# EVIDENCE SUMMARY

## RESEARCH QUESTION: Among COVID-19 patients, should fluvoxamine be used for the treatment?

Update by: Katherine Ruth O. Relato, MD, Natasha Ann R. Esteban-Ipac, MD, Mario M. Panaligan, MD, Ivan N. Villespin, MD, Arnel Gerald Q. Jiao, MD, Marissa M. Alejandria, MD, MSc
Initial Review by: Katherine Ruth O. Relato, MD, Carol Stephanie C. Tan-Lim, MD, MSc (Clinical Epidemiology), April P. Padua-Zamora, MD, Leonila F. Dans, MD, MSc, Marissa M. Alejandria, MD, MSc

## RECOMMENDATIONS

| Recommendations | Certainty of Evidence | Strength of Recommendation |
|---|---|---|
| We suggest against the use of fluvoxamine among adult patients with COVID-19 infection. | Very low | Weak |
| We suggest against the use of fluvoxamine among children and adolescent patients with mild to moderate COVID-19 infection. | Very low | Weak |

***Consensus Issues***

Current evidence showed that fluvoxamine had some benefit only on one critical outcome (need for hospitalization) and was inconclusive in terms of all-cause mortality and clinical deterioration. Although adverse events and serious adverse events were not significantly increased in the fluvoxamine group, there were reports of exacerbation of COVID-19 and respiratory failure. Hence, the panel unanimously agreed given the available evidence, the risk of harm, especially the serious adverse events outweighs the marginal benefit of reduction in the need for hospitalization.

## KEY FINDINGS

- Five (5) published randomized controlled trials (RCTs) (n=3,353) investigated the effectiveness of fluvoxamine compared to placebo among confirmed symptomatic non-hospitalized COVID-19 patients.
- There was a significant reduction in emergency room visits and the need for hospitalization among patients taking fluvoxamine, however, there were inconclusive evidence in terms of other critical outcomes such as all-cause mortality, clinical deterioration, healthcare utilization, and serious adverse events.
- The preliminary result of a Phase 2 published trial had issues on performance and detection bias. The serious risk of bias, serious inconsistency and serious imprecision led to the downgrading of evidence to very low certainty.

## WHAT'S NEW IN THIS VERSION?

Three new published RCTs (Seo 2022, Bramante 2022 and McCarthy 2023) are included in this update.

**PREVIOUS RECOMMENDATION**
*As of 08 November 2021*

There is insufficient evidence to recommend the use of fluvoxamine among COVID-19 patients. (Low certainty of evidence)

*Consensus Issues*
Current evidence showed that although fluvoxamine appeared to reduce the need for emergency room visit or hospitalization, there was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, clinical deterioration, adverse events, and serious adverse events. The sample size of the two randomized controlled trials may still be too small to reach a level of significance, precluding any recommendation to be made. As of writing, there are 9 ongoing clinical trials, results of which may further elucidate on fluvoxamine's effectiveness in the treatment of COVID-19.

## INTRODUCTION

Fluvoxamine is a selective serotonin re-uptake inhibitor used to treat obsessive compulsive disorder. The anti-viral and anti-inflammatory roles of fluvoxamine have been recently studied. The potential role of fluvoxamine on the treatment of COVID-19 include a decrease in serotonin levels leading to decreased platelet aggregation, reduced mast cell degranulation thus reducing cytokine release, interference in the lysosomal activity and entry of the virus, inhibition of hyperinflammation by sigma-1 receptor affinity, and mitigation of inflammation by increasing melatonin [1].

Common adverse reactions associated with fluvoxamine include nausea, insomnia, somnolence, headache, asthenia, dizziness, dry mouth, and vomiting. It should also be used with caution when used with other serotonergic drugs to avoid serotonin syndrome [2].

## REVIEW METHODS

A systematic search was done last January 18, 2023 using Medline, Cochrane Library, and Google scholar using free text, MeSH terms and advance search using the terms coronavirus infections, COVID-19 severe acute respiratory syndrome coronavirus 2, and fluvoxamine. Trials found in the COVID-NMA were included. Screening for ongoing trials was done in various trial registries. Medrxiv, chinaxiv and biorxiv was also searched for preprints. RCTs on fluvoxamine as treatment for COVID-19 compared to placebo were included. No limits were placed on age, severity, and dose.

## RESULTS

### Characteristics of included studies

Five (5) published RCTs (n=3,353) evaluated the effectiveness of fluvoxamine among confirmed symptomatic non-hospitalized COVID-19 patients compared to placebo. Two of the trials reviewed were also included in the COVID-NMA Living Data [3,4]. No available studies were found for children or adolescents.

Appendix 3 summarizes the characteristics of the included studies. Three studies were done in the US [3-5], one study was done in Brazil [6] and the other study was done in Korea [7]. Three studies are ongoing Phase 3 trial [4-6], while the two other studies are Phase 2 trials [3,5]. Of the Phase 2 trials, one study is a preliminary report of a suspended study due to closure of the community treatment center [7]. The study participants in all the included trials are confirmed COVID-19 symptomatic patients aged 18 years old and above. One of the studies [6] specified at least one co-morbidity and one of the studies included overweight and obesity[ 4] in the inclusion criteria. One of the studies included patients admitted at a community treatment center [7]. All studies excluded patients being referred for hospitalization at the start of the study [3-7]. One study excluded previous vaccination of COVID-19 [6]. One study included vaccinated and unvaccinated participants [5].

### Certainty of evidence

The overall certainty of evidence was rated very low due to serious risk of bias, serious inconsistency, and serious imprecision on one critical outcome (clinical deterioration). One trial has serious risk of performance and detection bias. The risk of bias summary is shown in Appendix 4. The GRADE evidence summary is in Appendix 5.

### Effectiveness outcomes

Fluvoxamine significantly reduced the need for hospitalization (RR 0.75, 95% CI 0.57-0.98; $I^2$=4%; 3 RCTs, n=2,980) [3,5,6] and the need for emergency room visits (RR 0.73, 95% CI 0.62-0.86; 1 RCT, n=1,497) among symptomatic COVID-19 patients compared to placebo [6]. However, fluvoxamine had no significant benefit on all-cause mortality (RR 0.69, 95% CI 0.38-1.27; 2 RCT, n=2,828) [5,6], clinical deterioration (RR 0.74, 95% CI 0.21-2.66, $I^2$=51%, 3 RCTs, 525 participants) [3,4,7], healthcare utilization (RR 0.89, 95% CI 0.59-1.36 $I^2$=53%, 3 RCTs, 3,149) [4,5,6], and viral negative conversion at day 7 (RR 0.70, 95% CI 0.48-1.04, 1 RCT, n=1,497) compared to placebo [5]. Results on clinical deterioration and healthcare utilization showed moderate heterogeneity.

### Safety

There was no significant difference between fluvoxamine and placebo on the adverse events (RR 1.04, 95% CI 0.83-1.30; $I^2$=47%; 4 RCTs) and serious adverse events (RR 0.77, 95% CI 0.58-1.01, $I^2$=26%, 3 RCTs), however, there is moderate heterogeneity for both results. Common adverse events reported were loss of sense of smell, fatigue, body aches, cough, subjective fever, and loss of appetite. Serious adverse events reported were dehydration, exacerbation of COVID-19, COPD exacerbation, respiratory failure, and pneumonia.

## RECOMMENDATIONS FROM OTHER GROUPS

**Table 1. Summary of recommendations from other groups**

| Group / Agency | Recommendation |
|---|---|
| US-NIH Guidelines as of December 1, 2022[9] | There is insufficient evidence to recommend either for or against the use of fluvoxamine for the treatment of COVID-19. |
| Australian Guideline on COVID-19 as of December 19, 2022[10] | Fluvoxamine for the treatment of COVID-19 should only be used in research settings. |
| Infectious Diseases Society of America (IDSA)as of November 21, 2022[11] | |
| WHO Living Guidelines as of January 13, 2023[12] | |

## RESEARCH GAPS

As of January 17, 2023, there are ten (10) ongoing trials on fluvoxamine registered on *clinicaltrials.gov* and EU Clinical Trials Register. One of the ongoing trials is a phase 4 trial in Thailand with 1,800 participants (Appendix 8).

## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

## COST

Fluvoxamine maleate is used in the Philippines for obsessive compulsive disorder. The local price of fluvoxamine is at ₱71.25 to ₱100.00 for 50mg/tab. Based on the five RCTs [3-7] for COVID-19, fluvoxamine should be taken orally, two to three times a day for 10 to 15 days at a maximum dose of 300mg/day. The total cost of treatment per patient would be ₱6,412.50 to ₱9,000. A cost-effectiveness study done in the United States showed that Fluvoxamine will cost approximately ₱447,600($8,000)/ Quality-Adjusted Life Year (QALY) gained or approximated ₱392,000 $7,000/life year gained [8].

## REFERENCES


[1] Sukhatme VP, Reiersen AM, Vayttaden SJ and Sukhatme VV. Fluvoxamine: A Review of Its Mechanism of Action and Its Role in COVID-19. Frontiers in Pharmacology. 2021; 12(652688). doi: 10.3389/fphar.2021.652688

[2] Fluvoxamine maleate [package insert]. Food and Drug Administration. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021519s012lbl.pdf.

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[4] Bramante CT, Huling JD, Tignanelli JB, Buse DM, Liebovitz JM, Nicklas K, et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. N Engl J Med 2022 Aug;387:599-610.

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[9] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: National Institutes of Health; 2022 December 1. Available from: https://www.covid19treatmentguidelines.nih.gov/

[10] Coronavirus Disease 2019 (COVID-19): Communicable Disease Network Australia National Guidelines for Public Health Units. 2022;62.1 [update 2022 December 19Available from: https://app.magicapp.org/#/guideline/EQ3k5L/rec/jxQg84

[11] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. [Internet]. Infectious Diseases Society of America 2022;Version 10.0.0.0. [updated 2022 November 21]. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#Recommendation28:Fluvoxamine

[12] World Health Organization. [Internet]. Therapeutics and COVID-19 Living Guidelines. [updated 2023 January 13. Available from: https://app.magicapp.org/#/guideline/nBkO1E/rec/nBMO8R

Appendix 1: Preliminary Evidence to Decision

**Table 1. Summary of initial judgements prior to the panel discussion (N=7/10)**

| FACTORS | JUDGEMENT | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|---|---|
| **Problem** | No | Yes (7) | | | | • COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity. |
| **Benefits** | Large | Moderate | Small (5) | Uncertain (2) | Trivial | • Fluvoxamine significantly reduced the need for hospitalization (RR 0.75, 95% CI 0.57-0.98; 3 RCTs, 2,980 participants) and need for emergency room visits (RR 0.73, 95% CI 0.62-0.86; 1 RCT, 1,497 participants) among symptomatic COVID-19 patients compared to placebo.<br>• However, fluvoxamine had no benefit on all-cause mortality (RR 0.69, 95% CI 0.38-1.27), clinical deterioration at day 15 (RR 0.74, 95% CI 0.21-2.66), and viral negative conversion at day 7 (RR 0.70, 95% CI 0.48-1.04) compared to placebo. |
| **Harm** | Large | Small (4) | Uncertain (3) | Varies | | • There was no significant difference on adverse events (RR 1.04, 95% CI 0.83-1.30) and serious adverse events (RR 0.77, 95% CI 0.58-1.01) between fluvoxamine and placebo |
| **Certainty of Evidence** | High | Moderate (1) | Low (4) | Very low (2) | | • The overall certainty of evidence is rated very low due to serious risk of bias, serious inconsistency and serious imprecision on one critical outcome(clinical deterioration) |
| **Balance of effects** | Favors drug (3) | Does not favor drug (2) | Uncertain (2) | | | • There appears to be trend towards benefit (need for hospitalization, need for ER visit) without significant harm<br>• There is still inconclusive evidence in terms of other critical outcomes (all-cause mortality, clinical deterioration, adverse events and serious adverse events) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Values** | Important uncertainty or variability (2) | Possibly important uncertainty or variability (4) | Possibly NO important uncertainty or variability (1) | No important uncertainty or variability | | | |
| **Resources Required** | Uncertain | Large cost | Moderate cost (7) | Negligible cost | Moderate savings | Large savings | ● The local price of fluvoxamine is at ₱75.25 for 50mg/tab. Taken orally, two to three times a day for 10 to 15 days at a maximum dose of 300 mg/day.<br>● The total cost of treatment per patient would be ₱6,772.50 |
| **Certainty of evidence of required resources** | No included studies (3) | Very low (2) | Low (1) | Moderate (1) | High | | ● The cost of fluvoxamine was quoted from a private tertiary hospital's drug price list available online |
| **Cost effectiveness** | No included studies (4) | Favors the comparison (1) | Does not favor either the intervention or the comparison (2) | Favors the intervention | | | |
| **Equity** | Uncertain (3) | Reduced (1) | Probably no impact (1) | Increased (2) | | | |
| **Acceptability** | Uncertain (5) | No | Yes (2) | | | | |
| **Feasibility** | Uncertain (3) | No | Yes (4) | | | | |

Appendix 2: Search Yield and Results

| DATABASE | SEARCH STRATEGY / SEARCH TERMS | DATE AND TIME OF SEARCH | RESULTS | |
|---|---|---|---|---|
| | | | Yield | Eligible |
| Medline | {"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Fluvoxamine Filter: October 10, 2021 to January 17, 2023 | January 17, 2023 10:34PM | 96 | 4 |
| CENTRAL | MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Fluvoxamine | January 17, 2023 11:23PM | 29 | 3 |
| COVID-NMA Initiative | Fluvoxamine | January 17, 2023 09:45PM | 2 | 2 |
| Google Scholar | Fluvoxamine AND COVID-19 AND “randomized trial”<br>Custom range: 2021 - 2023 | January 17, 2023 11:29PM | 377 | 4 |
| | | | | |
| ClinicalTrials.gov | COVID-19, COVID-19 Pneumonia, Investigational Trials, Fluvoxamine | January 17, 2023 11:45PM | 9 | 5 |
| Chinese Clinical Trial Registry | COVID, Fluvoxamine, Randomly Sampling | January 17, 2023 11:47PM | 0 | 0 |
| EU Clinical Trials Register | COVID AND Fluvoxamine | January 17, 2023 11:47PM | 1 | 0 |
| Republic of Korea - Clinical Research Information Service | COVID, fluvoxamine, investigational | January 17, 2023 11:49PM | 0 | 0 |
| Japan Primary Registries Network/ NIPH Clinical Trials Search | COVID AND Fluvoxamine | January 17, 2023 11:51PM | 0 | 0 |
| CenterWatch | COVID AND fluvoxamine | January 17, 2023 11:53PM | 0 | 0 |
| WHO database COVID-19 studies | COVID AND fluvoxamine | January 17, 2023 11:54PM | 6 | 2 |
| | | | | |
| chinaxiv.org | COVID AND fluvoxamine | January 17, 2023 11:57PM | 0 | 0 |
| Medrxiv.org | COVID AND fluvoxamine<br>Limit results (Date posted): October 21, 2021 to January 17, 2023 | January 17, 2023 11:57PM | 45 | 1 |
| Biorxiv.org | COVID AND fluvoxamine | January 17, 2023 11:59PM | 16 | 0 |

| | | | | |
|---|---|---|---|---|
| | Limit results (Date posted): October 21, 2021 to January 17, 2023 | | | |

## Appendix 3: Characteristics of Included Studies

| Title/Author | Study design | Country | Population | Intervention Group(s) | Control | Outcomes |
|---|---|---|---|---|---|---|
| Lenze 2020<br><br>STOP-COVID<br><br>Phase 2 | Double-blind, placebo-controlled, randomized trial | United States of America | ≥18 years old, outpatient, confirmed, symptomatic (N=152) | Fluvoxamine 50mg, then 100mg twice daily for 2 days, then 100mg 3 times daily through day 15 | Placebo | • Clinical deterioration<br>• Clinical Status on 7-point scale<br>• Adverse event<br>• Serious adverse events |
| Reis 2021<br><br>TOGETHER Trial<br><br>Phase 3 | Adaptive Placebo controlled randomized trial | Brazil | ≥18 years old, with acute symptomatic confirmed COVID-19, at least one additional criterion for comorbidity<br><br>(N=1,497) | Fluvoxamine 100mg twice daily for 10 days | Placebo | • Extended emergency room observation<br>• Hospitalization<br>• Viral clearance<br>• Time to clinical improvement<br>• Number of days with respiratory symptoms<br>• Time to hospitalization<br>• Clinical deterioration<br>• All-cause mortality<br>• Days in hospital or mechanical ventilator<br>• Adverse events |
| New studies | | | | | | |
| Seo 2022*<br><br>Phase 2 | Single-blind placebo-controlled randomized trial | Korea | ≥18 years old, admitted at a community treatment care, confirmed, symptomatic<br><br>(N=52) | Fluvoxamine 50mg, then 100mg twice daily until discharge (about 10 days) | Placebo | • Clinical deterioration<br>• Days to clinical deterioration<br>• Adverse events<br>• Serious adverse events |
| Bramante 2022<br><br>COVID-OUT<br><br>Phase 3 | Double-blind placebo-controlled randomized trial | United States of America | 30-84 years old, out-patient, confirmed, obese or overweight<br><br>(N=361) | Fluvoxamine 50mg on day 1 then 50mg twice daily for days 2-14 | Placebo | • Clinical deterioration<br>• Emergency room visit<br>• Hospitalization<br>• All-cause mortality<br>• Adverse events<br>• Serious adverse events |

| | | | | | | |
|---|---|---|---|---|---|---|
| McCarthy 2023<br><br>ACTIV-6<br><br>United States | Double-blind placebo-controlled adaptive randomized clinical trial | United States of America | 30 years or older,<br>Out-patient,<br>Confirmed, mild to moderate, symptom onset 7 days or less<br><br>Exclusion: hospitalization<br><br>(N=1,331)<br><br>Vaccinated and unvaccinated<br><br>Enrollment: August 6, 2021 to May 27, 2022 | Fluvoxamine 50mg BID for 10 days<br><br>Ivermectin<br><br>Fluticasone furoate | Placebo | • Time to sustained recovery<br>• Hospitalization or death by day 28<br>• COVID clinical progression scale day 7, 14, 28<br>• Mortality day 28<br>• Hospitalization, urgent care visit, emergency room visit or death day 28 |

Appendix 4: Study Appraisal

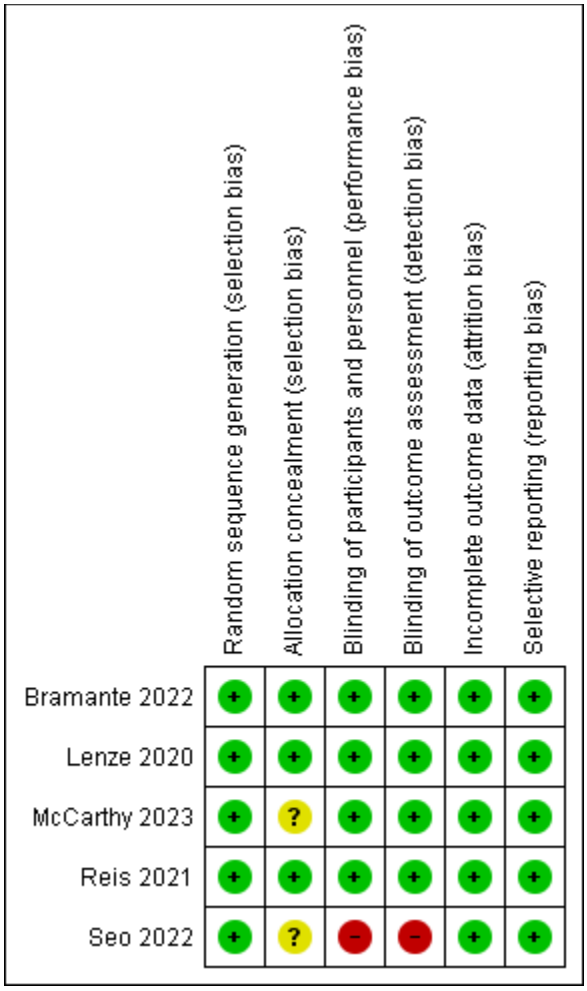


**Figure 1.** Risk of bias summary table

## Appendix 5: GRADE Evidence Profile

**Author(s): K. Relato**
**Question:** Fluvoxamine compared to Placebo for COVID-19

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fluvoxamine | Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Clinical Deterioration** | | | | | | | | | | | | |
| 3 | randomised trials | serious[a] | serious[b] | not serious | serious[c] | none | 47/262 (17.9%) | 48/263 (18.3%) | **RR 0.74** (0.21 to 2.66) | **47 fewer per 1,000** (from 144 fewer to 303 more) | ⨁◯◯◯ Very low | CRITICAL |
| **All-cause mortality** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | serious[c] | none | 17/1427 (1.2%) | 25/1401 (1.8%) | **RR 0.69** (0.38 to 1.27) | **6 fewer per 1,000** (from 11 fewer to 5 more) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Need for hospitalization** | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | not serious | none | 77/1507 (5.1%) | 105/1473 (7.1%) | **RR 0.75** (0.57 to 0.98) | **18 fewer per 1,000** (from 31 fewer to 1 fewer) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Adverse Effect** | | | | | | | | | | | | |
| 4 | randomised trials | serious[a,d] | not serious | not serious | serious[c] | none | 142/1533 (9.3%) | 135/1499 (9.0%) | **RR 1.04** (0.83 to 1.30) | **4 more per 1,000** (from 15 fewer to 27 more) | ⨁⨁◯◯ Low | IMPORTANT |
| **Serious Adverse Effect** | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | serious[c] | none | 81/1507 (5.4%) | 107/1473 (7.3%) | **RR 0.77** (0.58 to 1.01) | **17 fewer per 1,000** (from 31 fewer to 1 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Emergency Room Visit** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | not serious | none | 180/741 (24.3%) | 251/756 (33.2%) | **RR 0.73** (0.62 to 0.86) | **90 fewer per 1,000** (from 126 fewer to 46 fewer) | ⨁⨁⨁⨁ High | IMPORTANT |
| **Healthcare utilization (emergency room visit and need for hospitalization)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | serious[e] | not serious | serious[c] | none | 119/1583 (7.5%) | 153/1566 (9.8%) | **RR 0.89** (0.59 to 1.36) | **11 fewer per 1,000** (from 40 fewer to 35 more) | ⨁◯◯◯ Very low | IMPORTANT |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

## Explanations

a. Performance and detection bias
b. I2= 51%
c. wide confidence interval with possibility for benefit and harm.
d. selection bias
e. I2=53%

Appendix 6: Forest Plots

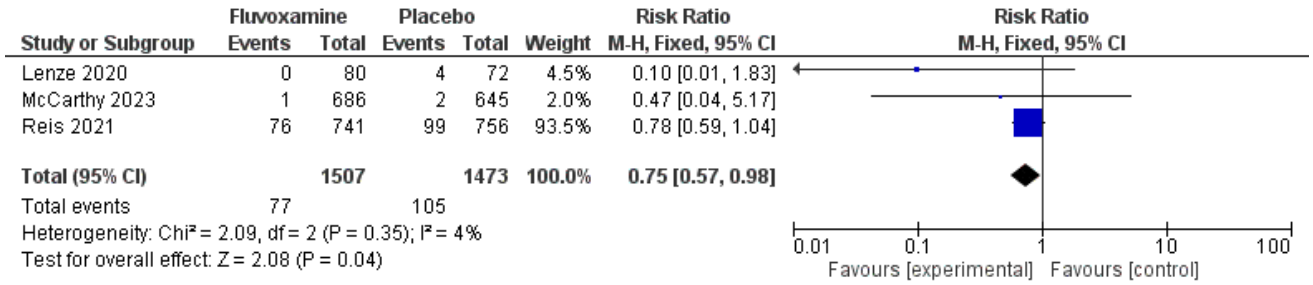


**Figure 2.** Need for hospitalization

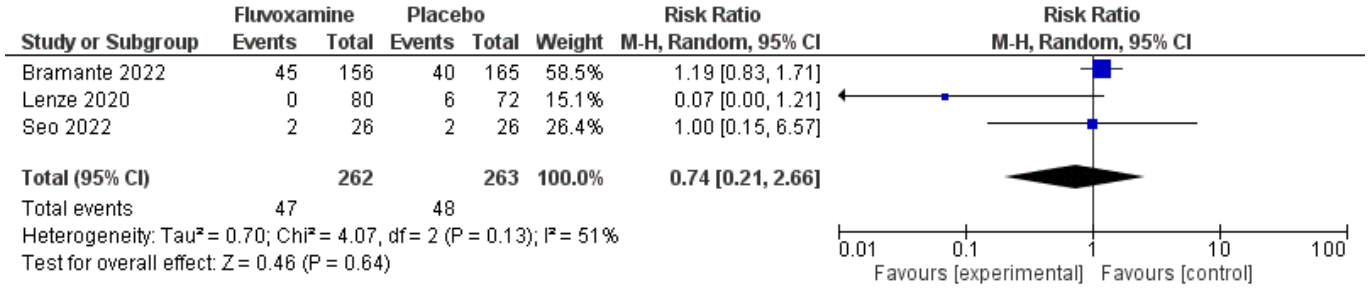


**Figure 3.** Clinical deterioration

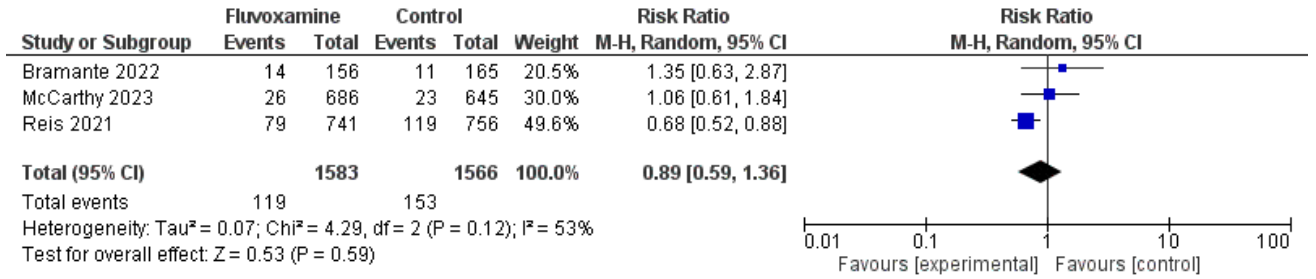


**Figure 4.** Healthcare Utilization (Emergency room visit, need for hospitalization)

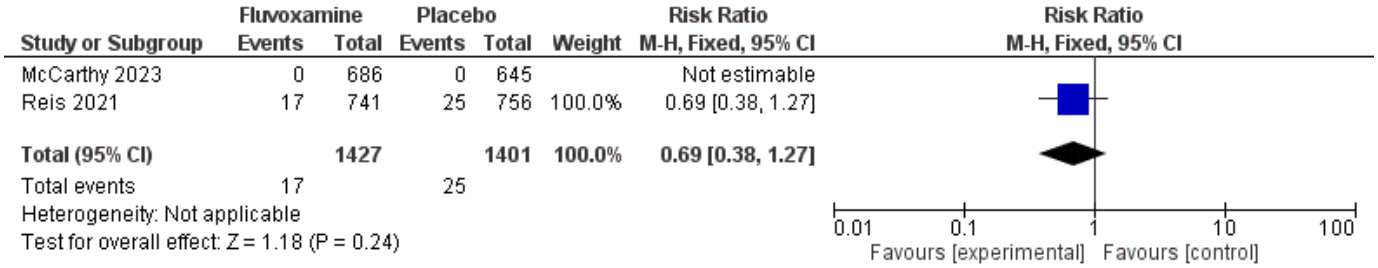


**Figure 5.** All-cause mortality

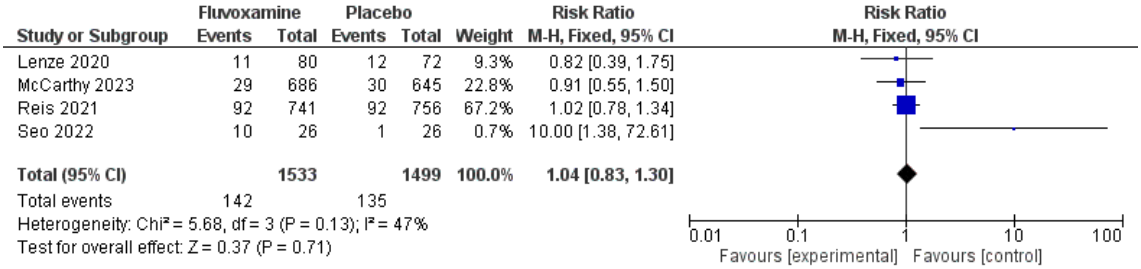


**Figure 6.** Adverse events

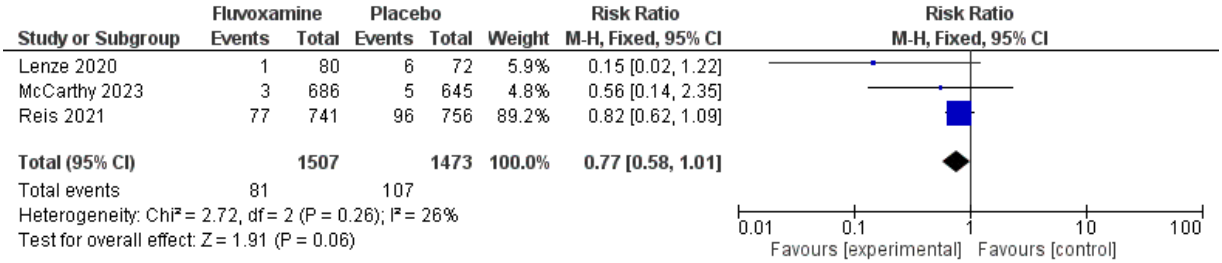


**Figure 7.** Serious adverse events

Appendix 7: Pooled Results of Trials

| Outcome | Pooled / Relative Risk | 95% CI | Certainty of evidence (GRADE) |
|---|---|---|---|
| **Need for hospitalization** (3 RCTs, n = 2,980) | 0.75 | 0.57 to 0.98 | Moderate |
| **Emergency Room visit** (1 RCT, n = 1,497) | 0.73 | 0.62 to 0.86 | High |
| **All-cause mortality** (2 RCT, n = 2,980) | 0.69 | 0.38 to 1.27 | Moderate |
| **Clinical Deterioration** (3 RCTs, n = 525) | 0.74 | 0.21 to 2.66 | Very Low |
| **Healthcare Utilization (3 RCTs, n = 3,149)** | 0.89 | 0.59 to 1.36 | Very Low |
| **Viral Negative Conversion** (1 RCT, n = 1,497) | 0.70 | 0.48 to 1.04 | Moderate |
| **Adverse events** (4 RCTs, n = 3,032) | 1.04 | 0.58 to 1.01 | Low |
| **Serious adverse events** (3 RCTs, n =2,980) | 0.77 | 0.58 to 1.01 | Low |

## Appendix 8: Characteristics of Ongoing Studies

| Study Title | Patients (n) | Interventions | Outcomes | Method |
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| 1. Effect of fluvoxamine medicine on cytokine level of COVID-19 patients, hospitalized in ICU ward<br><br>*Completed recruitment*<br>*Phase 2-3* | Hospitalized in ICU due to COVID-19 | Experimental: Fluvoxamine 50mg daily up to 300mg/week<br><br>Control: Standard of care | Primary: CRP, ESR, IL-6 level upon discharge from ICU | Randomized control open label |
| 2. Fluvoxamine for Early Treatment of Covid-19 (Stop Covid 2)<br><br>Recruitment completed<br><br>Phase 3 | ≥30 years old, not currently hospitalized, proven SARS-CoV-2 positive, currently symptomatic, one of the following risk factors for clinical deterioration: age≥40, racial/ethnic group African-American, Hispanic, or Native American or 1+ of the following medical conditions which increased risk for developing moderate-severe COVID illness: obesity, hypertension, diabetes, heart disease, lung disease, immune disorder | Experimental: Fluvoxamine 50mg once daily then 100mg twice daily approximately 15 days<br><br>Control: Placebo | Primary: Time to clinical deterioration | Randomized placebo controlled double-blind |
| 3. Repurposed Approved and Under Development Therapies for Patients With Early-Onset COVID-19 and Mild Symptoms<br><br>Recruiting<br>Phase 3 | ≥18 years old, flu-Like symptoms < 07 days, at least ONE enhancement criteria: 50 years; Diabetes mellitus, Systemic arterial hypertension, cardiovascular diseases, Symptomatic lung disease, Fever > 38 C at baseline, Obesity, Transplanted patients, chronic kidney disease, Immunosuppressed patients/ using corticosteroid therapy, Patients with a history of cancer Patients | Experimental: Group 1: Fluvoxamine 100mg twice daily through day 9<br><br>Group 2: Doxazosin<br><br>Group 3: Ivermectin<br><br>Group 4: Peg INF lambda<br><br>Group 5: Peg INF Beta<br><br>Control: Placebo | Primary: Need for emergency care and clinical worsening 28 days<br><br>Need for hospitalization | Randomized double blind placebo controlled |

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| | with important limitation of daily activities, positive rapid test for SARS-CoV2 antigen performed on occasion of the screening or patient with a positive SARS-CoV2 diagnostic test within 07 days of the onset of symptoms. | | | |
| 4. Effect of Combined Fluvoxamine with Favipiravir versus Favipiravir Monotherapy in Prevention of Clinical Deterioration among mild to moderate COVID-19 patients Monitoring by Telemedicine in Virtual Clinic: Open-label Randomized Controlled Trial<br><br>*Recruitment completed*<br>*Phase 2/3* | ≥18 years old, confirmed COVID-19 with 1 or more of the symptoms, Asymptomatic COVID-19, accept to perform chest CT, Nasopharyngeal swab or oropharyngeal swab detected ORF1 a/b gene E gene from SARS-CoV-2 PCR with Ct value, does not meet WHO criteria for hospitalization | Experimental: Fluvoxamine 100mg daily for 10 days plus Favipavir<br><br>Control: Favipavir | Primary: Clinical deterioration | Randomized open-label |
| 5. Fluvoxamine Administration in Moderate SARS-CoV-2 (COVID-19) Infected Patients<br><br>*Recruitment completed*<br>*Phase 2* | 18-70 years of age, Hospitalized patients with confirmed SARS-CoV-2 by PCR, Moderate cases (each of the followings met): showing dyspnea but not manifest respiratory distress, respiratory rate 22-29 / min; oxygen saturation at rest > 93%; with or without the need for oxygen supplementation; pneumonia on medical imaging with pulmonary infiltrates occupying ≤ 50% of the lung-fields | Experimental: Fluvoxamine 200mg daily over 74 days<br><br>Control: Placebo | Primary: Time to clinical recovery | Randomized double blind placebo-controlled |
| 6. A randomized, double-blind, placebo-controlled, adaptive-design study to assess the safety and efficacy of daily 200 | 18-80 years of age, hospitalized patients with confirmed SARS-CoV-2, Moderate cases (at least one of the following criteria is met): dyspnea/tachypnea, respiratory rate | Experimental: Fluvoxamine 50mg<br><br>Control: Placebo | Primary: Time to clinical recovery | Randomized double blind placebo-controlled |

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| mg fluvoxamine as add-on therapy to standard of care in moderate severity COVID-19 patients<br><br>*Recruiting*<br>*Phase 2* | 22-29 / min; with the need for oxygen supplementation; pulmonary infiltrates on medical imaging | | | |
| 7. ACTIV-6: COVID-19 Study of Repurposed Medications<br><br>Recruiting<br>Phase 3 | Age ≥30 years old, Confirmed SARS-CoV-2 infection within 10 days of screening, Two or more current symptoms of acute infection for ≤7 days: fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell | Experimental:<br>Group 1: Ivermectin<br><br>Group 2: Fluvoxamine 50mg twice daily for 10 days<br><br>Group 3 Fluticasone<br><br>Control: Placebo | Primary: Number of hospitalizations<br><br>Number of deaths<br><br>Number of symptoms | Randomized double blind placebo controlled |
| 8. COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19)<br><br>*Active, not recruiting*<br>*Phase 3* | 30 to 85 years old, positive RT PCR within 3 days, no known history of confirmed SARS-CoV-2 infection, BMI >= 25kg/m2, GFR>45ml/min within 2 weeks for patients >75 years old, or with history of heart, kidney, or liver failure. | Experimental:<br>Group 1: Metformin<br><br>Group 2: Ivermectin<br><br>Group 3: Fluvoxamine 50mg twice daily for 14 days<br><br>Group 4: Fluvoxamine and Metformin<br><br>Group 5: Metformin and Ivermectin<br><br>Control: Placebo | Primary: Decreased oxygenation<br><br>Emergency department utilization | Randomized double blind placebo-controlled |
| 9. Randomized-controlled Trial of the Effectiveness of COVID-19 Early Treatment in Community<br><br>Recruitment completed<br>Phase 4 | >18 years old, COVID-19 patients with mild symptoms and the results were confirmed by Antigen Test Kit or PCR for SARS-CoV-2. People who have symptoms consistent with COVID-19 and test positive for SARS-CoV-2 infection within 48 hours of being known | Experimental:<br>Group 1: Fluvoxamine 50mg in AM and 100mg in PM for 14 days<br><br>Group 2: Fluvoxamine and Bromhexine | Primary: Hospital admission or mortality (28-day)<br><br>Time to recovery | Randomized, parallel, open-label, adaptive trial |

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| | | Group 3: Fluvoxamine and Cyproheptadine<br><br>Group 4: Niclosamide<br><br>Group 5: Niclosamide and Bromhexine<br><br>Control: Standard of Care | Progression to severe disease | |
| 10. Fluvoxamine in Long COVID<br><br>Recruitment completed<br>Phase 3 | >15 years old, COVID-19 diagnosed by an Infectious Disease Specialist | Experimental: Fluvoxamine 50mg BID for 10 days<br><br>Control: Placebo | Primary: Frequency of any of the neuropsycological symptoms of Long COVID in patients (after 4 weeks) | Randomized, parallel, double-blind, placebo controlled |