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Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf



Letter to the Editor

A meta-analysis regarding fluvoxamine and hospitalization risk of COVID-19 patients: TOGETHER making a difference

Dear Editor,

We read with great interest the meta-analysis recently published by Cheema et al. in the *Journal of Infection* on the topic of

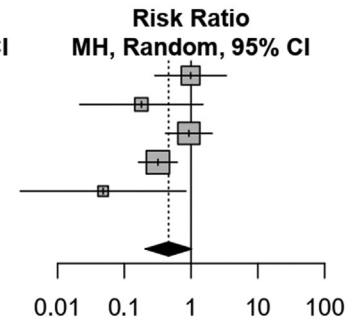
efficacy and safety of fluvoxamine for the treatment of COVID-19 patients.¹

In their meta-analysis Cheema et al. concluded that fluvoxamine does not decrease the risk of hospitalisation in patients with COVID-19 (RR 0.46; 95% CI: 0.21–1.02; $I^2 = 54%$; $p = 0.06$). This conclusion stands in contrast to conclusions of prior meta-analyses such as the meta-analysis published by Lee et al. in JAMA Network

A

Study	Intervention		Control		Weight	Risk Ratio MH, Random, 95% CI
	Events	Total	Events	Total		
Bramante 2022	5	329	5	324	20.9%	0.98 [0.29; 3.37]
Lenze 2020	1	80	5	72	10.5%	0.18 [0.02; 1.50]
Lenze 2022	11	272	12	275	29.5%	0.93 [0.42; 2.06]
Pineda 2022	30	594	10	63	32.5%	0.32 [0.16; 0.62]
Seftel 2021	0	77	6	48	6.5%	0.05 [0.00; 0.84]
Total (95% CI)	47	1352	38	782	100.0%	0.46 [0.21; 1.02]

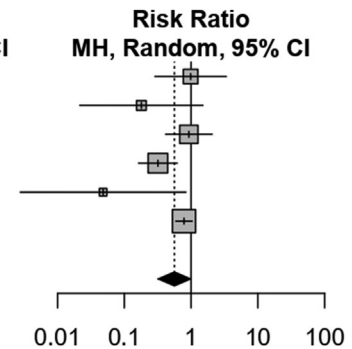
Heterogeneity: $\text{Tau}^2 = 0.3863$; $\text{Chi}^2 = 8.68$, $\text{df} = 4$ ($P = 0.07$); $I^2 = 54%$
 Test for overall effect: $Z = -1.92$ ($P = 0.06$)



B

Study	Intervention		Control		Weight	Risk Ratio MH, Random, 95% CI
	Events	Total	Events	Total		
Bramante 2022	5	329	5	324	13.1%	0.98 [0.29; 3.37]
Lenze 2020	1	80	5	72	5.8%	0.18 [0.02; 1.50]
Lenze 2022	11	272	12	275	20.7%	0.93 [0.42; 2.06]
Pineda 2022	30	594	10	63	23.8%	0.32 [0.16; 0.62]
Seftel 2021	0	77	6	48	3.4%	0.05 [0.00; 0.84]
Reis 2021	76	741	99	756	33.2%	0.78 [0.59; 1.04]
Total (95% CI)	123	2093	137	1538	100.0%	0.56 [0.32; 0.98]

Heterogeneity: $\text{Tau}^2 = 0.2218$; $\text{Chi}^2 = 11.68$, $\text{df} = 5$ ($P = 0.04$); $I^2 = 57%$
 Test for overall effect: $Z = -2.03$ ($P = 0.04$)



C

Study	Intervention		Control		Weight	Risk Ratio MH, Random, 95% CI
	Events	Total	Events	Total		
Bramante 2022	5	329	5	324	11.9%	0.98 [0.29; 3.37]
Lenze 2020	1	80	5	72	5.1%	0.18 [0.02; 1.50]
Lenze 2022	11	272	12	275	19.6%	0.93 [0.42; 2.06]
Pineda 2022	30	594	10	63	22.9%	0.32 [0.16; 0.62]
Seftel 2021	0	77	6	48	3.0%	0.05 [0.00; 0.84]
Reis 2021	76	741	99	756	33.4%	0.78 [0.59; 1.04]
ACTIV-6 2022	1	674	2	614	4.1%	0.46 [0.04; 5.01]
Total (95% CI)	124	2767	139	2152	100.0%	0.57 [0.34; 0.95]

Heterogeneity: $\text{Tau}^2 = 0.1860$; $\text{Chi}^2 = 11.79$, $\text{df} = 6$ ($P = 0.07$); $I^2 = 49%$
 Test for overall effect: $Z = -2.17$ ($P = 0.03$)

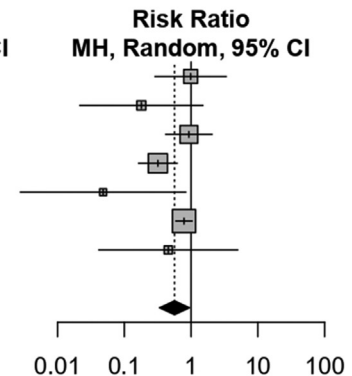


Fig. 1. Forest plot recreating the original meta-analysis by Cheema, H. A. et al.¹ regarding the effect of fluvoxamine on COVID-19 outpatient hospitalisation risk outcome (Fig. 1A). Reanalysis of the hospitalisation outcome with inclusion of data from the TOGETHER trial (Reis, 2021) on Fig. 1B and with the additional inclusion of data from the recently published preprint of the ACTIV-6 study on Fig. 1C.

Open which found that fluvoxamine showed a high probability of being associated with reduced hospitalization in outpatients with COVID-19.²

Upon further inspection of the meta-analysis by Cheema et al., it seems that the authors had made an unfortunate mistake and failed to include results from the TOGETHER trial³ (marked as Reis 2021 in the original meta-analysis and kept as such in this reanalysis) in their hospitalisation outcome meta-analysis, recreated on Fig. 1A. The TOGETHER trial was a placebo-controlled, randomised, adaptive platform trial conducted amongst 1497 high-risk symptomatic Brazilian COVID-19 outpatients, which found that fluvoxamine 100 mg twice daily for 10 days significantly reduced the need for hospitalisation defined as a composite outcome of either retention in a COVID-19 emergency setting or transfer to a tertiary hospital. Data regarding secondary outcomes such as mortality and hospitalisation rate is readily available in Table 3 of the TOGETHER study manuscript and Cheema et al. included results from the TOGETHER trial in their mortality outcome analysis but failed to do the same regarding the hospitalisation outcome.

We have thus reanalysed the hospitalisation outcome with the data presented by Cheema et al., but with the inclusion of hospitalisation data from the TOGETHER trial, Fig. 1B. According to our reanalysis, fluvoxamine does statistically significantly reduce the risk of hospitalisation in COVID-19 outpatients (RR 0.56; 95% CI: 0.32–0.98; $I^2=57\%$; $p=0.04$). Additionally, we have also included results from the recently published preprint of the ACTIV-6 trial on fluvoxamine⁴ which included 1331 COVID-19 positive randomised outpatients and found no statistically significant benefit of fluvoxamine, although in a predominantly vaccinated population (67%) and using a lower dose of 50 mg twice daily. Nevertheless, when we included the hospitalisation outcome data from the ACTIV-6 trial in the meta-analysis, the results remained statistically significant in favour of fluvoxamine (RR= 0.57; 95% CI: 0.34–0.95; $I^2=49\%$; $p=0.03$), Fig. 1C.

In conclusion, the failure to include the TOGETHER trial in the hospitalisation risk outcome meta-analysis by Cheema et al. significantly impacted the results of their analysis and resulted in an erroneous conclusion. Based on our reanalysis, it appears fluvoxamine is associated with a statistically significant decrease in the risk of hospitalisation when given to COVID-19 outpatients.

Authors' contributions

All authors participated equally in all parts of the manuscript.

Funding

No funding was received for this study.

Data disclosure statement

All analysed data is presented in the manuscript.

Declaration of Competing Interest

No conflicts of interest to declare.

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