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Fluvoxamine for the treatment of COVID-19 (Review)

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[Intervention Review]

Fluvoxamine for the treatment of COVID-19

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A B S T R A C T

Background

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that has been approved for the treatment of depression, obsessive–compulsive disorder, and a variety of anxiety disorders; it is available as an oral preparation. Fluvoxamine has not been approved for the treatment of infections, but has been used in the early treatment of people with mild to moderate COVID-19. As there are only a few effective therapies for people with COVID-19 in the community, a thorough understanding of the current evidence regarding the efficacy and safety of fluvoxamine as an anti-inflammatory and possible anti-viral treatment for COVID-19, based on randomised controlled trials (RCTs), is needed.

Objectives

To assess the efficacy and safety of fluvoxamine in addition to standard care, compared to standard care (alone or with placebo), or any other active pharmacological comparator with proven efficacy for the treatment of COVID-19 outpatients and inpatients.

Search methods

We searched the Cochrane COVID-19 Study Register (including Cochrane Central Register of Controlled Trials, MEDLINE, Embase, ClinicalTrials.gov, WHO ICTRP, medRxiv), Web of Science and WHO COVID-19 Global literature on COVID-19 to identify completed and ongoing studies up to 1 February 2022.

Selection criteria

We included RCTs that compared fluvoxamine in addition to standard care (also including no intervention), with standard care (alone or with placebo), or any other active pharmacological comparator with proven efficacy in clinical trials for the treatment of people with confirmed COVID-19, irrespective of disease severity, in both inpatients and outpatients. Co-interventions needed to be the same in both study arms. We excluded studies comparing fluvoxamine to other pharmacological interventions with unproven efficacy.

Data collection and analysis

We assessed risk of bias of primary outcomes using the Cochrane Risk of Bias 2 tool for RCTs. We used GRADE to rate the certainty of evidence to treat people with asymptomatic to severe COVID-19 for the primary outcomes including mortality, clinical deterioration, clinical improvement, quality of life, serious adverse events, adverse events of any grade, and suicide or suicide attempt.

Main results

We identified two completed studies with a total of 1649 symptomatic participants. One study was conducted in the USA (study with 152 participants, 80 and 72 participants per study arm) and the other study in Brazil (study with 1497 high-risk participants for progression to severe disease, 741 and 756 participants per study arm) among outpatients with mild COVID-19. Both studies were double-blind, placebo-controlled trials in which participants were prescribed 100 mg fluvoxamine two or three times daily for a maximum of 15 days.

We identified five ongoing studies and two studies awaiting classification (due to translation issues, and due to missing published data). We found no published studies comparing fluvoxamine to other pharmacological interventions of proven efficacy.

We assessed both included studies to have an overall high risk of bias.

Fluvoxamine for the treatment of COVID-19 in inpatients

We did not identify any completed studies of inpatients.

Fluvoxamine for the treatment of COVID-19 in outpatients

Fluvoxamine in addition to standard care may slightly reduce all-cause mortality at day 28 (RR 0.69, 95% CI 0.38 to 1.27; risk difference (RD) 9 per 1000; 2 studies, 1649 participants; low-certainty evidence), and may reduce clinical deterioration defined as all-cause hospital admission or death before hospital admission (RR 0.55, 95% CI 0.16 to 1.89; RD 57 per 1000; 2 studies, 1649 participants; low-certainty evidence). We are very uncertain regarding the effect of fluvoxamine on serious adverse events (RR 0.56, 95% CI 0.15 to 2.03; RD 54 per 1000; 2 studies, 1649 participants; very low-certainty evidence) or adverse events of any grade (RR 1.06, 95% CI 0.82 to 1.37; RD 7 per 1000; 2 studies, 1649 participants; very low-certainty evidence).

Neither of the studies reported on symptom resolution (clinical improvement), quality of life or suicide/suicide attempt.

Authors' conclusions

Based on a low-certainty evidence, fluvoxamine may slightly reduce all-cause mortality at day 28, and may reduce the risk of admission to hospital or death in outpatients with mild COVID-19. However, we are very uncertain regarding the effect of fluvoxamine on serious adverse events, or any adverse events.

In accordance with the living approach of this review, we will continually update our search and include eligible trials as they arise, to complete any gaps in the evidence.

PLAIN LANGUAGE SUMMARY

Fluvoxamine for treating COVID-19

Review question

Is fluvoxamine an effective treatment for people with COVID-19 and does it cause any unwanted effects?

Key messages

It is unclear whether fluvoxamine is an effective treatment for COVID-19 in people with mild to moderate COVID-19. This is because there is currently not enough research available to make a definite decision.
We found five ongoing studies that are currently investigating fluvoxamine as a possible treatment for COVID-19, and two studies for which we need more information. We will update this review if their results change our conclusions.

What is fluvoxamine?

Fluvoxamine is a type of medication known as a selective serotonin reuptake inhibitor (SSRI), available in tablet form. Recent research has found that fluvoxamine may have an effect on COVID-19. When the immune system fights the virus, the lungs and airways can become inflamed, causing breathing difficulties. Fluvoxamine could help reduce this inflammation, potentially reducing the risk of developing severe COVID-19 and its associated lung symptoms through its possible anti-inflammatory and anti-viral effects. We know that most people do not experience any serious side effects with fluvoxamine when it is taken as an antidepressant. Some people can, however, experience the following common side effects, especially when starting the medication: nausea, anxiety or restlessness, insomnia, or diarrhoea, and in rare cases, suicidal ideation.

What did we want to find out?

We wanted to know if fluvoxamine reduces death, severity of disease, and length of infection in people with COVID-19, if it has an effect on quality of life, or causes any unwanted effects. We included studies that compared fluvoxamine to placebo (dummy treatment), no treatment, usual care, or any other treatment for COVID-19 that is known to work to some extent, such as remdesivir or dexamethasone. We excluded treatments that we know do not work for COVID-19, such as hydroxychloroquine, or have an unknown effect on the disease.

We evaluated the effects of fluvoxamine in adults with COVID-19 on:

• people dying;

• whether people needed to be treated in a hospital;

• whether people's COVID-19 symptoms got better or worse;

• unwanted effects;

• quality of life;

• and whether there is a risk of suicide or suicide attempt when taking this medication.

What did we do?

We searched for studies that investigated fluvoxamine as a treatment for adults with COVID-19 in hospital or as outpatients. We compared and summarised the results of the studies and rated our confidence in the evidence, based on common criteria such as study methods and study sizes.

What did we find?

We found two studies that investigated fluvoxamine as an early treatment for mild COVID-19 in 1649 self-isolated people at home (outpatients). All studies compared fluvoxamine to placebo together with standard care. The studies used different durations of treatment (10 or 15 days).

We found five ongoing studies and two studies that are awaiting classification. We did not find any studies that investigated the effect of fluvoxamine on people in hospital with COVID-19.

Main results

• Compared to placebo, fluvoxamine may slightly reduce the number of people who die in the 28 days after starting treatment (2 studies, 1649 people).

• Compared to placebo, fluvoxamine may reduce number of people who are admitted to a hospital or who die before hospital admission (2 studies, 1649 people).

•The number of unwanted (serious) events did not clearly differ between fluvoxamine and placebo treatment (2 studies, 1649 people).

•Neither of the studies reported on quality of life, the time needed until all initial symptoms resolved, or suicide attempts.

What are the limitations of the evidence?

We cannot be confident in the current evidence for fluvoxamine in treating people with COVID-19, mainly due to the lack of studies that are currently available and some flaws in study design. We will continue to search for new studies to complete the current evidence gap.

It would also be important to find out the effects of a medication such as fluvoxamine on long-Covid. We are currently waiting for research on this to become available in the near future.

Unfortunately, the studies available did not focus on children and young adults, women who are planning or trying to conceive, women who are pregnant or breastfeeding, older adults, or those people who have a weakened immune system (immunocompromised people). Likewise, no information was available on whether women or men were more likely to benefit from fluvoxamine.

Search date

The evidence is current to February 2022.

SUMMARY OF FINDINGS

Summary of findings 1.   Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19

Patient or population: symptomatic people with COVID-19

Setting: outpatients

Intervention: fluvoxamine plus standard care

Comparison: placebo plus standard care

Outcomes		Anticipated absolute effects (95% CI)*		Relative effect (95% CI)	N of participants (studies)	Certainty in the evidence (GRADE)	Comment
		Risk with placebo plus standard care	Risk with fluvoxamine plus standard care				
All-cause mortality (at day 28)		30 per 1000 (95% CI 11 to 38)	21 per 1000 (95% CI 2 to 29)	RR 0.69 (0.38 to 1.27)	1649 (2 RCTs)	Low[a]	Fluvoxamine may slightly reduce all-cause mortality at day 28.
All-cause admission to hospital or death (before hospital admission)		126 per 1000 (95% CI 105 to 150)	94 per 1000 (95% CI 76 to 116)	RR 0.55 (0.16 to 1.89)	1649 (2 RCT)	Low[b]	Fluvoxamine may reduce admission to hospital or death (before hospital admission).
Symptom resolution	All initial symptoms resolved	Not reported					
	Time to symptom resolution	Numerical data not derivable, outcome was illustrated in a figure (graph) indicating an overlap of confidence intervals (TOGETHER 2021).					
Quality of life (at longest follow-up)		Not reported					
Serious adverse events (during study period)		122 per 1000 (95% CI 18 to 248)	95 per 1000 (95% CI 41 to 221)	RR 0.56 (0.15 to 2.03)	1649 (2 RCTs)	Very low[c]	The evidence is very uncertain about the effects of fluvoxamine on serious adverse events.
Any adverse events (during study period)		118 per 1000 (95% CI 97 to 162)	125 per 1000	RR 1.06 (0.82 to 1.37)	1649 (2 RCTs)	Very low[d]	The evidence is very uncertain about the effects of fluvoxamine on any adverse events.

	(95% CI 104 to 169)
Suicide or suicide attempt (at longest follow-up)	Not reported

*The risk in the intervention group and its 95% CI is based on the assumed risk in the comparison group and the relative effect of the intervention and its 95% CI.

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio

[a]Risk difference 9 per 1000 (19 fewer to 8 more), small important effect (since mortality is the most critical outcomes for patients and clinicians). Downgraded by 2 levels for very serious imprecision since CI suggests both potential benefit and no effect/potential harm, and number of events is small.
[b]Risk difference 57 per 1000 (106 fewer to 112 more), moderate effect. Downgraded by 2 levels for very serious imprecision since CI suggests both potential benefit and no effect/potential harm, and number of events is small.
[c]Risk difference 54 per 1000 (50 fewer to 4 more), moderate effect. Downgraded by 1 level for serious risk of bias and by 2 levels for very serious imprecision since CI suggests both potential benefit and potential harm.
[d]Risk difference 7 per 1000 (21 fewer to 44 more), small unimportant effect. Downgraded by 1 level for serious risk of bias and by 2 levels for very serious imprecision since CI suggests both potential benefit and potential harm.

BACKGROUND

This work constitutes part of a series of Cochrane Reviews investigating the use of potential pharmacotherapies for coronavirus disease 2019 (COVID-19) in both inpatients and outpatients. This particular review evaluates the efficacy and safety of fluvoxamine, specifically evaluating its possible use in ambulatory-managed patients, from here on referred to as outpatients, but also considers inpatients. Reviews in this series carry a degree of overlap with the background and methodology sections of other published reviews from the German research project 'CEOsys' (COVID-19 Evidence Ecosystem) on antibiotics (Popp 2021a), monoclonal antibodies (Kreuzberger 2021), convalescent plasma (Piechotta 2022), ivermectin (Popp 2021a), vitamin D supplementation (Stroehlein 2021), systemic corticosteroids (Wagner 2021), colchicine (Mikolajewska 2021) and remdesivir (Ansems 2021).

Description of the condition

COVID-19 is a rapidly spreading infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (WHO 2020a). COVID-19 is unprecedented in comparison to previous coronavirus outbreaks such as SARS and Middle East Respiratory Syndrome (MERS), which caused 813 and 858 deaths, respectively (WHO 2003; WHO 2019a). Despite international efforts to contain its spread, as of February 2022, COVID-19 had resulted in more than 420 million confirmed cases and over 5.9 million deaths worldwide (WHO2022a). The emergence of novel SARS-CoV-2 variants is also of great concern, with the potential for augmented transmission of the disease, a shortened incubation period and a negative impact on established and proven disease control methods (Grubaugh 2020; WHO 2021a).

Vaccination has been shown to be highly effective in reducing severe illness and death from COVID-19. More than 10.4 billion doses of vaccines had been administered globally as of February 2022, with additional vaccines in continuous development (WHO2022a). The majority of vaccines have been administered in high-income countries, leaving populations including health care workers and older people in other countries vulnerable.

The mean incubation period is estimated at five to six days, with 97.5% of cases developing symptoms within 11.5 days of exposure (Lauer 2020). Sore throat, cough, fever, headache, fatigue, myalgia (muscle pain) and arthralgia (joint pain) are the most commonly reported symptoms (Struyf 2020). Other symptoms may include dyspnoea, rigors, nausea and vomiting, diarrhoea, and nasal congestion (WHO 2020a). The majority of infected individuals develop mild symptoms not requiring hospitalisation, or remain completely asymptomatic (80% to 90%) depending on the timing of the investigation, the cohort investigated, and the virus variant (Chen 2020; Danza 2022; Funk 2021; Pan 2020; Wu 2020). The reported frequency of asymptomatic cases also varies greatly and ranges from 6% to 96% (Buitrago-Garcia 2020; Funk 2021; Oran 2020).

In the first two years of the pandemic (2020 to 2021), there were estimates that approximately 11% to 20% of infected individuals went on to develop severe disease, with 1% to 5% developing critical illness with respiratory failure, septic shock or multi-organ dysfunction syndrome requiring intensive care unit (ICU) treatment (Funk 2021; Huang 2020; Wu 2020). Furthermore,

COVID-19 case fatality rates varied widely between countries and reporting periods, from 0% to over 25% (Johns Hopkins University of Medicine 2022; Williamson 2020). These numbers may have been misleading, as they depended on testing frequency, delays in reporting dates and incomplete capture of case data at the time (Johns Hopkins University of Medicine 2022; Williamson 2020). Case definitions have been adjusted and modified during the course of the pandemic (WHO 2020b), whilst contemporary considerations such as the levels of immunity in the population and type of viral strains present at the time of data collection should also be taken into account (WHO 2022).

Description of the intervention

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and a σ-1 receptor (S1R) agonist that has been approved for the treatment of depression, obsessive–compulsive disorder, and a variety of anxiety disorders. Available as an oral preparation, it is widely prescribed in the primary care setting worldwide for major depressive and obsessive-compulsive disorders; in treating anxiety disorders such as panic disorder, social anxiety disorder, and post-traumatic stress (Figgit 2000); as well as for menopausal symptoms and functional gut disorders (off-label use). When fluvoxamine is used to treat psychiatric conditions, the most common adverse effect is nausea (particularly at the beginning of the treatment), but adverse effects can include other gastrointestinal effects (e.g. diarrhoea, indigestion), neurological effects (e.g. asthaenia, insomnia, somnolence, anxiety, headache), and suicidal ideation. There has been much discussion over the years about increased suicide rates in people taking serotonin reuptake inhibitors. Increased suicide rates are particularly evident in younger people (Friedman 2014).

Fluvoxamine can enhance the serotonergic effects of other SSRIs or monoamine oxidase inhibitors (MAOIs), resulting in serotonin syndrome; therefore, it should not be used within two weeks of administration of other SSRIs or MAOIs. Fluvoxamine may enhance the effects of antiplatelets and anticoagulants. Hence, people receiving these drugs should be closely monitored (Kam 1997).

How the intervention might work

There are many important mechanisms of action of fluvoxamine and other SSRIs that could play a role in COVID-19 treatment. These effects include: reduction in platelet aggregation, decreased mast cell degranulation, interference with endolysosomal viral trafficking, regulation of inositol-requiring enzyme 1α-driven inflammation and increased melatonin levels, collectively having a direct antiviral effect, as well as regulating coagulopathy or mitigating the cytokine storm, which are known hallmarks of severe COVID-19 (Sukhatme 2021).

Anti-inflammatory effects of certain pharmacological interventions are thought to be effective during phases of COVID-19 with high inflammatory activity. S1R is an endoplasmic reticulum (ER) chaperone membrane protein involved in many cellular functions, including regulation of ER stress response–unfolded protein response and regulation of cytokine production in response to inflammatory triggers. In a preclinical model of septic shock, fluvoxamine was found to bind to S1R on immune cells, resulting in a reduced inflammatory response with inhibited cytokine production (Rosen 2019). In the presence of fluvoxamine, S1R might prevent the ER stress sensor inositol-requiring enzyme 1α from

splicing and activating the mRNA of X-box protein 1, a key regulator of cytokine production including interleukins IL-6, IL-8, IL-1β, and IL-12.

The anti-inflammatory effects of fluvoxamine through activation of S1R observed in preclinical studies suggest fluvoxamine could be evaluated as a treatment option for COVID-19 in clinical settings (Rafiee 2016). The anti-inflammatory effects of fluvoxamine were also shown by a significantly decreased expression of some inflammatory genes, such as intracellular adhesion molecule (ICAM1), vascular cell adhesion molecule ($VCAM_1$), cyclooxygenase 2 (COX_2), and inducible nitric oxide synthase (iNOS) in human endothelial cells and macrophages (van Harten 1995).

In a murine sepsis model, fluvoxamine was found to bind to the S1R on immune cells, resulting in reduced production of inflammatory cytokines (Rosen 2019). Furthermore, in-vitro studies of human endothelial cells and macrophages showed that fluvoxamine reduced the expression of inflammatory genes (Sukhatme 2021). Ongoing studies are currently looking to establish whether the anti-inflammatory effects of fluvoxamine observed in non-clinical studies are relevant to the clinical setting of COVID-19 (Takenaka 2022).

Why it is important to do this review

The COVID-19 pandemic places healthcare systems under tremendous pressure to provide adequate care. The emergence of variants of concern (WHO 2021b; WHO 2022), with the potential for increased transmissibility and altered disease characteristics, combined with the ongoing scarcity of effective and established drug treatments, in addition to low global vaccination coverage (WHO 2020c), highlights the obvious and urgent need for effective and safe pharmacotherapies. The repurposing of existing medications that are also widely available, inexpensive, and with well-understood safety profiles, such as fluvoxamine, is of great importance. Evidence-based reviews are therefore needed to guide clinical decision-making for people with COVID-19.

Current treatment consists of supportive care with oxygen therapy in cases with moderate disease, and with respiratory support, such as mechanical ventilation, and extracorporeal membrane oxygenation in cases of severe disease (CDC 2020; WHO 2020b). Overall, data from randomised controlled trials (RCTs) do not demonstrate a clear, major clinical benefit with most of the drugs evaluated thus far. Data from RCTs at this stage support the role of corticosteroids for severe COVID-19 and clinical guidelines recommend their use (Agarwal 2020; National COVID-19 Clinical Evidence Taskforce 2021). Further, tocilizumab and janus kinase inhibitor baricitinib are recommended for certain patient groups, while other drugs, such as hydroxychloroquine, azithromycin and ivermectin, are not recommended for the treatment of COVID-19 (Agarwal 2020; National COVID-19 Clinical Evidence Taskforce 2021).

Effective therapy regimens are particularly necessary for the early viral phase of the disease in order to prevent a severe course of COVID-19. Evidence is emerging about the efficacy of anti-COVID-19 specific neutralising monoclonal antibodies as early treatments for COVID-19 (Kreuzberger 2021). If used in the early phase of the disease (up to day five to seven after the onset of symptoms), the neutralising monoclonal antibodies significantly reduce the risk of a severe course of the disease (Gupta 2021;

Weinreich 2021). However, a parenteral form of administration and currently limited availability represent an important challenge that makes widespread use in the non-hospitalised setting difficult. Furthermore, the effectiveness of many of the neutralising monoclonal antibodies against the new virus variants may be reduced (Hoffmann 2021; Planas 2022). Other antiviral drugs are promising, such as the ribonucleoside analogue molnupiravir or the protease inhibitor nirmatrelvir in combination with ritonavir, but are still under investigation and not yet widely available (Jayk Bernal 2021).

Systematic reviews for interventions to treat COVID-19 have already been undertaken, including treatment with fluvoxamine (Kacimi 2021; Lee 2021; Murchu 2022; Wen 2022). However, they did not fulfil all the methodological standards for evidence synthesis. For example, they did not apply the GRADE approach for rating the certainty of the evidence or assess the risk of bias (Kacimi 2021; Wen 2022). Furthermore, Murchu 2022 considered only preliminary data of a single study on fluvoxamine and Lee 2021 focused on unpublished data. Therefore, we aim to provide a complete evidence profile for oral fluvoxamine as a treatment for COVID-19, in both inpatients and outpatients.

OBJECTIVES

To assess the efficacy and safety of fluvoxamine in addition to standard care, compared to standard care (alone or with placebo), or any other active pharmacological comparator with proven efficacy for the treatment of COVID-19 outpatients and inpatients.

METHODS

Criteria for considering studies for this review

Types of studies

The main outline of the methods section is based on the standard template of the Cochrane Haematology review group and is in line with a series of Cochrane Reviews investigating treatments and therapies for COVID-19 (e.g. Kreuzberger 2021; Popp 2021a; Stroehlein 2021). The original review protocol for this review was registered with PROSPERO (CRD42022299758) on 4 January 2022. As this review and the other reviews of the Cochrane Review series are living systematic reviews during the COVID-19 pandemic, specific adaptations relating to the research question, including participants, interventions, comparators, outcomes, and methods may be necessary in further updates.

To assess the efficacy and safety of fluvoxamine for the treatment of people with COVID-19 in outpatient and inpatient settings, we included randomised controlled trials (RCTs), as this study design, if performed appropriately, provides the best evidence for experimental therapies in highly controlled therapeutic settings. We used the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b). In addition to observational studies, non-standard RCT designs, such as cluster-randomised and cross-over trials, were not eligible for the review. The latter are not appropriate in this context, since the underlying cause of COVID-19 is an infection with the SARS-CoV-2 virus and the medical condition evolves over time. Furthermore, we excluded controlled non-randomised studies of interventions, animal studies, pharmacokinetic studies, and in vitro studies.

We included the following formats, if sufficient information was available on study design, characteristics of participants, interventions, and outcomes.

- Full-text journal publications
- Abstract publications
- Preprint articles
- Results published in trial registries
- Additional personal communication with investigators, if results were available in any of the above-listed formats

We included preprints and conference abstracts to have a complete overview of the ongoing research activity, especially for tracking newly emerging studies on treatments for COVID-19. We did not apply any limitations with respect to the length of follow-up or language of the publication.

Types of participants

We included studies investigating adults with a confirmed diagnosis of COVID-19 (with reverse transcription-polymerase chain reaction (RT-PCR) or antigen testing) irrespective of age, sex, ethnicity and disease severity. If studies included participants with a confirmed or suspected COVID-19 diagnosis, we only used data for patient populations with a confirmed COVID-19 diagnosis. In cases where data were not reported separately for participants with confirmed or suspected COVID-19 diagnosis, we included the mixed population. The status of participants in the included studies, as well as the type of COVID-19 diagnosis, is reported in the section Included studies. If mixed population studies contributed data to the meta-analyses, we excluded these studies in Sensitivity analysis to test the robustness of the results.

We excluded studies that evaluated fluvoxamine for other coronavirus diseases such as SARS or MERS, or other viral diseases, such as influenza. If studies enrolled populations with, or exposed to, mixed viral diseases, we only planned to include studies if the trial authors provided subgroup data for COVID-19.

Types of interventions

The intervention was defined as treatment with fluvoxamine. All doses and therapeutic regimes were eligible.

We compared fluvoxamine in addition to standard care (including no intervention), to standard care (alone or with placebo), or any other active pharmacological comparator with proven efficacy (within clinical trials with a high weight of evidence) for the treatment of COVID-19.

For example, dexamethasone has been shown to reduce mortality from COVID-19 amongst participants who were randomised to receive dexamethasone compared to those who received standard care (Agarwal 2020; RECOVERY 2021), in people who were oxygenated or received respiratory support. Remdesivir showed some benefit for people hospitalised with COVID-19, though to a lesser extent (Beigel 2020). For people who qualify for dexamethasone therapy, for instance, or for any other intervention that is proven to be beneficial in the future, it would be unethical to further conduct trials that compare an intervention to placebo only. On the contrary, studies using comparators without proven efficacy, such as hydroxychloroquine, may confound the assessment of the efficacy or safety of fluvoxamine, so we excluded

these. Although these types of intervention were possibly used at certain time points during the pandemic with the best intentions, their use was never supported through the evidence, and they may also be associated with adverse effects (Singh 2021). From those comparisons, no reliable evidence could be obtained; therefore, active comparators without proven efficacy were not eligible for this review. For the current review, we did not find any studies using an active comparator with proven efficacy.

We excluded studies evaluating fluvoxamine in combination with other active treatments, if the same treatment was not used in the control group. We also excluded studies investigating its efficacy and safety in preventing COVID-19. We created the following comparisons.

- Fluvoxamine in addition to standard care (including no intervention) versus standard care (alone or with placebo)
- Fluvoxamine in addition to standard care (including no intervention) versus active pharmacological intervention for the treatment of COVID-19 with proven efficacy (no studies were available for the current review version)

Types of outcome measures

We evaluated core outcomes in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for people with COVID-19 (COMET 2021; Marshall 2020), and additional outcomes that have been prioritised by consumer representatives and the German guideline panel for inpatient therapy of people with COVID-19, as well as the German Primary Care Association Guidelines (DEGAM) for the treatment of acute COVID-19 in the outpatient setting (DEGAM 2022). The current outcome set is in alignment with the previous review in this series of Cochrane Reviews investigating the use of potential pharmacotherapies for COVID-19 in both inpatients and outpatients (Popp 2021a).

We defined outcome sets with primary and secondary outcomes for two populations.

- Inpatients (hospitalised individuals, secondary care) with moderate to severe (World Health Organization (WHO) severity score > 4) (WHO 2020e) COVID-19
- Outpatients (ambulatory-managed individuals, primary care) with asymptomatic or mild COVID-19 (WHO severity score ≤ 4) (WHO 2020e)

Primary outcomes were used to inform the Summary of findings 1.

Timing of outcome measurement

We collected information on outcomes from all time points reported in the publications. If only a few studies contributed data to an outcome, we pooled different time points, provided the studies had produced valid data and pooling was clinically reasonable.

In the case of time-to-event analysis, for instance as with 'time to death', we included the outcome measure based on the longest follow-up time and measured from randomisation.

We included serious adverse events and adverse events occurring during the study period, including both adverse events during active treatment and long-term adverse events. If sufficient data were available, we grouped the measurement time points of

eligible outcomes (e.g. adverse events and serious adverse events) into those measured directly after treatment (up to seven days after treatment), medium-term outcomes (up to 14 days after treatment) and longer-term outcomes (more than 28 days after treatment).

Primary outcomes

Inpatients with moderate to severe COVID-19

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge
- Clinical status at day 28, day 60, and up to the longest follow-up, including
  - worsening of clinical status
    - participants with clinical deterioration (new need for invasive mechanical ventilation) or death
  - improvement of clinical status
    - participants discharged alive (participants should be discharged without clinical deterioration or death)
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. with the WHO Quality of Life-100 (WHOQoL-100) scale) at up to seven days; up to 28 days, and longest follow-up available
- Serious adverse events during the study period
- Adverse events (any grade) during the study period, defined as the number of participants with any event

Outpatients with asymptomatic or mild COVID-19 (WHO < 4)

- All-cause mortality at day 28, day 60, time-to-event, and up to the longest follow-up
- All-cause admission to hospital or death (before hospital admission)
- Symptom resolution
  - all initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up
  - duration to symptom resolution
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at day seven, up to day 28, and the longest follow-up available
- Serious adverse events during the study period
- Adverse events (any grade) during the study period, defined as number of participants with any event
- Suicide or suicide attempt

Secondary outcomes

Inpatients with moderate to severe COVID-19

Additional outcomes

- Clinical status at day 15, day 28 and up to the longest follow-up
  - worsening of clinical status
    - need for invasive mechanical ventilation
    - need for non-invasive mechanical ventilation or high flow
    - need for oxygen by mask or nasal prongs
    - need for hospitalisation without oxygen therapy
  - improvement of clinical status
    - weaning or liberation from invasive mechanical ventilation in surviving patients
    - ventilator-free days

- duration to liberation from invasive mechanical ventilation
- liberation from supplemental oxygen in surviving patients
- duration to liberation from supplemental oxygen
- Need for dialysis at up to day 28
- Admission to the intensive care unit (ICU) at day 28
- Duration of hospitalisation
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to day three, day seven, and day 14
- Hospital-acquired infections up to day 28

Outpatients with asymptomatic or mild COVID-19 (WHO < 4)

Additional outcomes

- Clinical status at day 15, day 28 and up to the longest follow-up
  - worsening of clinical status (moderate to severe COVID-19 symptoms)
    - need for invasive mechanical ventilation
    - need for non-invasive mechanical ventilation or high flow
    - need for hospitalisation (with need for oxygen by mask or nasal prongs)
    - need for hospitalisation (without oxygen therapy)
- Viral clearance, assessed with RT-PCR for SARS-CoV-2 at baseline, up to day three, day seven, and day 14

Search methods for identification of studies

Electronic searches

Our Information Specialist (IM) designed systematic search strategies and a second Information Specialist peer reviewed them. We searched in the following sources from the inception of each database up to 1 February 2022 and did not place restrictions on the language of the publication.

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org)
  - Cochrane Central Register of Controlled Trials (CENTRAL) (monthly updates)
  - MEDLINE (PubMed) (weekly updates)
  - Embase.com (weekly updates)
  - ClinicalTrials.gov (www.clinicaltrials.gov) (daily updates)
  - WHO International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/) (monthly updates)
  - medRxiv (www.medrxiv.org) (weekly updates)
- Web of Science Core Collection
  - Science Citation Index Expanded (1945 to present)
  - Emerging Sources Citation Index (2015 to present)
- WHO COVID-19 Global literature on coronavirus disease (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/)

For detailed search strategies, see Appendix 1.

Searching other resources

We searched for other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews and meta-analyses. In addition, we contacted the investigators of included studies to obtain additional information on the retrieved studies when needed.
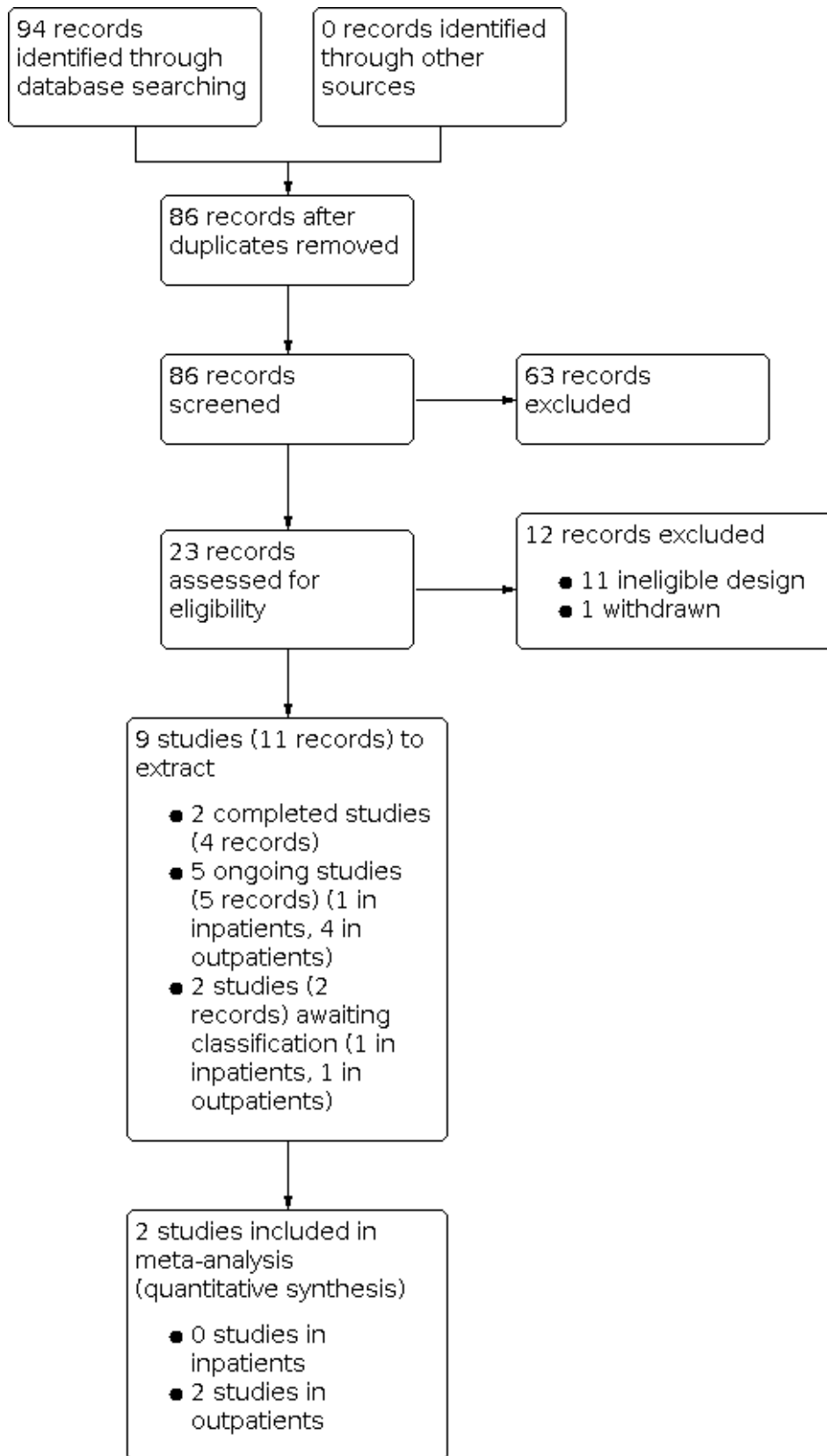
Data collection and analysis

Selection of studies

In accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2021), two review authors (JN, IT, AAT or CS) independently screened the results of the search strategies for eligibility of this review by reading the titles and abstracts using Covidence. We then retrieved full-text articles and assessed eligibility of the remaining records against predefined eligibility criteria in duplicate. We resolved discrepancies by discussion within the group of review authors. We included studies in the review irrespective of whether the measured outcome data were reported in a 'usable' way. We collated multiple reports of the same study, so that the study, rather than the report, was the unit of interest in the review.

We documented the study selection process in a flow diagram, as recommended in the PRISMA statement (Page 2021), and show the total number of retrieved references and the numbers of included, ongoing, excluded studies, as well as those awaiting classification in Figure 1. We listed all studies that we excluded after full-text assessment and the reasons for their exclusion in the Characteristics of excluded studies, and used the same procedure for the Studies awaiting classification.

Figure 1. Figure 1: PRISMA flow diagram of study selection

```
┌─────────────────────┐      ┌─────────────────────┐
│ 94 records          │      │ 0 records identified│
│ identified through  │      │ through other       │
│ database searching  │      │ sources             │
└──────────┬──────────┘      └──────────┬──────────┘
           │                            │
           └──────────────┬─────────────┘
                          │
              ┌───────────▼──────────┐
              │ 86 records after     │
              │ duplicates removed   │
              └───────────┬──────────┘
                          │
                          │
              ┌───────────▼──────────┐      ┌─────────────────────┐
              │ 86 records           │─────▶│ 63 records          │
              │ screened             │      │ excluded            │
              └───────────┬──────────┘      └─────────────────────┘
                          │
                          │
              ┌───────────▼──────────┐      ┌─────────────────────┐
              │ 23 records           │─────▶│ 12 records excluded │
              │ assessed for         │      │ ● 11 ineligible     │
              │ eligibility          │      │   design            │
              └───────────┬──────────┘      │ ● 1 withdrawn       │
                          │                 └─────────────────────┘
                          │
              ┌───────────▼──────────────┐
              │ 9 studies (11 records) to │
              │ extract                   │
              │                           │
              │  ● 2 completed studies    │
              │    (4 records)            │
              │  ● 5 ongoing studies      │
              │    (5 records) (1 in      │
              │    inpatients, 4 in       │
              │    outpatients)           │
              │  ● 2 studies (2           │
              │    records) awaiting      │
              │    classification (1 in   │
              │    inpatients, 1 in       │
              │    outpatients)           │
              └───────────┬──────────────┘
                          │
                          │
              ┌───────────▼──────────────┐
              │ 2 studies included in     │
              │ meta-analysis             │
              │ (quantitative synthesis)  │
              │                           │
              │  ● 0 studies in           │
              │    inpatients             │
              │  ● 2 studies in           │
              │    outpatients            │
              └───────────────────────────┘
```

Data extraction and management

We conducted data extraction according to the guidelines proposed by Cochrane (Li 2020). Two review authors (JN, IT or CS) extracted data independently and in duplicate, using a customised data extraction form developed in Microsoft Excel (Microsoft 2018). We solved disagreements by discussion. If no agreement was reached, we involved a third review author to resolve the disagreement.

We extracted the following information, if reported.

- General information: author, title, source, country, language, type of publication, publication date
- Study characteristics: setting and dates, inclusion/exclusion criteria, number of study arms, comparability of groups, treatment cross-overs, treatment tailoring, intervention modification, length of follow-up, funding
- Participant characteristics: number of participants randomised/ received intervention/analysed, COVID-19 diagnostics, severity of disease, age, gender, comorbidities (e.g. diabetes, immunosuppression), concurrent interventions, time since symptom onset
- Intervention: dose, frequency, duration, and route of administration
- Control intervention: type of control, frequency, duration, and route of administration
- Outcomes: as specified under Types of outcome measures

Assessment of risk of bias in included studies

We used the Risk of Bias 2 (RoB 2) tool to analyse the risk of bias of study results contributing information to our primary outcomes (risk of bias 2.0; Sterne 2019). Of interest for this review was the effect of the assignment to the intervention (the intention-to-treat (ITT) effect), so we performed all assessments with RoB 2 on this effect. The outcomes that we assessed are the primary outcomes specified for inclusion in the summary of findings tables.

Two review authors (JN, IT) independently assessed the risk of bias for each outcome. In case of discrepancies among their judgements and inability to reach consensus, we consulted the third review author to reach a final decision. We assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To address these types of bias we used the signalling questions recommended in RoB 2 and make a judgement using the following options.

- 'Yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias for the given direction of the question)
- 'Probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question)

- 'No': if there is firm evidence that the question is unfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question)
- 'Probably no': a judgement has been made that the question is unfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question)
- 'No information': if the study report does not provide sufficient information to allow any judgement

We used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias.

- Low risk of bias
- Some concerns
- High risk of bias

Subsequently, we derived an overall risk of bias rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judged the trial to be at low risk of bias for all domains for this result
- 'Some concerns': we judged the trial to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain
- 'High risk of bias': we judged the trial to be at high risk of bias in at least one domain for the result, or we judged the trial to have some concerns for multiple domains in a way that substantially lowers confidence in the results

To implement RoB 2, we used the RoB 2 Excel tool (available on the website www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2), and stored and presented our detailed RoB 2 assessments in the analyses section.

Measures of treatment effect

For dichotomous outcomes, we recorded the number of events and total number of participants in both treatment and control groups and reported the pooled risk ratio (RR) with 95% confidence intervals (CIs) and the risk difference (RD) (Deeks 2020).

For continuous outcomes, we recorded the mean, standard deviation and total number of participants in both treatment and control groups. Where continuous outcomes used the same scale, we performed analyses using the mean difference (MD) with 95% CIs (Deeks 2020). For continuous outcomes measured with different scales, we planned to perform analyses using the standardised mean difference (SMD) (Deeks 2020). For interpreting SMDs, we planned to re-express SMDs in the original units of a particular scale with the most clinical relevance and impact. For the current review, all outcomes were measured on comparable scales.

If available, we extracted and reported hazard ratios (HRs) for time-to-event outcomes (e.g. time to hospital discharge). If HRs were not available, we would have made every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar and Tierney (Parmar 1998; Tierney 2007). If sufficient studies provided HRs, we would have used HRs rather than RRs or MDs in a meta-analysis, as HRs provide more information.

Unit of analysis issues

The unit of analysis for this review is the individually-randomised participant. In studies with multiple intervention groups, we followed the recommendations in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a). For studies with multiple treatment groups of the same intervention (i.e. dose, route of administration), we combined the study arms if they were sufficiently homogeneous. If arms could not be pooled, which was not the case for the current review, we had planned to compare each arm with the common comparator separately. For pairwise meta-analysis, we had planned to split the 'shared' group into two or more groups with smaller sample size, and include two or more (independent) comparisons. For this purpose, in the case of dichotomous outcomes, we would have divided both the number of events and the total number of participants. For continuous outcomes, we would have divided the total number of participants and retained unchanged means and standard deviations (SDs).

Dealing with missing data

There are many potential sources of missing data in a systematic review or meta-analysis, which can affect the level of studies, outcomes, summary data, individuals, or study-level characteristics (Deeks 2020). Incomplete data can introduce bias into the meta-analysis if they are not missing at random, which is addressed in the section Assessment of risk of bias in included studies.

First, when data were missing at outcome and study level, we checked for any evidence for the data being missing at random. When we could not retrieve information about data being missing at random, we contacted principal investigators and requested these data (Table 1). If, after this, data were still missing, we would have assumed that data were not missing at random. On the other hand, if there were indications that data were not missing at random, we would have conducted complete case analysis for the primary analysis and would have discussed its potential impact in the discussion section. If we were concerned regarding missing data across studies, we would not have performed meta-analyses, but would have provided subtotals per study.

Assessment of heterogeneity

We used the descriptive statistics reported in the Characteristics of included studies to assess whether the studies within each pairwise comparison were homogenous enough, with respect to study and intervention details and population baseline characteristics, that the assumption of homogeneity might be plausible. In case of excessive clinical heterogeneity, we did not pool the findings of included studies.

We measured statistical heterogeneity using the Chi^2 test and the I^2 statistic (Deeks 2020), and the 95% prediction interval (PI) for random-effects meta-analysis (IntHout 2016). The prediction interval helps in the clinical interpretation of heterogeneity by estimating what true treatment effects can be expected in future settings (IntHout 2016).

We restricted the calculation of a 95% PI to meta-analyses with four or more studies (≥ 200 participants), since the interval would be imprecise if a summary estimate were based on only a few small studies. We planned to use the open-source statistical software R package Meta to calculate 95% PIs, and declare statistical heterogeneity if the P value was less than 0.1 for the Chi^2 statistic, or the I^2 statistic was 40% or more (40% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity) (Deeks 2020); or the range of the 95% PI revealed a different clinical interpretation of the effect estimate compared to the 95% CI.

Assessment of reporting biases

We sought to identify all research that meets our predefined eligibility criteria. Missing studies can introduce bias to the analysis. We searched for completed non-published trials in trials registers, contacted authors to seek assurance that the results will be made available, and classified them as 'awaiting classification' until the results are reported. We reported the number of completed non-published trials.

We planned to investigate the risk of reporting bias (publication bias) in pairwise meta-analyses using contour-enhanced funnel plots, when there were 10 or more relevant studies pooled in a meta-analysis. In the current review, there are no meta-analyses including 10 or more studies. For future review updates, if funnel plot asymmetry is suggested by a visual assessment, we plan to perform exploratory analyses (e.g. Ruecker's arcsine test for dichotomous data and Egger's linear regression test for continuous data) to further investigate funnel plot asymmetry (Egger 1997). A P value of less than 0.1 will be considered as the level of statistical significance. In future review updates, we will analyse reporting bias using the open-source statistical software R package Meta.

Data synthesis

We analysed trials including different severities of disease separately, grouping them into asymptomatic to mild, and moderate to severely ill, as these are different populations in different settings, resulting in different outcome sets (see Types of outcome measures). We analysed trials with the following participant populations separately.

- Inpatients with moderate to severe COVID-19
- Outpatients with asymptomatic or mild COVID-19

For these two distinct populations, we created the following comparisons.

- Fluvoxamine in addition to standard care versus standard care (alone or with placebo)
- Fluvoxamine in addition to standard care versus active pharmacological intervention for the treatment of COVID-19 with proven efficacy in clinical trials with a high weight of evidence (no studies were available for the current review version) in addition to standard care

Placebo and standard care alone (including no intervention) were treated as the same intervention, as well as standard care at different institutions and time points during the pandemic.

We performed meta-analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020). If clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data into meta-analyses. We used the RevMan Web software for meta-analyses (RevMan Web 2022). One review author entered the data in the software, and a second review author checked the data for accuracy. When meta-analysis was feasible, we used

the random-effects model as we assumed that the intervention effects were related but were not the same for the included studies. For dichotomous outcomes, we performed meta-analyses using the Mantel-Haenszel method under a random-effects model to calculate the summary (combined) intervention effect estimate as a weighted average of the intervention effects estimated in the individual studies. For continuous outcomes, we used the inverse-variance method.

We planned to present descriptive statistics only if we deemed meta-analysis inappropriate for a certain outcome because of heterogeneity or because of serious study limitations leading to a considerably high risk of bias (e.g competing risk of death not taken into account in outcome measurements). This was not the case for the current review version.

If meta-analysis was possible, we assessed the effects of potential biases in sensitivity analyses (see Sensitivity analysis) and considered investigating heterogeneity in subgroup analyses (see Subgroup analysis and investigation of heterogeneity). Subgroup analyses were not possible due to the low number of studies per outcome. For future review updates, if we cannot find a cause for the heterogeneity, we will not undertake a meta-analysis but will comment instead on the results as a narrative and present the results from all studies in tables.

We used forest plots to visualise meta-analyses of primary outcomes only, including risk of bias assessment. We reported secondary outcomes without risk of bias assessments in additional tables.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to investigate clinical heterogeneity for the following characteristics (considering primary outcomes):

- Disease severity at baseline as defined by the WHO Clinical Progression Scale (mild, moderate, severe)
- Dose of fluvoxamine (usual dose versus low dose versus high dose)

In the current review version, none of these analyses were possible due to a lack of data and trials (only two included studies).

If enough studies are identified during future review updates, we will also perform subgroup analyses, if statistical heterogeneity is present (P < 0.1 for the Chi^2 test of heterogeneity, I^2 ≥ 50%), or a different clinical conclusion (when comparing 95% CI with 95% PI). We also plan to undertake tests for interaction to test for differences between subgroup results.

Sensitivity analysis

We planned sensitivity analyses of the following characteristics (considering primary outcomes).

- Risk of bias assessment (only trials with a low risk of bias or some concerns)
- Comparison of preprint articles versus peer-reviewed publications (only trials published as journal articles)
- Confirmed versus mixed (suspected and confirmed) COVID-19 diagnosis (only trials/participants with confirmed COVID-19 diagnosis)

Similar to the subgroup analyses, such analyses were not possible in the current review version (due to the low number of trials).

Summary of findings and assessment of the certainty of the evidence

Summary of findings

We evaluated the certainty of the evidence using the GRADE approach for the interventions evaluated in RCTs.

We planned to create a separate summary of findings tables for the different patient populations (outpatients, inpatients) and for the different comparisons. For the current review version, there were no studies addressing inpatients or an active comparator.

We used the GRADEpro GDT to create a summary of findings table. For time-to-event outcomes, we planned to calculate absolute effects at specific time points, as recommended in the GRADE guidance 27 (Skoetz 2020). For the current review, there were no time-to-event data available. According to Chapter 14 of the updated *Cochrane Handbook for Systematic Reviews of Interventions*, the "most critical and/or important health outcomes, both desirable and undesirable, limited to seven or fewer outcomes" should be included in the summary of findings table (Schünemann 2020). We included the following outcomes prioritised according to the Core Outcome Set for intervention studies (COMET 2021, Marshall 2020) and patient relevance.

Inpatients with moderate to severe COVID-19

- All-cause mortality (most favourable time point: at hospital discharge, if not reported for this time point we considered day 60, followed by day 28, or time-to-event estimate)
- Worsening of clinical status at day 28
  - participants with clinical deterioration (new need for invasive mechanical ventilation) or death
- Improvement of clinical status at day 28
  - participants discharged alive
- Quality of life at longest follow-up available
- Serious adverse events during the study period
- Any adverse events during the study period
- Suicide or suicide attempt

Outpatients with asymptomatic or mild COVID-19

- All-cause mortality (most favourable at longest follow-up (> 60 days), if not reported at longest follow-up we considered day 60, followed by day 28, or time-to-event estimate)
- Admission to hospital (all cause) or death (combined outcome, within 28 days)
- Symptom resolution
  - all initial symptoms resolved (asymptomatic) at day 14
  - duration to symptom resolution
- Quality of life at longest follow-up available
- Serious adverse events during the study period
- Any adverse events during the study period
- Suicide or suicide attempt

Assessment of certainty in the evidence

We used the GRADE approach to assess the certainty in the evidence for the outcomes listed above. The GRADE approach

uses five domains (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty in the body of evidence for each prioritised outcome.

We downgraded our certainty of evidence as follows.

- Serious (-1) or very serious (- 2) risk of bias
- Serious (-1) or very serious (- 2) inconsistency
- Serious (-1) or very serious (- 2) uncertainty about directness
- Serious (-1) or very serious (- 2) imprecise or sparse data
- Serious (-1) or very serious (- 2) probability of reporting bias

The GRADE system used the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We followed the current GRADE guidance for these assessments in its entirety as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 14 (Schünemann 2020). We used the overall risk of bias judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading for risk of bias. We phrased the findings and certainty in the evidence as suggested in the informative statement guidance (Santesso 2020).

Methods for future updates (living systematic review considerations)

Our information specialists (IM, KG) will provide us with new search records each week, which two review authors will screen, extract, evaluate, and integrate following the guidance for Cochrane living systematic reviews (Cochrane LSR). We will also manually check platform trials that were previously identified and listed as Studies awaiting classification for additional relevant treatment arms.

We will wait until the accumulating evidence changes our conclusions of the implications of research and practice before republishing the review. We will consider one or more of the following components to inform this decision.

- The findings of one or more prioritised outcomes
- The credibility (e.g. GRADE rating) of one or more prioritised outcomes
- New settings, populations, interventions, comparisons or outcomes studied

In case of emerging policy relevance because of global controversies on the intervention, we will consider republishing an update the review even though our conclusions will remain unchanged. We will review the review scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (for example, when

additional comparisons, interventions, subgroups or outcomes, or new review methods become available).

RESULTS

Description of studies

Results of the search

The literature search resulted in 94 records. No records were identified via additional searches of reference lists. After removing duplicates, 86 records remained. During title and abstract screening, we judged 63 records to be irrelevant.

We proceeded to full-text screening with 23 records, considering published full texts or, if these were not available, trial register entries. From these 23 records, we excluded 12 records: one record (one study) was cancelled before starting patient recruitment and 11 records (11 studies) were not RCTs. From the 11 records (nine studies) that we considered to be relevant (included), five records referred to ongoing studies and two are awaiting classification. Finally, we included two studies (four records) in our quantitative synthesis, contributing data to the primary and secondary outcomes of this review. The flow of records is illustrated in Figure 1.

Inpatients

We did not include any clearly-eligible, completed studies that investigated fluvoxamine in the inpatient setting.

Studies awaiting classification

We considered one study conducted in the inpatient setting to be relevant (Safa 2020), and listed this study in the section Studies awaiting classification. This study was only available in the Persian language, and we will re-evaluate it once the study authors have clarified some translation issues.

Ongoing studies

The characteristics of ongoing studies are available in the section Ongoing studies. In the inpatient setting, we identified one ongoing study (NCT04718480). This trial is still active and compares fluvoxamine with placebo treatment (both in addition to standard care) in people hospitalised with COVID-19. The expected completion date is December 2022. The trial records refer to a planned sample size of 100.

Outpatients

Study design and publication status

Details of the included studies are available in the section Characteristics of included studies.

We included two randomised controlled trials in this review with a total of 1649 allocated participants, of whom 821 were allocated to fluvoxamine in addition to standard care and 828 to placebo and standard care (Lenze 2020; TOGETHER 2021). TOGETHER 2021 was a randomised, adaptive platform trial to investigate the efficacy of different repurposed treatments for non-hospitalised people with COVID-19, allocating 1497 participants to the comparison of interest. Lenze 2020 allocated 152 participants in total.

The study by Lenze 2020 was performed as a remote outpatient trial and the TOGETHER 2021 study used both in-person and remote

follow-up assessments (i.e. relying on physical examination or self-assessments via phone contact or video calls). Both studies were multicentric: Lenze 2020 was performed in two centres in the greater St. Louis metropolitan area, USA, while the TOGETHER 2021 study was conducted at 11 clinical sites in Brazil. With regard to equity, applicability, and resources, we must highlight that one of the included studies was performed in a high-income country while the other was performed in an upper-middle-income country. Both studies reported information about the responsible ethics committee and financial support. TOGETHER 2021 was supported by FastGrants and the Rainwater Foundation, while Lenze 2020 was supported by the Taylor Family Institute for Innovative Psychiatric Treatment at Washington University and the COVID-19 Early Treatment Fund, the Center for Brain Research in Mood Disorders at Washington University, the Bantly Foundation, and a grant from the National Institutes of Health. In both studies, a number of co-authors reported conflicts of interests.

Both trials were peer-reviewed publications in indexed journals and were prospectively registered.

Participants

Both studies recruited participants from the outpatient setting. Lenze 2020 used an electronic health record system, physician referrers, doctors' hotlines, COVID-19 Test Centres, Emergency Rooms (microbiology lab) as per the Healthy Mind Lab website (www.healthymind.wustl.edu), flyers, and email notifications. TOGETHER 2021 recruited participants at community health facilities (emergency settings, influenza-symptom referral centres, or primary care community centres), with the help of notices through physical and social media as per local public health authorities.

In Lenze 2020, all participants had a polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection, while in TOGETHER 2021 PCR for SARS-CoV-2 was not mandatory and participants were also included in the study if they had a positive rapid test for SARS-CoV-2 antigen done after obtaining informed consent.

Lenze 2020 performed randomisation and start of study medication within seven days of symptom onset, without further specification. In TOGETHER 2021, all patients had symptoms beginning within seven days of the screening date: 42.6% within the first three days of symptom onset and 34.5% between days four and seven. For the remaining participants, information on the duration of symptoms within the first seven days was missing.

In both studies, all participants were symptomatic adults. In Lenze 2020 the median age of participants was 46 years in the intervention group and 45 years in the control group (interquartile range (IQR) 35 to 58 and 36 to 54 years, respectively). In TOGETHER 2021 the median age of participants was 50 years (IQR 39 to 56) in the intervention group and 49 years (IQR 38 to 56) in the control group. In total, 50.9% of all participants in this study were less than 50 years old. The majority of participants were female (Lenze 2020: 71.7%; TOGETHER 2021: 58.7%).

The most common comorbidities in Lenze 2020 were asthma (21%) and hypertension (19%) in the intervention group and hypertension (21%) in the control group. In TOGETHER 2021 the most common risk factors were uncontrolled hypertension (in 14% of participants in the intervention group and 12% of participants

in the control group) and type 2 diabetes mellitus (in 14% of participants in the intervention group and 12% of participants in the control group).

The most common symptoms of COVID-19 in Lenze 2020 were loss of sense of smell (in 33% of participants in the intervention group and 25% of participants in the control group) and fatigue (in 21% of participants in the intervention group and 25% of participants in the control group). TOGETHER 2021 did not report the details of baseline symptoms.

Interventions and comparators

Both studies compared fluvoxamine in addition to standard care with placebo and standard care (Lenze 2020; TOGETHER 2021). In Lenze 2020 the dose of fluvoxamine (capsules manufactured by Apotex) was titrated from 50 mg on the day of randomisation to 100 mg twice daily on days two and three and finally 100 mg three times daily on the remaining days up to day 15. After the completion of 15 days of fluvoxamine or placebo, participants were given the option to receive a six-day open-label course of fluvoxamine. This was a change from the original study protocol, but no data collection was conducted for this phase. Matching placebo gelatin capsules contained microcrystalline cellulose and silica gel, micronised. All active drug and placebo preparations were performed by the same pharmacy. In TOGETHER 2021 participants were randomly assigned to fluvoxamine (manufactured by Abbott) at a dose of 100 mg twice daily for 10 days or a corresponding placebo starting directly after randomisation. Neither study specified the placebo.

In the TOGETHER 2021 study, standard care typically focused on the management of symptoms and provision of antipyretics, while antibiotics were provided when clinicians suspected bacterial pneumonia. Lenze 2020 did not report standard care, and the participants received either fluvoxamine or placebo during quarantine. However, taking immunosuppressant biological drugs or high-dose corticosteroids (> 20 mg/d of prednisone) were exclusion criteria in the Lenze 2020 study. TOGETHER 2021 did not allow current use of an SSRI.

Outcome measures

The primary outcome in Lenze 2020 was clinical deterioration, defined by meeting both criteria of (1) shortness of breath or hospitalisation for shortness of breath or pneumonia and (2) oxygen saturation < 92% on room air or need for supplemental oxygen to achieve oxygen saturation of 92% or greater (within 15 days). The primary outcome in TOGETHER 2021 was admission to hospital, defined as COVID-19 emergency setting visits (participants remaining under observation for over six hours) or admission to hospitalisation due to progression of COVID-19 (within 28 days).

Secondary outcomes included in Lenze 2020 were 30 days of post-trial observation events (emergency department visit, hospitalisation, or both) and ventilator support. All outcomes were measured using participants' self-reported responses on twice-daily surveys during the 15 days after randomisation and assessed remotely (via Zoom videoconference, phone, text, email, as well as REDCap surveys pushed out to participants via their smartphones or other devices). In order to standardise the procedure, criteria were formulated for which an emergency department visit was indicated (a decrease in oxygen saturation < 90% on room air on more than two readings, persistent increase in respiratory rate to > 30 breaths per minute, persistent increase in heart rate to > 120

beats per minute, alteration in mentation, or severe worsening in shortness of breath). At 30 days after the conclusion of the 15-day trial, a follow-up survey was performed by phone, email, or electronic medical record review. In the follow-up, the participants were asked if they were hospitalised or had visited a hospital or emergency department since the last study survey.

In TOGETHER 2021, secondary outcomes included time to clinical improvement, number of days with respiratory symptoms, time to hospitalisation (for any cause or due to COVID-19 progression), length of hospitalisation (days), proportion of participants with mechanical ventilation, time on mechanical ventilator (days), proportion of participants who were non-adherent with the study drugs, and adverse reactions to the study medications. Study personnel collected outcome data on days one, two, three, four, five, seven, ten, 14, and 28 in-person or via telephone or social media using video-teleconferencing. At the baseline visit, a six-lead electrocardiogram (Kardiamobile, Mountain View, CA, USA) was performed for all participants and transferred to a central facility (Cardresearch, Belo Horizonte, Brazil) for reading. Vital signs included oxygen status assessed by means of a pulse oximeter for non-invasive arterial oxygen saturation and pulse (Jumper Medical Equipment, Shenzhen, China), and temperature by a standard digital oral thermometer.

Studies awaiting classification

We considered one study conducted in the outpatient setting to be relevant (NCT04668950), and listed it in the section Studies awaiting classification. Although the study is related to the included and published study of Lenze 2020 (but conducted across the United States and two provinces of Canada), we have not yet identified any published reports.

Ongoing Studies

The characteristics of ongoing studies in outpatients are available in the section Ongoing studies. We classified four trials as ongoing: three are still active and are currently recruiting (NCT04510194; NCT04885530; NCT05087381), while the other trial (TCTR20210615002) is pending (not yet recruiting). In all trials, fluvoxamine is being compared to placebo or standard care or with other pharmacological interventions in the outpatient setting. Ongoing studies are evaluating participants aged 18 years and older. The original completion date for the TCTR20210615002 trial was December 2021, and the expected completion date for NCT05087381 was March 2022, while those for NCT04885530 and NCT04510194 are in early 2023. These four trial records refer to planned sample sizes of 296 (TCTR20210615002), 1350 (NCT04510194), 1800 (NCT05087381), and 15000 (NCT04885530), respectively.

Excluded studies

We excluded 12 records after full-text assessment, and these are listed in the section Excluded studies. One record (one study) was cancelled before starting participant recruitment and 11 records (11 studies) were not RCTs.

Risk of bias in included studies

We assessed methodological quality and risk of bias for two RCTs contributing results to our primary outcomes using the RoB 2 tool. The RoB 2 judgements for all study results per outcome and for all domains are available in an interactive risk of bias table (Risk of

bias table for Analysis 1.1; Risk of bias table for Analysis 1.2; Risk of bias table for Analysis 1.3; Risk of bias table for Analysis 1.4) and are briefly summarised below.

Overall risk of bias by study

We assessed both studies to have an overall high risk of bias (Lenze 2020; TOGETHER 2021), mainly due to concerns with the outcome measurement (mostly self-reported outcomes collected remotely), and due to missing participant data. In Lenze 2020, 20% of study participants stopped responding to surveys during the 15-day trial. The possibility that some of these participants (n = 6) received care at an urgent care centre outside the trial could not be excluded. For 31 participants, it was confirmed that they did not receive any medical care for worsening of COVID-19.

Overall risk of bias by outcome

The following section summarises the risk of bias per outcome for all primary outcomes included in the summary of findings table (Summary of findings 1.)

We have no concerns regarding the risk of bias across studies for the outcome 'all-cause mortality at day 28'. We identified a high risk of bias due to missing outcome data for one trial that contributed data to this outcome (18 out of 80 (22.5%) in the intervention group and 19 out of 72 (26.4%) in the placebo group did not complete the study and reasons for missing data were not provided) (Lenze 2020). However, this study did not impact the result of the analysis (zero event study, Analysis 1.1), so we based the bias summary on TOGETHER 2021, where the dropout rate was less than 12%.

We also have no concerns regarding risk of bias for the outcome 'admission to hospital and death' reported by one study (TOGETHER 2021). Although hospital admission rates may be more frequent in trials with a remote patient assessment, particularly when patients are diagnosed with an infectious disease, and direct (face-to-face) contact with a clinician is lacking, the randomised allocation of participants should balance this issue between study arms.

For 'serious adverse events' and 'adverse events', we also identified a high risk of bias due to the measurement of the outcome. All (serious and non-serious) adverse events appear to be self-reported, and it is unclear whether they were verified by medical records or practitioner reports, which may be associated with an under- or overestimation of such events. Furthermore, the results could be impacted due to missing participant data, particularly in the study of Lenze 2020.

Effects of interventions

See: **Summary of findings 1** Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19

on time to ssssAs we did not include any studies investigating efficacy and safety of fluvoxamine in the inpatient setting, this section effectively only addresses the outpatient setting.

Primary outcomes are displayed in the summary of findings table (Summary of findings 1 'Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19').

We included two placebo-controlled studies in both qualitative synthesis and quantitative synthesis (meta-analysis) of this review (Lenze 2020; TOGETHER 2021). Both studies investigated outpatients with confirmed mild COVID-19.

We did not conduct sensitivity analysis regarding the risk of bias, since only one study had a low risk of bias for the outcome 'all-cause mortality' (TOGETHER 2021). Lenze 2020 did not report any events reported for this outcome. So the study with a low risk of bias contributed 100% to the weight of the meta-analysis.

There were no indications of data not missing at random, so predefined analyses for such cases were not applicable.

In the current review, there are not enough studies available to perform the planned subgroup analyses to investigate heterogeneity for study characteristics (such as differing doses and severity of the disease).

Primary outcomes

All-cause mortality at day 28

Both studies reported on all-cause mortality either at day 15 (Lenze 2020) or day 28 (TOGETHER 2021). Fluvoxamine may slightly reduce all-cause mortality (RR 0.69, 95% CI 0.38 to 1.27; 1649 participants; RD 9 per 1000; Analysis 1.1). While no deaths were recorded in either the treatment group or placebo group at day 15 (Lenze 2020), at day 28 the risk with fluvoxamine and standard care was 21 per 1000 and the risk in the placebo group was 30 per 1000 (TOGETHER 2021). Certainty of the evidence for this outcome was low. While we did not downgrade for risk of bias (as the study with a high risk of bias had a weight of 0% (Lenze 2020), we did downgrade for very serious imprecision because the 95% CI suggests both potential benefit and no effect or potential harm, and the number of events was small.

All-cause admission to a hospital or death (before hospital admission)

Both studies reported data on admission to hospital or death within 28 days for participants with symptomatic COVID-19. Fluvoxamine may reduce admission to hospital or death (RR 0.55, 95% CI 0.16 to 1.89; 1649 participants; RD 57 per 1000; Analysis 1.2). Certainty of the evidence for this outcome was low. We downgraded this by two levels due to concerns of very serious imprecision because the 95% CI suggests both potential benefit and no effect or potential harm, and the number of events was small.

Symptom resolution

Neither of the studies reported numerical data for this outcome. One study illustrated data in a graph that indicated an overlap of confidence intervals (TOGETHER 2021).

Quality of life

Neither of the studies reported this outcome.

Serious adverse events

Both studies reported data for this outcome (Lenze 2020; TOGETHER 2021). There is very low-certainty evidence on fluvoxamine regarding the number of participants with serious adverse events during the study period (RR 0.56, 95% CI 0.15 to 2.03; 1649 participants; RD 54 per 1000; Analysis 1.3). We downgraded the certainty of the evidence by three levels: by one level for serious

concerns due to high risk of bias (measurement of the outcome), and by two levels for very serious concerns due to imprecision. The 95% CI includes a potential benefit and harm.

Any adverse events (any grade)

The studies of Lenze 2020 and TOGETHER 2021 also reported data for any adverse events. There is very low-certainty evidence on fluvoxamine regarding adverse events of any grade during the short-term follow-up (RR 1.06, 95% CI 0.82 to 1.37; 1649 participants; RD 7 per 1000; Analysis 1.4). We downgraded the certainty of the evidence by three levels: by one level for serious concerns due to high risk of bias (measurement of the outcome), and by two levels for very serious concerns due to imprecision. The 95% CI includes a potential benefit and harm.

Suicide or suicide attempt

None of the included studies reported this outcome.

Secondary outcomes

The secondary outcomes reported included 'clinical status' at day 15, 28 or the longest follow-up and 'viral clearance'. Clinical status was measured in one study each as 'need for invasive mechanical ventilation', 'need for non-invasive mechanical ventilation or high flow' and 'need for hospitalisation with oxygen therapy'. Quantitative data for the secondary outcomes are listed in Table 2.

Need for invasive mechanical ventilation

TOGETHER 2021 reported that 26 of 741 fluvoxamine treated patients versus 34 of 756 participants in the placebo group needed mechanical ventilation (RR 0.77, 95% CI 0.45 to 1.30; 1497 participants; RD 10 per 1000; Table 2).

Need for non-invasive mechanical ventilation or high flow

Lenze 2020 reported that none of the 80 fluvoxamine treated participants versus three of 72 participants in the placebo group required supplemental oxygen plus ventilator support for three days or more (absolute difference 0.00, 95% CI -8.41 to 0.49; 152 participants; RD 0 per 1000; Table 2). This outcome was assessed with a 7-point scale.

Need for hospitalisation with oxygen therapy by masks or nasal prongs

Lenze 2020 also reported that none of the 80 participants treated with fluvoxamine versus three of 72 participants in the placebo group needed hospitalisation and required supplemental oxygen therapy by masks or nasal prongs (absolute difference -4.21, 95% CI -13.22 to 2.04; 152 participants; RD 42 per 1000; Table 2). Again, this outcome was assessed with a 7-point scale.

Viral clearance (assessed with PCR) at day 7

TOGETHER 2021 reported that 40 of 207 fluvoxamine treated patients versus 58 of 221 participants in the placebo group showed successful viral clearance at day seven (OR 0.67, 95% CI 0.42 to 1.06; 428 participants; RD 70 per 1000; Table 2).

DISCUSSION

Summary of main results

The aim of this review was to investigate the efficacy and safety of fluvoxamine in people with COVID-19. We identified two RCTs including more than 1500 non-hospitalised people (outpatients) with symptomatic COVID-19 (Lenze 2020; TOGETHER 2021). We did not find any RCTs that investigated asymptomatic people or those hospitalised with COVID-19 who were being treated with fluvoxamine.

Both included studies evaluated composite endpoints including clinical worsening according to the definition of the respective study and retention in a COVID-19 emergency setting or inpatient setting. From the prioritised primary endpoints of this review, the studies reported all-cause mortality at day 28 (Lenze 2020; TOGETHER 2021), admission to hospital (all cause) or death (before hospital admission) (TOGETHER 2021), serious adverse events (Lenze 2020; TOGETHER 2021) and adverse events (any grade) (Lenze 2020; TOGETHER 2021). Furthermore, the studies also reported data for the secondary outcomes: need for mechanical ventilation (TOGETHER 2021), need for non-invasive mechanical ventilation or high flow oxygen supplementation (Lenze 2020), need for hospitalisation with need for oxygen therapy (by masks or nasal prongs) (Lenze 2020), and viral clearance at day 7 (TOGETHER 2021).

Our analyses show that fluvoxamine compared to placebo (both in addition to standard care) may slightly reduce all-cause mortality at day 28 (RR 0.69, 95% CI 0.38 to 1.27; 2 studies, 1649 participants; low-certainty evidence) and may reduce the number of people admitted to a hospital or who died beforehand (RR 0.55, 95% CI 0.16 to 1.89; 2 studies, 57 participants; low-certainty evidence). The number of serious adverse events did not clearly differ between fluvoxamine and placebo, and we are very uncertain about the effect of fluvoxamine on serious adverse events during the study period (RR 0.56, 95% CI 0.15 to 2.03; 2 studies, 1649 participants; very low-certainty evidence). Likewise, we are very uncertain about the effect of fluvoxamine on adverse events of any grade (RR 1.06, 95% CI 0.82 to 1.37; 2 studies, 1649 participants; very low-certainty evidence). Although TOGETHER 2021 mentioned that there was no difference in time to symptom resolution between the groups, we could not derive any numerical data from this study and contacting the authors was unsuccessful. Neither study reported on quality of life or suicide and suicide attempt.

Overall completeness and applicability of evidence

The evidence summarised in this review applies to the use of fluvoxamine in symptomatic COVID-19 outpatients. It is mainly restricted to unvaccinated people at high-risk and the virus variants of concern that were present at the time of the conducted trials (up to August 2021). We did not identify any randomised trials for inpatients with moderate, severe and critical COVID-19, or any studies reporting on fluvoxamine versus other active pharmacological comparators with proven effectiveness.

One small study was conducted in a single geographical area of the USA, with recruitment between April and August 2020 (the first phase of the pandemic) (Lenze 2020). The other, much larger, study was conducted in high-risk people in Brazil and recruitment took place between January and August 2021 (TOGETHER 2021).

The recruitment period in Lenze 2020 was before the start of the vaccination campaign, and in TOGETHER 2021 only 6% of recruited participants reported one dose of a COVID-19 vaccine at the end of the trial. Taking into account that widespread vaccination programmes have now become established in some areas, it is very unclear whether the results of the studies can be transferred to a predominantly immunised population in case of a breakthrough infection.

Particularly for immunocompromised people, who have a relevant risk of an inadequate immune response to vaccination, an effective treatment reducing disease progression would be clinically important. However, immunosuppression was an exclusion criterion in Lenze 2020, and in TOGETHER 2021 the number of immunosuppressed participants was unclear. Older people were also underrepresented in both studies: the median age of participants was 46 years (intervention arm) and 45 years (control arm) in Lenze 2020, and 50% of participants in the TOGETHER 2021 trial were younger than 50 years old. Because the focus of the study of TOGETHER 2021 was people at high-risk, the applicability of our findings for subgroups including the immunocompromised or older people must be applied with caution.

Since recruitment in TOGETHER 2021 was based on the results of rapid SARS-CoV-2 antigen testing, diagnostic uncertainty may be another limitation in the interpretation of the results of this study. However, the concordance of positive COVID-19 rapid antigen tests with RT-PCR was evaluated in a group of participants who underwent PCR testing. A concordance rate of greater than 99% for both tests collected at baseline was found.

Furthermore, the changing dynamics in the development of virus variants, with possible limitations on the effectiveness of antiviral therapies, needs to be considered when interpreting these results. There are no studies to date that evaluate the efficacy of fluvoxamine in the presence of virus variants of concern. Furthermore, we currently we do not know how immunomodulators will be affected by viral variants.

Certainty of the evidence

We assessed the certainty of evidence for primary outcomes presented in the Summary of findings 1 according to Schünemann 2020, and this ranged from low to very low. We found all-cause mortality and admission to hospital, or death prior to hospital admission, to have low-certainty evidence. The certainty of evidence for the outcomes 'serious adverse events' and 'adverse events of any grade' was very low. Downgrading was due to very serious imprecision (because the 95% CI suggests both potential benefit and no effect or potential harm) and a serious risk of bias (because of concerns in measurement of the outcome 'adverse events' which were self-reported in both studies). Although our findings are mainly restricted to unvaccinated persons and virus variants of concern that were present up to August 2021, we did not downgrade due to indirectness. The reason for not downgrading was due to the ongoing and still dynamic pandemic. Judging the effectiveness of current anti-COVID-19 therapies against emerging variants poses an enormous challenge, as has been seen with the assessment of vaccine effectiveness over the last year (Altmann 2021).

In the current phase of the pandemic, it is also impossible to reliably assess the risk of publication bias. There are registered studies

that are ongoing. We will follow the publication and trial history of each ongoing study, including those awaiting classification. We do not suspect any current publication bias to be present, for any of the outcomes. However, this may change in future updates of this review.

Potential biases in the review process

To avoid potential bias in the review process, we committed ourselves to conducting this systematic review according to published guidance provided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b).

Furthermore, this review is part of a Cochrane Living Systematic Reviews Series on different interventions for treatment of COVID-19 (Ansems 2021; Kreuzberger 2021; Popp 2021a; Popp 2021b; Stroehlein 2021; Wagner 2021). Initially, a common core outcome set was established for all reviews in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for people with COVID-19 (COMET 2021; Marshall 2020). These outcomes are continuously discussed and modified as necessary, taking into account the dynamics of the pandemic.

Although we did not exclude preprint studies, this review contains data from peer-reviewed journal publications only. We contacted study authors if the publication included unclear or missing information. Details of communication with authors are provided in Table 1.

Two trials are classified as awaiting classification either due to inconclusive information regarding outcome measures related to the language of the study (trial in Persian language in an inpatient setting), or because the study was stopped for futility by a data safety monitoring board and results have not been published (trial in an inpatient setting). We will closely monitor these trials for further publications in the near future.

None of the authors has an affiliation with a stakeholder group that favours or disapproves of any selective serotonin reuptake inhibitors, or any of the comparators used in relevant studies.

Agreements and disagreements with other studies or reviews

We have identified two published reviews dedicated solely to the efficacy and safety of fluvoxamine in the treatment of COVID-19 (Kacimi 2021; Lee 2021). Only one review, published as a preprint, analysed randomised trials (Lee 2021), while Kacimi 2021 also considered observational studies.

Lee 2021 came to similar conclusions as our review. However, that review included three randomised trials. Besides the study of TOGETHER 2021 and Lenze 2020, the review considered a third completed, but not published, trial (NCT04668950). The authors stated that they obtained outcome data directly from the principal investigators (who were co-authors of the cited review).

Kacimi 2021 (a preprint labelled as a living systematic review) also focused on fluvoxamine and included two randomised trials and one observational study. The authors concluded that repurposing of fluvoxamine for the treatment of people with COVID-19 had not shown any efficacy in reducing the mortality rate or the rate of progress to mechanical ventilation. Although the authors described a reduced risk of hospitalisation amongst people with COVID-19,

they stressed that there was still an urgent need for more clinical studies to determine the extent of the effectiveness of fluvoxamine, and to know more about its mechanism of action in people with COVID-19.

There are several reviews analysing fluvoxamine as one of the therapeutics for COVID-19.

A systematic review by Murchu 2022 focused on differing oral interventions (including fluvoxamine, bamlanivimab as monotherapy and combined with etesevimab, casirivimab plus imdevimab, ivermectin, nitazoxanide, and peginterferon lambda) in the outpatient setting to prevent progression to severe disease in people with COVID-19. Although this review did not include the large TOGETHER trial on fluvoxamine (TOGETHER 2021), and most findings of the evaluated medications were based on single study results, the authors concluded that promising results in relation to clinical deterioration (defined by dyspnoea or hospitalisation), oxygen saturation (on room air) or need for supplemental oxygen (in the ambulatory setting) are available.

Wen 2022 conducted a meta-analysis to investigate the effectiveness of fluvoxamine and other oral antivirals (molnupiravir and nirmatrelvir/ritonavir). The authors included both randomised and non-randomised trials and concluded that each oral medication assessed was effective in reducing mortality and hospitalisation rates in people with COVID-19. In addition, they found that the risk of adverse events did not increase whilst taking medication compared to placebo or standard care. Taking into account that no bias assessment had been conducted, and the study results were combined without differentiating between inpatient and outpatient settings, these findings needed to be interpreted with caution.

Based on their review of trials, including two RCTs which had the greatest impact on the Panel's recommendation (Lenze 2020; TOGETHER 2021), the U.S. National Institutes of Health COVID-19 Treatment Guidelines Panel stated that there is insufficient evidence to recommend either for or against the use of fluvoxamine in the treatment of COVID-19 (National Institutes of Health 2022).

Although there are some published reviews on fluvoxamine as early treatment for COVID-19, none fulfilled all the methodological standards for evidence syntheses, and they did not apply the GRADE approach for rating the certainty of the evidence. But, overall, the findings of these reviews are in alignment with our review, indicating that the current evidence for fluvoxamine is limited, especially considering that only two randomised controlled trials currently exist.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the current evidence, the use of fluvoxamine plus standard care in comparison to standard care plus placebo in outpatients with mild COVID-19 may reduce slightly all cause mortality (at day 28) and may reduce admission to hospital or death. However, we are very uncertain regarding the effect on serious adverse events. These findings are restricted to unvaccinated symptomatic outpatients and virus variants of concern that were present at the time that the trials were conducted. There were no numerical data currently available for

other prioritised outcomes, including symptom resolution, quality of life, and suicide. No completed studies were identified that focused on inpatients, hence no statements could be made on this aspect of fluvoxamine use.

Implications for research

Effective pharmacological therapies to treat COVID-19 in the outpatient setting are important to reduce the risk of progression to severe disease in people with COVID-19, and reduce the need for hospital admission. Trials considering both prioritised outcomes, such as quality of life, and current vaccination status, as well as older populations, women who are pregnant or breastfeeding, or people who have a weakened immune system are needed to further investigate the role of fluvoxamine in the treatment of COVID-19. Furthermore, it would be important to establish the efficacy and safety of fluvoxamine as compared to other active pharmacotherapies targeting novel COVID-19 variants, and whether closely related selective serotonin reuptake inhibitors could be used interchangeably.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Lenze 2020

Study characteristics	
Methods	• Trial design: randomised, double-blind, placebo-controlled, remote design • Type of publication: journal publication • Setting: non-hospitalised outpatients • Recruitment dates: April to August 2020 • Country: USA • Language: English • Number of centres: 2 • Trial registration number: NCT04342663 • Date of trial registration: 8 April 2020

Participants	• Number of participants (randomised/analysed): 181/152 (115 completed 15-day assessment)
	• Age (median, years): fluvoxamine group: 46 (range 20 to 75); control group: 45 (range 21 to 69)
	• Gender (males, n (%)): fluvoxamine group: 24 (30); control group: 19 (26)
	• Severity of condition according to study definition: non-hospitalised adults with confirmed COVID-19
	• Comorbidities: asthma, hypertension, diabetes, high cholesterol, hyperthyroidism, anxiety, osteoarthritis or rheumatoid arthritis, depression
	• Virus detection performed at baseline (RT-PCR positive at baseline, %): 100%
	• Inclusion criteria
	  ◦ outpatients (age 18 and older)
	  ◦ proven SARS-CoV-2 positive (per lab or physician report)
	  ◦ currently symptomatic, with at least 1 of the following symptoms: fever, cough, myalgia, mild dyspnoea, diarrhoea, vomiting, anosmia (inability to smell), ageusia (inability to taste), sore throat
	• Exclusion criteria
	  ◦ illness severe enough to require hospitalisation or already meeting study's primary endpoint for clinical worsening
	  ◦ unstable medical comorbidities (including, but not limited to, severe underlying lung disease)
	  ◦ decompensated cirrhosis
	  ◦ congestive heart failure (stage 3 or 4)

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Lenze 2020 *(Continued)*

○ immunocompromised (solid organ transplant, BMT, AIDS, on biologics and/or high dose steroids (> 20 mg prednisone per day))

○ currently taking chloroquine, hydroxychloroquine, azithromycin or colchicine.

Interventions	• Details of interventions for relevant arms ○ type and dose: fluvoxamine 50 mg (initial dose), then 100 mg (2 times daily, for 2 days as tolerated), then 100 mg (3 times daily, through day 15) ○ route of administration: oral • Treatment details of a control group (e.g. type, dose, route of administration) ○ placebo (same dose and administration as intervention) • Concomitant medications: all patients received standard care (which was not further defined) • Duration of follow-up: 15 days (after randomisation) • Treatment cross-overs: none

Outcomes	• Primary study outcome
	○ clinical deterioration defined as:
	  ■ presence of dyspnoea or hospitalisation (for dyspnoea) or pneumonia; and
	  ■ decrease in oxygen saturation (< 92%) on room air or supplemental oxygen requirement to maintain oxygen saturation of 92% or greater.
	• Relevant review outcomes reported
	○ mortality (all cause)
	○ serious adverse events
	○ adverse events (any grade)
	○ need for non-invasive mechanical ventilation or high flow (ventilator support)
	○ need for hospitalisation with need for oxygen therapy (by masks or nasal prongs)
	• Additional study outcomes reported
	○ clinical deterioration/worsening of clinical status defined by a 7-points scale at day 15:
	  ■ 0 = none, 1 = shortness of breath and oxygen saturation < 92% (no supplemental oxygen), 2 = shortness of breath and oxygen saturation < 92% + supplemental oxygen, 3 = oxygen saturation < 92% + supplemental oxygen and hospitalisation related to dyspnoea or hypoxia, 4 = oxygen saturation < 92% + supplemental oxygen and hospitalisations related to dyspnoea or hypoxia + ventilator support (< 3 days), 5 = oxygen saturation < 92% + supplemental oxygen and hospitalisation related to dyspnoea or hypoxia + ventilator support (≥ 3 days), 6 = death
	○ Post-trial observation events at day 30 (emergency department visit, hospitalisation, or both)

Notes	• Date of Publication: 12 November 2020 • Assessment: remotely • Sponsorship source: Taylor Family Institute for Innovative Psychiatric Treatment and Center for Brain Research in Mood Disorders(Washington University), COVID-19 Early Treatment Fund, Bantly Foundation, and the National Institutes of Health • Conflicts of interest ○ Dr Lenze reported receiving grants from the Patient-Centered Outcomes Research Institute, Takeda, Alkermes, Janssen, Acadia, and the Barnes Jewish Hospital Foundation; and receiving consulting fees from Janssen and Jazz Pharmaceuticals; ○ Dr Zorumski reported being on the scientific advisory board for and having stock and stock options with Sage Therapeutics, and receiving personal fees from CME Outfitters and JAMA Psychiatry; ○ Dr Nicol reported receiving grants from Alkermes, the Center for Brain Research in Mood Disorders, the Center for Diabetes Translational Research, the Institute for Public Health, the McDonnell Center for Neuroscience, and the Barnes Jewish Hospital Foundation; and serving as a consultant to Sunovion, Alkermes, and Elira; ○ Mr Miller reported receiving research funding from the Patient-Centered Outcomes Research Institute; ○ Dr Avidan reported receiving grants from the COVID-19 Therapeutics Accelerator. • Ethics approval: approved by the institutional review board at Washington University in St Louis • Correspondence with the study authors: request sent (see Table 1)

TOGETHER 2021 *(Continued)*

Study characteristics	
Methods	• Trial design: randomised, double-blind placebo-controlled, partly remote design (follow-up was either in person or via telephone contact or social media applications using video-teleconferencing) • Type of publication: journal publication • Setting: non-hospitalised, outpatients • Recruitment dates: January to August 2021 • Country: Brazil • Language: English • Number of centres: 11 • Trial registration number: NCT04727424 • Date of trial registration: 2 June 2020

Participants	• Number of participants (randomised/analysed): 1497/1497
	• Age (median, years): fluvoxamine group: 50 (interquartile range 39 to 56); control group: 49 (interquartile range 38 to 56)
	• Gender (males, n (%)): fluvoxamine group: 332 (45); control group: 303 (40)
	• Severity of condition according to study definition: confirmed RT-PCR positive for SARS-CoV-2 with a known risk factor for progression to severe disease
	• Comorbidities: chronic cardiac disease, hypertension, chronic pulmonary disease, asthma, chronic kidney disease, rheumatological disorder, chronic neurological disorder, diabetes (type 1 and 2), autoimmune disease
	• Virus detection performed at baseline (RT-PCR positive at baseline (%)): rapid test for SARS-CoV-2 antigen (all included participants) after obtaining informed consent; the concordance of COVID-19 positive rapid tests with RT-PCR was evaluated on the group of participants with PCR evaluations and a concordance rate of greater than 99% on both tests collected at baseline was found
	• Inclusion criteria
	  ○ outpatients (age 18 and older) with ≥ 1 enhancement criterion: age > 50 years, diabetes mellitus, systemic arterial hypertension, cardiovascular diseases, symptomatic lung disease, symptomatic asthma patients, obesity, transplanted patients, patient with stage IV chronic kidney disease or on dialysis, immunosuppressed patients, patients undergoing treatment of current cancer, chronic renal disease or end-stage renal disease
	• Exclusion criteria
	  ○ flu-like symptom onset (8 days or more);
	  ○ > 14 days of vaccination for SARS-CoV-2;
	  ○ acute respiratory conditions;
	  ○ dyspnoea due to other causes or infections;
	  ○ people with clinical evidence of moderate disease and/or hospitalisation indication;
	  ○ people using serotonin reception inhibitors;
	  ○ use of antiretroviral agents;
	  ○ people with severe psychiatric disorders;
	  ○ history of severe ventricular cardiac arrhythmia, symptomatic orthostatic hypotension, postural orthostatic tachycardia syndrome, myocardial infarction, cardiovascular intervention, moderate to severe mitral or aortic stenosis.

Interventions	• Details of intervention for relevant arms
	  ○ type and dose: fluvoxamine 100 mg (2 times daily, for 10 days)
	  ○ route of administration: oral
	• Treatment details of control group (e.g. type, dose, route of administration): placebo (same dose and administration as intervention)
	• Concomitant medications: standard care for COVID-19 provided by healthcare professionals (with a focus on symptom management, antipyretics or antibiotics only as needed); 86/1497 (6%) reported ≥ 1 dose of a COVID-19 vaccine at the end of the trial.

TOGETHER 2021 *(Continued)*

	• Duration of follow up: 28 days (after randomisation) • Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ admission to hospital defined as
	    ■ COVID-19 emergency setting visits (participants remaining under observation for > 6 h); or
	    ■ referral to further hospitalisation due to the progression of COVID-19 (within 28 days).
	• Relevant review outcomes reported
	  ○ all-cause mortality (at day 28)
	  ○ admission to hospital or death (before hospital submission)
	  ○ symptom resolution (mentioned in the study, but no numerical data reported; therefore not further considered in our review see also 'Notes' below)
	  ○ serious adverse events
	  ○ adverse events (any grade)
	  ○ need for mechanical ventilation
	  ○ viral clearance (assessed with RT-PCR for SARS-CoV-2) at day 7
	• Additional study outcomes reported
	  ○ respiratory symptoms (number of days)
	  ○ time to hospitalisation (for any cause or due to COVID-19 progression)
	  ○ time in hospital (number of days)
	  ○ mechanical ventilator (number of days)
	  ○ adherence (number of participants)

Notes	• Date of Publication: 28 October 2021
	• Sponsorship/funding source: FastGrants and the Rainwater Foundation
	• Conflicts of interest
	  ○ Prof. Mills, Dr Glushchenko, Dr. Sprague, have been employed by Platform Life Sciences
	  ○ Prof. Mills, Dr Harari and Mrs. Ruton have been employed by Cytel
	  ○ Mr Rayner has been employed by Certara;
	  ○ Dr Reis has been employed by Cardresearch
	  ○ Mrs. Ribeiro Nogueira and Prof. Lenze are co-inventors on a patent application filed by Washington University for methods of treating COVID-19
	  ○ No other disclosures were reported.
	• Ethics approval: local and national ethics boards in Brazil (CONEP CAAE: 41174620.0.1001.5120, approval letter 5.501.284) and the Hamilton Integrated Research Ethics Board (HiREB, approval letter 13390) in Canada
	• Others: the trial was stopped on 5 August 2021 due to superiority.
	• Correspondence with the study authors: request sent (see Table 1).

COVID-19: coronavirus disease 2019; RT-PCR: reverse transcription-polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Assanovich 2021	**Ineligible study design:** a description of properties of fluvoxamine
Brown University 2021	**Ineligible study design:** not original study publication, rather a commentary on how fluvoxamine may limit deterioration from COVID-19
Glebov 2021	**Ineligible study design:** a highlight of protective effect of fluvoxamine antidepressant against COVID-19, highlighting therapeutic and prophylactic potential

Study	Reason for exclusion
Hashimoto 2021	**Ineligible study design:** a commentary on mechanisms of action of fluvoxamine for COVID-19
Khosravi 2022	**Ineligible study design:** a narrative review
Marcec 2021	**Ineligible study design:** description of fluvoxamine mechanisms of action and potential use in COVID-19 treatment
McCarthy 2021	**Ineligible study design:** paper reviewed the pleiotropic properties of fluvoxamine and explored how the drug may be used to treat the inflammatory sequelae of COVID-19 in the future
Medical Letter 2021	**Ineligible study design:** a commentary on properties of fluvoxamine
Murchu 2021	**Ineligible study design:** not an original publication
NCT04711863	**Suspended Trial:** trial was suspended due to closure of the main treatment centre
Seftel 2021	**Ineligible study design:** a prospective cohort study in real-world experience using fluvoxamine
Sukhatme 2021	**Ineligible study design:** description of fluvoxamine mechanisms of action and potential use in COVID-19 treatment

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT04668950

Methods	- Trial design: randomised, triple-blind, placebo-controlled - Type of record: trial register entry and published protocol - Sample size: 683 - Setting: non-hospitalised, outpatients - Country: Canada, USA - Language: English - Number of centres: 5 - Trial registration number: NCT04342663 - Date of trial registration: 16 December 2020
Participants	Inclusion criteria - Adult (30 years and older) - Proven SARS-CoV-2 positive (per lab or physician report) - Symptomatic: fever, cough, myalgia, mild dyspnoea, chest pain, diarrhoea, nausea, vomiting, anosmia (inability to smell), ageusia (inability to taste), sore throat, nasal congestion - Risk factors for clinical deterioration Exclusion criteria - Unstable medical comorbidities (e.g. decompensated cirrhosis), per patient report and/or medical records - Immunocompromised; e.g. solid organ transplant, BMT, high dose steroids (>20 mg prednisone per day), or tocilizumab - Already enrolled in another COVID-19 medication trial (not including vaccination or prophylaxis trials) - Unable to perform the study procedures - Taking other medications like donepezil, or sertraline, or warfarin (Coumadin), or taking SSRIs or tricyclic antidepressants at high dose, or taking alprazolam or diazepam

NCT04668950 *(Continued)*

- Received vaccine for COVID-19

Interventions	Details of intervention
	• Fluvoxamine 50 mg once daily, then 100 mg twice daily; up to 200 mg per day as tolerated, for approximately 15 days; reduce dose for tolerability reasons
	Treatment details of control group (e.g. type, dose, route of administration)
	• Placebo one capsule, twice daily, for approximately 15 days; may reduce dose for tolerability reasons
Outcomes	Primary study outcomes
	• Clinical deterioration at 15 days defined as 1) presence of dyspnoea and/or hospitalisation for shortness of breath or pneumonia and 2) decrease in O_2 saturation (< 92% on room air) and/or supplemental oxygen requirement (to keep O_2 saturation ≥ 92%
	Relevant study outcomes planned
	• Quality of life
	Secondary outcomes
	• Post-Covid function at day 15 and day 90
Notes	• Reason for awaiting classification: as of 13 January 2022, completed recruitment, but no results have been published
	• Recruitment status: completed
	• Prospective completion date: 28 September 2021
	• Data last update was posted: 13 January 2022
	• Sponsorship/funding source: Washington University School of Medicine

Safa 2020

Methods	• Trial design: randomised clinical trial
	• Type of record: trial register entry and published protocol
	• Sample size: 40
	• Setting: hospitalised, inpatients
	• Country: Iran
	• Language: Persian
	• Number of centres: 1
	• Trial registration number: IRCT20131115015405N4
	• Date of trial registration: 03 October 2020 (retrospective registration)
Participants	Inclusion criteria
	• Adult (18 years and older)
	• COVID-19 patients on intensive care unit
	• Being conscious
	• Informed consent
	• Definite diagnosis of COVID-19 in medical records of the patient
	Exclusion criteria
	• Being pregnant

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Safa 2020 *(Continued)*

	• Simultaneous consumption of any kind of alcohol or substance
Interventions	Details of intervention of relevant arms
	• Fluvoxamine 50 mg capsule per night (dose to be increased to 300 mg/day if tolerated)
	Treatment details of control group (e.g. type, dose, route of administration)
	• Standard care
Outcomes	Primary study outcomes
	• quality of life
	• mortality
Notes	• Reasons for awaiting classification
	○ publication is in the Persian language
	○ contacting the authors was not successful
	○ automated translations was insufficient for a formal assessment or inclusion of the study
	• Recruitment Status: completed and results published
	• Prospective completion date: 5 September 2020
	• Date last update was posted: 6 October 2020
	• Sponsorship/funding source: Shahid Beheshti University of Medical Sciences

COVID-19: coronavirus disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SSRIs: selective serotonin reuptake inhibitors

Characteristics of ongoing studies *[ordered by study ID]*

NCT04510194

Study name	COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19)
Methods	• Trial design: randomised, triple-blinded
	• Type of record: trial register entry and published protocol
	• Sample size: 1350
	• Setting: outpatients
	• Country: Canada, USA
	• Language: English
	• Number of centres: 5
	• Trial registration number: NCT04510194
	• Date of trial registration: 12 August 2020
Participants	Inclusion Criteria
	• Both male and female aged 30 years to 85 years
	• Positive laboratory test for active SARS-CoV-2 viral infection based on local laboratory standard (PCR)
	• No known history of confirmed SARS-CoV-2 infection
	• Electronic device for communication
	Exclusion Criteria
	• Hospitalised, for COVID-19 or other reasons
	• History of severe kidney disease
	• Unstable heart failure

NCT04510194 *(Continued)*

Interventions	Details of intervention

	• Eligible patients shall be randomised to receive one of the antibiotics/combinations.
	  ◦ metformin only
	  ◦ fluvoxamine only
	  ◦ ivermectin only
	  ◦ metformin + fluvoxamine
	  ◦ metformin + ivermectin
	• Route of administration: oral
	
	Treatment details of control group (e.g. dose, route of administration)
	
	• Placebo

Outcomes	• Primary study outcomes
	  ◦ clinical progression at 14 days; defined as emergency department visit for any COVID-19 related symptom (including hospitalisation or death) or decrease in O2 saturation (≤ 93% on room air, or need for supplemental oxygen to maintain an O2 saturation > 93%)
	• Relevant review outcomes planned
	  ◦ quality of life
	  ◦ hospitalisation or death
	• Secondary outcome
	  ◦ maximum symptom severity at 14 days and 28 days
	  ◦ clinical progression at 14 days and 28 days
	  ◦ time to meaningful recovery at 14 days and 28 days

Starting date	1 January 2021
Contact information	covidout@umn.edu
Notes	• Recruitment status: recruiting • Prospective completion date: February 2023 • Date last update was posted: 16 January 2022 • Sponsorship/funding source: University of Minnesota

NCT04718480

Study name	Fluvoxamine Administration in Moderate SARS-CoV-2 (COVID-19) Infected Patients
Methods	• Trial design: randomised, double-blind, placebo-controlled, adaptive-design • Type of record: trial register entry and published protocol • Sample size: 100 • Setting: hospitalised, inpatients • Country: Hungary • Language: English • Number of centres: 4 • Trial registration number: NCT04718480 • Date of trial registration: 22 January 2021
Participants	Inclusion criteria • Adults (18 to 70 years) • Hospitalised patients with confirmed SARS-CoV-2 by PCR

NCT04718480 *(Continued)*

	Exclusion criteria
	• Mild, severe or critical COVID-19 at randomisation
	• Standard care treatment planned with chloroquine or hydroxychloroquine
	• History of bleeding diathesis or other bleeding disorders, or present malignancy
Interventions	Details of intervention
	• 2 x 100 mg fluvoxamine daily (with careful dose escalation and tapered dose reduction)
	• Overall treatment period: 74 days
	• Route of administration: oral
	Treatment details of control group (e.g. dose, route of administration)
	• 2 x 100 mg placebo daily (with careful dose escalation and tapered dose reduction)
	• Overall treatment period: 74 days
	• Standard care
Outcomes	• Primary study outcomes
	○ time to clinical recovery after treatment at 74 days
	■ resolution from fever
	■ return of respiratory rate to normal (≤ 20 per min)
	■ cough remission
	• Relevant review outcomes planned
	○ clinical status
	○ quality of life
	• Secondary outcomes
	○ maximum symptom severity at 14 and 28 days
	○ clinical progression at 14 and 28 days
	○ time to meaningful recovery at 14 and 28 days
Starting date	18 January 2021
Contact information	andrea.fekete@sigmadrugs.com
Notes	• Recruitment Status: recruiting
	• Prospective completion date: August 2022
	• Date last update was posted: 27 September 2021
	• Sponsorship/funding source: Sigma Drugs Research Ltd

NCT04885530

Study name	ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications
Methods	• Trial design: randomised, double-blind, placebo-controlled
	• Type of record: trial register entry and published protocol
	• Sample size: 15000
	• Setting: non-hospitalised, outpatients
	• Country: USA
	• Language: English
	• Number of centres: 74
	• Trial registration number: NCT04885530
	• Date of trial registration: 13 May 2021

NCT04885530 *(Continued)*

Participants	**Inclusion criteria** • Adults aged ≥ 30 years old • PCR confirmed SARS-CoV-2 infection or antigen test collected within 10 days of screening • Two or more current symptoms of acute infection for ≤ 7 days **Exclusion criteria** • Prior diagnosis of COVID-19 infection • Current or recent hospitalisation • Known allergy/sensitivity or any hypersensitivity to components of the study drug or placebo • Known contraindications to study drugs, including prohibited concomitant medications

Interventions	**Details of intervention**
	
	• Eligible patients shall be randomised to receive one of 3 antibiotics:
	  ○ ivermectin (7 mg): prespecified number of tablets for 3 consecutive days based on weight for a daily dose of approximately 300 to 400 µg per kg
	  ○ fluvoxamine: 50 mg twice a day for 10 days
	  ○ fluticasone: 200 µg (1 blister) once daily for 14 days
	• Route of administration: oral
	
	Treatment details of control group (e.g. dose, route of administration)
	
	• Placebo doses matched to respective study drug

Outcomes	• Primary study outcomes
	  ○ number of hospitalisations at 14 days
	  ○ number of deaths at 14 days
	  ○ number of symptoms at 14 days
	• Relevant review outcomes planned
	  ○ clinical status
	  ○ quality of life
	  ○ symptom resolution
	  ○ hospitalisation
	• Secondary outcome
	  ○ number of deaths at 28 days
	  ○ number of symptom resolution at 28 days
	  ○ change in quality of life
	  ○ composite score of hospitalisations, urgent care visits, and emergency room visits at 28 days

Starting date	13 May 2021
Contact information	sybil.wilson@duke.edu, and april.ray@duke.edu
Notes	• Recruitment Status: recruiting • Prospective completion date: December 2022 • Date last update was posted: 13 May 2021 • Sponsorship/funding source: Susanna Naggie, MD

NCT05087381

Study name	Randomized-controlled Trial of the Effectiveness of COVID-19 Early Treatment in Community

NCT05087381 *(Continued)*

Methods	• Trial design: randomised, open-label • Type of record: trial register entry and published protocol • Sample size: 15000 • Setting: non-hospitalised, outpatients • Country: Thailand • Language: English • Number of centres: 2 • Trial registration number: NCT05087381 • Date of trial registration: 21 October 2021
Participants	Inclusion criteria • Adults 18 years or older • Antigen Test Kit or PCR for SARS-CoV-2 positive patients with mild symptoms Exclusion criteria • Recovered (generally much improved and symptoms now mild or almost absent) • Clinician deems ineligible • Pregnancy and breastfeeding
Interventions	Details of intervention • Fluvoxamine • Fluvoxamine + bromhexine • Fluvoxamine + cyproheptadine • Route of administration: oral Treatment details of control group (e.g. dose, route of administration) • Standard care

Outcomes	• Primary outcomes
	  ○ hospital admission related to COVID-19 at 28 days
	  ○ time taken to self-report recovery
	  ○ progression to severe COVID-19
	  ○ mortality
	• Relevant review outcomes planned:
	  ○ clinical worsening
	  ○ quality of life
	  ○ symptom resolution
	  ○ hospitalisation
	  ○ mortality
	• Secondary outcomes
	  ○ change in respiratory viral clearance at 0, 7, 14 days
	  ○ time to resolution of fever

Starting date	21 October 2021
Contact information	Dhammika.L@chula.ac.th, Phatthranit.pha@mahidol.edu
Notes	• Recruitment Status: recruiting • Prospective completion date: March 2022 • Date last update was posted: 26 January 2022 • Sponsorship/funding source: Chulalongkorn University

TCTR20210615002

Study name	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
Methods	• Trial design: randomised, open-label • Type of record: trial register entry and published protocol • Sample size: 296 • Setting: outpatients • Country: Thailand • Language: English • Number of centres: 2 • Trial registration number: TCTR20210615002 • Date of trial registration: 14 June 2021
Participants	Inclusion criteria • Thai people aged 18 years or over • Confirmed COVID-19 • Asymptomatic COVID-19 • Nasopharyngeal swab or oropharyngeal swab Exclusion criteria • Respiratory tract symptoms compatible with a bacterial infection • Previous receiving anti-SARS-CoV-2 agents • Complete coronavirus vaccination • History of favipiravir or fluvoxamine allergy • Need oxygen therapy • Previous use of immunosuppressive agents, a corticosteroid, azathioprine, mycophenolate mofetil, cyclosporin, JAK inhibitor • Cannot home quarantine • Unable to receive enteral nutrition • Pregnancy or breastfeeding • Terminal illness, heart failure, end-stage renal disease • Taking the antibiotics, anti-inflammatory drugs, or herb within 48 hours • Depression or suicidal idea • Glaucoma • Receiving chemotherapy • Organ transplantation • Evidence of any respiratory viral infection other than coronavirus
Interventions	Details of intervention • Fluvoxamine + favipiravir: favipiravir 3600 mg in the initial day, then 1600 mg per day for 4 days, and fluvoxamine 100 mg per day for 10 days • Favipiravir: 3600 mg in the initial day then 1600 mg per day for 4 days • Fluvoxamine + favipiravir + dexamethasone: favipiravir 3600 mg in the initial day, then 1600 mg per day for 9 days, fluvoxamine 100 mg per day and dexamethasone 6 mg per day orally for 10 days • Favipiravir + dexamethasone: favipiravir 3600 mg in the initial day, then 1600 mg per day for 9 days, and dexamethasone 6 mg per day orally for 10 days • Route of administration: oral Treatment details of control group (e.g. dose, route of administration)

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TCTR20210615002 *(Continued)*

	• Standard care

Outcomes	• Primary outcome
	  ○ clinical deterioration in moderate COVID-19
	  ○ clinical deterioration in moderate COVID-19 (pneumonia)
	• Relevant review outcomes planned
	  ○ clinical worsening
	  ○ quality of life
	  ○ symptom resolution
	  ○ hospitalisation
	  ○ mortality
	  ○ adverse events (any grade)
	  ○ viral clearance
	• Secondary outcomes
	  ○ duration from initial treatment to clinical deterioration
	  ○ changing of inflammatory marker at 0, 2, 5, 14 days
	  ○ adverse events at any time

Starting date	16 June 2021
Contact information	taweegrit.sir@pccms.ac.th.
Notes	• Recruitment status: pending • Prospective completion date: none • Date last update was posted: 15 June 2021 • Sponsorship/funding source: Chulabhorn Royal Academy

COVID-19: Coronavirus Disease 2019; JAK: Janus Kinase; PCR: Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

RISK OF BIAS

Legend: ✅ Low risk of bias   ❌ High risk of bias   〜 Some concerns

Risk of bias for analysis 1.1 All-cause mortality (at day 28)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Lenze 2020	✅	✅	❌	✅	✅	❌
TOGETHER 2021	✅	✅	✅	✅	✅	✅

Risk of bias for analysis 1.2 All-cause hospital admission or death (before hospital admission)

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Lenze 2020	✅	✅	✅	✅	✅	✅
TOGETHER 2021	✅	✅	✅	✅	✅	✅

Risk of bias for analysis 1.3 Serious adverse events

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Lenze 2020	✅	✅	❌	❌	✅	❌
TOGETHER 2021	✅	✅	✅	❌	✅	❌

Risk of bias for analysis 1.4 Adverse events (any grade)

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Lenze 2020	✅	✅	❌	❌	✅	❌
TOGETHER 2021	✅	✅	✅	❌	✅	❌

DATA AND ANALYSES

Comparison 1. Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality (at day 28)	2	1649	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.38, 1.27]
1.2 All-cause hospital admission or death (before hospital admission)	2	1649	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.16, 1.89]
1.3 Serious adverse events	2	1649	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.15, 2.03]
1.4 Adverse events (any grade)	2	1649	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.82, 1.37]

Analysis 1.1. Comparison 1: Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19, Outcome 1: All-cause mortality (at day 28)
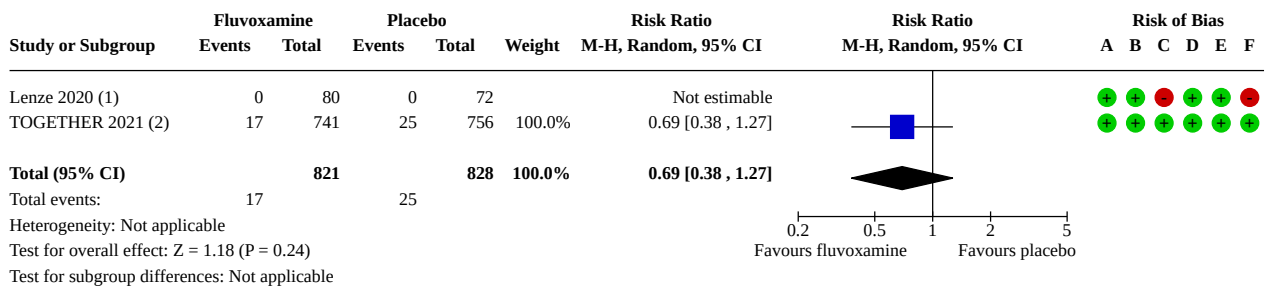
Study or Subgroup	Fluvoxamine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lenze 2020 (1)	0	80	0	72		Not estimable
TOGETHER 2021 (2)	17	741	25	756	100.0%	0.69 [0.38 , 1.27]
Total (95% CI)		821		828	100.0%	**0.69 [0.38 , 1.27]**
Total events:	17		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable

Favours fluvoxamine ← → Favours placebo

Footnotes
(1) Patient recruitment between 04/2020 and 08/2020. No vaccination was available at this time.
(2) Participant recruitment between January 2021 and August 2021. Vaccination was introduced during this time (6% of entire study population received at least 1 vaccine).

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19, Outcome 2: All-cause hospital admission or death (before hospital admission)

Study or Subgroup	Fluvoxamine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Lenze 2020 (1)	1	80	5	72	23.5%	0.18 [0.02 , 1.50]		+ + + + + +
TOGETHER 2021 (2)	76	741	99	756	76.5%	0.78 [0.59 , 1.04]		+ + + + + +
Total (95% CI)		**821**		**828**	**100.0%**	**0.55 [0.16 , 1.89]**		
Total events:	77		104					

Heterogeneity: Tau² = 0.49; Chi² = 1.82, df = 1 (P = 0.18); I² = 45%

Test for overall effect: Z = 0.94 (P = 0.35)

Test for subgroup differences: Not applicable

Favours fluvoxamine   Favours placebo

Footnotes

(1) Participant recruitment between April 2020 and August 2020. No vaccination was available at this time.

(2) Participant recruitment between January 2021 and August 2021. Vaccination was introduced during this time (6% of entire study population received at least 1 vaccine).

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

Analysis 1.3. Comparison 1: Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19, Outcome 3: Serious adverse events

Study or Subgroup	Fluvoxamine Events	Total	Standard care/placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Lenze 2020 (1)	1	80	5	72	25.0%	0.18 [0.02 , 1.50]		+ + − − + −
TOGETHER 2021 (2)	77	741	96	756	75.0%	0.82 [0.62 , 1.09]		+ + + − + −
Total (95% CI)		**821**		**828**	**100.0%**	**0.56 [0.15 , 2.03]**		
Total events:	78		101					

Heterogeneity: Tau² = 0.56; Chi² = 1.93, df = 1 (P = 0.16); I² = 48%

Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable
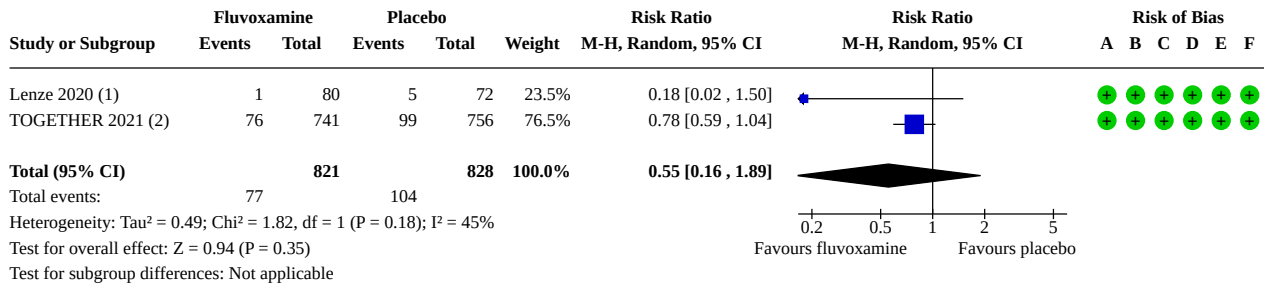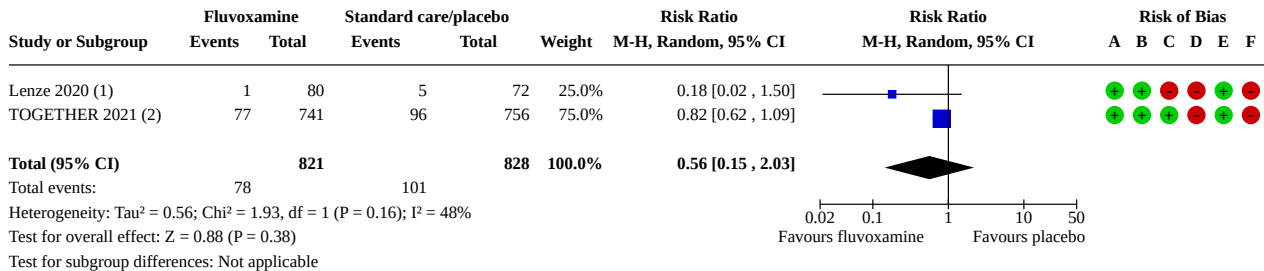
Favours fluvoxamine   Favours placebo

Footnotes

(1) Patient recruitment between 04/2020 and 08/2020. No vaccination was available at this time.

(2) Participant recruitment between January 2021 and August 2021. Vaccination was introduced during this time (6% of entire study population received at least 1 vaccine).

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

Analysis 1.4. Comparison 1: Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19, Outcome 4: Adverse events (any grade)
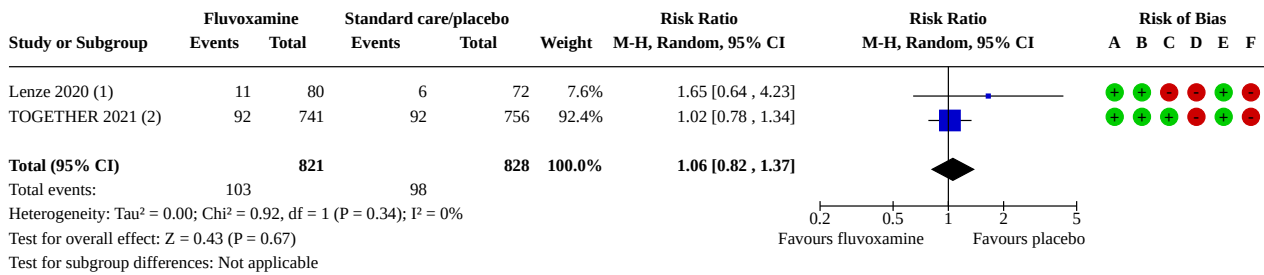
Study or Subgroup	Fluvoxamine Events	Total	Standard care/placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Lenze 2020 (1)	11	80	6	72	7.6%	1.65 [0.64 , 4.23]		+ + – – + –
TOGETHER 2021 (2)	92	741	92	756	92.4%	1.02 [0.78 , 1.34]		+ + + – + –
Total (95% CI)		**821**		**828**	**100.0%**	**1.06 [0.82 , 1.37]**		
Total events:	103		98					

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
Favours fluvoxamine   Favours placebo

Footnotes
(1) Participant recruitment between April 2020 and August 2020. No vaccination was available at this time.
(2) Participant recruitment between January 2021 and August 2021. Vaccination was introduced during this time (6% of entire study population received at least 1 vaccine).

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Author communication

Study ID	Date of request and question of the authors' of this review	Date when feedback was received and author response provided
Lenze 2020	9 June 2022: Question regarding the outcome 'all-cause hospitalisation', which is mentioned in the primary study, but definite numerical data were missing.	9 June 2022: Numbers for all-cause hospitalisation: 1 participant in the fluvoxamine and 5 participants in the placebo group.
TOGETHER 2021	27 January 2022: Question regarding the outcome 'symptom resolution' which is mentioned in the primary study, but definite numerical data are not reported.	Feedback was not provided.

Communications are listed after considering communication date

Table 2. Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19

Outcomes	Effect estimate (95% CI)	N of participants (studies)	Fluvoxamine n/N	Placebo n/N	Measures of heterogeneity	Comment
Need for invasive mechanical ventilation	RR: 0.77 (0.45 to 1.30)	1497ᵃ(1)	26/741 (3,5%)	34/756 (4,5%)	NA	TOGETHER 2021 no significant difference
Need for non-invasive mechanical ventilation or high flow (ventilator support)	AD: 0.00 (-8.41 to 0.49)	152 (1)	0/80 (0%)	0/72 (0%)	NA	Lenze 2020

Table 2.   Fluvoxamine plus standard care compared to placebo plus standard care for outpatients with mild COVID-19 *(Continued)*

						no significant difference
Need for hospitalisation (with oxygen therapy by masks or nasal prongs)	AD: -4.21 (-13.22 to 2.04)	152 (1)	0/80 (0%)	3/72 (4.2%)	NA	Lenze 2020 no significant difference
Viral clearance (assessed with RT-PCR) at day 7	OR: 0.67 (0.42 to 1.06)	428[b] (1)	40/207 (19%)	58/221 (26%)	NA	TOGETHER 2021 no significant difference

AD: absolute difference; n: number of events; N: number of participants; NA: not applicable; OR: odds ratio; RR: relative risk; RT-PCR: reverse transcription-polymerase chain reaction
[a] Number of participants hospitalised.
[b] Number of participants available for outcome assessment.

APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register

fluvoxamin* or luvox* or floxyfral* or fevarin* or faverin* or fluvoxadura* or dumirox* or desiflu*

Web of Science (Core Collection) – Science Citation Index and Emerging Sources Citation Index

#1 TI=((COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2"))) OR AB=((COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#2 (TI=((fluvoxamin* or luvox* or floxyfral* or fevarin* or faverin* or fluvoxadura* or dumirox* or desiflu*))) OR AB=((fluvoxamin* or luvox* or floxyfral* or fevarin* or faverin* or fluvoxadura* or dumirox* or desiflu*))

#3 #1 AND #2

WHO COVID-19 Global literature on coronavirus disease

(fluvoxamin* or luvox* or floxyfral* or fevarin* or faverin* or fluvoxadura or dumirox* or desiflu*)

CONTRIBUTIONS OF AUTHORS

John Nyirenda (JN)*: search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies; analysis of data; assessment of the certainty in the body of evidence; writing and proofreading of the review.

Mario Sofroniou (MSo)*: conception of the review; interpretation of data; writing and proofreading of the review.

Ingrid Toews (IT): conception of the review; search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies; assessment of the certainty in the body of evidence, writing and proofreading the review.

Agata Mikolajewska (AMi): conception of the review; interpretation of data; writing and proofreading of the review.

Cornelius Lehane (CL): interpretation of data and proofreading the review.

Ina Monsef (IM): search strategy design; running the searches and writing the review.

Aesha Abu-taha (AA): search and selection of studies for inclusion in the review.

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Miriam Stegemann (MSt): conception of the review; interpretation of data; writing and proofreading of the review.

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*Shared first authorship.

DECLARATIONS OF INTEREST

John Nyirenda (JN): has no known conflicts of interest to declare.

Mario Sofroniou (MSo): has no known conflicts of interest to declare.

Ingrid Toews (IT): has no known conflicts of interest to declare.

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Christine Schmucker (CS): has no known conflicts of interest to declare.

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- Federal Ministry of Education and Research, Germany

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no changes between the initial review protocol and the final review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Clinical Deterioration; *COVID-19 Drug Treatment; Fluvoxamine [pharmacology] [therapeutic use]; Randomized Controlled Trials as Topic; Selective Serotonin Reuptake Inhibitors [therapeutic use]

MeSH check words

Humans