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Clinical Efficacy and Safety of Fluvoxamine in COVID-19 Patients: An Umbrella Review of Systematic Reviews and Meta-Analyses

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ABSTRACT

Introduction Fluvoxamine is an agonist for the sigma-1 receptor, through which it controls inflammation. It helps reduce the cytokine storm associated with the COVID-19 virus by regulating the production of IL-6 and gene expression. This review of systematic reviews (SRs) aims to summarize the effects of fluvoxamine in treatment of COVID-19.

Methods This umbrella review (CRD42025592203) of SRs and meta-analyses investigated the safety and efficacy of fluvoxamine for treatment in COVID-19 patients, irrespective of disease severity and age. Comprehensive searches were conducted from inception to December 12, 2024, covering PubMed, Cochrane CENTRAL, Google Scholar, and Cochrane COVID-19 resources. A qualitative synthesis of evidence was performed. The AMSTAR2 tool was used to assess the methodological quality of the included SRs.

Results Eleven reviews published in 12 publications that reported the use of fluvoxamine in COVID-19 patients were finally included as part of the synthesis. The studies reported a lower mortality rate with fluvoxamine than with placebo, but only four studies reported statistical significance. Five reported a statistically significant reduction in hospitalization risk for patients treated with fluvoxamine compared to controls. Only one review evaluated COVID-19 progression, reporting a non-significant decrease in the risk of disease progression with fluvoxamine compared to placebo. Higher dosages of fluvoxamine compared to lower doses yielded better outcomes.

Conclusion Although fluvoxamine may have potential benefits in reducing COVID-19-associated mortality and hospitalization, our findings do not support a significant role in preventing disease progression or clinical deterioration. Further research is needed to compare the efficacies of different dosages.

1. Introduction

The coronavirus disease 2019 (COVID-19) infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an acute respiratory syndrome that rapidly escalated into a global pandemic after first appearing in Wuhan, China, during late December 2019 [1]. Due to its highly contagious and severe nature, it has had a catastrophic impact, resulting in more than 6 million deaths globally [1]. To minimize its spread, various vaccines, including mRNA and inactivated vaccines, were developed in addition to preventive measures such as social distancing [2].

Supportive care, along with close monitoring of high-risk patients, remains the primary treatment approach for individuals with COVID-19 [3]. Antivirals and antimicrobials have also been considered as part of treatment plans; however, their effectiveness remains uncertain, as studies have shown mixed results [4].

Repurposed drugs are medications already approved by the Food and Drug Administration (FDA) for other indications that may be used in the management of COVID-19. Fluvoxamine is one of four FDA-approved medications being tested in the ACTIV-6 trial, owing to its affordability and accessibility, particularly in resource-limited settings [5]. Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI), commonly used to treat depression, anxiety disorders, and obsessive-compulsive disorder (OCD). It is being investigated as a potential treatment option for COVID-19 due to its anti-inflammatory properties [6]. One proposed mechanism is through

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fluvoxamine's interaction with the sigma-1 receptors (S1Rs). S1R is a multifunctional chaperone protein that plays an important role in cellular survival by mediating calcium influx into mitochondria during cellular stress, such as in viral infections [7]. Fluvoxamine is a ligand of S1R and plays a protective role in COVID-19 infection by reducing oxidative stress response and counteracting pro-apoptotic signals, consequently reducing the severity of infection [8]. Additionally, fluvoxamine is a lysosomotropic agent and inhibitor of acid sphingomyelinase in the lysosomes. This could inhibit the formation of viral replication complexes and negatively affect viral trafficking and budding, justifying its potential as a treatment option in COVID-19 [6]. Apart from its role as an antiviral, fluvoxamine also exhibits anti-inflammatory properties, which help reduce the severity of cytokine storms associated with COVID-19 infections. Mast cells possess ACE-2 receptors acting as hosts for SARS-CoV-2 and mediating the cytokine storm. SSRIs like fluvoxamine are known to decrease mRNA levels of protease-1 in mast cells, therefore, inhibiting the release of histamine from mast cells [9].

This overview of systematic reviews (SRs) and meta-analyses was conducted to compile and analyze existing evidence on the use of fluvoxamine in treating COVID-19. It also aims to assess its potential efficacy in terms of affordability and compare it with other available COVID-19 treatments.

2. Methods

The protocol for this review has been registered with PROSPERO (CRD42025592203) on January 7th, 2025. This overview adheres to the PRISMA 2020 standards for SRs. The results are reported following the PRISMA guidelines for SRs and meta-analyses that focus on healthcare interventions.

2.1. Objectives

This umbrella review of SRs and meta-analyses was conducted to qualitatively consolidate and analyze current evidence regarding the use of fluvoxamine in treating COVID-19. The findings will be crucial to gauge their potential effectiveness in comparison to the cost and accessibility challenges associated with other treatment options for COVID-19.

2.2. Eligibility Criteria

2.2.1. Inclusion criteria

We included SRs that examined both the effectiveness and safety of fluvoxamine in patients with COVID-19 without restrictions on patient age or disease severity. Reviews addressing COVID-19 at all stages, from asymptomatic cases to severe infections, and in all care settings (both outpatient and inpatient) were considered. Inclusion was not limited by the type of study designs included in the SRs.

2.2.2. Exclusion criteria

Reviews that were not SRs or meta-analyses, narrative reviews, editorials, conference abstracts, non-English publications, reviews focusing solely on other interventions without fluvoxamine data, and duplicate publications were excluded.

2.2.3. Information Sources and Search Strategy

Comprehensive search strategies were designed to identify relevant studies in the PubMed and Cochrane databases. The search was further supplemented by exploring additional literature sources, including the Cochrane COVID-19 resource and Google Scholar, as well as cross-referencing the SRs identified. Detailed search strategies for each electronic database are provided in Supplement 1. To avoid missing SRs that reported combined therapies, search terms were not limited to fluvoxamine-specific keywords. The electronic databases and other literature sources were initially searched for records published between January 1st, 2020, and July 30th, 2024. An updated supplemental literature search was conducted on December 12th, 2024. Only publications in the English language were included.

2.2.4. Screening and Selection

All retrieved records from the database search were assessed for relevance using predetermined inclusion criteria. Two reviewers independently screened the titles and abstracts, followed by a full-text review. Any disagreements between the reviewers were resolved through discussion and, if necessary, by consulting a third reviewer.

2.2.5. Data Collection, Extraction, and Quality Evaluation

Data from the SRs were gathered using a standardized extraction form. Extracted details included general characteristics of each review, descriptions of the target populations, dosing regimens, and frequency of fluvoxamine, comparators, outcome measures, and findings related to safety and effectiveness. The methodological quality of each included review was assessed using the AMSTAR2 tool. Reviews were categorized as high quality (no or one minor weakness), moderate quality (multiple minor weaknesses), low quality (one major flaw with or without minor weaknesses), or critically low (multiple major flaws). Two reviewers independently performed the full-text data extraction and quality evaluation.

2.2.6. Data Analysis

The findings from this umbrella review were summarized narratively only. Quantitative synthesis was not feasible due to the overlap of individual studies in the included SRs, heterogeneity in the inclusion criteria of the included SRs, and variation in the reporting of outcomes. This qualitative synthesis outlines the publication years of the SRs, the populations studied (including COVID-19 severity levels), the countries of origin, the outcomes measured, and the overall conclusions regarding fluvoxamine's effectiveness and safety in managing COVID-19.

3. Results

3.1. Study Selection

The initial systematic search identified 3,624 records from various databases. After removing duplicates, 3,591 records underwent title and abstract screening based on eligibility criteria. Of these, 3,581 records were excluded, leaving 10 records for full-text review. Additionally, two reviews were identified through additional literature searches. A total of 12 publications [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21] were included: 11 original SRs and 1 updated review of a previously included SR [16]. The selection process is presented in **(Figure 1)**.

3.2. Characteristics of included SRs

The majority of included reviews were published in 2022 and 2023 (four each), with three reviews published in 2024. The most recent search in one of the reviews was conducted on January 31, 2024. All reviews, except one, included meta-analyses. Only one review involved pediatric populations. Severity levels across studies varied, covering both inpatient and outpatient cases, and included mild, moderate, and severe COVID-19 infections. One review also reported data on patients with underlying health conditions such as chronic kidney disease, cardiovascular disease,

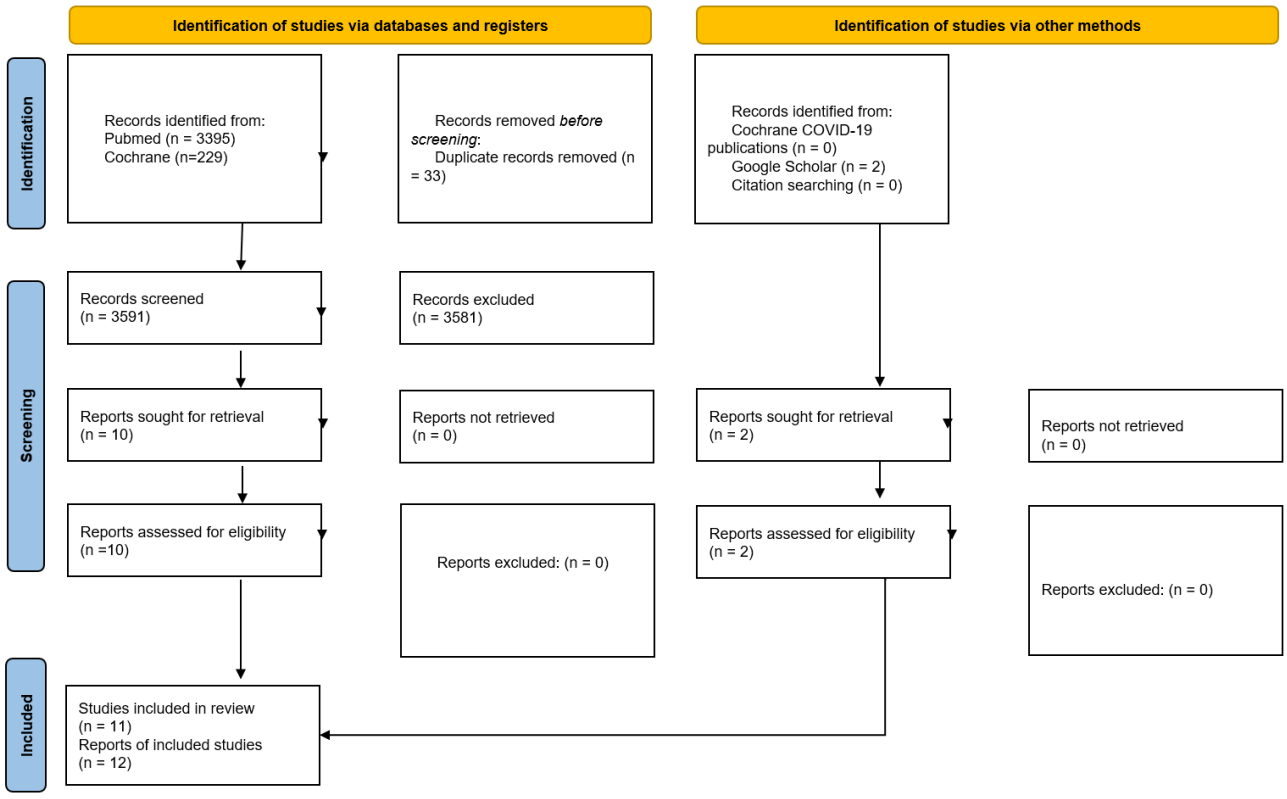

Figure 1: Flowchart of Study Selection Process for Systematic Review.

hypertension, smoking status, and obesity [11]. Further details on study characteristics are reported in **(Table 1)**.

3.3. Summary of the Effects and Safety of Interventions

3.3.1. Mortality

Nine of the reviews reported all-cause mortality as an outcome. All analyses revealed a lower mortality rate with fluvoxamine compared to placebo. However, the results reached statistical significance in only three of the included reports [12, 13, 18, 20]. Effect estimates of primary outcomes are presented in (**Table** 2.). Four reviews published in 2022 reported mortality as an outcome, with three [10, 15, 17] reporting a non-significant reduction, while Zheng et al. [20] did not pool the study outcomes. In their review, Zheng et al. [20] concluded a reduced risk of mortality based on the estimates from individual studies. In contrast, other studies, such as Nyirenda et al. [17], reported a risk ratio (RR) of 0.69 (95% CI, 0.38-1.27; p = 0.24) with 1,649 participants, indicating a non-statistically significant difference. The certainty of the evidence was described as low in that study. Two reviews published in 2023 (Deng et al. [12] and Fico et al. [13]) reported mortality as an outcome, and both revealed a statistically significant decrease. Deng et al. [12] included six randomized controlled trials (RCTs) with 1,470 participants and found that fluvoxamine reduced mortality with an RR of 0.72 (95% CI, 0.63 to 0.82) among outpatients with COVID-19. Similarly, the pooled odds ratio (OR) for Fico 2023 was calculated to be 0.15 (95% CI, 0.02 to 0.95; p = 0.31) [13]. Finally, three reviews published in 2024 [11, 18, 21] reported mortality outcomes, with only Prasanth et al. [18] finding a significant reduction in mortality at doses ≥ 200 mg per day; log odds ratio 1.593 (95% CI 0.530 to 2.656; p = 0.003).

3.3.2. Hospitalization

Ten of the included reviews reported hospitalization outcomes, and five of these showed a statistically significant reduction in the risk of hospitalization with fluvoxamine compared to placebo [11, 14, 15, 20, 21]. Five reviews published in 2022 reported hospitalization rates [10, 14, 15, 17, 20]. The results from Cheema et al. [10] were updated with data from the TOGETHER trial in the review by Marcec et al. [16]. Lu et al. [15] (OR 0.69; 95% CI, 0.51 to 0.94; p = 0.02) and Marcec et al. [16] (RR 0.57; 95% CI, 0.34 to 0.95; p = 0.03) both demonstrated significantly lower hospitalization rates in the fluvoxamine group compared to control. Lee et al. [14] also reported a higher probability of reduced hospitalization rates in outpatient COVID-19 patients (RR: 0.75; 95% CI 0.58 to 0.97) using fluvoxamine. For Vatvani et al. [19], the hospitalization rate between the placebo and fluvoxamine groups was comparable (p = 0.09). Finally, two reviews published in 2024 by Deng et al. [11] and Zhou et al. [21] demonstrated a significantly lower risk of hospitalization with fluvoxamine compared to placebo. Deng et al. [11] reported a reduction in risk ratio (RR: 0.77; 95% CI (0.60 to 0.97); p = 0.03), while Zhou et al. [21] reported a decrease in risk ratio (RR 0.76; 95% CI, 0.59 to 0.99; p = 0.04), indicating decreased hospitalization rates in the intervention group in both cases.

3.3.3. COVID-19 Progression/Clinical Deterioration

One review [10] reported a non-significant decrease in the risk of disease progression in the fluvoxamine group compared to placebo (RR 0.74; 95% CI, 0.21 to 2.57; p = 0.64) [10]. Similarly, Vatvani et al. [19] also examined clinical deterioration and found that fluvoxamine did not offer a significant benefit over placebo (RR 0.83; 95% CI, 0.65 to 1.06; p = 0.14). However, Zheng et al. [20] found fluvoxamine to be associated with a lower likelihood

Table 1: Systematic Reviews on Fluvoxamine for COVID-19

Study (Author, Year)	Search Date	No. of Databases	Total Number Of Studies (N) And Study Designs Included	Total Number of Patients Included (N)	Countries	Interventions Assessed	Outcomes Assessed	Conclusion	AMSTAR 2 Rating
Cheema 2022 [7]	2022	4	N=8 RCTs=5 Prospective cohort=2 Quasi-randomized trial=1	3,781 Mild Moderate Severe (requiring ICU admission) Outpatient Inpatient	USA Canada Croatia Korea Honduras Brazil	Fluvoxamine	Primary: all-cause mortality Secondary: ROH, COVID-19 progression, incidence of AE	Fluvoxamine use showed a large but statistically non-significant reduction in mortality and hospitalization rates and no increase in incidence of AEs. It may be beneficial due to easy accessibility and affordable price.	Critically Low
Deng 2024 [8]	2024	6	N=27 RCTs=9	5,861 Mild Moderate Outpatient	USA Egypt South Korea Thailand Brazil	Fluvoxamine	Incidence of hospitalization, healthcare utilization (ER visits or hospitalization), mortality, supplemental oxygen and mechanical ventilation requirements, SAEs and non-adherence	Fluvoxamine twice a day may reduce ROH and healthcare utilization but absolute benefits are modest and associated with increased risk of treatment non-adherence. It's a potential alternative due to low cost and wide availability. It reduced healthcare utilization in outpatients with obesity range BMI (30 kg/m²) but not in lower BMI patients.	Low
Deng 2023 [11]	2023	7	N=11 RCTs=6 Observational=5	With Controls=5353 Without Controls=2958 Severe(ICU-hospitalized) Inpatients Outpatients	USA Canada Brazil Croatia South Korea Honduras Hungary	Fluvoxamine	Mortality, hospitalization, composite of hospitalization/ERs visits, hypoxemia, requirement for supplemental oxygen, ventilator support, and SAEs	Fluvoxamine may reduce mortality and hospitalization. Medium-dose was associated with reduced mortality, hospitalization, and composite of hospitalization and ER visits but not low-dose. It was not associated with increased AEs.	Low

Table 1 (continued): Systematic Reviews on Fluvoxamine for COVID-19

Study (Author, Year)	Search Date	No. of Databases	Total Number Of Studies (N) And Study Designs Included	Total Number of Patients Included (N)	Countries	Interventions Assessed	Outcomes Assessed	Conclusion	AMSTAR 2 Rating
Fico 2023 [12]	2023	7	N=9 RCTs=2 Cohort=5 Retrospective Cross-sectional=6 Case-control=2	With Controls=215173 Mild Moderate Severe Inpatient	USA Brazil Europe Sweden UK	Psychotropic drugs in COVID-19 treatment: Anti-depressants (Fluvoxamine) Antipsychotics	Primary and Secondary outcomes (i.e., risk of SARS-CoV-2 infection, hospitalization rates, CD, risk of delirium, use of restraints, intubation or mechanical ventilation, mortality due to any cause), risk of severe COVID-19 (considered as risk of intubation or death), and mortality due to any cause among people diagnosed with COVID-19	Preclinical evidence suggests antipsychotics and antidepressants may inhibit SARS-CoV-2 replication and modulate the immune response. Fluvoxamine may reduce severe COVID-19 outcomes and mortality, especially in early treatment to prevent psychiatric symptoms in long-COVID. The increased risk of severe COVID-19 and mortality with antipsychotics is not absolute and should be assessed on a case-by-case basis. Ongoing antipsychotic treatment should not be discontinued in psychiatric patients.	Critically Low
Lu 2022 [13]	2022	7	N=4 RCTs=3 Prospective Nonrandomized Cohort=1	1814 Outpatient	Brazil USA South korea	Fluvoxamine	The primary outcome was ROH or ED visits. Secondary outcomes were requirement of mechanical ventilation, ICU admission, risk of mortality, and risk of AEs	Fluvoxamine use can help reduce the risk of hospitalization or ED visits for nonhospitalized patients. It's use was associated with a similar risk of AEs as that observed in the control group.	Critically Low
Nyirenda 2022 [15]	2022	7	N=2 RCT=2	1649 Mild Outpatient	Brazil USA	Fluvoxamine	SAE, Quality of Life, Clinical status, Death, Adverse Event, Need for dialysis at up to day 28, Admission to the ICU at day 28, Duration of hospitalization, Viral clearance, assessed with RT-PCR test for SARS-CoV-2,Hospital-acquired infections up to day 28	Fluvoxamine may reduce all-cause mortality at day 28, and the ROH or death in outpatients with mild COVID-19. However, there is uncertainty regarding the effect of fluvoxamine on AEs or SAEs.	Low

Table 1 (continued): Systematic Reviews on Fluvoxamine for COVID-19

Study (Author, Year)	Search Date	No. of Databases	Total Number Of Studies (N) And Study Designs Included	Total Number of Patients Included (N)	Countries	Interventions Assessed	Outcomes Assessed	Conclusion	AMSTAR 2 Rating
Prasanth 2024 [16]	2024	4	N=14 RCTs=7 Retrospective cohort=1 Real world studies=7	7153 Varying degrees of severity	Not specified	Fluvoxamine	Primary outcome of this study was time to sustained recovery. Secondary outcomes such as hospitalization, clinical deterioration, and death	Fluvoxamine has shown some potential for treating COVID-19, preventing CD and mortality, with early treatment and higher doses being optimal. The results suggest that treatment within three days of infection is optimal in the prevention of CD and mortality. There is potential for the prevention of Long-covid symptoms in those initially treated for COVID-19 with fluvoxamine.	Critically Low
Vatvani 2023 [17]	2023	4	N=6 RCTs	4197 Outpatient	South Korea Brazil USA	Fluvoxamine	Clinical deterioration, hospitalization rate, and mortality from Covid-19	Fluvoxamine although safe is not effective as outpatient treatment as it does not reduce the ROH or CD rate. It did not offer any significant benefit when compared with placebo. This study did not encourage the use of fluvoxamine for patients with SARS-CoV-2 infection in outpatient settings.	Low
Zhou 2024 [18]	2024	4	N=6 RCTs	4,711 -	USA Canada Brazil Korea	Fluvoxamine	The number of patients who experience clinical deterioration, the number of patients who require hospitalization, the number of patients who require mechanical breathing, and the length of time before clinical deterioration(included hypoxemia, a trip to the ED, an urgent care visit, a hospital stay, or death), AEs, SAEs, mortality	Fluvoxamine is a promising therapy for patients with COVID-19, especially those who take 200 mg or more daily, and is superior to the placebo group in reducing CD and hospitalization. It did not show any higher risk of AEs or SAEs.	Critically Low

Table 1 (continued): Systematic Reviews on Fluvoxamine for COVID-19

Study (Author, Year)	Search Date	No. of Databases	Total Number Of Studies (N) And Study Designs Included	Total Number of Patients Included (N)	Countries	Interventions Assessed	Outcomes Assessed	Conclusion	AMSTAR 2 Rating
Zheng 2022 [9]	2022	6	N=7 RCTs=2 Retrospective=3 Prospective Cohort=2	92,947 Inpatients Outpatients	USA, Brazil, Croatia, France, Hungary	The efficacy and safety of antidepressants in treatment for COVID-19 patients	Primary outcome: clinical deterioration, hospitalization Additional outcomes: all-cause mortality, ADRs, and dropout rate	Antidepressants could reduce the risk of CD and hospitalization. Being a widely available and inexpensive SSRI, fluvoxamine has shown promise as an adjunct treatment for COVID-19. There is evidence for fluvoxamine in reducing the risk of mortality and the need for hospitalization but inconsistent evidence for the safety of adjunctive fluvoxamine for COVID-19 patients.	Critically Low
Lee 2022 [10]	2022	2	N=3 RCTs=3	2196 Outpatients Mild-to-moderate	USA Canada Brazil	Fluvoxamine	All-cause hospitalization emergency department visits that were 24 hours or longer	The probability that fluvoxamine was associated with reduced hospitalization ranged from 94.1% to 98.6% and the probability of moderate association ranged from 81.6% to 91.8%. It could be recommended as a treatment option for patients without contraindication, particularly in resource-limited settings or for individuals without access to monoclonal antibodies or direct antivirals.	Critically Low

RCT: Randomized Controlled Trials; mg: milligrams; AEs: Adverse events; SAEs: Serious adverse events; ADRs: adverse drug reactions; ICU: Intensive care units; BMI: Basal metabolic rate; SSRIs: Selective serotonin reuptake inhibitors; ROH: Risk of hospitalization; CD: Clinical deterioration; ER: Emergency room; ED: Emergency department

Table 2: Effect estimates and number of studies for efficacy and safety outcomes in the included SRs

Study Name	Quality	All-cause mortality	Hospitalization in COVID-19 patients.	Covid 19 progression/ Clinical Deterioration	Risk of Serious Adverse Events
Deng 2024 [8]	Low	RR (0.73; 95%CI (0.42 to 1.28); p=0.99); N=8	RR (0.77; 95%CI (0.60 to 0.97); p=0.03); N=9	NA	RR (0.72; 95% CI (0.40 to 1.30); p=0.79); N=7
Deng 2023 [11]	Low	RR (0.72; 95%CI (0.63 to 0.82)); N=6	RR (0.79; 95%CI (0.64 to 0.99)); N=6	NA	RR (0.77; 95%CI (0.34 to 1.71); N=5
Nyirenda 2022 [15]	Low	RR (0.69; 95%CI (0.38 to 1.27); p=0.24); N=2	Absolute Difference (-4.21; 95%CI (-13.22 to 2.04); N=1	NA	RR (0.56; 95%CI (0.15 to 2.03) p=0.38); N=2
Vatvani 2023 [17]	Low	NA	RR (0.80; 95% CI (0.62 to 1.04); P = 0.09); N=6	RR (0.83; 95%CI (0.65 to 1.06); p = 0.14); N=6	RR (0.82; 95%CI (0.63 to 1.06); p=0.12); N=4
Fico 2023 [12]	Critically Low	OR (0.15; 95%CI (0.02 to 0.95); p=0.04); N=2	NA	NA	NA
Lu 2022 [13]	Critically Low	OR (0.66; 95 % CI (0.36–1.21)); N= NA	OR (0.69; 95% CI (0.51 to 0.94); p=0.02); N=4	NA	OR (0.47; 95%CI (0.09 to 2.54); p=0.38); N=3
Prasanth 2024 [16]	Critically Low	LogOR (1.502; 95%CI (0.621 to 2.391); p < 0.001); N=5	NA	LogOR (0.359; 95%CI (0.1111 to 0.5294); p=0.002); N=7	NA
Cheema 2022 [7]	Critically Low	RR (0.49; 95%CI (0.21 to 1.17); p=0.11); N=3	RR (0.46; 95% CI 0.21 to 1.02; p=0.05); N=5	RR (0.74; 95%CI (0.21 to 2.57); p=0.64); N=3	NA
Zhou 2024 [18]	Critically Low	RR (0.69; 95%CI (0.38 to 1.27); p=0.24); N=6	RR (0.76; 95%CI (0.59 to 0.99); p=0.04); N=5	RR (0.73; 95% CI (0.59 to 0.90); p = 0.004); N=6	RR (0.97; 95%CI (0.59 to 1.60); p=0.91); N=6
Zheng 2022 [9]	Critically Low	Meta-analysis not performed	Meta-analysis not performed	Meta-analysis not performed	Meta-analysis not performed
Lee 2022 [10]	Critically Low	NA	RR (0.75; 95% CI (0.58 to 0.97)); N=3	NA	NA
Marcec 2023 [14]	Not Applicable	NA	RR (0.57; 95% CI (0.34 to 0.95); p = 0.03); N= 7	NA	NA

OR, Odds ratios; RR, Risk Ratios; CI, Confidence Intervals; NA, Not Available

of clinical deterioration based on one clinical trial. Likewise, Zhou et al. [21] also found that fluvoxamine provides reduced clinical deterioration than placebo (RR 0.73; 95% CI, 0.59 to 0.90; p = 0.004). Finally, Prasanth et al. also suggested that fluvoxamine provides reduced clinical deterioration (Log OR 0.359 (95% CI 0.1111 to 0.5294) (z = 3.103; p=0.002)).

3.3.4. Risk of Serious Adverse Events (SAEs)

Seven of the included reviews reported risks of SAEs in the fluvoxamine and placebo groups. In most cases, the risk of serious AEs was similar in both groups, with no statistically significant differences observed [10, 11, 12, 15, 17, 19, 21]. Zheng et al. [20] concluded there was "inconsistent evidence" regarding the safety of fluvoxamine for COVID-19.

3.4. Subgroup results

3.4.1. Age

The SRs included adult populations, with most studies specifying inclusion of patients aged 18 years or older. The mean age of patients per SR ranged from 46.2 to 52.3 years. No age-related effects were reported.

3.4.2. Disease severity

Most of the included SRs consisted of studies that recruited non-hospitalized patients. Cheema et al. [7] and Deng et al. [8] also included patients in the ICU and those hospitalized. Higher doses, including >200mg/day, were linked with a reduction in mortality and clinical deterioration in these patients.

3.4.3. Dosages

Subgroup analyses based on dosages were conducted by one SR published in 2023 and three reviews published in 2024 [11, 12, 18, 21]. Improved efficacy outcomes were reported at higher dosages compared to lower dosages, with a comparable safety profile. For fluvoxamine 50 mg twice daily, as reported by Deng et al. [11] and Deng et al. [12] did not observe significant reductions in hospitalization or healthcare utilization. Furthermore, Deng et al. [12] reported no increase in SAEs for this dosage group compared to the placebo (RR 0.72; 95% CI 0.40 to 1.30). For 100 mg twice daily, Deng et al. [12] found significant reductions in hospitalization (RR 0.75; 95% CI 0.58–0.97) and healthcare use (RR 0.68; 95% CI 0.53–0.86], and Deng et al. [11] reported similar findings. However, Deng et al. [11] noted that this dosage group was not associated with reduced mortality from COVID-19. No increase in SAEs was observed at this dosage level in either study. For the 100 mg regimen administered three times a day, Deng et al. [12] reported no significant decrease in hospitalization, as reported in one study only. Furthermore, no increase in SAEs was observed with fluvoxamine compared to placebo. Prasanth et al. [18] stratified dosages into three groups: up to 100 mg/day, up to 200 mg/day, and up to 300 mg/day. For clinical deterioration, dosages of up to 200 mg/day and 300 mg/day demonstrated significant benefits (p < 0.05). For mortality, interventions of ≥200 mg per day were associated with statistically significant improvements (p < 0.001), whereas doses below 200 mg per day were not. Finally, Zhou et al. [21] classified dosages as low dose (<100 mg twice daily) and high dose (≥ 100 mg twice daily). Their findings indicated that the high dose of fluvoxamine significantly reduced hospitalization (RR 0.77; 95% CI 0.59 to 1.00; p = 0.05) and clinical deterioration rates

(RR 0.69; 95% CI 0.55 to 0.87; p = 0.001), whereas low doses did not. Additionally, no statistically significant differences in adverse events were observed for either dosage level compared to placebo [21].

3.5. Methodological Quality (AMSTAR2) of Included SRs

The AMSTAR2 tool was used to assess the methodological quality of the 11 original SRs included in this study. Out of these, seven SRs were rated as critically low quality, while the remaining four were assessed as low quality. The most common reasons for downgrading quality were inappropriate methods of pooling the studies including inconsistent study designs, sample sizes being pooled together, failure to provide a list of excluded studies with justifications, lack of reporting on funding sources, not evaluating the impact of bias in individual studies on meta-analysis outcomes, and not investigating publication bias (small study effects). The complete AMSTAR2 grading results are provided in the Supplement.

4. Discussion

This umbrella review suggests that fluvoxamine may have potential in reducing COVID-19-related mortality and hospitalizations. Overall, the results indicate that fluvoxamine does not significantly prevent the progression or clinical worsening of the disease. However, most of the included SRs reported no major difference in adverse events between fluvoxamine and placebo, suggesting that fluvoxamine is generally safe. Notably, our analysis showed that higher doses of fluvoxamine were linked with greater benefits, including reductions in hospitalization rates, clinical deterioration, and possibly overall mortality [21].

Several studies support the idea that fluvoxamine can reduce mortality and decrease the risk of clinical deterioration and hospitalization, particularly by preventing the progression from mild to severe illness. For instance, one RCT reported that none of the patients treated with fluvoxamine experienced disease progression, compared to 8.3% in the placebo group [22]. Another meta-analysis of RCTs demonstrated a 30% reduction in hospitalization risk among high-risk patients, largely attributed to adherence to prescribed medication [23]. Additionally, another meta-analysis concluded that fluvoxamine, when combined with antiviral treatments, significantly reduces mortality and hospitalization in COVID-19 patients [11]. When compared with our findings, it appears that fluvoxamine's effectiveness may be more pronounced at higher dosages, with limited positive outcomes observed at lower doses [21]. A recent meta-analysis of 7153 patients across 14 studies concluded that earlier treatment with higher doses was more effective than treatment with lower doses. They conducted a subgroup analysis, dividing the data into two groups: high (200 mg or more per day) and low dose (less than 200 mg). In the high-dose group, the average outcome differed significantly from zero ($z=4.2882$, $p< 0.0001$). However, in the low-dose group, the outcome did not differ significantly from zero ($z=1.082$, $p=0.279$)[18]. Fluvoxamine acts as an agonist for the sigma-1 receptor, through which it exerts anti-inflammatory effects. It has been shown to possess direct antiviral properties, regulate coagulation issues, and reduce the severity of cytokine storms [2]. The drug helps limit the inflammatory cytokine surge by reducing interleukin-6 (IL-6) production and regulating gene expression in cell models of inflammation. Fluvoxamine has demonstrated strong activity at the sigma-1 receptor, which functions as a chaperone protein within the endoplasmic reticulum, modulating both innate and adaptive immune responses. This mechanism may help reduce disease severity and progression in COVID-19 patients [22].

In reviewing prior trials, we noted significant variations in outcomes. For example, one clinical trial demonstrated that early treatment with combinations of fluvoxamine and bromhexine, fluvoxamine and cyproheptadine, or niclosamide and bromhexine led to no clinical worsening during the acute phase (28 days) compared to standard care. Furthermore, these combination therapies were more effective than fluvoxamine alone, as nine participants in the fluvoxamine-only group experienced clinical deterioration requiring low-flow oxygen between days 14 and 28 (post-treatment completion). Additionally, the early use of combination therapies in that trial was associated with a reduced burden of Post-Acute Sequelae of COVID-19 (PASC) symptoms in long-term follow-up. There is also evidence suggesting that sigma-1 receptor agonists, such as fluvoxamine, may help lower the risk of developing PASC symptoms [24].

Conversely, another trial by Bhimraj et al. [25] found that administering 50 mg of fluvoxamine twice daily for 10 days to outpatients with mild to moderate COVID-19 did not significantly improve the time to sustained recovery. In that trial, which included 1,288 participants, the median recovery time was 12 days in the fluvoxamine group compared to 13 days in the placebo group. No significant benefit was observed for the primary outcome, indicating that fluvoxamine may not be effective in treating mild to moderate COVID-19 [25].

4.1. Strengths and Limitations

This review included an extensive search for SRs from multiple sources, encompassing studies with both inpatient and outpatient populations. Additionally, the use of the AMSTAR2 tool ensured that rigorous quality assessment of included SRs was performed. Findings of this synthesis require caution due to certain limitations. Multiple SRs included the same primary studies, potentially leading to the overestimation of treatment effects in our narrative synthesis. Secondly, the included reviews covered different phases of the pandemic (2022-2024) with varying patient populations, vaccination rates, dominant virus variants, and standard care practices, limiting generalizability. Thirdly, the SRs reported different statistical measures (risk ratios vs. odds ratios), making direct comparison and synthesis of results across studies challenging. Most included SRs (7 out of 11) were rated as critically low quality using AMSTAR2, significantly limiting confidence in the findings. Furthermore, the SRs included mixed patient populations (inpatient vs. outpatient, varying severity levels, and different comorbidities) without adequate subgroup analysis. Lastly, a wide variation in fluvoxamine dosing regimens (50-300 mg daily) was observed across studies.

4.2. Implications for Clinical Practice

Fluvoxamine, an SSRI, has shown promise in managing severe COVID-19 symptoms due to its anti-inflammatory properties, particularly its ability to modulate cytokine production, such as IL-6, which plays a role in the cytokine storm [26]. Clinical trials like STOP-COVID and TOGETHER suggest that early use of fluvoxamine can help prevent disease progression, reducing severe outcomes, hospitalizations, and the need for mechanical ventilation [27]. As an affordable and widely accessible generic medication, fluvoxamine offers potential antiviral, anti-inflammatory, and anticoagulant effects [27]. It is easy to administer orally and has a generally favorable safety profile, with mild and transient side effects [28, 29].

However, fluvoxamine also has limitations in treating COVID-19. Some studies have shown that it does not effectively prevent clinical deterioration in unvaccinated symptomatic outpatients [29]. While side effects like nausea, dizziness, and insomnia are usually mild and short-term, drug interactions with other medications can complicate its use in patients with multiple prescriptions [30]. Additionally, the long-term effects of fluvoxamine use in COVID-19 remain unclear due to limited data [31]. Our findings also suggest that higher doses of fluvoxamine may be more beneficial, but such dosing regimens could decrease patient adherence, similar to challenges observed in antibiotic treatments [31]. Given its affordability and accessibility, fluvoxamine could be a valuable treatment option, especially in resource-limited settings where other COVID-19 therapies are not readily available. When compared to lower doses, studies observed that higher daily dosages of fluvoxamine are superior to the placebo group in reducing clinical deterioration and hospitalization, with comparable safety concerns. Future studies should aim to determine the optimal dosage, identify patient populations most likely to benefit from fluvoxamine, and explore the role of fluvoxamine in combination therapies. Large-scale international trials are necessary to confirm the clinical utility of this treatment for COVID-19.

5. Conclusions

While the reductions in mortality and hospitalizations were observed in several included SRs, only a few demonstrated statistical significance, with all of them either of low or critically low quality. Mixed evidence was reported on COVID-19-related mortality, hospitalizations, disease progression, clinical deterioration, and the impact of dosage. In summary, while the anti-inflammatory effects of fluvoxamine offer a promising therapeutic rationale, the synthesized evidence is insufficient to fully justify its routine use as a therapeutic agent in COVID-19 patients. Although it is not currently part of standard COVID-19 treatment protocols, it is a promising candidate for early outpatient management. Further, larger RCTs are needed to clarify their role in COVID-19 treatment.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Authors Contribution

OI and AR conceptualized the study design and objectives. OI, MJ, WM, MSK, MBH, RD, NK, AA, and MAQ conducted the literature search, study screening, selection, and data extraction. OI, ABSZ, JAK, and AR designed the data extraction template, extracted data, and carried out data analysis. OI, MJ, WM, MSK, MBH, RD, NK, AA, and MAQ drafted the initial manuscript. OI, ABSZ, JAK, and AR critically reviewed and revised the final manuscript. ABSZ, JAK, and AR are the guarantors and critically reviewed the manuscript. All authors approve the final manuscript as submitted for publication.

Data Availability

All studies used in the research are available in various databases.

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