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Review article

Antidepressants for COVID-19: A systematic review

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ABSTRACT

Objective: To systematically examine the efficacy and safety of antidepressants for the treatment of coronavirus disease 2019 (COVID-19).

Methods: A systematic search was performed independently by two researchers based on Chinese Journal Net, WanFang, PsycINFO, Cochrane Library, PubMed, and EMBASE.

Results: Seven studies ($n = 92,947$) including three retrospective studies ($n = 91,083$), two randomized clinical trials (RCTs, $n = 1649$), two prospective cohort study ($n = 215$) involving ($n = 92,947$) patients with COVID-19 were examined. For RCTs, fluvoxamine outperformed placebo in reducing clinical deterioration and hospitalisation for COVID-19 patients. For retrospective studies, antidepressants (2 studies) and fluoxetine (1 study) possibly reduced the risk of mortality in patients with COVID-19. Results from two remaining studies supported the superiority of fluvoxamine in reducing risk of mortality in COVID-19 patients. The two RCTs that examined the safety of fluvoxamine for COVID-19 patients found inconsistent results but no significant group differences in the dropout rate.

Conclusion: This systematic review found emerging evidence for fluvoxamine in reducing the risk of mortality and hospitalisation in COVID-19 patients, but inconsistent evidence for the safety of fluvoxamine in COVID-19 patients. More studies are needed to determine the efficacy and safety of antidepressants for the treatment of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a rapid and substantial increase in the rates of hospitalisation, intensive care unit admission, and death globally (Wiersinga et al., 2020). Although a number of safe and effective COVID-19 vaccines have been developed, major challenges remained with regard to their production, distribution, and affordability particularly in many developing countries (Torres et al., 2020). Accumulating evidence has indicated that lung damage caused by COVID-19 is associated with an

uncontrolled immune-mediated inflammatory response, which has led to a growing interest in anti-COVID-19 immunomodulatory drugs (Asif et al., 2020; Mehta et al., 2020; Rizk et al., 2020).

Current evidence suggests that the nonopioid receptor sigma 1 receptor (encoded by SIGMAR1) could be a promising inhibitor of SARS-CoV-2 replication (Gordon DE, 2020a, Gordon DE, 2020b). As a single polypeptide composed of 223 amino acids, the sigma-1 receptor contains an endoplasmic reticulum-retention signal (Hanner et al., 1996; Hashimoto, 2021). The sigma-1 receptor (S1R) might play a role in interfering with the early steps of virus-induced host cell reprogramming (Vela, 2020). A preclinical study found that S1R could restrict the

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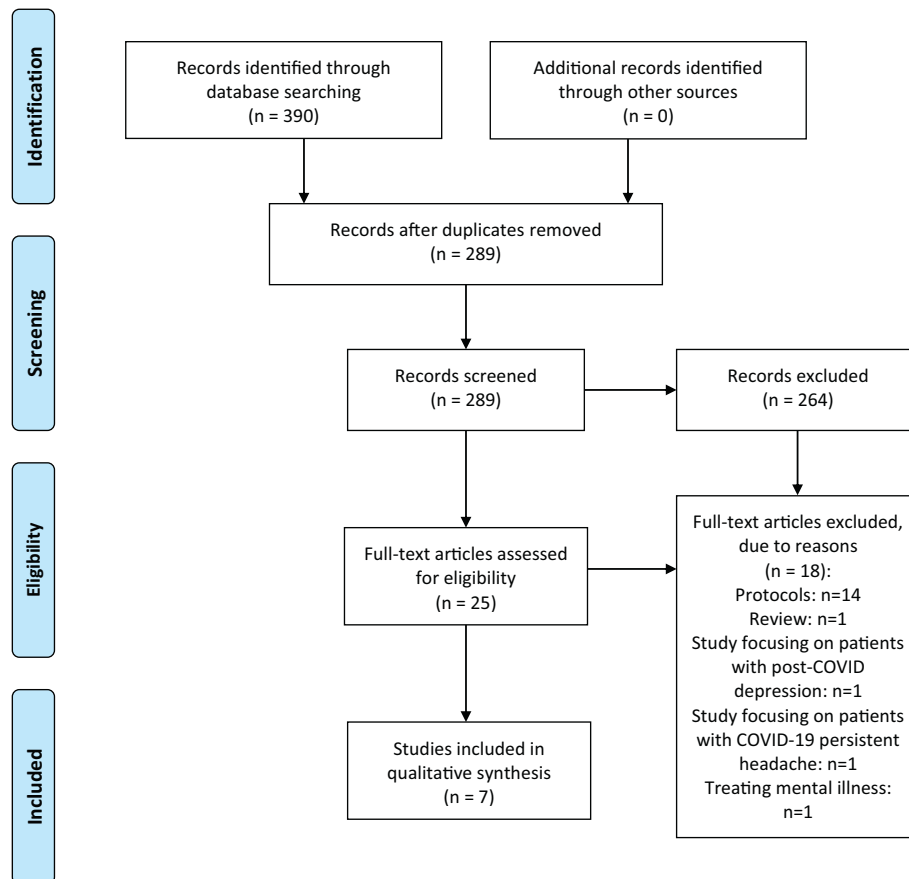


Fig. 1. Flow chart of study selection.

endonuclease activity of endoplasmic reticulum (ER) stress sensor inositol-requiring enzyme 1 (IRE1) and cytokine expression, but does not inhibit the classical inflammatory signalling pathways (Rosen et al., 2019b). Thus, drugs with sigma affinity could be useful in the early intervention for those suffering from COVID-19 via interactions with the sigma-1 receptor (Brimson et al., 2021; Hashimoto et al., 2022; Rosen et al., 2019b; Vela, 2020).

Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), are widely used in the clinical treatment of psychiatric disorders such as major depressive disorder and anxiety disorders (Cipriani et al., 2018; Zhou et al., 2020). The anti-inflammatory properties of antidepressants may be associated with decreased levels of proinflammatory cytokines (Hannestad et al., 2011), including interleukin (IL)-10 and tumor necrosis factor alpha (TNF- α) and monocyte chemoattractant protein-1 (MCP-1), which are related to the severity of COVID-19 (Hoertel et al., 2021; Hojyo et al., 2020). Two recent randomized controlled studies (RCTs) found that fluvoxamine, an SSRI with high affinity for the sigma-1 receptor, could potentially prevent clinical deterioration and reduce the need for hospitalisation (Lenze et al., 2020; Reis et al., 2021) in COVID-19 patients. However, they reported inconsistent findings regarding the safety of adjunctive fluvoxamine for COVID-19.

A recent review (Facente et al., 2021) of two RCTs (Lenze et al., 2020; Reis et al., 2021) and one prospective cohort study (Seftel and Boulware, 2021) found that fluvoxamine could effectively reduce morbidity and mortality caused by COVID-19. To date, however, there is no published systematic review that examined the efficacy and safety of antidepressants for treating COVID-19. Thus, this systematic review evaluated the efficacy and safety of adjunctive antidepressants for COVID-19 patients.

2. Methods

This systematic review was conducted following the PRISMA guidelines (Moher et al., 2009). The registration number of this systematic review was INPLASY202210030 (<https://inplasy.com/>).

2.1. Study selection

All types of studies that examined the efficacy and safety of antidepressants added to treatment as usual (TAU) for COVID-19 patients were eligible for inclusion such as case report/series, RCTs, prospective cohort studies, prospective observational studies (single-group or with matched controls) and open-label retrospective studies. Review articles were excluded. The primary outcome was clinical deterioration as defined by respective studies. Additional outcomes reported in this systematic review were all-cause mortality, adverse drug reactions (ADRs), and dropout rate.

2.2. Search strategy

Both Chinese (Chinese Journal Net, WanFang) and international (PsycINFO, Cochrane Library, PubMed, and EMBASE) databases were independently searched by two researchers (HLS and HC) for published studies on antidepressants for COVID-19, from their inceptions until December 9, 2021 using the following search terms: (Coronavirus OR COVID-19 OR SARS-CoV-2 OR 2019-nCoV OR coronavirus disease 2019) AND (agomelatine OR amitriptyline OR bupropion OR citalopram OR clomipramine OR desvenlafaxine OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR levomilnacipran OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR reboxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetin OR

Table 1
Summary of the study and patient characteristics.

Study (country)	N	Design: -Blinding -Setting	Trial duration (d)	Patients: -Diagnosis -Criteria	Age: mean years (IQR/range/SD)	Sex: Male (%)	Treatment dosages: mg/d (range); Number of patients (n);	Quality assessment
RCT								
Lenze et al., 2020 (USA)	152	- Double-blind - Outpatients	15	- Living in the community with SARS-CoV-2 infection - PCR	46.0 (range = 20–75)	28.3	1.Flvoxamine (100 mg 2 times/d to 100 mg 3 times/d); n = 80 2.Placebo (100 mg 2 times/d to 100 mg 3 times/d); n = 72	Jadad scores = 5
Reis et al., 2021 (Brazil)	1,497 ^a	- Double blind - Outpatients	10	- Positive SARS-CoV-2 diagnostic test within 7 days of symptom onset - SARS-CoV-2 antigen	50.0* (range = 18–102) ^a	42.4 ^a	1.Flvoxamine (100 mg 2 times/d for 10 days); n = 741 2.Placebo (100 mg 2 times/d for 10 d); n = 756	Jadad scores = 5
Prospective cohort study								
Seftel and Boulware, 2021 (USA)	113	- Nonrandom control study - Outpatients	14	- SARS-CoV-2 infection - PCR	42.0* (IQR = 33–56)	75.0	1.Flvoxamine (50–100 mg loading dose, then 50 mg 2 times/d); n = 65 2.No Therapy; n = 48	NOS scores n = 7
Calusic et al., 2021a, 2021b (Croatia)	102	- Prospective cohort trial - Inpatients	15 days +7 days	- COVID-19 patients who met criteria for severe disease were admitted into ICUs - SARS-CoV-2 PCR test	65.8 (SD = 11.65)	66.7	1.Flvoxamine (100 mg 3 times/d for 15 days+50 mg 2 times/d for the followed 7 days); n = 51 2.Standard therapy; n = 51	NOS scores = 8
Retrospective study								
Németh et al., 2021 (Budapest)	269	- Retrospective case-control study - Inpatients	28	- SARS-CoV-2 infection - PCR or SARS-CoV-2 antigen	64.1 (range = 19–96)	54.6	1.Flvoxetine (20 mg capsules 1 times/d); n = 110 2.Not receive fluoxetine; n = 159	NOS scores = 6
Hoertel et al., 2021 (France)	7230	- Retrospective study - Inpatients	18.4	- Inpatient visits for COVID-19 - COVID-19 RT-PCR test	73.7 (SD = 15.80)	50.8	1.Any antidepressant (mean (SD) = 21.6 (14.1) mg/d; range (1.64–81.22); n = 345 2.No antidepressant (mean (SD) = NR; range = NR; n = 6885	NOS scores = 8
Oskotsky et al., 2021 (USA)	83,584	- Retrospective cohort study - Both inpatients and outpatients	NR	- Patients with a diagnosis of COVID-19 or COVID-19 exposure - Laboratory test for SARS-CoV-2 and/or ICD-10 code	52.1 (SD = 19.31)	49.8	1.SSRIs (mean (SD) = NR; range = NR fluoxetine-equivalent dose was 30.2 (22.6) mg/d; n = 3401 2.Not treated with SSRIs mean (SD) = NR; range = NR; n = 80,183	NOS scores = 8

Abbreviations: Age* = median age; Both = inpatients and outpatients; COVID-19 = coronavirus disease 2019; d = days; ICUs = the intensive care units; ICD-10 = International Classification of Diseases,10th edition; IQR = interquartile range; M = mean; NOS = the Newcastle-Ottawa Scale; NR = not reported; PCR = transcriptase-polymerase-chain-reaction; RCT = randomized controlled trial; RT-PCR test = positive reverse-transcriptase-polymerase-chain-reaction test; SARS-CoV-2 = severe acute respiratory syndrome and causative agent of coronavirus disease 2019; SSRIs = selective serotonin reuptake inhibitors; SD=Standard Deviation; R = range.

^a Data collected from fluvoxamine (n = 741) and placebo (n = 756) treatment groups.

antidepressive agents). The reference lists of included studies ([Calusic et al., 2021a](#); [Hoertel et al., 2021](#); [Lenze et al., 2020](#); [Németh et al., 2021](#); [Oskotsky et al., 2021](#); [Reis et al., 2021](#); [Seftel and Boulware, 2021](#)) and relevant reviews ([Facente et al., 2021](#); [Sukhatme et al., 2021](#)) were manually searched for additional studies.

2.3. Data extraction

The same two researchers independently screened studies and extracted data. If there was any ambiguity, it was resolved by a discussion with a senior researcher. We contacted with the first/corresponding authors to obtain any missing data if necessary.

2.4. Quality assessment

Literature quality was also evaluated by two researchers (HLS and HC). For RCTs, the Cochrane risk of bias ([Higgins et al., 2011](#)) and the Jadad scale ([Jadad et al., 1996](#)) were used to assess the study quality. For other types of studies (i.e., open-label retrospective studies), Newcastle-Ottawa Scale (NOS) ([Stang, 2010](#)) was used to assess the study quality.

3. Results

3.1. Literature search

As shown in [Fig. 1](#), the literature search yielded 390 trials. Finally, seven studies ([Calusic et al., 2021a](#); [Hoertel et al., 2021](#); [Lenze et al., 2020](#); [Németh et al., 2021](#); [Oskotsky et al., 2021](#); [Reis et al., 2021](#); [Seftel and Boulware, 2021](#)) that investigated the efficacy and safety of antidepressants for COVID-19 patients met the study entry criteria and were included in this systematic review. Meta-analysis was not performed due to the substantial heterogeneity between the included studies, particularly in terms of study design (RCTs versus prospective cohort studies versus retrospective studies).

3.2. Included studies and participant details

The seven studies (n = 92,947) included three retrospective studies (n = 91,083) ([Hoertel et al., 2021](#); [Németh et al., 2021](#); [Oskotsky et al., 2021](#)), two RCTs (n = 1649) ([Lenze et al., 2020](#); [Reis et al., 2021](#)) and two prospective cohort study (n = 215) ([Calusic et al., 2021b](#); [Seftel and Boulware, 2021](#)), all of which are summarized in [Table 1](#). Among the seven included studies, antidepressants included fluvoxamine (4 studies,

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel	Blinding of outcome assessment (Symptom reduction, response)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other sources of bias
Lenze et al., 2021	+	+	+	+	+	+	+
Reis et al., 2021	+	+	+	+	+	+	+

Fig. 2. The Cochrane risk of bias for RCTs.

Abbreviations: RCT = randomized controlled trial; +: Low risk of bias; -: High risk of bias; ?: Unclear risk of bias.

Table 2

Clinical deterioration and all-cause mortality.

Study	Clinical outcomes	Treatment, n (%)	Control, n (%)	P-value
RCT				
Lenze et al., 2021	Clinical deterioration	Fluvoxamine, 0	Placebo, 6 (8.3)	0.009
	Mortality	NR	NR	NR
Reis et al., 2021	Hospitalisation	Fluvoxamine, 75 (10.1)	Placebo, 97 (12.8)	0.10
	Mortality	Fluvoxamine, 17 (2.3)	Placebo, 25 (3.3)	0.24
Prospective cohort study				
Seftel et al., 2021	Hospitalisation	Fluvoxamine, 0	No therapy, 6 (12.5)	0.005
	Mortality	Fluvoxamine, 0	No therapy, 1 (2.1)	NR
	Residual symptoms	Fluvoxamine, 0	No therapy, 29 (60.0)	<0.001
Calusic et al., 2021a, 2021b	Clinical deterioration	NR	NR	NR
	Mortality	Fluvoxamine + standard therapy, 30 (58.8)	Standard therapy, 39 (76.5)	0.027
Retrospective study				
Németh et al., 2021	Clinical deterioration	NR	NR	NR
	Mortality	Fluoxetine, 15 (13.6)	Not treated with fluoxetine, 49 (30.8)	0.001
Hoertel et al., 2021	Intubation or death	Any antidepressants, 84 (24.3)	Not treated with any antidepressants, 1,188 (17.3)	NR
Oskotsky et al., 2021	Clinical deterioration	NR	NR	NR
	Mortality	Any SSRI antidepressants, 497 (14.6)	Not treated with SSRIs, 6,698 (8.4)	NR

Bolded values are $P < 0.05$.

Abbreviations: COVID-19 = coronavirus disease 2019; NR = not reported; RCT = randomized controlled trial; SSRIs = selective serotonin reuptake inhibitors.

$n = 1864$) (Calusic et al., 2021a; Lenze et al., 2020; Reis et al., 2021; Seftel and Boulware, 2021), fluoxetine (1 study, $n = 269$) (Németh et al., 2021) and multiple antidepressants (2 studies, $n = 90,814$) (Hoertel et al., 2021; Oskotsky et al., 2021).

3.3. Assessment of study quality

Fig. 2 depicts the Cochrane risk of bias of two double-blinded RCTs. As shown in Table 1, Jadad total scores were 5 for two RCTs and NOS total scores ranged from 6 to 8 for other types of studies.

3.4. Clinical deterioration and all-cause mortality

Table 2 shows the rates of clinical deterioration and all-cause mortality for the included studies. In the two RCTs, fluvoxamine was associated with a lower likelihood of clinical deterioration (Lenze et al., 2020) and hospitalisation (Reis et al., 2021) in patients with COVID-19 when compared with placebo groups. In the three retrospective studies, antidepressants (2 studies) (Hoertel et al., 2021; Oskotsky et al., 2021) and fluoxetine (1 study) (Németh et al., 2021) possibly reduced the risk of all-cause mortality. The remaining two studies (Calusic et al., 2021a; Seftel and Boulware, 2021) found that fluvoxamine had a positive effect in reducing mortality in patients with COVID-19.

3.5. ADRs and dropout rate

Compared to placebo, fluvoxamine was associated with less frequent pneumonia and gastrointestinal symptoms such as nausea and vomiting in one RCT (Lenze et al., 2020). Another RCT reported similar rates of ADRs in both fluvoxamine and placebo groups (Reis et al., 2021) (Table 3). In two prospective studies, no serious ADRs occurred with fluvoxamine. ADRs were not reported in the three retrospective studies (Calusic et al., 2021b; Hoertel et al., 2021; Németh et al., 2021; Oskotsky et al., 2021).

In the two RCTs, no significant difference was found between the fluvoxamine than placebo groups regarding the dropout rate (all $P_s > 0.05$) (Lenze et al., 2020; Reis et al., 2021). The two prospective cohort studies (Calusic et al., 2021b; Seftel and Boulware, 2021) did not describe discontinuation rates.

4. Discussion

This systematic review (7 studies with 92,947 COVID-19 patients) examined the efficacy and safety of antidepressants for the treatment of COVID-19. Clinical deterioration of patients with COVID-19 typically occurs during the second week of illness (Cummings et al., 2020; Lenze et al., 2020). This systematic review found that antidepressants, especially fluvoxamine, could reduce the risk of clinical deterioration and hospitalisation, which is consistent with the findings of a recent review (Facente et al., 2021). All included studies were published within one year, suggesting that antidepressants as an adjunct treatment for COVID-19 is a novel and clinically important focus. Four incomplete RCTs (NCT04668950, NCT04718480, NCT04510194 and NCT04885530) are currently underway, including three in the USA and one in the Hungary (Facente et al., 2021).

Although many drugs were trialled in treating COVID-19, most had disappointing findings (WHO Solidarity Trial Consortium, 2021). For example, the Interim WHO Solidarity Trial results found that interferon beta-1a, remdesivir, lopinavir, and hydroxychloroquine had small or no effect on the mortality, duration of hospital stay or initiation of ventilation in hospitalized patients with COVID-19 (Iqbal et al., 2021; Ivbijaro et al., 2021; WHO Solidarity Trial Consortium, 2021). Other drugs such as azithromycin (Hinks et al., 2021), favipiravir (Hassanipour et al.,

Table 3
Adverse drug reactions and dropout rate.

Study	ADRs			Dropout rate (%)		
	Events	Treatment (%)	Control (%)	Total (%)	Treatment (%)	Control (%)
RCTs						
Lenze et al., 2021	Pneumonia	3 (3.8)	6 (8.3)	Fluvoxamine-treated participants, 18 of 80 stopped responding to the surveys prior to day 15 compared with 19 of 72 who were randomized to placebo	18 (22.5)	19 (26.4)
	Shortness of breath	2 (2.5)	4 (5.6)			
	Headache or head pain	2 (2.5)	1 (1.4)			
	Gastroenteritis, nausea, or vomiting	1 (1.3)	5 (6.9)			
	Muscle aches	1 (1.3)	0			
	Bacterial infection	1 (1.3)	0			
	Vasovagal syncope	1 (1.3)	0			
	Teeth chattering	1 (1.3)	0			
	Dehydration	1 (1.3)	0			
	Low oxygen saturation or hypoxia	0	6 (8.3)			
	Chest pain or tightness	0	2 (2.8)			
	Fever	0	2 (2.8)			
	Acute respiratory failure	0	1 (1.4)			
	Hypercapnia	0	1 (1.4)			
	Flank pain	0	1 (1.4)			
	Serious adverse events ^a	1 (1.3)	5 (6.9)			
	Other adverse events ^b	11 (13.8)	6 (8.3)			
Reis et al., 2021	No significant differences in the fluvoxamine and placebo groups			330 (22.0)	193 (26.0)	137 (18.0)
Prospective cohort study						
Seftel et al., 2021	No serious ADRs occurred with fluvoxamine			NR		
Calusic et al., 2021a, 2021b	NR	NR	NR	NR		
Retrospective study						
Németh et al., 2021	NR	NR	NR	NA		
Hoertel et al., 2021	NR	NR	NR	NA		
Oskotsky et al., 2021	NR	NR	NR	NA		

Abbreviations: ADRs = adverse drug reactions; NR = not reported; NA = not applicable; RCT = randomized controlled trial.

^a Serious adverse events = One patient in the placebo group had more than 1 serious adverse event. The total No. of serious adverse events was 1 in the fluvoxamine group and 6 in the placebo group.

^b Other adverse events = There were patients in the placebo group who had more than 1 other adverse event.

2021), and metformin (Reis et al., 2022) did not provide any clinical benefit in treating COVID-19 patients. However, being a widely available and inexpensive SSRI, fluvoxamine has shown promise as an adjunct treatment for COVID-19 (Calusic et al., 2021a; Lenze et al., 2020; Reis et al., 2021).

The potential mechanisms of therapeutic role for the antidepressants for COVID-19 symptoms are still not clear (Hashimoto et al., 2022). COVID-19 induced by SARS-CoV-2 is primarily triggered by an intense proinflammatory host response (Costela-Ruiz et al., 2020; Iqbal et al., 2021). Further evidence found that severe outcomes of COVID-19 resulted an increased plasma concentrations of pro-inflammatory cytokines and chemokines such as interleukin IL-2, IL-6, IL-7, IL-10, TNF- α , MCP1, C-reactive protein, ferritin, D-dimers and macrophage inflammatory protein 1 alpha (MIP1 α) (Costela-Ruiz et al., 2020; Hojyo et al., 2020; Singh and Tikka, 2021). Numerous studies suggested that antidepressants could decrease the concentrations of IL-6, IL-10, and TNF- α (Köhler et al., 2018). Additionally, modulation of the sigma-1 receptor-Inositol-Requiring Enzyme 1 α (IRE1) pathway by antidepressants and specifically fluvoxamine and fluoxetine were associated" to "antidepressants, specifically fluvoxamine and fluoxetine, were associated with decreased damaging aspects of the inflammatory response (Rosen et al., 2019a). Other mechanisms of actions could be involved. SSRIs, such as fluoxetine, could decrease mRNA levels of protease-1 in mast cells (MCs), and hence reduce cytokine storms in COVID-19 patients (Chen et al., 2008). Treatment of mice with S1R agonists, such as fluoxetine

(Hashimoto, 2015), may reduce acid sphingomyelinase activity and protein levels in neurons (Gulbins et al., 2013). Fluoxetine may also inhibit entry and spread of SARS-CoV-2 in the Vero-E6 cell line (Schloer et al., 2020). S1R agonists, such as escitalopram and fluoxetine (Hashimoto, 2015), could prevent the SARS-CoV-2 from infecting Vero cells (Carpinteiro et al., 2020). Certain antidepressants (e.g., amitriptyline) may prevent infection of human Caco-2 cells with SARS-CoV-2, and low-dose amitriptyline could prevent freshly isolated nasal epithelial cells from being infected by pp-VSV-SARS-CoV-2 (Carpinteiro et al., 2020; Sukhatme et al., 2021).

Several limitations should be noted. First, the small number of RCTs limited our capacity to conduct a meta-analysis. Second, the dose of fluvoxamine ranged from a 50–100 mg loading dose to 100 mg taken three times daily in the included studies (Calusic et al., 2021a; Lenze et al., 2020; Reis et al., 2021; Seftel and Boulware, 2021). The optimal doses of fluvoxamine for COVID-19 should be further examined. Only two (28.6%; 2/7) high quality RCTs were conducted in the USA and Brazil but have not been replicated elsewhere.

In conclusion, there was emerging evidence for fluvoxamine in reducing the risk of mortality and the need for hospitalisation in COVID-19 patients but inconsistent evidence for the safety of adjunctive fluvoxamine for COVID-19 patients. More high-quality studies with larger sample sizes and longer follow-up periods, are needed to provide definitive evidence for the efficacy and safety of antidepressants for the treatment of COVID-19.

CRedit authorship contribution statement

Study design: Wei Zheng, Yu-Tao Xiang.

Data collection, analysis and interpretation: Wei Zheng, He-Li Sun, Hong Cai, Qinge Zhang.

Drafting of the manuscript: Wei Zheng, Yu-Tao Xiang.

Critical revision of the manuscript: Chee H. Ng.

Approval of the final version for publication: all authors.

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Declaration of competing interest

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