



Fluvoxamine for the Early Treatment of SARS-CoV-2 Infection: A Review of Current Evidence

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Abstract

SARS-CoV-2 infection causes COVID-19, which frequently leads to clinical deterioration and/or long-lasting morbidity. Academic and governmental experts throughout the USA met in 2021 to discuss the potential for use of fluvoxamine as early treatment of SARS-CoV-2 infection. Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is a strong sigma-1 receptor agonist, and this may effectively reduce cytokine production, preventing clinical deterioration. This repurposed psychiatric medication has a well-known safety record, is inexpensive, easy to use, and widely available, all of which are advantages during this global COVID-19 pandemic. At the meeting, experts reviewed the existing published literature on the use of fluvoxamine as experimental COVID-19 treatment, as well as prior research on the potential mechanisms for anti-inflammatory effects of fluvoxamine, including for other conditions including sepsis. Investigators shared current trials underway and existing gaps in knowledge. Two randomized controlled trials and one observational study examining the effect of fluvoxamine in COVID-19 treatment have found high efficacy. Four larger randomized clinical trials are currently underway, including three in the USA and Canada. More data are needed on dosing and mechanisms of effect; however, fluvoxamine appears to have substantial potential as a safe and widely available medication that could be repurposed to ameliorate serious COVID-19-related morbidity and mortality. As of April 2021, fluvoxamine was mentioned in the NIH COVID-19 treatment guidelines, although no recommendation is made for or against use. Available data may warrant clinician discussion of fluvoxamine as a treatment option for COVID-19, using shared decision making.

Key Points

Fluvoxamine appears to have potential as a safe, inexpensive, and widely available medication that could be effectively repurposed to ameliorate serious COVID-19-related morbidity and mortality.

Fluvoxamine prevented clinical deterioration and long-lasting symptoms related to COVID-19 in initial studies and one large clinical trial, with several large clinical trials underway globally.

Current information may warrant clinician discussion of fluvoxamine as a treatment option for COVID-19, using shared decision making.

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1 Introduction

SARS-CoV-2 infection causes coronavirus disease 2019 (COVID-19), which frequently leads to clinical deterioration around the second week of illness [1, 2], and/or long-lasting morbidity after initial infection [3, 4]. While some treatment options have come to light for those who have already progressed to severe disease, increasingly there are calls for discovery of effective early treatments that can prevent clinical deterioration and/or long-term morbidity in the first place [5].

Evidence is steadily accumulating that points to the role of excessive immune response in SARS-CoV-2 infection as a key factor in clinical deterioration or long-term symptoms. A leading theory is that SARS-CoV-2 replicates in an intermediate compartment between the endoplasmic reticulum (ER) and Golgi complex, leading to ER stress and increased cytokine production causing an excessive inflammatory response [6]. In late 2020, Gordon and colleagues [7] identified that knockout or knockdown of *SIGMAR1* gene, which encodes the sigma-1 receptor (S1R), caused substantial reduction in SARS-CoV-2 replication. The S1R is already well established as influencing the pathophysiology of multiple psychiatric, neurodegenerative, and central nervous system disorders [8–12]. The findings of Gordon and colleagues, along with prior research indicating a potential role for S1R ligands in preventing sepsis—also associated with excessive inflammatory cytokine production [13]—has led to an interest in exploring the potential for the repurposing of existing drugs that target the S1R as early treatment for SARS-CoV-2 infection.

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that has been widely used globally since the 1990s. Previous studies have shown high affinity for the S1R [14], and in multiple comparative studies fluvoxamine has been consistently ranked as one of the most potent S1R agonists clinically available [6, 10, 15]; therefore, it may effectively reduce cytokine production and prevent clinical deterioration. It is inexpensive, easy to use, widely available globally, and highly lipophilic, with rapid intracellular uptake into lung epithelial cells [16].

1.1 Safety Profile

Fluvoxamine has a well-known safety profile [17, 18], with nausea as the most common adverse event. In a global database of 35,368 people who had taken fluvoxamine across 66 studies in 11 countries, nausea was reported in 15.7% of patients, followed by somnolence (6.4%), asthenia (5.1%), headache (4.8%), and dry mouth (4.8%). Serious adverse events occurred in approximately 2.0% of people who were taking this medication for a psychiatric disorder, with 1.6%

requiring hospitalization and < 0.4% experiencing another serious adverse event, including a suicide attempt, depression, death, or accidental injury [17].

2 Current Evidence on Fluvoxamine as COVID-19 Treatment

Several studies have examined the efficacy of fluvoxamine for improvement in the clinical progression of SARS-CoV-2 infection or have explored the potential mechanisms by which fluvoxamine may have a beneficial effect as early COVID-19 treatment (Table 1). In a small randomized clinical trial known as STOP COVID, participants were randomly assigned to receive 100 mg of fluvoxamine ($n = 80$) or placebo ($n = 72$) up to three times per day, for 15 days [1]. Lenze and colleagues hypothesized that fluvoxamine would prevent clinical deterioration if prescribed early in COVID-19 (i.e., within 7 days of symptoms onset). All participants were aged ≥ 18 years, were not already hospitalized or living in an institutional setting (but were self-isolated per public health guidance), and had diagnosed, symptomatic SARS-CoV-2 infection, with symptoms onset of a median of 4 days prior to enrollment (interquartile range, 3–5; maximum 7 days). The primary endpoint of this study was clinical deterioration, as defined by both (1) presence of dyspnea (i.e., shortness of breath) or hospitalization for dyspnea or pneumonia, and (2) presence of hypoxia with pulse oxygen saturation < 92% on room air. At study completion, none (0%) of the 80 participants receiving fluvoxamine met the criteria for clinical deterioration, but 6 (8.3%) of the 72 participants receiving placebo deteriorated clinically (absolute difference from survival analysis 8.7%, 95% CI, 1.8% to 16.4%; log-rank $p = 0.009$). Despite the high dose of fluvoxamine administered during this trial, only one serious adverse event occurred, of a person with no respiratory deterioration, hospitalized for dehydration. Overall, 11 other adverse events occurred in the treatment group; the placebo group had 6 serious adverse events (all hospitalizations for COVID-19) and 12 other adverse events, including higher reports of pneumonia and gastrointestinal symptoms.

Inspired by the newly published results from Lenze and colleagues, during a large occupational outbreak of COVID-19 in late 2020, Seftel and Boulware conducted a real-world observational study of early SARS-CoV-2 treatment with fluvoxamine [19]. A total of 113 people in a work-associated congregate living environment were offered fluvoxamine on the same day that they tested positive for SARS-CoV-2. Testing used a rapid antigen test during one of three rounds of mass testing during the outbreak, regardless of symptoms. Participants could choose whether or not to accept the medication, given the limited data in support of its use for this purpose. A total of 65 people (57.5%) opted for treatment

Table 1 Key characteristics of completed studies on fluvoxamine for treatment of SARS-CoV-2 infection

| Study, first author [references] | Design | Sample size | Intervention | Study population and inclusion criteria | Duration | Findings |
|----------------------------------|---|-------------|---|--|----------|---|
| Lenze [1] | Randomized controlled trial (participants were randomized 1:1 to a fluvoxamine arm or a placebo arm) | 152 | Fluvoxamine 100 mg, 3x/day × 14 days | Aged ≥ 18, not hospitalized or living in an institutional setting, diagnosed, symptomatic SARS-CoV-2 infection < 7 days from symptoms onset | 15 days | Zero (0%) of the participants receiving fluvoxamine met the criteria for clinical deterioration (dyspnea and hypoxia) within 15 days, but 6 (8.3%) of the participants receiving placebo deteriorated clinically (absolute difference of 8.7%, 95% CI 1.8 to 16.4%) 65 people opted into fluvoxamine treatment; at 14 days, 0% (0/65) of those receiving fluvoxamine had been hospitalized for clinical deterioration, and 12.5% (6/48) of those declining treatment had been hospitalized ($p = 0.005$). By Day 14, 0% (0/65) of those in the fluvoxamine group reported ongoing symptoms related to COVID-19, whereas 60% (29/48) of those receiving no treatment reported symptoms ($p < 0.001$), with 21% (10/48) reporting ≥ 5 ongoing symptoms at 14 days |
| Seftel [19] | Observational cohort (participants were given a free choice of fluvoxamine treatment same day as diagnosis, or observation only) | 113 | Fluvoxamine 50–100 mg load, then 50 mg 2x/day × 14 days | Workers with a congregate living environment during a mass outbreak of COVID-19; patients tested positive for SARS-CoV-2 during mass testing | 14 days | |
| Reis [21] | Phase III: quadruple-blind randomized controlled trial (participants randomized 1:1:1 to treatment with fluvoxamine, metformin HCL, ivermectin, or placebo) | 3323 | Fluvoxamine 100 mg, 2x day × 10 days | Brazil. Aged > 18, positive SARS-CoV-2 test, acute flu-like symptoms for < 7 days, and at least one of the following: aged > 50, diabetes mellitus requiring oral medication or insulin, systemic arterial hypertension requiring at least one medication for control, known cardiovascular disease (e.g. heart failure, congenital heart disease, cardiomyopathies), symptomatic lung disease (emphysema or chronic bronchitis), symptomatic asthma requiring chronic use of agents for symptoms control, smoking, body mass index > 30 kg/m ² body weight, organ transplant, stage IV chronic kidney disease or need for dialysis, immunosuppression or receiving corticosteroid therapy equivalent to ≥ 10 mg of prednisone/day, history of cancer in the last 5 years or currently undergoing cancer treatment, or SARS-CoV-2 vaccination | 28 days | Primary endpoints were: (1) rate of emergency visits with observation unit stay > 6 h, and (2) rate of hospitalization due to lower respiratory tract infection related to COVID-19 Secondary endpoints included: (1) change in viral load on Days 3 and 7 after randomization, (2) time to clinical improvement (self-reported improvement > 50% compared to baseline symptoms), (3) time to hospitalization due to progression of COVID-19, (4) number of days with respiratory symptoms since randomization, (5) rate of all-cause hospitalizations, (6) rate of COVID-19-related hospitalizations, (7) rate of all-cause mortality, (8) rate of cardiovascular death, (9) rate of respiratory death, (10) rating on the PROMIS Global-10 Scale [28], (11) rating on the WHO Clinical Progression Scale [29], (12) rate of adverse events, and (13) percent adherence to study drug |

with a 50–100 mg loading dose of fluvoxamine, followed by 50 mg twice daily (50 mg was a lower dose than the Lenze trial), and 48 (42.5%) opted for observation alone. Participants received in-person follow-up at 7 and 14 days, with 100% retention. At 14 days, no patients receiving fluvoxamine had been hospitalized for clinical deterioration; however, 12.5% (6/48) of patients who declined treatment had been hospitalized ($p = 0.005$). Notably, by Day 14, 0% (0/65) of those in the fluvoxamine group reported ongoing symptoms related to SARS-CoV-2 infection, whereas 60% (29/48) of those receiving no treatment reported symptoms ($p < 0.001$), with 21% (10/48) reporting five or more ongoing symptoms at 14 days.

Most recently, investigators from the TOGETHER trial in Brazil published results of their Phase III clinical trial. The trial comprised four treatment arms aimed to evaluate the effect of various medications to reduce the need for emergency care requiring observation for > 6 h due to the worsening COVID-19, and/or hospitalization due to COVID-19-related lower respiratory tract infection. Adults with a positive SARS-CoV-2 test, acute flu-like symptoms for < 7 days, and at least one enhancement factor (e.g., older age, diabetes mellitus, immunosuppression, etc.) were randomized to 10 days of treatment in one of four treatment arms: fluvoxamine (100 mg twice daily), metformin, ivermectin, or placebo. At the second interim analysis in April 2021, metformin was dropped, yet fluvoxamine was retained [20], and on August 6, 2021, the trial arms were stopped for superiority of fluvoxamine, with a total of 3323 patients enrolled. The relative risk (RR) of hospital admission or emergency room observation for more than 6 hours was determined to be 0.68 (95% Bayesian Credible Interval [BCI] 0.52–0.88) for participants receiving fluvoxamine versus the placebo control in the intention-to-treat sample. In a per-protocol analysis of participants who were adherent to at least 80% of pills, fluvoxamine was effective against both deterioration and mortality, with an RR of 0.34 for hospitalization (95% BCI 0.21–0.54) and an odds ratio of 0.09 (95% CI 0.01–0.47) for mortality [21].

Further study is needed to investigate potential anti-viral and anti-inflammatory, and other mechanisms of fluvoxamine in the context of SARS-CoV-2 infection. One theory of its mechanism of action is a reduction in the ER stress response and reduction in cytokine production as a result of sigma-1 activation, given fluvoxamine's potency as a S1R agonist. The S1R is an ER chaperone protein that regulates the ER stress response as well as production of cytokines in response to infection and other inflammatory triggers; S1R agonists prevent Inositol Requiring Enzyme 1 α (IRE1) from activating X-Box Binding Protein-1 (XBP-1) mRNA, therefore regulating the ER stress response, and reducing cytokine production [13]. In a recent study of affinity of various antidepressant drugs for the S1R in rat brains, Ishima

and colleagues found that fluvoxamine was the most potent S1R agonist among ten different antidepressants tested [14]. In a 2019 study of fluvoxamine's effectiveness in preventing lethal septic shock in mice, Rosen and colleagues found that only 9% of wild-type (WT) mice died after injection with lipopolysaccharide (LPS), known to rapidly induce pro-inflammatory cytokines in mice and humans, compared to 62% of mice with sigma-1 knockout (KO). Similar results were found after infection with fecal slurry (1 g/kg of body-weight), which resulted in septic shock and death in substantially more of the S1R KO mice than WT mice ($p < 0.05$). However, in the presence of an IRE1 inhibitor, survival rates of S1R KO mice and WT mice were similar, further demonstrating the potential mechanistic effects of S1R agonism to dampen inflammatory response [13].

Rather than just anti-inflammatory effects, another possible mechanism of fluvoxamine's effect is antiviral properties through lysosomotropic effects [22]. Cationic amphiphilic drugs (CADs) such as fluvoxamine tend to accumulate in the lysosomes, altering the pH, interfering with viral proteins that accumulate, and/or preventing mature virus from using lysosomes to escape the cell, which is one characteristic of coronaviruses [23]. It is also possible that lysosomotropic antidepressants may interfere with viral entry through inhibition of acid sphingomyelinase activity [24]. Functional inhibitors of acid sphingomyelinase (FIASMs) prevent sphingomyelin from being converted to ceramide, which makes it more difficult for a virus like SARS-CoV-2 to enter the cell [25].

Others have theorized that the inhibition of platelet aggregation and mast cell degranulation may be likely mechanisms of action [26, 27]. SSRIs like fluvoxamine have been shown to decrease platelet aggregation and increase bleeding time. Since hyperactive platelets can release excessive serotonin, and serotonin clearance requires healthy pulmonary endothelium, beginning SSRIs early in SARS-CoV-2 infection—before the pulmonary endothelium is damaged by COVID-19—may prevent the effect of potentially damaging platelet hyperactivation, inflammatory thrombosis, and platelet serotonin storm, therefore reducing the risk of a hyperserotonergic state leading to acute respiratory distress [26, 27]. Furthermore, SSRIs decrease histamine release from human mast cells, and reduce mRNA levels of protease-1 in mast cells; this is important, as postmortem lung biopsies of patients with COVID-19 have linked activated mast cells to pulmonary thromboses and edema [26].

3 Additional Studies Underway

On December 17, 2020, Lenze and colleagues began a new nationwide, fully remote (internet-based) Phase III randomized controlled trial named STOP COVID 2

(StopCovidTrial.com; ClinicalTrials.gov: NCT04668950) to confirm the initial results from their preliminary trial. This trial is taking place in the USA and Canada, with nation-wide internet-based enrollment and telemedicine appointments for all study interactions. The preliminary trial (STOP COVID) resulted in few cases of clinical deterioration overall due to limited sample size and relatively young and healthy participants, resulting in low precision of the effect size estimate [1]. STOP COVID 2 aimed to recruit 1100 participants with eligibility criteria similar to the first trial (SARS-CoV-2 positive and symptomatic within 7 days of symptoms onset, residing in the community rather than in a hospital or other institutional setting); however, in this trial the sample was enriched, with participants needing to have one or more of the following risk factors for more severe COVID-19: aged ≥ 40 years, obesity, diabetes, hypertension, heart disease, lung disease, an immune condition, and/or being African American, Latinx, or Native American.

On May 19, 2021, STOP COVID 2 stopped enrolling new participants on the advice of the Data and Safety Monitoring Board, based on an overall lower rate of clinical deterioration than anticipated (leading to a much larger sample size necessary to observe the *a priori* minimum detectable effect), the decreasing number of volunteers enrolling in the trial, and their review of the unblinded interim results to date. There were no adverse safety signals, but due to successful vaccination roll-out in the USA and Canada, the trial was no longer expected to accrue the needed number of participants. Participants already enrolled in the trial finished their assigned doses of therapy and will complete the planned follow-up questionnaires at 15 and ~90 days to assess short- and long-term secondary outcomes. This trial has the same duration and primary outcome as the initial trial (clinical deterioration within 15 days of enrollment, defined by dyspnea and hypoxia), but has lower dosing: 100 mg twice/day, instead of three times daily for 15 days, of either fluvoxamine or placebo. With enrollment halted, the trial will not have the required sample size and statistical power to detect an effect of fluvoxamine on the primary outcome. However, this trial also includes a secondary outcome of health functioning and symptoms assessed at 15 days and again at 3 months, measured by the Global Health Scale [28], and an exploratory symptom questionnaire to assess any effect of fluvoxamine on long-term COVID-19 morbidity.

In January 2021, Drs Bramante, Boulware, and colleagues at the University of Minnesota; Northwestern University; University of Colorado, Denver; UCLA Olive View; and OptumLabs began stage 1 of a Phase III, factorial randomized clinical trial known as COVID-19-OUT (covidout.com; ClinicalTrials.gov: NCT04510194). The initial stage of the quadruple-blinded trial enrolled 70 patients, with the fully enrolled trial having a planned 1160 participants. This

factorial trial has five experimental arms (fluvoxamine only, metformin only, ivermectin only, metformin plus fluvoxamine, or metformin plus ivermectin), with one placebo arm. Adults aged 30 to 85 years are eligible for inclusion within ≤ 3 days of a positive PCR test for SARS-CoV-2 infection if they are asymptomatic or have had symptoms for < 7 days before randomization, enroll within 3 days of testing, have a body mass index ≥ 25 kg/m² by self-report height/weight or ≥ 23 kg/m² for patients who self-identify as South Asian or Latinx. A glomerular filtration rate (GFR) will be obtained in persons older than age 75 years or who have a history of heart, kidney, or liver failure if a GFR is not visible within the electronic health record within 2 weeks, to ensure these high-risk individuals have a GFR > 45 mL/min. The primary outcome measures are (1) decreased oxygenation at 14 days (defined as pulse oxygen saturation ≤ 93 % on home monitoring), (2) emergency department utilization for COVID-19 symptoms at 14 days (and/or hospitalization/death), and (3) post-acute sequelae of SARS-CoV-2 infection (PASC) assessment at 6 and 12 months. This trial is currently enrolling.

Another trial also enrolling is ACTIV-6 (ClinicalTrials.gov: NCT04885530), which is a Phase III, placebo-controlled, randomized trial, run by Dr. Naggie at Duke Clinical Research Institute. This trial has three experimental arms (ivermectin, fluvoxamine, and fluticasone), with a placebo comparator arm matched to each experimental arm. Both participants and the study teams know which study drug they have been allocated but are blinded to whether they are in the experimental or placebo comparator arms for that study drug. Adults aged ≥ 30 years with SARS-CoV-2 infection confirmed within 10 days of study screening with two or more current symptoms of acute SARS-CoV-2 infection (fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, or new loss of sense of taste or smell) began enrolling in this study on June 8, 2021, with a goal of enrolling 15,000 participants before a primary completion date of December 2022. The primary outcome measures of this trial are the number of hospitalizations, number of deaths, and number of symptoms within 14 days, as measured by patient reports.

Finally, another randomized controlled trial of fluvoxamine and COVID-19 is underway in Hungary: SigmaDrugs Research Ltd. is currently recruiting for a Phase II trial (ClinicalTrials.gov: NCT04718480), studying the time to clinical recovery after treatment with 74 days of fluvoxamine 100 mg taken twice daily, compared to placebo. Up to 100 adults who have moderately severe cases of COVID-19 (having each of the following: dyspnea without respiratory distress, a respiration rate 22–29 times per minute, resting pulse oxygen saturation ≥ 93 %, and pneumonia with pulmonary infiltrates occupying ≤ 50 % of the lung-fields) will be enrolled. The primary endpoint of clinical recovery includes

Table 2 Key characteristics of studies in progress on fluvoxamine for treatment of SARS-CoV-2 infection, Sept 2021

| Study, PI | Design | Sample size | Intervention | Study population and inclusion criteria | Duration | Endpoints |
|---|--|---|---|--|----------------------|---|
| STOP COVID 2, Lenze (NCT04668950) | Phase III: triple-blind, fully remote (internet-based) randomized controlled trial (participants randomized 1:1 to a fluvoxamine arm or a placebo arm) | 1100 (planned) 677 (actual at time trial enrollment was stopped) | Fluvoxamine 100 mg, 2x/day x 14 days | USA and Canada Aged ≥ 18 , not hospitalized or living in an institutional setting, diagnosed, symptomatic SARS-CoV-2 infection < 7 days from symptoms onset, one or more of the following risk factors: aged ≥ 40 , obesity, diabetes, hypertension, heart disease, lung disease, an immune condition, and/or being African American, Latinx, or Native American | 15 days/ 3 months | Primary endpoint is clinical deterioration, defined by both (1) dyspnea or hospitalization and (2) hypoxia with oxygen saturation < 92% Secondary endpoint is function by the PROMIS Global Health Scale [28], assessed at 15 days and 3 months |
| Fluvoxamine Administration in Moderate SARS-CoV-2 Infected Patients, Fekete (NCT04718480) | Phase II: quadruple-blind randomized controlled trial (participants randomized 1:1 to a fluvoxamine arm or a placebo arm) | 100 | Fluvoxamine 100 mg, 2x/day x 74 days | Hungary. Aged 18–70, hospitalized with confirmed SARS-CoV-2, with moderate symptoms (dyspnea without respiratory distress, respiration rate 22–29 times per minute, resting pulse oxygen saturation $\geq 93\%$, and pneumonia on medical imaging with pulmonary infiltrates occupying $\leq 50\%$ of the lung-fields) | 74 days | Primary endpoint is time to clinical recovery after treatment, defined as having any three of the following four items: (1) fever resolution for at least 48 hours with antipyretics, (2) respiration rate ≤ 20 /min, (3) pulse oxygen saturation $\geq 95\%$ on room air, and (4) any reduction on the cough-burden visual analogue scale, compared to baseline |
| COVID-19-OUT, Bramente (NCT04510194) | Phase III: quadruple-blind, factorial randomized controlled trial (participants randomized 1:1 to one of five treatment arms or a placebo arm) | 1160 | Fluvoxamine 50 mg, 2x/day x 14 days, with or within 1500 mg daily of metformin depending on arm Other arms include treatment with Ivermectin and/or metformin) | USA nationwide; aged 30–85, not hospitalized or symptomatic > 7 days from randomization, body mass index ≥ 25 kg/m ² by self-report height/weight or ≥ 23 kg/m ² for patients who self-identify as South Asian or Latinx, and a glomerular filtration rate > 45 mL/min within 2 weeks for patients older than aged 75 years or who have a history of heart, kidney, or liver failure | 12 months | Primary endpoints are (1) decreased oxygenation at 14 days (defined as pulse oxygen saturation $\leq 93\%$ on home monitoring), (2) emergency department utilization for COVID-19 symptoms at 14 days, and (3) post-acute sequelae of SARS-CoV-2 infection (PASC) assessment at 6 and 12 months, to assess long COVID Secondary endpoints include (1) maximum symptom severity at 14 and 28 days, (2) maximum clinical support needed on the Clinical Progression Scale at 14 and 28 days, (3) time to meaningful recovery, and a series of laboratory outcomes on Days 1, 5, and 10 |

Table 2 (continued)

| Study, PI | Design | Sample size | Intervention | Study population and inclusion criteria | Duration | Endpoints |
|---|---|-------------|-------------------------------------|---|----------|--|
| ACTIV-6: COVID-19 Out-patient Randomized Trial to Evaluate Efficacy of Repurposed Medications (NCT04885530) | Phase III: double-blind randomized controlled trial (participants randomized 1:1:1:1:1 to treatment with ivermectin, fluvoxamine, fluticasone, or placebo comparators of each of these experimental arms) | 15,000 | Fluvoxamine 50 mg, 2x day x 10 days | U.S. nationwide; aged ≥ 30 years, not hospitalized currently or within 10 days of screening, or previously diagnosed with COVID-19 infection (> 10 days from screening). Must have SARS-CoV-2 infection confirmed within 10 days of screening, and two or more current symptoms of acute infection for at least 7 days (including fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, or new loss of sense of taste or smell | 29 days | Primary endpoints are: (1) number of hospitalizations, (2) number of deaths, and (3) number of symptoms, all within 14 days and as measured by patient reports Secondary endpoints include: (1) change in COVID Clinical Progression Scale [29], (2) Number of hospitalizations within 28 days, (3) Number of deaths within 28 days, (4) Number of symptom resolutions (first of at least 3 consecutive days without symptoms) within 28 days, (5) Change in quality of life as measured by the PROMIS-29 from baseline, day 7, 14, 28, and 29 [30], and (6) Composite score of hospitalizations, urgent care visits, and emergency room visits, within 28 days |

resolving to normal any three of the following four clinical indicators: fever, respiratory rate, pulse oxygen saturation, and cough burden. This study has an estimated completion date of December 2021.

Multiple studies of the mechanisms of fluvoxamine's effect on SARS-CoV-2 are also currently underway, including in vitro and animal studies at multiple institutions. Publication of findings from these pending studies is eagerly awaited, as they will offer meaningful contributions to our understanding of how and why early treatment with fluvoxamine may have a beneficial effect on COVID-19-related morbidity and mortality.

4 Knowledge Gaps and Challenges

The studies described above (Table 2) are designed to address two key gaps in knowledge, which must be better understood to inform widespread use of fluvoxamine as early treatment for COVID-19.

4.1 Efficacy

With publication of the TOGETHER trial results, along with the first STOP COVID trial, the efficacy of fluvoxamine for preventing clinical deterioration and/or long-term morbidity due to SARS-CoV-2 infection has been demonstrated in two randomized placebo-controlled trials. The extent of fluvoxamine's efficacy remains unclear; in both the STOP COVID and Seftel and Boulware studies, *no* participant who received fluvoxamine experienced the primary adverse outcome—respiratory deterioration (in the case of STOP COVID) or hospitalization (Seftel and Boulware)—for their COVID-19 infection, compared with 8.3% or 12.5% of participants in the control arm, respectively. Similarly, in the TOGETHER trial per-protocol analysis, the fluvoxamine arm was associated with a 66% reduction in clinical deterioration requiring hospitalization or extended emergency contact, and a 91% reduction in mortality [21]. In addition to these primary endpoints, the Seftel study also found that zero participants in the fluvoxamine group had ongoing symptoms at 14 days, compared to 60% of people in the control group; however, STOP COVID found no differences in short-term symptomatic recovery and saw some lingering symptoms reported after 4 months in both the fluvoxamine and placebo arms, although numbers were too small to allow for statistical comparisons. While mortality due to COVID-19 has received the most attention to date among the media and general public, both short-term and long-term morbidity from SARS-CoV-2 infection is a substantial burden worldwide.

Fig. 1 Recommendations for research activities

- **Clinical efficacy:** It is imperative that these promising preliminary results are challenged in a larger clinical trial, to test the robustness of these findings. Further studies are needed to collect serial cytokine and virologic data for patients randomized to fluvoxamine prescription compared to placebo, which will also further our understanding of how the drug may be working relative to the clinical outcomes observed in the existing studies. Fluvoxamine should also be tested later in the course of COVID-19, as it may be beneficial in preventing further deterioration in those already hospitalized, as has been shown with dexamethasone.
- **Dosing strategies:** The optimal dosing of fluvoxamine to maximize effect while minimizing toxicity is still under investigation. Particularly, further exploration is needed regarding the best methods for offering fluvoxamine to patients with SARS-CoV-2 infection if they are already taking a different SSRI. In the STOP COVID trial, people already on SSRIs are not excluded, but risk of serotonin syndrome is assessed on a case-by-case basis. Given the high prevalence of SSRI uptake in the U.S. and around the world, this will be an important consideration if the effects of fluvoxamine on SARS-CoV-2 prognosis persist in further studies.
- **Mechanisms of action:** The findings of the preliminary human studies of fluvoxamine are quite impressive, and the safety and logistical ease of fluvoxamine prescription early in SARS-CoV-2 infection is attractive. However, the mechanism of effect is not well understood, and more data is needed to understand why and how this repurposed medication appears to have such a substantial impact on COVID-19.

4.2 Mechanisms of Action

The anti-inflammatory effects of fluvoxamine are well understood, but the mechanism by which it could have such a strong effect on morbidity and mortality—especially without more clearly demonstrated anti-viral effects—is still unclear. The *in vitro* and animal studies currently underway will greatly improve our understanding of the biological effect of this drug, and further explore any potential for the prolongation of the viral phase of infection as a result of fluvoxamine's inhibition of the inflammatory response, which would warrant caution with its use. Since fluvoxamine seems to have anti-inflammatory and immune modulatory actions without substantial suppression of the immune response, it may be much safer to use in the earliest stages of COVID-19, as compared to systemic steroids.

5 Research Priorities and Future Directions

As of April 2021, fluvoxamine is now mentioned in the NIH COVID-19 treatment guidelines, although no recommendation is yet made for or against use, due to insufficient available evidence. Based on our review of the current evidence and studies in progress, there are several key research priorities (Fig. 1). In summary, fluvoxamine is seen as a highly promising drug for COVID-19, but more studies are needed to elucidate its mechanism of action and possible deleterious effects.

Declarations

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Competing interests Dr. Reiersen and Dr. Lenze are listed on a patent application related to methods of treating COVID-19, that was filed by Washington University in St. Louis. No other authors report any conflicts of interest.

Availability of data and material As this is a narrative review of available scientific evidence, all included data and material are available through the cited literature.

Code availability Not applicable.

Author contributions SNF: Overall synthesis of material and first draft of manuscript; AMR, EJM, DRB: conceptualization, curatorship of data and findings; JDK: conceptualization, project leadership, and funding. All authors read and approved the manuscript.

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