in men); also, $d=-0.122$ regarding history of diabetes, $d= -0.350$ regarding history of treated hypertension, $d=-0.11$ regarding on-admission APACHE score – all suggesting a considerable imbalance between the two cohorts (lower values in the fluvoxamine cohort). The authors provide Kaplan-Meier curves of time-to-death (or ICU discharge) but without the numbers at risk[1]. Still, data could be read from the graphs and curves reconstructed (Figure 1A):(i) the first marked difference between the treated and controls occurs during the first 7 days of observation – 3 patients died and 3 were censored in the former, and 11 died and 4 were censored the latter cohort (Figure 1A). This difference in deaths (3 vs. 11) did not change over the entire later period since the overall difference in the number of deaths was 9 (30/51 in treated vs. 39/51 in controls). This would indicate a very rapid-onset (and subsequently "lost") effect of fluvoxamine, which does not seem pharmacologically plausible. The assumed fluvoxamine mechanisms[1] are not of the immediate-onset type; with a 3x100 mg/day dosing, elimination half-life is likely to extend well beyond 30 hours, hence steady-state would be achieved only after 7-10 days [3]. Combined with the baseline imbalance between groups, this indicates that the initial separation of the two curves – more

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or less preserved throughout the entire subsequent period - was likely not attributable to fluvoxamine; (ii) after day 21, and particularly after day 28, the numbers at risk were very low, and after day 35 there were no further events (Figure 1A), hence accounting for the entire curve is likely misleading [4]; (iii) although the curves do not cross (Figure 1A), they indicate a possibility that hazard ratio varied over time. Hazard ratio as generated in a Cox proportional hazard model (as done by the authors) is an average of values that can change over time[5]; it is also inherently prone to selection bias and, even in absence of confounding its interpretation is not straightforward[5]. This holds for randomized and particularly for non-randomized settings [5]. Reconstructed data depicted in Figure 1A were used to fit a complementary log-log model for continuous time process taking into account the first 35 days (no events after that point): the method treats time as a continuous but more "coarsely" measured variable, in intervals of identical length (in this case 7-day intervals, i.e., weeks); based on assumption of constant hazard within the interval, the method provides period-specific (for weeks 1-5) hazard ratios [6], which is likely a preferable option [5]. Figure 1B depicts estimated probabilities of death and HRs: it is only during week 1 that the hazard appeared lower in treated – a period during which, as elaborated, fluvoxamine most likely had no effect. Finally, authors fitted a multivariable Cox model [1] to substantiate the fluvoxamine effect. With a total of 15 independents in a study with 102 subjects, the model was likely overfitted and susceptible to bias arising from over(unnecessary)-adjustments [7]. But more importantly, it included adjustment for renal replacement therapy (RRT), which was actually one of the outcomes. Inadequacy of adjustments for post-exposure outcomes as if they were baseline covariates has been extensively elaborated [8] and almost inevitably results in a considerable bias, regardless of whether the respective variable was actually a mediator or a collider [8]. Such adjustments require implementation of marginal structural models or some of the *g-estimation* methods [9].

Overall, the reported difference between the two cohorts of patients is more likely bias arising from design and analysis than evidence supporting a causal effect of fluvoxamine.

References

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Figure 1 . Summary of re-analysis of survival data published in ref. 1. **A** . Reconstructed curves of Kaplan-Meier product-limit estimates. Data[1] were read using a digitizing software, and were re-analyzed and curves were drawn using JMP 13 software (SAS Institute Inc., Cary, NC). Upward oriented ticks indicate censorings, downward oriented ticks indicate failures. ICU – intensive care unit. **B** . Estimated probabilities of death during weeks 1 to 5 by treatment (Fluvox – fluvoxamine) and period-specific hazard ratios (HR) with confidence intervals. A complementary log-log model was fitted to reconstituted data using SAS 9.4 for Windows (SAS Inc., Cary, NC).

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