South African National Department of Health
Rapid Review Report
Component: COVID-19

TITLE: Should fluvoxamine be used to treat COVID-19?

Date: 27 May 2022 ***(first update of initial report of 5 November 2021)***

Key findings

- We conducted a rapid review of available evidence on the efficacy and safety of fluvoxamine in patients with COVID-19.
- Two randomised controlled trials were identified for inclusion.
- Compared to placebo, there is no clear evidence that fluvoxamine results in a difference in mortality, progression to hospitalisation, duration of hospitalisation, progression to mechanical ventilation, duration of mechanical ventilation or adverse events.
- The current evidence is limited, but does not support the inclusion of fluvoxamine to treat patients with COVID-19.

NEML MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation		X			

Recommendation: The Committee suggests that fluvoxamine not be used for the treatment of COVID-19, except in the context of clinical trials.
Rationale: There remains significant uncertainty whether fluvoxamine is more effective and safer than placebo in treating patients with COVID-19.
Level of Evidence: Low certainty of evidence
Review indicator: Evidence of safety and/or efficacy that is sufficient to change the recommendation.

(Refer to appendix 2 for the evidence to decision framework)

NEML MAC on COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees. Secretariat: Trudy Leong, Milli Reddy (BHPSA).

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

PROSPERO registration: CRD42021286710

BACKGROUND

An excessive inflammatory response from irregular cytokine production has been implicated in COVID-19 associated lung damage prompting investigation of immunomodulatory medicines [1-2]. Fluvoxamine, a Selective Serotonin Reuptake Inhibitor, is an antidepressant with possible immunomodulatory effects that may decrease the harmful effects of the inflammatory response during sepsis [3-4]. Case reports of COVID-19 patients with severe depression found reduced plasma levels of inflammatory mediators [3,5]. This review aims to determine whether fluvoxamine reduces the risk of disease progression and mortality among COVID-19 patients.

RESEARCH QUESTION: Should fluvoxamine be used for managing COVID-19?

METHODS

Eligibility criteria for review

Population:
All patients with confirmed SARS-CoV-2 infection, no restriction to age, disease severity or setting.

Intervention:
Fluvoxamine, alone or in combination with any other agent; no restriction on dose, frequency, or timing with respect to onset of symptoms.

Comparators:
Standard of care +/- placebo.

Outcomes:
Mortality; progression to hospitalization; duration of hospitalization; progression to ICU admission; progression to mechanical ventilation; duration of mechanical ventilation; duration of ICU stay; clinical outcome on an ordinal scale, adverse events, adverse reactions.

Study designs:
Randomised controlled trials, and systematic reviews of randomised controlled trials.

Data sources

On 16 September 2021 we searched the following databases:

- PubMed
- COVID-19 LOVE platform
- Cochrane COVID-19 Study Register

Search strategy: Refer to appendix 1.

Selecting studies for inclusion
Title and abstract and full-text screening were done in duplicate using COVIDENCE software (SvW and VN).

Data extraction
Data extraction was done by a single reviewer (VN) and checked by a second reviewer (SvW). We extracted data on the methods; participants including population, age, risk and setting; interventions including type of intervention, comparator and delivery; and primary and secondary outcomes.

Appraisal of study quality
Quality assessment was done in duplicate, and conflicts were resolved with discussion (SvW and VN). We appraised randomized controlled trials using the standard Cochrane risk of bias assessment tool 2.0 which considers: random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting and other sources of bias.
(https://training.cochrane.org/handbook/current/chapter-08).

Data synthesis
The relevant measures of effect with 95% confidence intervals (CIs) were reported for all outcomes. Pooled estimates were calculated in Review manager 5.4 where applicable, and we used available data to conduct GRADE assessments of the overall certainty of the evidence for these outcomes.

On 6 May 2022, an updated search was conducted.

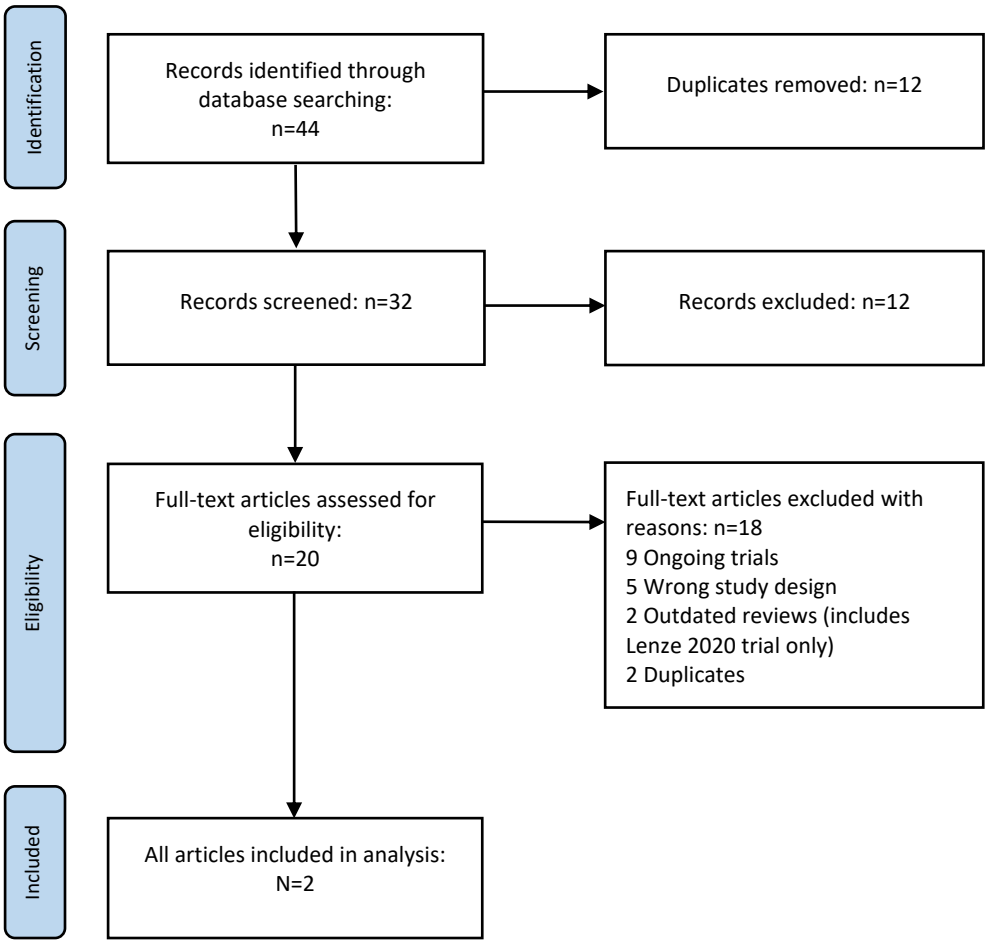
RESULTS

- **Initial review (16 September 2021)**

Identification of studies

Two randomized controlled trials (see Figure 1) were identified.

Figure 1: PRISMA flow diagram



Description of studies

We identified two randomized placebo-controlled trials: Lenze 2020[6] and the TOGETHER trial 2021[7] (the preprint of the TOGETHER trial was subsequently published in peer-review format on the 27 October 2021). Both trials recruited adults with acute symptomatic confirmed COVID-19 infection in an outpatient setting. Participants in the TOGETHER trial were unvaccinated and had at least one high-risk factor for severe COVID-19. Fluvoxamine 100mg was given three times daily for 15 days in the Lenze trial and twice daily for 10 days in the TOGETHER trial. Participants were followed up for 15 days in the Lenze trial and 28 days in the TOGETHER trial. Both trials reported clinical deterioration as a primary outcome (see definitions in Table 1).

Risk of bias of included studies

Both trials had low risk of bias due to randomization, deviations from intended interventions, missing outcome data and in measurement of the outcome data.

The TOGETHER trial protocol reported two primary outcomes: 1) extended emergency room observation (>6 hours) and 2) hospitalization. These outcomes have been combined into a non-prespecified composite outcome in the publication. The combined outcome relative risk (RR) was statistically significantly lower with 87% of this outcome comprising hospitalizations; however, RR for hospitalization alone was not statistically significant.

- **Review update (6 May 2022)**

Sixty-one new records were identified from the updated search conducted on 6 May 2022. After deduplication, 46 records were screened. Two new randomised controlled trials and two systematic reviews were identified and

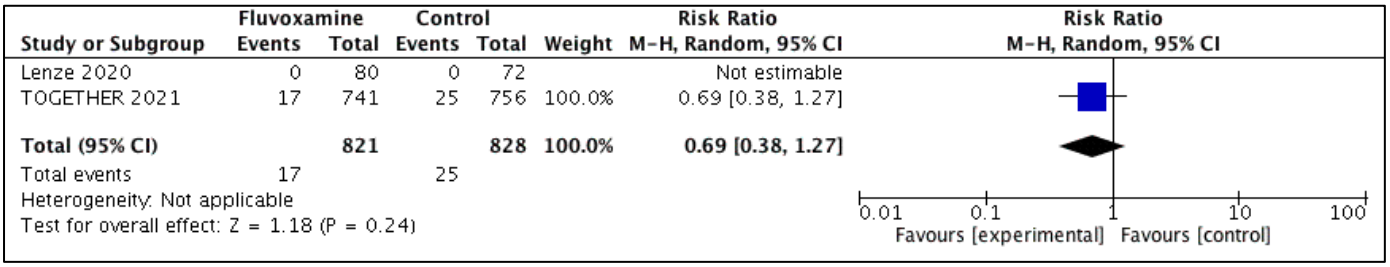
reviewed. Including the results from these studies to the rapid review, however, would not change the initial recommendation (5 November 2021) nor the strength of this recommendation.
This finding is in line with a recent summary from the FDA explaining why the request for Emergency Use Authorization of fluvoxamine was not approved.
https://protect-za.mimecast.com/s/_63WC2RrOjiVYDGpfnENhn?domain=accessdata.fda.gov

EFFECT OF THE INTERVENTION

Mortality

Fluvoxamine may result in little to no difference in mortality, relative risk (RR) 0.69 (95% CI 0.38 to 1.27), 2 trials, low certainty evidence.

Figure 2: Forest plot for fluvoxamine versus placebo; outcome: mortality

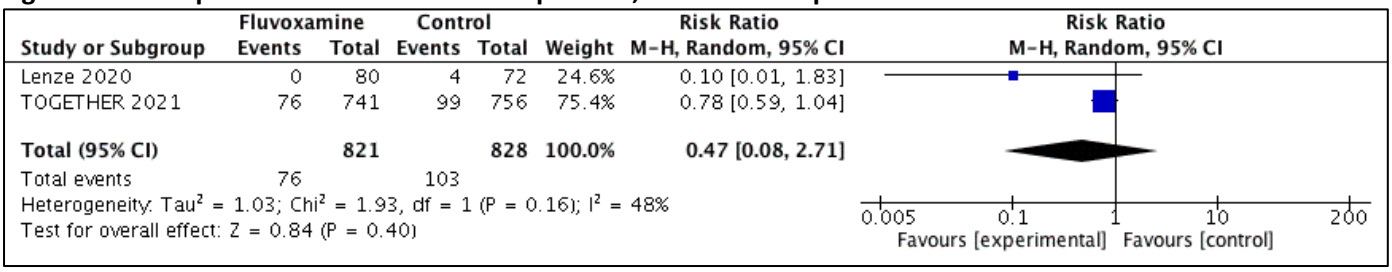


Progression to hospitalisation

Fluvoxamine may result in little to no difference in hospitalisation, relative risk (RR) 0.47 (0.08 to 2.71), 2 trials, low certainty evidence.

Of note, the TOGETHER publication combined 'emergency setting visit for at least 6 hours' with 'hospitalisation' as their non-prespecified primary outcome and found lower rates in the fluvoxamine group (79 [11%] of 741 vs 119 [16%] of 756); relative risk [RR] 0·68; 95% Bayesian credible interval [95% BCI]: 0·52–0·88)). Their justification for this was that hospitals were at capacity during the study period and patients that would normally have been referred for admission were observed for prolonged periods of time before admission or referral. This composite measure is not one of our pre-specified outcomes and is of questionable clinical relevance.

Figure 3: Forest plot for fluvoxamine versus placebo; outcome: hospitalisation



Duration of hospitalisation

Fluvoxamine may result in little or no difference in duration of hospitalization (see Table 4).

Progression to ICU admission

Not reported.

Progression to mechanical ventilation

Fluvoxamine may result in little or no difference in progression to mechanical ventilation (see Table 4).

Duration of mechanical ventilation

Fluvoxamine may result in little or no difference in duration of mechanical ventilation (see Table 4).

Duration of ICU stay

Not reported

Clinical outcome on an ordinal scale

Not reported

Adverse events
Fluvoxamine may result in little or no difference in adverse events (see Table 4).

Adverse reactions
Not reported.

CONCLUSION

There is no clear evidence that fluvoxamine compared to placebo results in a difference in clinically relevant outcomes.

The current evidence does not support the inclusion of fluvoxamine to treat COVID-19. This review will be updated as further evidence becomes available.

Reviewers:

Initial review (November 2020): Jeremy Nel, Gary Reubenson, Susanna S van Wyk, Veranyuy D. Ngah, Tamara Kredo.
Review update (May 2022): Jeremy Nel, Gary Reubenson, Susanna S van Wyk, Veranyuy D. Ngah, Tamara Kredo, Marli Mc Allister.

Affiliations & Declaration of interests:

JN (Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand), GR (Department of Paediatrics & Child Health, University of the Witwatersrand), SvW and MMA (Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University), VN (Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University), TK (Cochrane South Africa, South African Medical Research Council; Division Clinical Pharmacology, Faculty of Medicine and Health Sciences, Stellenbosch University) have no interests related to fluvoxamine.
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Acknowledgements:

Trudy Leong (TL): Essential Drugs Programme, National Department of Health supported the review team.

Table 1. Characteristics of included studies

Study	Design	Population	Intervention	Outcomes	Risk of bias
Lenze 2020[6]	RCT Participants, outcome assessors and research staff were blinded **Recruitment:** April 10, 2020 to August 5, 2020 **Final follow-up:** September 19, 2020 **Follow up:** Twice daily surveys x 15 days	United States Community-living, non-hospitalized adults with confirmed SARS-CoV-2 infection with COVID-19 symptom onset within 7 days and oxygen saturation 92% or greater Mean age: 46 years	Fluvoxamine 100mg 8-hourly x 15 days Control: placebo	**Primary:** Clinical deterioration within 15 days of randomization defined by meeting both criteria of (1) shortness of breath or hospitalization for shortness of breath or pneumonia and (2) oxygen saturation less than 92% on room air or need for supplemental oxygen to achieve oxygen saturation of 92%or greater. **Secondary:** Adverse events	Low risk of bias in all domains of Cochrane RoB2 tool
TOGETHER 2021[7]	RCT Trial team, site staff and patients were blinded **Recruitment:** Jan 15, 2021 to Aug 6, 2021 **Follow up:** 1,2,3,4,5,7,10,14 and 28 days	Brazilian adults Acutely symptomatic outpatients (symptoms onset within 7 days of screening) with confirmed COVID-19 At least one additional criterion for high-risk [a] and unvaccinated status Average age 50 years (18 to 102) 58% Female	Fluvoxamine 100mg 12-hourly x 10 days Control: placebo	**Primary:** Composite outcome of extended emergency room observation (>6 hours) or hospitalization up to 28 days post randomization **Secondary:** Viral clearance at day 7 Time to hospitalization Mortality Days in hospital and on ventilator Adverse drug reactions	Low risk of bias in all domains of Cochrane RoB2 tool
[a] Included DM, HPT, CVD, symptomatic lung disease, transplant patients, stage IV kidney disease/dialysis, immunosuppressed, history of cancer, age >=50 years					

Table 2. Characteristics of planned and ongoing studies

Treatment (per arm)	N	Severity at enrollment	Sponsor/Funder	Reg. number	Full text link
(1) Fluticasone vs (2) Placebo vs (3) Ivermectin vs (4) Placebo vs (5) Ivermectin vs (6) Placebo vs (7) Fluvoxamine vs (8) Placebo	15000	Moderate	Susanna Naggie, MD	NCT04885530	https://clinicaltrials.gov/show/NCT04885530
(1) Fluvoxamine vs (2) Doxazosin vs (3) Ivermectin vs (4) Peginterferon lambda vs (5) Peginterferon beta-1a vs (6) Placebo	4669	Mild	Cardresearch	NCT04727424	https://clinicaltrials.gov/show/NCT04727424
(1) Fluvoxamine vs (2) Bromhexine + fluvoxamine vs (3) Cyproheptadine hydrochloride + fluvoxamine vs (4) Niclosamide vs (5) Bromhexine + niclosamide vs (6) Standard of care	1800	Mild	Chulalongkorn University	NCT05087381	https://clinicaltrials.gov/show/NCT05087381
(1) Fluvoxamine vs (2) Placebo	400	Mild/ moderate	Asan Medical Center	NCT04711863	https://clinicaltrials.gov/show/NCT04711863
(1) Favipiravir + fluvoxamine vs (2) Favipiravir vs (3) Dexamethasone + favipiravir + fluvoxamine vs (4) Dexamethasone + favipiravir	296	Mild	Chulabhorn Royal Academy	TCTR20210615002	https://www.thaiclinicaltrials.org/show/TCTR20210615002
(1) Fluvoxamine vs (2) Placebo	100	Moderate	SigmaDrugs Research Ltd.	NCT04718480	https://clinicaltrials.gov/show/NCT04718480
(1) Fluvoxamine vs (2) Placebo	100	Moderate	SigmaDrugs Research Ltd.	EUCTR2020-002299-11-HU	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002299-11/HU

Table 3: Summary of findings

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluvoxamine	placebo	Relative (95% CI)	Absolute (95% CI)	
Mortality											
2	randomised trials	not serious	not serious	not serious[a]	very serious[b]	none	17/821 (2.1%)	25/828 (3.0%)	**RR 0.69** (0.38 to 1.27)	**9 fewer per 1,000** (from 19 fewer to 8 more)	⊕⊕◯◯ Low
Hospitalisation											
2	randomised trials	not serious	not serious	not serious[a]	very serious[c]	none	76/821 (9.3%)	103/828 (12.4%)	**RR 0.47** (0.08 to 2.71)	**66 fewer per 1,000** (from 114 fewer to 213 more)	⊕⊕◯◯ Low

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not downgraded for indirectness. Populations, intervention and outcome are relevant. Dosing was different: Lenze 100mg tds x 15 days and TOGETHER 100mg bd x 10 days.

b. Downgraded by 2 levels for imprecision. Few events in each arm. Confidence interval ranges from 62% reduction to 27% increase in mortality.

c. Downgraded by 2 levels for imprecision. Few events in each arm. Confidence interval ranges from 92% reduction to 2.7 fold increase in hospitalisation.

Table 4. Effect estimates of fluvoxamine vs placebo for number of days in hospital, progression to mechanical ventilation, number of days on ventilator and adverse events

Outcome	Study	Fluvoxamine Events/Total (%)	Placebo Events/Total (%)	Effect estimate (95% CI)
Days in hospital	TOGETHER[7]	Med 8 days [IQR 5 to 13]	Med 6 days [IQR 3 to 10.75]	Exponentiated estimates from a log-transformed linear regression 1.23 (0.99; 1.53)
Progression to mechanical ventilation	Lenze[6] TOGETHER	0/80 (0%) 26	1/72 (1.39%) 34	RR 0.30 (0.01; 7.27) OR 0·77 (0·45–1·30)
Days on mechanical ventilator	TOGETHER[7]	Med 5.5 days [IQR 3 to 12.75]	Med 6.5 days [IQR 2.25 to 12]	Exponentiated estimates from a log-transformed linear regression 1.03 (0.64; 1.67)
Serious adverse events	Lenze[6]	1/80 (1.25%)	6/72 (8.33%)	RR 0.14 (0.02; 1.15)
Other adverse events	Lenze[6]	11/80 (13.75%)	12/72 (16.67%)	RR 0.83 (0.39; 1.75)
Grade 1 AE	TOGETHER[7]	20/741 (3%)	11/756 (1%)	OR 1.88 (0.91; 4.09)
Grade 2 AE	TOGETHER[7]	72/741 (10%)	81/756 (11%)	OR 0.91 (0.64; 1.215)
Grade 3 AE	TOGETHER[7]	38/741 (5%)	50/756 (7%)	OR 0.76 (0.49; 1.18)
Grade 4 AE	TOGETHER[7]	21/741 (3%)	20/756 (3%)	OR 1.07 (0.58; 2.01)
Grade 5 AE	TOGETHER[7]	18/741 (2%)	26/756 (3%)	OR 0.70 (0.37; 1.28)

Appendix 1: Search strategy

Database: PubMed

Search	Query	Results
#7	Search: #4 OR #6	17
#6	Search: #3 AND #5	16
#5	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]	5,190,872
#4	Search: #1 AND #2 Filters: Systematic Review	1
#3	Search: #1 AND #2	28
#2	Search: Fluvoxamine[mh] OR Fluvoxamin*[tiab] OR Luvox[tiab] OR Floxyfral[tiab] OR Fevarin[tiab] OR Dumirox[tiab] OR Faverin[tiab]	3,082
#1	Search: Coronavirus[mh:noexp] OR coronavirus*[tiab] OR corona virus*[tiab] OR COVID-19[mh] OR covid-19[tiab] OR covid19[tiab] OR covid 2019[tiab] OR SARS-Cov-2[mh] OR SARS-CoV-2[tiab] OR SARS-CoV2[tiab] OR SARSCoV2[tiab] OR SARsCov-2[tiab] OR SARS-coronavirus*[tiab] OR severe acute respiratory syndrome coronavirus 2[nm] OR severe acute respiratory syndrome coronavirus 2[tiab] OR 2019-nCov[tiab] OR 2019nCov[tiab] OR nCov2019[tiab] OR nCOV-2019[tiab] OR hCOV*[tiab] OR n-cov[tiab] OR ncov*[tiab]	187,252

Database: **LOVE Platform** https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=aile
Search Strategy: (Fluvoxamine OR Fluvoxamin* OR Luvox OR Floxyfral OR Fevarin OR Dumirox OR Faverin)
Filtered by: Systematic reviews and Primary studies (RCTs and Pending)
Number of studies: 15 studies

Database: **Cochrane COVID-19 Study Register**
https://covid-19.cochrane.org/
Search Strategy: Fluvoxamine or Fluvoxamin* or Luvox or Floxyfral or Fevarin or Dumirox or Faverin
Filtered by: Intervention Assignment - randomised
Number of studies: 9 studies

Appendix 2: Evidence to decision framework

Desirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate o Large o Varies **X Don't know**	A composite outcome (need for admission and observation for more than 6 hours) suggesting potential benefit but no clear benefit in any prespecified clinically relevant outcomes:	

№ of RCTs	Fluvox- (n)	Placebo (n)	Relative effect (95% CI)	Absolute effect (95% CI)	Certainty
Mortality					
2	17/821 (2.1%)	25/828 (3.0%)	**RR 0.69** (0.38 to 1.27)	**9 fewer per 1,000** (from 19 fewer to 8 more)	⊕⊕◯◯ Low
Hospitalisation					
2	76/821 (9.3%)	103/828 (12.4%)	**RR 0.47** (0.08 to 2.71)	**66 fewer per 1,000** (from 114 fewer to 213 more)	⊕⊕◯◯ Low

Undesirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small **X Trivial** o Varies o Don't know	Well-tolerated (similar to placebo) Fluvoxamine may result in little or no difference in adverse events, compared to placebo (see Table 4).	Has an established safety record

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low **X Low** o Moderate o High o No included studies	No demonstrated benefit, however trends generally in favour of fluvoxamine Certainty of the evidence was downgraded for imprecision. There were few events in each arm and 95% confidence intervals were wide.	

Values: Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability **X Possibly important uncertainty or variability** o Probably no important uncertainty or variability o No important uncertainty or variability	Unclear how people would value treatment associated with lower risk of prolonged stay in emergency setting	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison **X Does not favor either the intervention or the comparison** o Probably favors the intervention o Favors the intervention o Varies o Don't know		

Resources required: How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs **X Moderate costs** o Negligible costs and savings o Moderate savings o Large savings	Fluvoxamine is SAHPRA-registered but it is not currently an EML item nor on public sector tender <u>SEP (unit price) of fluvoxamine 100 mg tablet:</u> • Faverin 100® = R11.38 • Luvox 100® = R16.64	

○ Varies ○ Don't know	• Fluvoxamine 100 Oethmaan® = R11.39 • Fluvoxamine- Hexal® = R11.55 *SEP database, 28 December 2020* Using average SEP (R12.74), cost of a treatment course is as follows: • Fluvoxamine 100mg 8-hourly x 15 days = **R573.30** • Fluvoxamine 100mg 12-hourly x 10 days = **R254.80**	

Cost-effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**Not applicable**	

Equity: What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Not applicable.**	

Acceptability: Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	**Not applicable.**	

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	**Not applicable.**	

Appendix 3: Updating of rapid report

Date	Signal	Rationale
8 April 2022	Published systematic review of fluvoxamine in JAMA, 6 April 2022	Systematic review suggests that fluvoxamine for mild COVID-19 may reduce hospitalisations.

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	5 November 2021	SVW, GR, JN, VDN, TK	Fluvoxamine is not recommended for the treatment of COVID-19. There remains significant uncertainty whether fluvoxamine is more effective and safer than placebo in treating patients with COVID-19.
Second	27 May 2022	SVW, GR, JN, VDN, MMA, TK	No change to the recommendation and the rationale.This finding is in line with a recent summary from the FDA explaining why the request for Emergency Use Authorization of fluvoxamine was rejected: https://protect-za.mimecast.com/s/_63WC2RrOjiVYDGpfnENhn?domain=accessdata.fda.gov.

For internal NDoH use:
WHO INN: Fluvoxamine
ATC: N06AB08
ICD10: U07.1/U07.2

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