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# Psychotropic drug repurposing for COVID-19: a Systematic Review and Meta-Analysis

--Manuscript Draft--

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| **Abstract:** | Several psychotropic drugs, including antidepressants (AD), mood stabilizers, and antipsychotics (AP) have been suggested to have favorable effects in the treatment of COVID-19. The aim of this systematic review and meta-analysis was to collect evidence from studies concerning the scientific evidence for the repurposing of psychotropic drugs in COVID-19 treatment. Two independent authors searched PubMed-MEDLINE, Scopus, PsycINFO, and ClinicalTrials.gov databases, and reviewed the reference lists of articles for eligible articles published up to 13th December, 2021. All computational, preclinical and clinical (observational and/or RCTs) studies on the effect of any psychotropic drug on Sars-CoV-2 or patients with COVID-19 were considered for inclusion. We conducted random effect meta-analyses on clinical studies reporting the effect of AD or AP on COVID-19 outcomes. 29 studies were included in the synthesis: 15 clinical, 9 preclinical, and 5 computational studies. 9 clinical studies could be included in the quantitative analyses. AD did not increase the risk of severe COVID-19 (RR= 1.71; CI 0.65-4.51) or mortality (RR=0.94; CI 0.81-1.09). Fluvoxamine was associated with a reduced risk of mortality for COVID-19 (OR=0.15; CI 0.02-0.95). AP increased the risk of severe COVID-19 (RR=3.66; CI 2.76-4.85) and mortality (OR=1.53; CI 1.15-2.03). Fluvoxamine might be a possible candidate for psychotropic drug repurposing in COVID-19 due to its anti-inflammatory and antiviral potential, while evidence on other AD is still controversial. Although AP are associated with worse COVID-19 outcomes, their use should be evaluated case to case and ongoing treatment with antipsychotics should be not discontinued in psychiatric patients. |

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Barcelona, June 9th, 2022

**To the European Neuropsychopharmacology Editorial Board**

Please find enclosed our work entitled "**Psychotropic drug repurposing for COVID-19: a Systematic Review and Meta-Analysis"**, which aims to collect the available preclinical and clinical evidence grounding psychotropic drug-repurposing for COVID-19 and to quantify the association between psychotropic drugs and COVID-19 outcomes.

Drug repurposing has the potential to bring existing de-risked drugs for effective intervention in an ongoing pandemic of COVID-19. In this perspective, psychotropic compounds, including antidepressants, antipsychotics, or mood stabilizers, have potentially significant antiviral and anti-inflammatory properties which might be effective against Sars-CoV-2 infection. Our main findings show that fluvoxamine, due to its anti-inflammatory and antiviral potential might be a possible candidate for COVID-19 treatment, since it reduces both mortality and severe COVID-19 outcomes, while evidence on the effect of other antidepressants is still controversial. Also, antipsychotics seem to increase the risk of severe COVID-19.

We believe that our results might extend current knowledge on COVID-19 treatment and open new translational research perspectives on the mechanisms of psychotropic drugs and related inflammation pathways.

We declare that this manuscript is original and is not currently being considered for publication elsewhere. We confirm that all listed authors have contributed significantly to the manuscript and that the manuscript has been read and approved by all named authors. We have each approved the order of authors listed in the manuscript. My co-authors and I hope that this paper will be of interest and look forward to hearing from you in due course.

Yours sincerely,

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**Comments from the editors and reviewers**

Dear Dr. Salagre,
Thank you for evaluating our manuscript submitted to "European Neuropsychopharmacology". We are grateful for your interest and time. Following, we will answer in detail each observation and/or commentary made by Reviewers 1 and 2 (all changes are in track-mode).

**Reviewer 1:** In the their systematic review and meta-analysis "Psychotropic drug repurposing for COVID-19: a Systematic Review and Meta-Analysis", Dr Fico and colleagues investigate preclinical and clinical evidence for psychotropic drug-repurposing for COVID-19 and assess the association between psychotropic drugs and COVID-19 outcomes. Their main findings are that fluvoxamine is a promising candidate for COVID-19 treatment, reducing mortality and severe illness outcomes. In contrast, the evidence for effect of other antidepressants was deemed controversial. Further, antipsychotic use was associated with increased risk of severe COVID-19 outcomes. The manuscript is timely, reads well, is methodologically sound and presents new important evidence for potential repurposing of psychotropic drugs, especially fluvoxamine, for COVID-19. It is also well-balanced in the conclusions regarding use of antipsychotics. I have only one minor comment, which is to rephrase the sentence "in
conclusion, ..." in the section before the limitations since this is a bit confusing for the reader given the conclusion sines after the limitations section. Overall a well-written, important and interesting paper for which the authors should be commended.

**We thank Reviewer 1 for his/her comment. We have changed the manuscript accordingly (page 17).**

**Reviewer 2:** The aim of the submitted study was to conduct a systematic review and meta-analysis of the preclinical and clinical studies for the repurposing of psychotropic drugs in the COVID-19 treatment. This is an important and timely study since the repurposing of existing drugs has proven to be the fastest and safest way to address the pandemic and some psychotropic drugs have shown to present anti-inflammatory and immune-modulatory effects with potential clinical benefits in patients presenting COVID-19. They found that antidepressants did not increase the risk of severe COVID-19 or mortality and antipsychotics increased the risk of severe COVID-19 and mortality. Finally, fluvoxamine was associated with reduced risk of mortality for COVID-19.

The manuscript presents a well conducted systematic review and meta-analysis. It is clearly written and methods are well described. However, there are specific issues that need to be addressed to better understand their methods, results an discussion, as listed below.

**We are grateful to Reviewer 2 for his/her comments. We will provide a detailed answer to each point below and change the manuscript accordingly in track change mode.**

Comment 1: In materials and methods, the Prospero protocol number is missing.
We add the PROSPERO ID according to Reviewer's 2 comment (page 4).

2. In literature search, the authors list the databases they performed the search. Please, explain why other databases were not used, such as EMBASE, Web of Science, PsycInfo, CINAHL and The Cochrane Library?

**We thank Reviewer 2 for his comment. In the supplementary material we have dedicated a paragraph to the search strings in several databases: MEDLINE/PubMed/Index Medicus, Embase, Scopus, Psycinfo, and ClinicalTrials. We added this information in the manuscript since we noticed that the specific information was missing in the main text but specified in the supplementary material.**

3. In inclusion and exclusion criteria, they mention anti-anxiety medications. Do they mean benzodiazepines only or other classes of drugs?

**We agree with Reviewer 2 that the term "anti-anxiety" is generic and might be confounding. Since we incorrectly used this term as referred to benzodiazepines, we changed the text in the manuscript accordingly (page 5).**

4. In data extraction, item 4 it is written "the number of the sample". Do they mean sample size? Please clarify.

**With "the number of the sample" we meant "sample size". We have changed the manuscript according to Reviewer's 2 comment (please see page 6).**

5. The inclusion of computational studies in the analysis is not clear. In the abstract they are not mentioned as only preclinical and clinical studies were listed. Does it make sense to add computational studies in this meta-analysis? Please justify.

**We thank Reviewer 2 for his/her insightful comment. In the past decade, there has been a dramatic increase in the number of computational applications and tools that have improved the process of drug discovery thereby enhancing the speed and efficiency of the design–make–test–analyze cycle. Modern computational applications and tools transcend all areas of drug discovery and repurposing, thus we believe that computational study should be included to have a wider view on this topic. Therefore, we agree with Reviewer 2 that the word "preclinical" should not include computational studies, so we have changed the manuscript accordingly in track change mode, adding "computational" where appropriate (see abstract and methodology).**

6. In the quality assessment, they mention that the quality of preclinical studies was evaluated with the OHAT Risk of Bias tool. What about clinical studies? Were they assessed by the same method? Why OHAT Risk of Bias tool was used instead of the more widely used Cochrane Risk of Bias tool?

**We have used three different methods to evaluate respectively computational, preclinical and clinical studies, as specified in the methodology section, please see below and in the specific section in the manuscript:**

***"The quality of preclinical studies was evaluated with the OHAT Risk of Bias tool (Eick et al., 2020). The Newcastle-Ottawa scale (NOS) was applied (Herzog et al., 2013; Zeng et al., 2015) for observational studies and the Cochrane risk of bias (RoB) tool for randomized studies (Higgins et al., 2011). We adopted the thresholds for converting Newcastle-Ottawa Scale scores into "good," "fair," and "poor" quality criteria, previously described ("AHRQ Comparative Effectiveness Reviews - NCBI Bookshelf," 2005). "***

7. In statistical analysis, when mention "COVID severe outcomes" would be good for the reader to have a list of which outcomes were considered severe (ICU hospitalization? intubation? others?).

**We thank Reviewer 2 for his/her comment. With COVID server outcome we considered considered as risk of intubation or death. We have mentioned this aspect in the methodology section (see page 13).**

8. In discussion, I suggest a further debate whether the differences on COVID-19 outcomes between fluvoxamine and other antidepressants had to do with a much better quality clinical trials using fluvoxamine compared with a lower quality clinical and observational studies using other antidepressants.

**We thank Reviewer 2 for his/her comment. We agree that the lack of further clinical trials on other AD rather than fluvoxamine might be a limitation since we cannot say that other AD are not effective or useful in COVID-19. The lack of clinical trials for the treatment of COVID-19 is not uncommon in systematic reviews and meta-analysis, due to the nature of the previously unknown disease and the rapid outbreak. However, we have added a paragraph in our limitation section to better address this aspect following Reviewer'2 suggestion (please see page 18).**

Minor points:

1. In statistical analysis, "random-effect" should be "random-effects". **Thank you. We have changed the manuscript accordingly.**

2. The title of Supplementary Table 1 is incomplete. "Characteristics of the included computational studies and narrative synthesis of". **Thank you. We have changed the supplementary material accordingly.**

# Psychotropic drug repurposing for COVID-19: a Systematic Review and Meta-Analysis

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**Abstract**

Several psychotropic drugs, including antidepressants (AD), mood stabilizers, and antipsychotics (AP) have been suggested to have favorable effects in the treatment of COVID-19. The aim of this systematic review and meta-analysis was to collect evidence from studies concerning the scientific evidence for the repurposing of psychotropic drugs in COVID-19 treatment. Two independent authors searched PubMed-MEDLINE, Scopus, PsycINFO, and ClinicalTrials.gov databases, and reviewed the reference lists of articles for eligible articles published up to 13th December, 2021. All computational, preclinical and clinical (observational and/or RCTs) studies on the effect of any psychotropic drug on Sars-CoV-2 or patients with COVID-19 were considered for inclusion. We conducted random effect meta-analyses on clinical studies reporting the effect of AD or AP on COVID-19 outcomes. 29 studies were included in the synthesis: 15 clinical, 9 preclinical, and 5 computational studies. 9 clinical studies could be included in the quantitative analyses. AD did not increase the risk of severe COVID-19 (RR= 1.71; CI 0.65-4.51) or mortality (RR=0.94; CI 0.81-1.09). Fluvoxamine was associated with a reduced risk of mortality for COVID-19 (OR=0.15; CI 0.02-0.95). AP increased the risk of severe COVID-19 (RR=3.66; CI 2.76-4.85) and mortality (OR=1.53; CI 1.15-2.03). Fluvoxamine might be a possible candidate for psychotropic drug repurposing in COVID-19 due to its anti-inflammatory and antiviral potential, while evidence on other AD is still controversial. Although AP are associated with worse COVID-19 outcomes, their use should be evaluated case to case and ongoing treatment with antipsychotics should be not discontinued in psychiatric patients.

**Keywords**: **Covid-19, psychotropic drugs, antidepressants, antipsychotics, anti-inflammatory, antiviral**

## 1. Introduction

The spreading infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused over 6 million deaths for COVID-19 worldwide so far (WHO, 2022) despite the unprecedented joint effort to study and treat this illness. The spectrum of COVID-19 clinical manifestations is very broad, ranging from the absence of symptoms to severe pneumonia with respiratory failure (Zhu et al., 2020). Notwithstanding the fast development and ongoing massive administration of vaccines, which proved to be safe and effective (Polack et al., 2020), a high number of people are still at risk for COVID-19 and related severe complications (Carbonell et al., 2021). Currently, the elevation of the pro-inflammatory cytokines and chemokines, the so-called cytokine storm (Fajgenbaum and June, 2020), is the main pathophysiological mechanism underlying the severity of COVID-19. Also, alterations of both the serotonin and dopamine synthetic pathways (Attademo and Bernardini, 2021) might be involved in COVID-19 pathophysiology and related to the documented neurological long-term sequelae observed (Chou et al., 2021; L. Liu et al., 2021). The repurposing of existing drugs proved to be the fastest and safest way to clinically tackle the pandemic, representing a cost-efficient alternative to the classic drug development process, also disclosing potential mechanisms of action for novel indications (Smith et al., 2021). Repurposed drugs mainly target RNA polymerase inhibition (Jiang et al., 2021), angiotensin-converting enzyme-2 (ACE-2), and transmembrane serine protease-2 (TMPRSS2) inhibitors (Hoffmann et al., 2020). Indeed, FDA approved remdesivir, an antiviral with in vitro inhibitory activity against SARS-CoV-1 and the Middle East respiratory syndrome (MERS-CoV) (Sheahan et al., 2020), and tocilizumab, an inhibitor of interleukin-6 (IL-6) used in several diseases including rheumatoid arthritis (Hennigan and Kavanaugh, 2008) for hospitalized patients with COVID-19 (Beigel et al., 2020; Salama et al., 2020). Among other available drugs, psychotropic medications have well-understood safety profiles, and showed anti-inflammatory properties (Baumeister et al., 2016), being possible candidates for drug repurposing in COVID-19. For instance, lithium shows immune-modulatory properties, increasing neutrophil, but also lymphocytes, leukocytes, and natural killer cells count

(Pietruczuk et al., 2018), while directly impeding viral replication in both animals and in vitro studies (Murru et al., 2020). Some antidepressants (AD) such as clomipramine and fluoxetine decrease inflammatory cytokines (IL-6), interferon γ, and tumor necrosis factor (TNF) (Caiaffo et al., 2016), while fluvoxamine reduces the production of pro-inflammatory cytokines and showed a possible antiviral effect (Sukhatme et al., 2021). Studies on the effects of antipsychotics (AP) on inflammation are somewhat conflicting, showing both pro- and anti-inflammatory activity (Baumeister et al., 2016; Mondelli and Howes, 2013). Also, SARS-CoV-2 may be sensitive to GSK-3 inhibitors, including lithium (X. Liu et al., 2021).

### *1.1. Aims*

The aim of this Systematic Review (SR) and meta-analysis (MA) is threefold: 1) to collect the available computational, preclinical and clinical evidence grounding the possible drug-repurposing of psychotropic drugs for the treatment of COVID-19 and its related outcomes; 2) to quantify the association between psychotropic drugs and COVID-19 outcomes; 3) to depict possible recommendations for future clinical studies on this topic.

## 2. Material and methods

We followed the procedures outlined in the 2020 update of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) (Page et al., 2021) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Brooke et al., 2021), following an a priori protocol. The protocol of this systematic review and meta-analysis was posted on PROSPERO(ID 336944).

### *2.1. Literature search*

To identify studies for this review, a systematic search was performed using MEDLINE/PubMed/Index Medicus, EMBASE, Scopus, Psycinfo, and www.clinicaltrials.gov considering those articles published until December 13$^{th}$, 2021, cross-checking the references

obtained. Secondary literature derived from the primary sources was also reviewed. The full search strategy is given in the Supplementary material (Supplementary 3).

*2.2. Studies selection*

First, studies of potential interest were evaluated by 2 blind independent researchers (GF and UI), based on the abstract or full text. Grey literature was included if sufficient information was provided. No language restriction was applied.

*2.3. Inclusion and exclusion criteria*

We limited our search to preclinical studies assessing the effect of any psychotropic drug on SARS-CoV-2, including in vitro or animal or clinical (i.e., cohort, case-control, RCT) studies concerning the exposure to any psychotropic drug in patients with COVID-19. Psychotropic drugs included AD, benzodiazepines, AP, lithium, other mood stabilizers, and stimulants. In order to be considered for this SR and MA, articles had to report details on the design, sample description, inclusion criteria, defined aims, clear methodological procedures, and clear outcome definitions. Case-reports, case-series, review articles, commentaries, and letters to the editors were excluded.

*2.4. Data collection process and items and data extraction*

Following the PRISMA statement (Supplementary 1), articles were selected based on title and abstract and, when necessary, on examination of the full text to assess relevance. After the elimination of duplicated sources, the full texts of the potentially eligible studies were retrieved and independently assessed for eligibility. References and additional records identified through other sources were also reviewed to identify further possible studies of interest. Any disagreement between the two raters was resolved through consensus or, when an agreement was not achieved, through discussion with a third reviewer (AM). The following information was

extracted: 1) reference details (i.e., author, year, geographical region, country); 2) type of cell or animal studied (applicable only to in vitro or animal study); 3) study design; 4) sample size; 5) inclusion and exclusion criteria; 6) treatment with psychotropic drugs; 7) primary and secondary outcomes (i.e., risk of SARS-CoV-2 infection, hospitalization rates, clinical deterioration, risk of delirium, use of restraints, intubation or mechanical ventilation, mortality due to any cause); 8) study results. Corresponding authors were contacted for clarification where necessary.

*2.5. Methodological quality assessment*

GF and UI evaluated, blinded to each other, the quality of the included studies. Any disagreement of the judgment of the two reviewers was solved through discussion among study authors. Computational studies were evaluated with a specific tool assessing five main aspects: design, target template modeling, docking tools, molecular dynamics simulation, and the resource for approved drugs (Mohamed et al., 2021). The quality of preclinical studies was evaluated with the OHAT Risk of Bias tool (Eick et al., 2020). The Newcastle-Ottawa scale (NOS) was applied (Herzog et al., 2013; Zeng et al., 2015) for observational studies and the Cochrane risk of bias (RoB) tool for randomized studies (Higgins et al., 2011). We adopted the thresholds for converting Newcastle-Ottawa Scale scores into “good,” “fair,” and “poor” quality criteria, previously described (“AHRQ Comparative Effectiveness Reviews - NCBI Bookshelf,” 2005).

*2.6. Outcomes*

Included clinical studies reported adjusted relative risk (RR), hazard ratio (HR), odds ratio (OR), and 95 % confidence intervals (CI) as their measures of association between psychotropic drugs and COVID-19.

*2.7. Statistical analysis*

Analyses were performed using RStudio R version 3.6.3 (R Development Core Team 2010), and MA was conducted through the *metafor* R-package (Viechtbauer and Viechtbauer 2015) using a random-effects model (restricted maximum-likelihood estimator). Heterogeneity between studies was assessed by the χ2 test of fit (Cochrane Q test) and I2 statistics. A χ2 statistics having a $p < 0.05$, and I2 statistics >50% (Higgins, Thompson et al. 2003) were considered suggestive of high heterogeneity. To examine the association of AD or AP with COVID-19 severe outcomes, patients treated with AD or AP and with COVID-19 were compared to patients with COVID-19 not treated with psychotropics. To examine the association of AD or AP with COVID-19 mortality, patients treated with AD or AP and with COVID-19 were compared to patients with COVID-19 not treated with psychotropics. Since outcomes were reported with different types of effect sizes among included studies, we calculated Risk Ratio (RR) or Odds Ratio (OR) from raw data when necessary. We did not evaluate publication bias according to Cochrane Collaboration recommendations, suggesting that the tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis.

## 3. Results

### *3.1. Study description*

Our literature search identified 390 studies, of which 358 were considered for inclusion after the removal of duplicates. After abstract screening, 47 studies were included for full-text screening. Last, 29 studies fulfilled the selection criteria and were included: 5 computational studies (Khater et al., 2021a; Loschwitz et al., 2021; Naasani, 2021; Pandey et al., 2020; Udrea et al., 2020) (Supplementary Table 1), 9 preclinical studies (Brunotte et al., 2021; Carpinteiro et al., 2020; Creeden et al., 2021; Gordon et al., 2020; Lu et al., 2021; Plaze et al., 2020; Schloer et al., 2021, 2020; Viel et al., 2020) (Supplementary Table 2), and 15 clinical studies (Clelland et al., 2021ì; Diez-Quevedo et al., 2021; Fei et al., 2021; Govind et al., 2021; Harrison et al., 2021; Hoertel et al., 2021, n.d.; Lenze et al., 2020; McKeigue et al., 2021; Nemani et al., 2021; Ohlis et

al., 2021; Oskotsky et al., 2021; Poblador-Plou et al., 2020; Pun et al., 2021; Reis et al., 2021) (Table 1). A flowchart of the review process is presented in Figure 1.

*3.2. Computational studies*

Of the 5 included studies, 4 explored AP and one fluoxetine antiviral activity against SARS-CoV-2 (Supplementary Table 1).

In a molecular docking-based molecular dynamics simulation study exploring the potential mechanisms of binding and activity of haloperidol and dextromethorphan towards the non-structural protein 6 (NSP6), linked to RNA replication of SARS-CoV-2, haloperidol bond more strongly to NSP6 and induced minimal changes in its structure and dynamics (Pandey et al., 2020). In another molecular docking study, thioridazine and its photoproducts mesoridazine and sulphoridazine showed significant biological activity on the SARS-CoV-2 main protease (Udrea et al., 2020). Also, a molecular dynamics simulation-guided study showed that eight compounds including lurasidone have high activity inhibiting the 3CLpro enzyme of SARS-CoV-2 (Loschwitz et al., 2021). A COMPARE analysis study, a novel bioinformatic approach for drug repurposing, confirmed the antiviral activity of several drugs, including valproic acid and thiothixene (Naasani, 2021). Lastly, a molecular docking study showed that fluoxetine bind with SARS-COV-2 main proteas, especially when loaded in lipid polymer hybrid (LPH) nanoparticles to enhance its activity (Khater et al., 2021).

*3.3. Preclinical studies*

Among the 9 included preclinical studies on the therapeutic potential of psychotropic drugs against SARS-CoV-2, 3 studies focused on AP, 5 on AD, and one on lithium (Supplementary Table 2).

In an extensive human protein-protein interaction (PPI) study, inhibitors of mRNA translation and predicted regulators of the Sigma1 and Sigma2 receptors, including haloperidol, acted as

inhibitors of Sars-CoV-2 virus replication and growth (Gordon et al., 2020). Another study using ACE2-HEK293T cell membrane chromatography found an *in-vitro* antiviral activity against SARS-CoV-2 of 19 AP (Lu et al., 2021). Tiapride, aripiprazole, chlorpromazine, thioridazine, and trifluoperazine showed significant viral entry inhibition and high affinity binding with ACE2 protein with Kd: (7.03 ± 3.28)e− 6 M, (8.91 ± 5.25)e− 5 M, (1.38 ± 0.38)e− 5 M, (7.88 ± 0.49)e− 6 M, and (3.33 ± 3.13)e− 5 M, respectively. Furthermore, in another *in-vitro* study using monkey VeroE6 cells, chlorpromazine showed antiviral properties against SARS-CoV-2 (IC50 of 8.2 μM, IC90 of 15.2 μM, CC50 of 13.5 μM and SI of 1.65) and human alveolar basal epithelial A549-ACE2 cells (IC50 of 11.3 μM and IC90 of 14.3 μM) (Plaze et al., 2020).

Several studies explored the effect of fluoxetine or other AD on SARS-CoV-2 infection. Evidence showed that fluoxetine may disrupt NF-kappaB/IL6ST axis and thereby mitigate the cytokine storm (Creeden et al., 2021). Furthermore, both fluoxetine and imipramine strongly reduced SARS-Cov-2 and Influenza A virus titers in Vero E6 and Calu-3 cells without cytotoxic effects (Schloer et al., 2020). Two studies showed that the combination of remdesivir with fluoxetine had an antiviral synergistic effect against bronchial epithelial cell lines Calu-3 and the Vero E6 cells (Brunotte et al., 2021; Schloer et al., 2021). In another *in-vitro* study, different AD including amitriptyline, imipramine, fluoxetine, sertraline, escitalopram, and maprotiline inhibited acid sphingomyelinase, significantly reduced the infection of Vero cells in pp-VSV-SARS-Cov-2 spike particles, and prevented the upregulation of ACE2 expression as a marker of the infection (Carpinteiro et al., 2020).

Only one study on human iPSCs-derived astrocytes explored the effect of lithium against SARS-CoV-2, showing that low doses of lithium (2.5 μM, 10 μM, and 25 μM) protect against SARS-CoV-2 (Viel et al., 2020).

*3.4. Clinical studies*

Among the 15 clinical studies, 2 randomized controlled trials (RCT), 5 cohort studies, 6 retrospective cross-sectional studies, and 2 case-control studies were included (Table 1). A total of 145628 patients were included in the synthesis. Of these, 44770 received psychotropic medication. The diagnosis of COVID-19 was confirmed by the polymerase chain reaction (PCR) test in all these studies.

**Table 1. Characteristics of the included clinical studies and narrative synthesis of results**

| Study and Location | Inclusion Criteria | End Points/Aims | Sample | Treatment regimens (only for experimental studies) | Results highlights |
|---|---|---|---|---|---|
| **Randomized Clinical Trials** | | | | | |
| **Lenze et al., 2020, USA** | Adults with SARS-CoV-2 infection confirmed by PCR; symptomatic within 7 days of the first dose of the study medication | Clinical deterioration defined as the presence of dyspnea or pneumonia and decrease of SO2 < 92% | 152 patients randomized 1:1 to fluvoxamine or placebo | Fluvoxamine up to 100mg 3 times daily v.s. placebo for 15 days | Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and 6 of 72 patients in the placebo group (AD=8.7%, CI 95% 1.8%-16.4%; p=0.009) |
| **Reis et al., 2021, Brazil** | 7-days symptomatic adults with SARS-CoV-2 infection confirmed by PCR or antigen test. At least one additional criterion for high risk for COVID-19 (e.g., diabetes, cardiovascular disease, among others) | A composite endpoint of admission to hospital setting for COVID-19 remaining under observation >6h or referral to further hospitalization within 28 days of randomization | 741 randomized to fluvoxamine, 756 to placebo | Fluvoxamine 100 mg twice daily v.s. placebo for 10 days | The proportion of patients observed in a COVID-19 emergency setting for more than 6 h or transferred to a tertiary hospital due to COVID-19 was lower for the fluvoxamine group compared with placebo (RR=0.68; 95% CI 0.52–0.88) |
| **Retrospective Cohort Studies** | | | | | |
| **Clelland et al., 2021, USA** | 165 psychiatric inpatients hospitalized from January to July 2020 | Assess if AD or vitamin D modifies the risk of COVID-19 infection | 165 inpatients (91, 55%, positive for COVID-19) | Not applicable | A significant protective association was observed between AD use and COVID-19 infection (OR= 0.33, 95% CI 0.15–0.70, adjusted p<0.05). |
| **Fei et al., 2021, Europe** | Adults hospitalized for COVID-19 | Differences among IL-6 blood levels in patients treated with SSRI and/or SNRI during hospitalization vs non treated | 402 patients (34, 8.45%, treated with AD) | Not applicable | ARDS (p<0.02), intubation (p<0.04) were significantly lower in the subgroup of patients with AD, while no differences in mortality rates were found among the two groups. |
| **Nemani et al., 2021, USA** | Adults with SARS-CoV-2 infection confirmed by PCR from March 3, 2020, and February 17, 2021. Diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder | Association between AP use and mortality for COVID-19 | 464 patients (196, 42.2%, treated with AP) | Not applicable | AP treatment was not significantly associated with mortality (OR=1; 95% CI, 0.48-2.08) |
| **Ohlis et al, 2011, Sweden** | A psychotic disorder diagnosis registered between 1 January 2019 and 29 February 2020 and prescribed AP during 2020 | Compare the risk of severe COVID-19 outcomes between patients on clozapine or other AP | 8233 patients (966, 11.7%, on clozapine) | Not applicable | No statistically significant differences in outcome rates were found between the two groups of patients [inpatient care (HR= 0.96, 95% CI 0.54-1.70), ICU care (HR=1.69, 95% CI 0.48-5.93) or death (HR=0.86, 95% CI 0.26-2.8) |

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| **Oskotsky et al., 2021, USA** | Adults with SARS-CoV-2 infection from January to September 2020 | Assess the association between SSRIs use and severe COVID-19 outcomes | 83584 patients recruited across 87 health care centers | Not applicable | Mortality was reduced among patients prescribed any SSRI (RR= 0.92, 95% CI, 0.85-0.99); fluoxetine (RR= 0.72, 95% CI, 0.54-0.97); and fluoxetine or fluvoxamine (RR= 0.74, 95% CI, 0.55-0.99) |
| **Cross-Sectional Studies** | | | | | |
| **Govind et al. 2020, UK** | Diagnosis of schizophrenia spectrum disorder (ICD-10); taking AP between 1 December 2019 to 1 March 2020 | Assess the association between clozapine and risk of COVID-19 infection | 6309 participants (n=1282, 20.32% on clozapine) | Not applicable | Individuals on clozapine had increased risk of COVID-19 infection compared with those who were on other AP medication (HR= 2.62, 95% CI 1.73–3.96) |
| **Hoertel et al., 2021a, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR from January 24th to April 1st, 2020. | Assess the association between AD use and severe COVID-19 | 7230 adults hospitalized for COVID-19 (n=345, 4.8% received an AD within 48h of hospital admission) | Not applicable | AD use was associated with a reduced risk of intubation or death (adjusted HR=0.56; 95% CI 0.43–0.73, p<0.001). The association was significant specifically for fluoxetine, paroxetine, escitalopram, venlafaxine, and mirtazapine (all p<0.05) |
| **Hoertel et al., 2021b, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR | Assess the association between haloperidol treatment and severe COVID-19 | 15,121 inpatients with COVID-19 (n=39, 0.03%, received haloperidol within the first 48h of admission, mean dose of 4.5 mg/day (SD = 5.2) for 8.4 days (SD = 7.2) | Not applicable | No significant association between haloperidol treatment and severe COVID-19 outcomes was found |
| **Pobladór-Plou et al., 2021, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR | Assess the risk factors for COVID-19 mortality | 4412 individuals | Not applicable | AP were amongst the medications associated the most with an increased likelihood of mortality both in men (OR=1.66, 95% CI 1.13-2.43), and women (OR=1.81, 95% CI 1.29-2.53). |
| **Pun et al., 2021** | Adult SARS-CoV-2 patients admitted to ICUs | Investigate risk factors for delirium in critically ill patients with COVID-19 | 2088 inpatients with COVID (19 admitted to ICUs) | Not applicable | Mechanical ventilation, use of restraints, benzodiazepine, opioid, and vasopressor infusions, and AP were each associated with a higher risk of delirium the next day (all p≤0.04) |
| **Diez-Quevedo et al., 2021, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR | Assess the association between psychotropic drugs and mortality in COVID-19 | 2150 adult inpatients (n=1011 received psychotropic medications during admission) | Not applicable | Previous year's treatment with anxiolytics/hypnotics and AD were independently associated with lower mortality risk (HR=0.47 and 0.43 respectively) |
| **Case-Control Studies** | | | | | |
| **Harrison et al., 2021, UK** | First cohort: Patients ≥ 65 | Assess the association | 8414 individuals with | Not applicable | People with dementia and COVID-19 who |

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| | years with dementia and COVID-19; used AP in the 30 days prior to COVID-19 Second cohort: Controls ≥ 65 years with dementia; used AP 30 days prior to or on a visit to a healthcare organization | between AP use and COVID-19 related thromboembolic events or all-cause mortality | COVID-19, dementia, and use of AP<br><br>31,963 controls | | received AP had significantly higher odds of 30-day thromboembolic events (OR=1.36, 95% CI: 1.21–1.52), and all-cause mortality (OR=1.93, 95% CI 1.71–2.17) than controls. |
| **McKeigue et al. 2021, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR, with severe COVID-19 and matched controls | Assess the association between prior drug prescribing and severe COVID-19 | 4251 cases of severe COVID-19<br>36,738 matched controls for age and sex | Not applicable | Several drugs were significantly associated with severe COVID-19. The largest effect was for AP (RR= 4.18, 95% CI 3.42-5.11) |

Abbreviations: AD=antidepressants; AP=antipsychotics; OR=Odds Ratio; CI=confidence intervals; SSRI=serotonin selective reuptake inhibitors; SNRI=serotonin and norepinephrine reuptake inhibitors; ADRS=Acute Respiratory Distress Syndrome; RRa=rate ratio; RR=relative risk; HR=hazard ratio; SD=standard deviation).

Nine studies involving 7188 patients treated with AD or AP and 19119 controls were included in the MA. Four studies focused on AD (Fei et al., 2021; Lenze et al., 2020; Oskotsky et al., 2021; Reis et al., 2021), one study explored the role of AP (Nemani et al., 2021), and four studies included both medications (Diez-Quevedo et al., 2021; Hoertel et al., 2021; McKeigue et al., 2021; Poblador-Plou et al., 2020). MA was possible for the following outcomes: risk of **severe** COVID-19 (considered as risk of intubation or death), and mortality due to any cause among people diagnosed with COVID-19.

*3.4.1. Antidepressant or antipsychotic use and risk of severe COVID-19*

Two observational studies (Hoertel et al., 2021; McKeigue et al., 2021) explored the risk of severe COVID-19 among people with or without AD use. The pooled RR was 1.71 (0.65-4.51 CI). High heterogeneity was found between studies ($I^2$ = 96.9%; Q=32.22, p<0.01). Results are reported in Figure 2. Results of the analysis split according to the class of AD assumed (SSRI vs other antidepressants) using unadjusted data are reported in the supplementary material

(Supplementary Figure 3). The pooled RR was 1.56 (1.40-1.73 CI). No heterogeneity was found between studies ($I^2$ = 0%; Q=2.67, p=0.45).

The same studies (Hoertel et al., 2021a; McKeigue et al., 2021) also explored the risk of severe COVID-19 among people with or without AP use. The pooled RR was 3.66 (2.76-4.85 CI). No significant heterogeneity was found between studies ($I^2$ = 67.4%; Q=3.07, p=0.08). Results are shown in Figure 3.

*3.4.2. Antidepressant or antipsychotic use and mortality*

Two RCTs (Lenze et al., 2020; Reis et al., 2021) observed the mortality rates among people with COVID-19 and treated with fluvoxamine compared to placebo. The pooled OR was 0.15 (0.02-0.95 CI). No heterogeneity was found between studies ($I^2$ = 1.5%; Q=1.01, p=0.31). Results are shown in Figure 4.

Four observational studies (Diez-Quevedo et al., 2021; FEIei et al., 2021a; Oskotsky et al., 2021; Poblador-Plou et al., 2020) observed the mortality rates among people with COVID-19, treated with AD. The pooled RR was 0.94 (0.81-1.09 CI). No significant heterogeneity was found between studies ($I^2$ = 0%; Q=0.99, p=0.8). Results are shown in Figure 5.

Three observational studies (Diez-Quevedo et al., 2021; Nemani et al., 2021; Poblador-Plou et al., 2020) observed the mortality rates among people with COVID-19, treated with AP. The pooled OR was 1.53 (1.15-2.03 CI). No significant heterogeneity was found between studies ($I^2$ = 52.2%; Q=4.04, p=0.13). Results are shown in Figure 6.

*3.5. Quality of the Included Studies*

Regarding the quality of computational studies, high-quality items including the use of two or more approved drug databases, analysis of molecular dynamic simulation, the use of crystal structure for the generation of the target sequence, and the use of AutoDock Vina combined with other docking tools occurred in about 20%, 60%, 20%, and 80% of included studies

(Supplementary Table 3). All preclinical studies show a low risk of bias (Supplementary Table 4). Overall, among clinical case-control studies and cohort studies, 11 had “good” quality, one was of “fair” quality, and three were of "poor quality", based on the Newcastle-Ottawa Scale (see Supplementary Table 5). The Cochrane risk of bias tool indicated a low risk for bias for both RCTs included (Supplementary Table 6).

**4. Discussion**

This is the first meta-analysis on psychotropic drug repurposing for COVID-19. The urgency to find effective drugs against COVID-19 has pushed research in different fields to face the ongoing pandemic. In our data synthesis, preclinical evidence showed that both antipsychotics and antidepressants, in particular SSRI, inhibit Sars-CoV-2 replication or activity, either directly or by anti-inflammatory response modulation. Computational approaches might play an important role in exploring the efficacy of effective psychotropic drugs against SARS-CoV-2, but according to our findings, they do not appear to fulfill clinical expectations. Based on preclinical evidence, several RCTs were conducted to explore the effectiveness of psychotropic drug repurposing for COVID-19.

The two RCTs included (Lenze et al., 2020; Reis et al., 2021) showed that fluvoxamine is effective in reducing the risk of COVID-19 progression or hospitalization when taken at appropriate doses during 10-15 days compared with placebo. Since the two studies had different primary outcomes, we conducted a meta-analysis on the association between fluvoxamine use and all-cause mortality, which showed reduced mortality in patients taking fluvoxamine compared with placebo. Fluvoxamine seems to be effective for COVID-19 treatment given its anti-inflammatory potential, mediated by the endoplasmatic reticulum protein (S1R) activation that might regulate cytokine production (Rosen et al., 2019; Sukhatme et al., 2021), as well as its antiplatelet activity, possibly reducing thrombosis’s risk (Cloutier et al., 2018; Sukhatme et al., 2021). Not only fluvoxamine is well tolerated, available and a low-cost drug, but it could be used as early

treatment for COVID-19 in high-risk populations preventing clinical deterioration. Furthermore, besides fluvoxamine, other SSRIs, including fluoxetine, can decrease levels of proinflammatory cytokines (e.g., IL-6) (Yoshimura et al., 2017)which contribute to the cytokine storm associated with fatal outcomes in COVID-19 (Fajgenbaum and June, 2020). Evidence from our systematic review points to AD protective effect from Sars-CoV-2 infection (Clelland et al., 2021), COVID-19 severe outcomes (FEeiI et al., 2021b; Hoertel et al., 2021a), and mortality (Diez-Quevedo et al., 2021; Oskotsky et al., 2021). However, we found no significant association between the use of AD and the risk of severe COVID-19 or mortality in the two meta-analyses. First, it should be noted the meta-analysis on the association of AD with severe COVID-19 was conducted on a population with high rates of polypharmacy, including other psychotropics (McKeigue et al., 2021), thus complicating the observation of a univocal effect of AD against severe COVID-19. in addition, several studies lacked relevant information such as, among the others, the reason for prescribing the AD, the presence of possible psychiatric comorbidities, treatment adherence before COVID-19 symptoms, thus preventing causal inferences.

On the other side, AP use significantly increased the risk of severe COVID-19 and mortality in our analyses. Coherently, a meta-analysis on the association of mental illness, psychotropics, and COVID-19 risk outlined a strong association between exposure to antipsychotics and COVID-19 mortality (OD=3.71, 1.74–7.91 CI) (Vai et al., 2021).

Undoubtedly, in all the included studies, AP treatments were usually prescribed during hospitalization, thereby indirectly associating with a more severely affected subpopulation of COVID-19 patients or with forthcoming deterioration. Furthermore, in all the included studies AP were given independently of diagnosis, they were considered as a homogenous group without any differentiation or stratification (e.g., based on metabolic side effects), and AP polypharmacotherapy was detected in most cases. However, these results and their implications for the clinical management of COVID-19 have to be taken into account under a careful global clinical evaluation, especially in patients with psychiatric disorders. Indeed, individuals with

severe mental disorders represent a highly vulnerable population to COVID-19 infection and its adverse outcomes (Wang et al., 2021) and should likely be prioritized for vaccination and treatment (Reininghaus et al., 2022). On the other side, patients with good adherence to AP are less likely to get infected from Sars-CoV-2 and show better COVID-19 outcomes compared with the general population(Canal-Rivero et al., 2021). Also, the possibility of a spurious result concerning the association of AP use and negative COVID-19 outcomes cannot be ruled out. AP show a heterogeneous but significant positive association with metabolic complications (Pillinger et al., 2020; Zhang et al., 2017), and the presence of metabolic comorbidities such as diabetes or metabolic syndrome among COVID-19 patients significantly increased the risk of mortality, respiratory failure, duration of ventilator dependence, severe/critical COVID-19, ICU admission, and length of hospital stay (Denson et al., 2021; Espiritu et al., 2021).

Our suggestion is that patients with psychiatric disorders should maintain psychotropic treatment to avoid both relapses of their baseline condition and the higher risk to get infected with COVID-19, in particular when considering treatment with AD such as fluvoxamine. Considering the absence of high-quality evidence or RCT on the use of AP for COVID-19, we recommend maintaining AP ongoing treatment in patients with COVID-19 and a psychiatric illness. The use of AP in people without psychiatric conditions should be evaluated on an individual basis, considering also that some AP showed benefits over placebo for treatment of delirium in patients with COVID-19 (Ostuzzi et al., 2020), and their use is considered safe and recommended (Anmella et al., 2020).

**5. Limitations**

There are some shortcomings in this SR and MA that should be pointed out. Due to the characteristics of observational studies, it was difficult to collect data in all of them about possible confounders. Adjusting for polypharmacotherapy, psychiatric diagnosis, and high-risk conditions for severe COVID-19 (age, sex, previous medical comorbidities) was not possible for

every study included in the meta-analyses. Moreover, we could not assess publication bias due to the low number of studies in each meta-analysis (n<10), since Egger's test might have lacked the statistical power to detect bias. In addition, some of the included studies were assessed to be of poor quality, which varied widely in the effect size measures. In particular, studies on fluvoxamine were of a higher quality and there were no clinical trials on on other AD, thus we cannot exclude the potential positive effect of other AD in patients with COVID-19.

## 6. Conclusion

Preclinical evidence showed that both antipsychotics and antidepressants, in particular SSRI, inhibit Sars-CoV-2 replication or activity, either directly or by anti-inflammatory response modulation. However, the translation of these results into clinical practice needs to be further explored. Regarding antidepressants, fluvoxamine may reduce the risk of severe COVID-19 outcomes and mortality, and therefore, SSRI might be good candidates for drug repurposing in COVID-19. Especially in the early treatment of the disease, they might be useful to prevent psychiatric symptoms in complications such as long-Covid (Llach and Anmella, 2022; Llach and Vieta, 2021). Increased risk for severe COVID-19 and mortality with antipsychotics is not absolute and should be contextualized to individual cases. Ongoing treatment with antipsychotics should not be discontinued in psychiatric patients.

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# Psychotropic drug repurposing for COVID-19: a Systematic Review and Meta-Analysis

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**Abstract**

Several psychotropic drugs, including antidepressants (AD), mood stabilizers, and antipsychotics (AP) have been suggested to have favorable effects in the treatment of COVID-19. The aim of this systematic review and meta-analysis was to collect evidence from ~~preclinical and clinical~~ studies concerning the scientific evidence for the repurposing of psychotropic drugs in COVID-19 treatment. Two independent authors searched PubMed-MEDLINE, Scopus, PsycINFO, and ClinicalTrials.gov databases, and reviewed the reference lists of articles for eligible articles published up to 13th December, 2021. All computational, preclinical and clinical (observational and/or RCTs) studies on the effect of any psychotropic drug on Sars-CoV-2 or patients with COVID-19 were considered for inclusion. We conducted random effect meta-analyses on clinical studies reporting the effect of AD or AP on COVID-19 outcomes. 29 studies were included in the synthesis: 15 clinical, 9 preclinical, and 5 computational studies. 9 clinical studies could be included in the quantitative analyses. AD did not increase the risk of severe COVID-19 (RR= 1.71; CI 0.65-4.51) or mortality (RR=0.94; CI 0.81-1.09). Fluvoxamine was associated with a reduced risk of mortality for COVID-19 (OR=0.15; CI 0.02-0.95). AP increased the risk of severe COVID-19 (RR=3.66; CI 2.76-4.85) and mortality (OR=1.53; CI 1.15-2.03). Fluvoxamine might be a possible candidate for psychotropic drug repurposing in COVID-19 due to its anti-inflammatory and antiviral potential, while evidence on other AD is still controversial. Although AP are associated with worse COVID-19 outcomes, their use should be evaluated case to case and ongoing treatment with antipsychotics should be not discontinued in psychiatric patients.

**Keywords**: **Covid-19, psychotropic drugs, antidepressants, antipsychotics, anti-inflammatory, antiviral**

## 1. Introduction

The spreading infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused over 6 million deaths for COVID-19 worldwide so far (WHO, 2022) despite the unprecedented joint effort to study and treat this illness. The spectrum of COVID-19 clinical manifestations is very broad, ranging from the absence of symptoms to severe pneumonia with respiratory failure (Zhu et al., 2020). Notwithstanding the fast development and ongoing massive administration of vaccines, which proved to be safe and effective (Polack et al., 2020), a high number of people are still at risk for COVID-19 and related severe complications (Carbonell et al., 2021). Currently, the elevation of the pro-inflammatory cytokines and chemokines, the so-called cytokine storm (Fajgenbaum and June, 2020), is the main pathophysiological mechanism underlying the severity of COVID-19. Also, alterations of both the serotonin and dopamine synthetic pathways (Attademo and Bernardini, 2021) might be involved in COVID-19 pathophysiology and related to the documented neurological long-term sequelae observed (Chou et al., 2021; L. Liu et al., 2021). The repurposing of existing drugs proved to be the fastest and safest way to clinically tackle the pandemic, representing a cost-efficient alternative to the classic drug development process, also disclosing potential mechanisms of action for novel indications (Smith et al., 2021). Repurposed drugs mainly target RNA polymerase inhibition (Jiang et al., 2021), angiotensin-converting enzyme-2 (ACE-2), and transmembrane serine protease-2 (TMPRSS2) inhibitors (Hoffmann et al., 2020). Indeed, FDA approved remdesivir, an antiviral with in vitro inhibitory activity against SARS-CoV-1 and the Middle East respiratory syndrome (MERS-CoV) (Sheahan et al., 2020), and tocilizumab, an inhibitor of interleukin-6 (IL-6) used in several diseases including rheumatoid arthritis (Hennigan and Kavanaugh, 2008) for hospitalized patients with COVID-19 (Beigel et al., 2020; Salama et al., 2020). Among other available drugs, psychotropic medications have well-understood safety profiles, and showed anti-inflammatory prop~~ri~~erties (Baumeister et al., 2016), being possible candidates for drug repurposing in COVID-19. For instance, lithium shows immune-modulatory properties, increasing neutrophil, but also lymphocytes, leukocytes, and natural killer cells count

(Pietruczuk et al., 2018), while directly impeding viral replication in both animals and in vitro studies (Murru et al., 2020). Some antidepressants (AD) such as clomipramine and fluoxetine decrease inflammatory cytokines (IL-6), interferon γ, and tumor necrosis factor (TNF) (Caiaffo et al., 2016), while fluvoxamine reduces the production of pro-inflammatory cytokines and showed a possible antiviral effect (Sukhatme et al., 2021). Studies on the effects of antipsychotics (AP) on inflammation are somewhat conflicting, showing both pro- and anti-inflammatory activity (Baumeister et al., 2016; Mondelli and Howes, 2013). Also, SARS-CoV-2 may be sensitive to GSK-3 inhibitors, including lithium (X. Liu et al., 2021).

### *1.1. Aims*

The aim of this Systematic Review (SR) and meta-analysis (MA) is threefold: 1) to collect the available computational, preclinical and clinical evidence grounding the possible drug-repurposing of psychotropic drugs for the treatment of COVID-19 and its related outcomes; 2) to quantify the association between psychotropic drugs and COVID-19 outcomes; 3) to depict possible recommendations for future clinical studies on this topic.

## 2. Material and methods

We followed the procedures outlined in the 2020 update of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) (Page et al., 2021) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Brooke et al., 2021), following an a priori protocol. The protocol of this systematic review and meta-analysis was posted on PROSPERO (ID 336944).

### *2.1. Literature search*

To identify studies for this review, a systematic search was performed using MEDLINE/PubMed/Index Medicus, EMBASE, Scopus, Psycinfo, and www.clinicaltrials.gov considering those articles published until December 13th, 2021, cross-checking the references

obtained. Secondary literature derived from the primary sources was also reviewed. The full search strategy is given in the Supplementary material (Supplementary 3).

*2.2. Studies selection*

First, studies of potential interest were evaluated by 2 blind independent researchers (GF and UI), based on the abstract or full text. Grey literature was included if sufficient information was provided. No language restriction was applied.

*2.3. Inclusion and exclusion criteria*

We limited our search to preclinical studies assessing the effect of any psychotropic drug on SARS-CoV-2, including in vitro or animal or clinical (i.e., cohort, case-control, RCT) studies concerning the exposure to any psychotropic drug in patients with COVID-19. Psychotropic drugs included AD, ~~anti-anxiety medications~~benzodiazepines, AP, lithium, other mood stabilizers, and stimulants. In order to be considered for this SR and MA, articles had to report details on the design, sample description, inclusion criteria, defined aims, clear methodological procedures, and clear outcome definitions. Case-reports, case-series, review articles, commentaries, and letters to the editors were excluded.

*2.4. Data collection process and items and data extraction*

Following the PRISMA statement (Supplementary 1), articles were selected based on title and abstract and, when necessary, on examination of the full text to assess relevance. After the elimination of duplicated sources, the full texts of the potentially eligible studies were retrieved and independently assessed for eligibility. References and additional records identified through other sources were also reviewed to identify further possible studies of interest. Any disagreement between the two raters was resolved through consensus or, when an agreement was not achieved, through discussion with a third reviewer (AM). The following information was

extracted: 1) reference details (i.e., author, year, geographical region, country); 2) type of cell or animal studied (applicable only to in vitro or animal study); 3) study design; 4) ~~the number of the sample~~sample size; 5) inclusion and exclusion criteria; 6) treatment with psychotropic drugs; 7) primary and secondary outcomes (i.e., risk of SARS-CoV-2 infection, hospitalization rates, clinical deterioration, risk of delirium, use of restraints, intubation or mechanical ventilation, mortality due to any cause); 8) study results. Corresponding authors were contacted for clarification where necessary.

*2.5. Methodological quality assessment*

GF and UI evaluated, blinded to each other, the quality of the included studies. Any disagreement of the judgment of the two reviewers was solved through discussion among study authors. Computational studies were evaluated with a specific tool assessing five main aspects: design, target template modeling, docking tools, molecular dynamics simulation, and the resource for approved drugs (Mohamed et al., 2021). The quality of preclinical studies was evaluated with the OHAT Risk of Bias tool (Eick et al., 2020). The Newcastle-Ottawa scale (NOS) was applied (Herzog et al., 2013; Zeng et al., 2015) for observational studies and the Cochrane risk of bias (RoB) tool for randomized studies (Higgins et al., 2011). We adopted the thresholds for converting Newcastle-Ottawa Scale scores into “good,” “fair,” and “poor” quality criteria, previously described (“AHRQ Comparative Effectiveness Reviews - NCBI Bookshelf,” 2005).

*2.6. Outcomes*

Included clinical studies reported adjusted relative risk (RR), hazard ratio (HR), odds ratio (OR), and 95 % confidence intervals (CI) as their measures of association between psychotropic drugs and COVID-19.

*2.7. Statistical analysis*

Analyses were performed using RStudio R version 3.6.3 (R Development Core Team 2010), and MA was conducted through the *metafor* R-package (Viechtbauer and Viechtbauer 2015) using a random-effects model (restricted maximum-likelihood estimator). Heterogeneity between studies was assessed by the χ2 test of fit (Cochrane Q test) and I2 statistics. A χ2 statistics having a $p < 0.05$, and I2 statistics >50% (Higgins, Thompson et al. 2003) were considered suggestive of high heterogeneity. To examine the association of AD or AP with COVID-19 severe outcomes, patients treated with AD or AP and with COVID-19 were compared to patients with COVID-19 not treated with psychotropics. To examine the association of AD or AP with COVID-19 mortality, patients treated with AD or AP and with COVID-19 were compared to patients with COVID-19 not treated with psychotropics. Since outcomes were reported with different types of effect sizes among included studies, we calculated Risk Ratio (RR) or Odds Ratio (OR) from raw data when necessary. We did not evaluate publication bias according to Cochrane Collaboration recommendations, suggesting that the tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis.

## 3. Results

### *3.1. Study description*

Our literature search identified 390 studies, of which 358 were considered for inclusion after the removal of duplicates. After abstract screening, 47 studies were included for full-text screening. Last, 29 studies fulfilled the selection criteria and were included: 5 computational studies (Khater et al., 2021a; Loschwitz et al., 2021; Naasani, 2021; Pandey et al., 2020; Udrea et al., 2020) (Supplementary Table 1), 9 preclinical studies (Brunotte et al., 2021; Carpinteiro et al., 2020; Creeden et al., 2021; Gordon et al., 2020; Lu et al., 2021; Plaze et al., 2020; Schloer et al., 2021, 2020; Viel et al., 2020) (Supplementary Table 2), and 15 clinical studies (Clelland et al., 2021ì; Diez-Quevedo et al., 2021; Fei et al., 2021; Govind et al., 2021; Harrison et al., 2021; Hoertel et al., 2021, n.d.; Lenze et al., 2020; McKeigue et al., 2021; Nemani et al., 2021; Ohlis et

al., 2021; Oskotsky et al., 2021; Poblador-Plou et al., 2020; Pun et al., 2021; Reis et al., 2021) (Table 1). A flowchart of the review process is presented in Figure 1.

*3.2. Computational studies*

Of the 5 included studies, 4 explored AP and one fluoxetine antiviral activity against SARS-CoV-2 (Supplementary Table 1).

In a molecular docking-based molecular dynamics simulation study exploring the potential mechanisms of binding and activity of haloperidol and dextromethorphan towards the non-structural protein 6 (NSP6), linked to RNA replication of SARS-CoV-2, haloperidol bond more strongly to NSP6 and induced minimal changes in its structure and dynamics (Pandey et al., 2020). In another molecular docking study, thioridazine and its photoproducts mesoridazine and sulphoridazine showed significant biological activity on the SARS-CoV-2 main protease (Udrea et al., 2020). Also, a molecular dynamics simulation-guided study showed that eight compounds including lurasidone have high activity inhibiting the 3CLpro enzyme of SARS-CoV-2 (Loschwitz et al., 2021). A COMPARE analysis study, a novel bioinformatic approach for drug repurposing, confirmed the antiviral activity of several drugs, including valproic acid and thiothixene (Naasani, 2021). Lastly, a molecular docking study showed that fluoxetine bind with SARS-COV-2 main proteas, especially when loaded in lipid polymer hybrid (LPH) nanoparticles to enhance its activity (Khater et al., 2021).

*3.3. Preclinical studies*

Among the 9 included preclinical studies on the therapeutic potential of psychotropic drugs against SARS-CoV-2, 3 studies focused on AP, 5 on AD, and one on lithium (Supplementary Table 2).

In an extensive human protein-protein interaction (PPI) study, inhibitors of mRNA translation and predicted regulators of the Sigma1 and Sigma2 receptors, including haloperidol, acted as

inhibitors of Sars-CoV-2 virus replication and growth (Gordon et al., 2020). Another study using ACE2-HEK293T cell membrane chromatography found an *in-vitro* antiviral activity against SARS-CoV-2 of 19 AP (Lu et al., 2021). Tiapride, aripiprazole, chlorpromazine, thioridazine, and trifluoperazine showed significant viral entry inhibition and high affinity binding with ACE2 protein with Kd: (7.03 ± 3.28)e− 6 M, (8.91 ± 5.25)e− 5 M, (1.38 ± 0.38)e− 5 M, (7.88 ± 0.49)e− 6 M, and (3.33 ± 3.13)e− 5 M, respectively. Furthermore, in another *in-vitro* study using monkey VeroE6 cells, chlorpromazine showed antiviral properties against SARS-CoV-2 (IC50 of 8.2 μM, IC90 of 15.2 μM, CC50 of 13.5 μM and SI of 1.65) and human alveolar basal epithelial A549-ACE2 cells (IC50 of 11.3 μM and IC90 of 14.3 μM) (Plaze et al., 2020).

Several studies explored the effect of fluoxetine or other AD on SARS-CoV-2 infection. Evidence showed that fluoxetine may disrupt NF-kappaB/IL6ST axis and thereby mitigate the cytokine storm (Creeden et al., 2021). Furthermore, both fluoxetine and imipramine strongly reduced SARS-Cov-2 and Influenza A virus titers in Vero E6 and Calu-3 cells without cytotoxic effects (Schloer et al., 2020). Two studies showed that the combination of remdesivir with fluoxetine had an antiviral synergistic effect against bronchial epithelial cell lines Calu-3 and the Vero E6 cells (Brunotte et al., 2021; Schloer et al., 2021). In another *in-vitro* study, different AD including amitriptyline, imipramine, fluoxetine, sertraline, escitalopram, and maprotiline inhibited acid sphingomyelinase, significantly reduced the infection of Vero cells in pp-VSV-SARS-Cov-2 spike particles, and prevented the upregulation of ACE2 expression as a marker of the infection (Carpinteiro et al., 2020).

Only one study on human iPSCs-derived astrocytes explored the effect of lithium against SARS-CoV-2, showing that low doses of lithium (2.5 μM, 10 μM, and 25 μM) protect against SARS-CoV-2 (Viel et al., 2020).

*3.4. Clinical studies*

Among the 15 clinical studies, 2 randomized controlled trials (RCT), 5 cohort studies, 6 retrospective cross-sectional studies, and 2 case-control studies were included (Table 1). A total of 145628 patients were included in the synthesis. Of these, 44770 received psychotropic medication. The diagnosis of COVID-19 was confirmed by the polymerase chain reaction (PCR) test in all these studies.

**Table 1. Characteristics of the included clinical studies and narrative synthesis of results**

| Study and Location | Inclusion Criteria | End Points/Aims | Sample | Treatment regimens (only for experimental studies) | Results highlights |
|---|---|---|---|---|---|
| **Randomized Clinical Trials** | | | | | |
| **Lenze et al., 2020, USA** | Adults with SARS-CoV-2 infection confirmed by PCR; symptomatic within 7 days of the first dose of the study medication | Clinical deterioration defined as the presence of dyspnea or pneumonia and decrease of SO2 < 92% | 152 patients randomized 1:1 to fluvoxamine or placebo | Fluvoxamine up to 100mg 3 times daily v.s. placebo for 15 days | Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and 6 of 72 patients in the placebo group (AD=8.7%, CI 95% 1.8%-16.4%; p=0.009) |
| **Reis et al., 2021, Brazil** | 7-days symptomatic adults with SARS-CoV-2 infection confirmed by PCR or antigen test. At least one additional criterion for high risk for COVID-19 (e.g., diabetes, cardiovascular disease, among others) | A composite endpoint of admission to hospital setting for COVID-19 remaining under observation >6h or referral to further hospitalization within 28 days of randomization | 741 randomized to fluvoxamine, 756 to placebo | Fluvoxamine 100 mg twice daily v.s. placebo for 10 days | The proportion of patients observed in a COVID-19 emergency setting for more than 6 h or transferred to a tertiary hospital due to COVID-19 was lower for the fluvoxamine group compared with placebo (RR=0.68; 95% CI 0.52–0.88) |
| **Retrospective Cohort Studies** | | | | | |
| **Clelland et al., 2021, USA** | 165 psychiatric inpatients hospitalized from January to July 2020 | Assess if AD or vitamin D modifies the risk of COVID-19 infection | 165 inpatients (91, 55%, positive for COVID-19) | Not applicable | A significant protective association was observed between AD use and COVID-19 infection (OR= 0.33, 95% CI 0.15–0.70, adjusted p<0.05). |
| **Fei et al., 2021, Europe** | Adults hospitalized for COVID-19 | Differences among IL-6 blood levels in patients treated with SSRI and/or SNRI during hospitalization vs non treated | 402 patients (34, 8.45%, treated with AD) | Not applicable | ARDS (p<0.02), intubation (p<0.04) were significantly lower in the subgroup of patients with AD, while no differences in mortality rates were found among the two groups. |
| **Nemani et al., 2021, USA** | Adults with SARS-CoV-2 infection confirmed by PCR from March 3, 2020, and February 17, 2021. Diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder | Association between AP use and mortality for COVID-19 | 464 patients (196, 42.2%, treated with AP) | Not applicable | AP treatment was not significantly associated with mortality (OR=1; 95% CI, 0.48-2.08) |
| **Ohlis et al, 2011, Sweden** | A psychotic disorder diagnosis registered between 1 January 2019 and 29 February 2020 and prescribed AP during 2020 | Compare the risk of severe COVID-19 outcomes between patients on clozapine or other AP | 8233 patients (966, 11.7%, on clozapine) | Not applicable | No statistically significant differences in outcome rates were found between the two groups of patients [inpatient care (HR= 0.96, 95% CI 0.54-1.70), ICU care (HR=1.69, 95% CI 0.48-5.93) or death (HR=0.86, 95% CI 0.26-2.8) |

| | | | | | |
|---|---|---|---|---|---|
| **Oskotsky et al., 2021, USA** | Adults with SARS-CoV-2 infection from January to September 2020 | Assess the association between SSRIs use and severe COVID-19 outcomes | 83584 patients recruited across 87 health care centers | Not applicable | Mortality was reduced among patients prescribed any SSRI (RR= 0.92, 95% CI, 0.85-0.99); fluoxetine (RR= 0.72, 95% CI, 0.54-0.97); and fluoxetine or fluvoxamine (RR= 0.74, 95% CI, 0.55-0.99) |
| **Cross-Sectional Studies** | | | | | |
| **Govind et al. 2020, UK** | Diagnosis of schizophrenia spectrum disorder (ICD-10); taking AP between 1 December 2019 to 1 March 2020 | Assess the association between clozapine and risk of COVID-19 infection | 6309 participants (n=1282, 20.32% on clozapine) | Not applicable | Individuals on clozapine had increased risk of COVID-19 infection compared with those who were on other AP medication (HR= 2.62, 95% CI 1.73–3.96) |
| **Hoertel et al., 2021a, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR from January 24th to April 1st, 2020. | Assess the association between AD use and severe COVID-19 | 7230 adults hospitalized for COVID-19 (n=345, 4.8% received an AD within 48h of hospital admission) | Not applicable | AD use was associated with a reduced risk of intubation or death (adjusted HR=0.56; 95% CI 0.43–0.73, p<0.001). The association was significant specifically for fluoxetine, paroxetine, escitalopram, venlafaxine, and mirtazapine (all p<0.05) |
| **Hoertel et al., 2021b, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR | Assess the association between haloperidol treatment and severe COVID-19 | 15,121 inpatients with COVID-19 (n=39, 0.03%, received haloperidol within the first 48h of admission, mean dose of 4.5 mg/day (SD = 5.2) for 8.4 days (SD = 7.2) | Not applicable | No significant association between haloperidol treatment and severe COVID-19 outcomes was found |
| **Pobladór-Plou et al., 2021, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR | Assess the risk factors for COVID-19 mortality | 4412 individuals | Not applicable | AP were amongst the medications associated the most with an increased likelihood of mortality both in men (OR=1.66, 95% CI 1.13-2.43), and women (OR=1.81, 95% CI 1.29-2.53). |
| **Pun et al., 2021** | Adult SARS-CoV-2 patients admitted to ICUs | Investigate risk factors for delirium in critically ill patients with COVID-19 | 2088 inpatients with COVID (19 admitted to ICUs) | Not applicable | Mechanical ventilation, use of restraints, benzodiazepine, opioid, and vasopressor infusions, and AP were each associated with a higher risk of delirium the next day (all p≤0.04) |
| **Diez-Quevedo et al., 2021, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR | Assess the association between psychotropic drugs and mortality in COVID-19 | 2150 adult inpatients (n=1011 received psychotropic medications during admission) | Not applicable | Previous year's treatment with anxiolytics/hypnotics and AD were independently associated with lower mortality risk (HR=0.47 and 0.43 respectively) |
| **Case-Control Studies** | | | | | |
| **Harrison et al., 2021, UK** | First cohort: Patients ≥ 65 | Assess the association | 8414 individuals with | Not applicable | People with dementia and COVID-19 who |

| | | | | | |
|---|---|---|---|---|---|
| | years with dementia and COVID-19; used AP in the 30 days prior to COVID-19 Second cohort: Controls ≥ 65 years with dementia; used AP 30 days prior to or on a visit to a healthcare organization | between AP use and COVID-19 related thromboembolic events or all-cause mortality | COVID-19, dementia, and use of AP<br><br>31,963 controls | | received AP had significantly higher odds of 30-day thromboembolic events (OR=1.36, 95% CI: 1.21–1.52), and all-cause mortality (OR=1.93, 95% CI 1.71–2.17) than controls. |
| **McKeigue et al. 2021, Europe** | Adults with SARS-CoV-2 infection confirmed by PCR, with severe COVID-19 and matched controls | Assess the association between prior drug prescribing and severe COVID-19 | 4251 cases of severe COVID-19<br>36,738 matched controls for age and sex | Not applicable | Several drugs were significantly associated with severe COVID-19. The largest effect was for AP (RR= 4.18, 95% CI 3.42-5.11) |

Abbreviations: AD=antidepressants; AP=antipsychotics; OR=Odds Ratio; CI=confidence intervals; SSRI=serotonin selective reuptake inhibitors; SNRI=serotonin and norepinephrine reuptake inhibitors; ADRS=Acute Respiratory Distress Syndrome; RRa=rate ratio; RR=relative risk; HR=hazard ratio; SD=standard deviation).

Nine studies involving 7188 patients treated with AD or AP and 19119 controls were included in the MA. Four studies focused on AD (Fei et al., 2021; Lenze et al., 2020; Oskotsky et al., 2021; Reis et al., 2021), one study explored the role of AP (Nemani et al., 2021), and four studies included both medications (Diez-Quevedo et al., 2021; Hoertel et al., 2021; McKeigue et al., 2021; Poblador-Plou et al., 2020). MA was possible for the following outcomes: risk of **severe** COVID-19 (considered as risk of intubation or death), and mortality due to any cause among people diagnosed with COVID-19.

*3.4.1. Antidepressant or antipsychotic use and risk of severe COVID-19*

Two observational studies (Hoertel et al., 2021; McKeigue et al., 2021) explored the risk of severe COVID-19 among people with or without AD use. The pooled RR was 1.71 (0.65-4.51 CI). High heterogeneity was found between studies ($I^2$ = 96.9%; Q=32.22, p<0.01). Results are reported in Figure 2. Results of the analysis split according to the class of AD assumed (SSRI vs other antidepressants) using unadjusted data are reported in the supplementary material

(Supplementary Figure 3). The pooled RR was 1.56 (1.40-1.73 CI). No heterogeneity was found between studies ($I^2$ = 0%; Q=2.67, p=0.45).

The same studies (Hoertel et al., 2021a; McKeigue et al., 2021) also explored the risk of severe COVID-19 among people with or without AP use. The pooled RR was 3.66 (2.76-4.85 CI). No significant heterogeneity was found between studies ($I^2$ = 67.4%; Q=3.07, p=0.08). Results are shown in Figure 3.

*3.4.2. Antidepressant or antipsychotic use and mortality*

Two RCTs (Lenze et al., 2020; Reis et al., 2021) observed the mortality rates among people with COVID-19 and treated with fluvoxamine compared to placebo. The pooled OR was 0.15 (0.02-0.95 CI). No heterogeneity was found between studies ($I^2$ = 1.5%; Q=1.01, p=0.31). Results are shown in Figure 4.

Four observational studies (Diez-Quevedo et al., 2021; FEIei et al., 2021a; Oskotsky et al., 2021; Poblador-Plou et al., 2020) observed the mortality rates among people with COVID-19, treated with AD. The pooled RR was 0.94 (0.81-1.09 CI). No significant heterogeneity was found between studies ($I^2$ = 0%; Q=0.99, p=0.8). Results are shown in Figure 5.

Three observational studies (Diez-Quevedo et al., 2021; Nemani et al., 2021; Poblador-Plou et al., 2020) observed the mortality rates among people with COVID-19, treated with AP. The pooled OR was 1.53 (1.15-2.03 CI). No significant heterogeneity was found between studies ($I^2$ = 52.2%; Q=4.04, p=0.13). Results are shown in Figure 6.

*3.5. Quality of the Included Studies*

Regarding the quality of computational studies, high-quality items including the use of two or more approved drug databases, analysis of molecular dynamic simulation, the use of crystal structure for the generation of the target sequence, and the use of AutoDock Vina combined with other docking tools occurred in about 20%, 60%, 20%, and 80% of included studies

(Supplementary Table 3). All preclinical studies show a low risk of bias (Supplementary Table 4). Overall, among clinical case-control studies and cohort studies, 11 had “good” quality, one was of “fair” quality, and three were of "poor quality", based on the Newcastle-Ottawa Scale (see Supplementary Table 5). The Cochrane risk of bias tool indicated a low risk for bias for both RCTs included (Supplementary Table 6).

**4. Discussion**

This is the first meta-analysis on psychotropic drug repurposing for COVID-19. The urgency to find effective drugs against COVID-19 has pushed research in different fields to face the ongoing pandemic. In our data synthesis, preclinical evidence showed that both antipsychotics and antidepressants, in particular SSRI, inhibit Sars-CoV-2 replication or activity, either directly or by anti-inflammatory response modulation. Computational approaches might play an important role in exploring the efficacy of effective psychotropic drugs against SARS-CoV-2, but according to our findings, they do not appear to fulfill clinical expectations. Based on preclinical evidence, several RCTs were conducted to explore the effectiveness of psychotropic drug repurposing for COVID-19.

The two RCTs included (Lenze et al., 2020; Reis et al., 2021) showed that fluvoxamine is effective in reducing the risk of COVID-19 progression or hospitalization when taken at appropriate doses during 10-15 days compared with placebo. Since the two studies had different primary outcomes, we conducted a meta-analysis on the association between fluvoxamine use and all-cause mortality, which showed reduced mortality in patients taking fluvoxamine compared with placebo. Fluvoxamine seems to be effective for COVID-19 treatment given its anti-inflammatory potential, mediated by the endoplasmatic reticulum protein (S1R) activation that might regulate cytokine production (Rosen et al., 2019; Sukhatme et al., 2021), as well as its antiplatelet activity, possibly reducing thrombosis’s risk (Cloutier et al., 2018; Sukhatme et al., 2021). Not only fluvoxamine is well tolerated, available and a low-cost drug, but it could be used as early

treatment for COVID-19 in high-risk populations preventing clinical deterioration. Furthermore, besides fluvoxamine, other SSRIs, including fluoxetine, can decrease levels of proinflammatory cytokines (e.g., IL-6) (Yoshimura et al., 2017)which contribute to the cytokine storm associated with fatal outcomes in COVID-19 (Fajgenbaum and June, 2020). Evidence from our systematic review points to AD protective effect from Sars-CoV-2 infection (Clelland et al., 2021), COVID-19 severe outcomes (FEeiI et al., 2021b; Hoertel et al., 2021a), and mortality (Diez-Quevedo et al., 2021; Oskotsky et al., 2021). However, we found no significant association between the use of AD and the risk of severe COVID-19 or mortality in the two meta-analyses. First, it should be noted the meta-analysis on the association of AD with severe COVID-19 was conducted on a population with high rates of polypharmacy, including other psychotropics (McKeigue et al., 2021), thus complicating the observation of a univocal effect of AD against severe COVID-19. in addition, several studies lacked relevant information such as, among the others, the reason for prescribing the AD, the presence of possible psychiatric comorbidities, treatment adherence before COVID-19 symptoms, thus preventing causal inferences.

On the other side, AP use significantly increased the risk of severe COVID-19 and mortality in our analyses. Coherently, a meta-analysis on the association of mental illness, psychotropics, and COVID-19 risk outlined a strong association between exposure to antipsychotics and COVID-19 mortality (OD=3.71, 1.74–7.91 CI) (Vai et al., 2021).

Undoubtedly, in all the included studies, AP treatments were usually prescribed during hospitalization, thereby indirectly associating with a more severely affected subpopulation of COVID-19 patients or with forthcoming deterioration. Furthermore, in all the included studies AP were given independently of diagnosis, they were considered as a homogenous group without any differentiation or stratification (e.g., based on metabolic side effects), and AP polypharmacotherapy was detected in most cases. However, these results and their implications for the clinical management of COVID-19 have to be taken into account under a careful global clinical evaluation, especially in patients with psychiatric disorders. Indeed, individuals with

severe mental disorders represent a highly vulnerable population to COVID-19 infection and its adverse outcomes (Wang et al., 2021) and should likely be prioritized for vaccination and treatment (Reininghaus et al., 2022). On the other side, patients with good adherence to AP are less likely to get infected from Sars-CoV-2 and show better COVID-19 outcomes compared with the general population(Canal-Rivero et al., 2021). Also, the possibility of a spurious result concerning the association of AP use and negative COVID-19 outcomes cannot be ruled out. AP show a heterogeneous but significant positive association with metabolic complications (Pillinger et al., 2020; Zhang et al., 2017), and the presence of metabolic comorbidities such as diabetes or metabolic syndrome among COVID-19 patients significantly increased the risk of mortality, respiratory failure, duration of ventilator dependence, severe/critical COVID-19, ICU admission, and length of hospital stay (Denson et al., 2021; Espiritu et al., 2021).

Our suggestion is that patients with psychiatric disorders should maintain psychotropic treatment to avoid both relapses of their baseline condition and the higher risk to get infected with COVID-19, in particular when considering treatment with AD such as fluvoxamine. Considering the absence of high-quality evidence or RCT on the use of AP for COVID-19, we recommend maintaining AP ongoing treatment in patients with COVID-19 and a psychiatric illness. The use of AP in people without psychiatric conditions should be evaluated on an individual basis, considering also that some AP showed benefits over placebo for treatment of delirium in patients with COVID-19 (Ostuzzi et al., 2020), and their use is considered safe and recommended (Anmella et al., 2020).

**5. Limitations**

There are some shortcomings in this SR and MA that should be pointed out. Due to the characteristics of observational studies, it was difficult to collect data in all of them about possible confounders. Adjusting for polypharmacotherapy, psychiatric diagnosis, and high-risk conditions for severe COVID-19 (age, sex, previous medical comorbidities) was not possible for

every study included in the meta-analyses. Moreover, we could not assess publication bias due to the low number of studies in each meta-analysis (n<10), since Egger's test might have lacked the statistical power to detect bias. In addition, some of the included studies were assessed to be of poor quality ~~using the NOS score~~, which varied widely in the effect size measures. In particular, studies on fluvoxamine were of a higher quality and there were no clinical trials on on other AD, thus we cannot exclude the potential positive effect of other AD in patients with COVID-19.

**6. Conclusion**

Preclinical evidence showed that both antipsychotics and antidepressants, in particular SSRI, inhibit Sars-CoV-2 replication or activity, either directly or by anti-inflammatory response modulation. However, the translation of these results into clinical practice needs to be further explored. Regarding antidepressants, fluvoxamine may reduce the risk of severe COVID-19 outcomes and mortality, and therefore, SSRI might be good candidates for drug repurposing in COVID-19. Especially in the early treatment of the disease, they might be useful to prevent psychiatric symptoms in complications such as long-Covid (Llach and Anmella, 2022; Llach and Vieta, 2021). Increased risk for severe COVID-19 and mortality with antipsychotics is not absolute and should be contextualized to individual cases. Ongoing treatment with antipsychotics should not be discontinued in psychiatric patients.

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**Figure 1.** **Flow diagram of systematic review selection criteria**

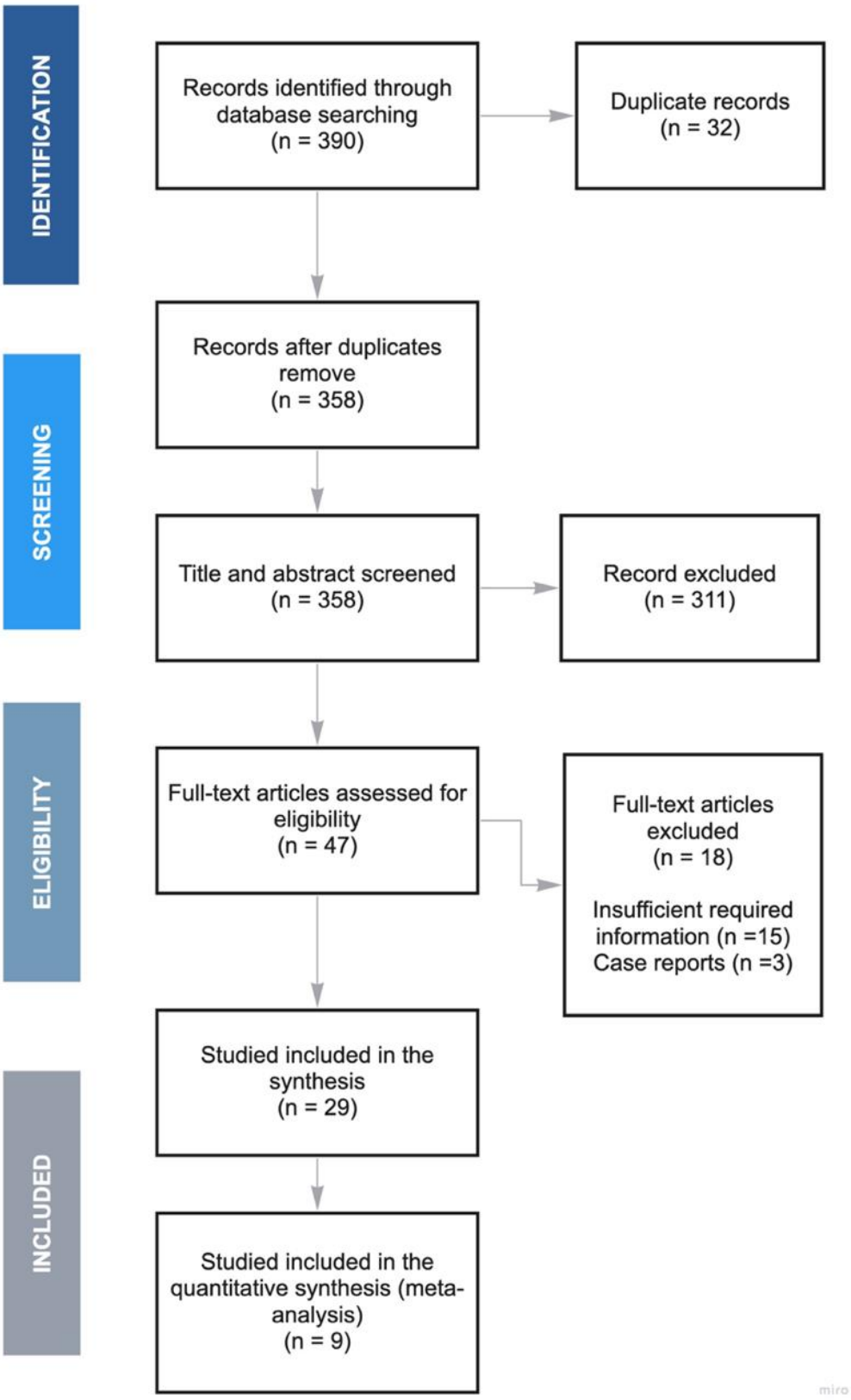


**Figure 2. Meta-analysis of the association between antidepressant use and severe COVID-19.** *Risk of severe COVID-19 is expressed as risk ratio (RR), adjusted. The diamond represents the pooled RR for the association of AD and severe COVID-19 and the corresponding 95 % CI.*

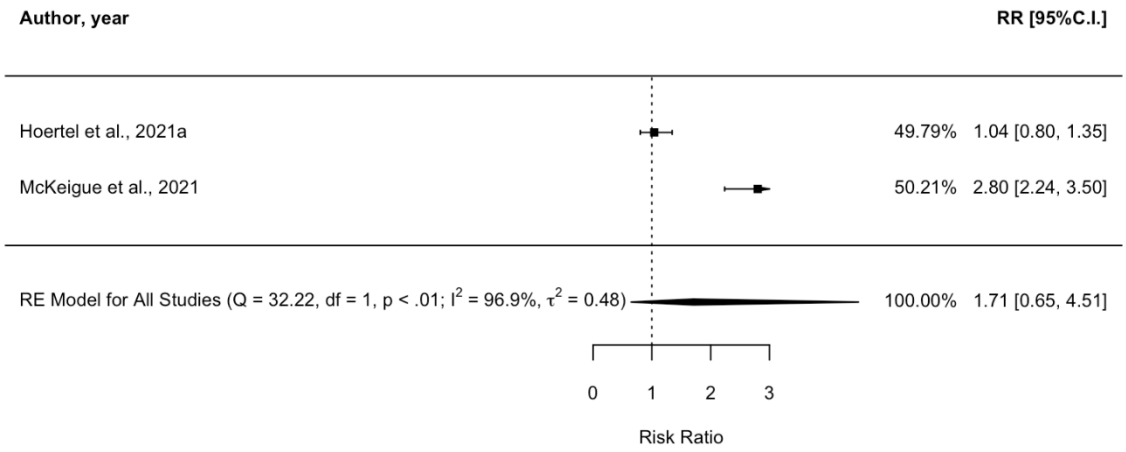



**Figure 3. Meta-analysis of the association between antipsychotic use and severe COVID-19.** *Risk of severe COVID-19 is expressed as risk ratio (RR), unadjusted. The diamond represents the pooled RR and corresponding 95 % CI.*

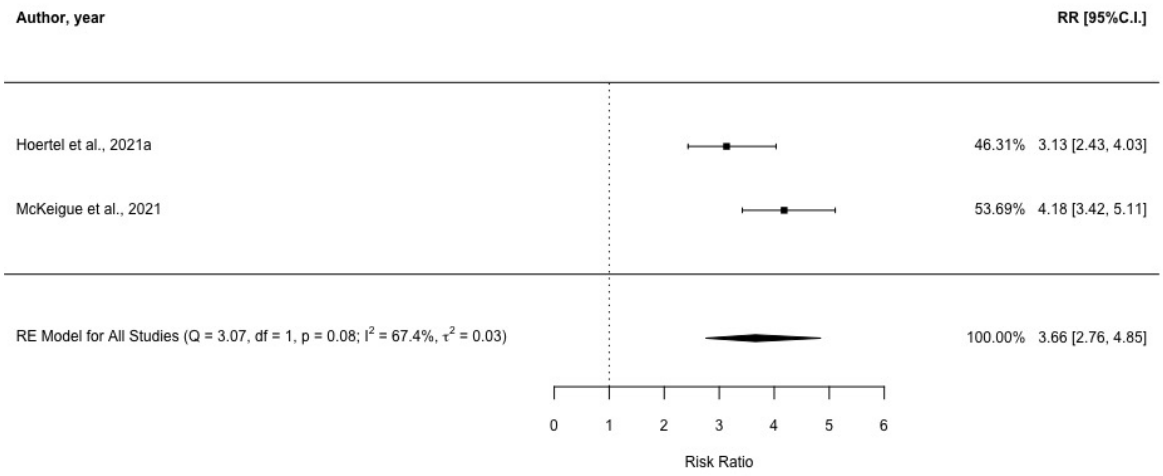


**Figure 4. Meta-analysis of the association between treatment with fluvoxamine and mortality in patients with COVID-19.** *COVID-19 mortality is expressed as Odds Ratio (OR). The diamond represents the pooled OR and corresponding 95 % CI.*

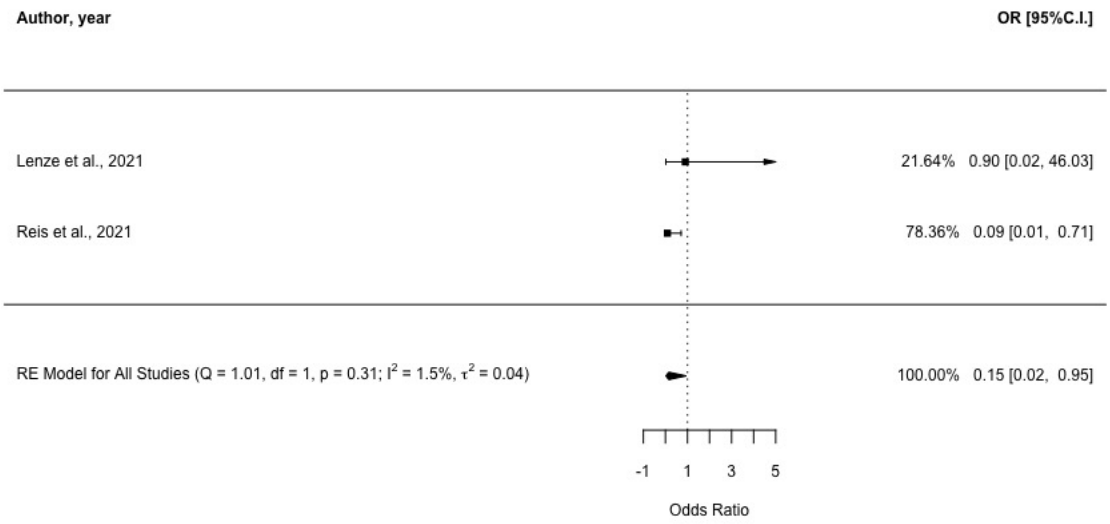



**Figure 5. Meta-analysis of the association between treatment with antidepressants and mortality in patients with COVID-19.** *COVID-19 mortality is expressed as Risk Ratio (RR), adjusted. The diamond represents the pooled RR and corresponding 95 % CI.*

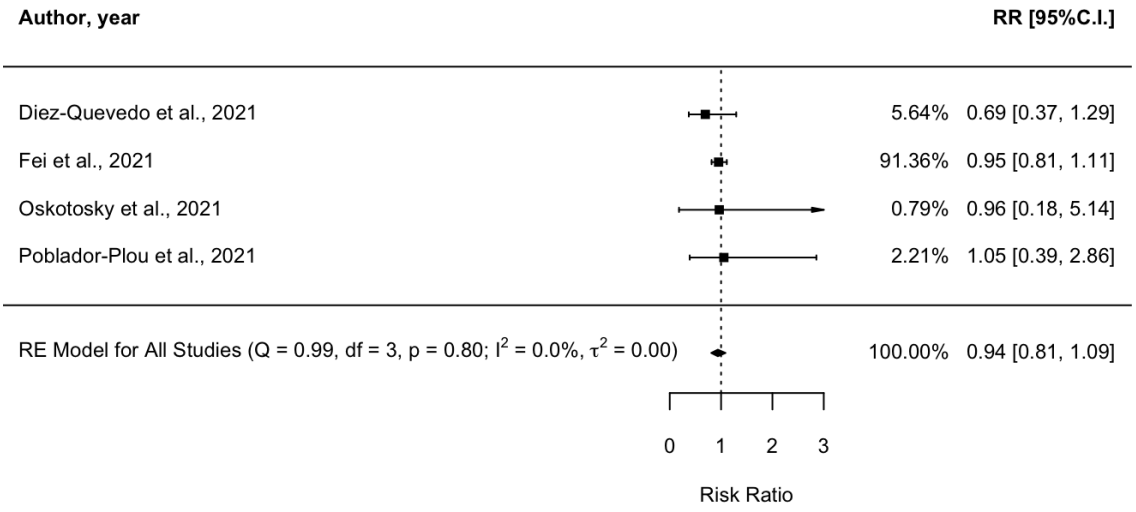
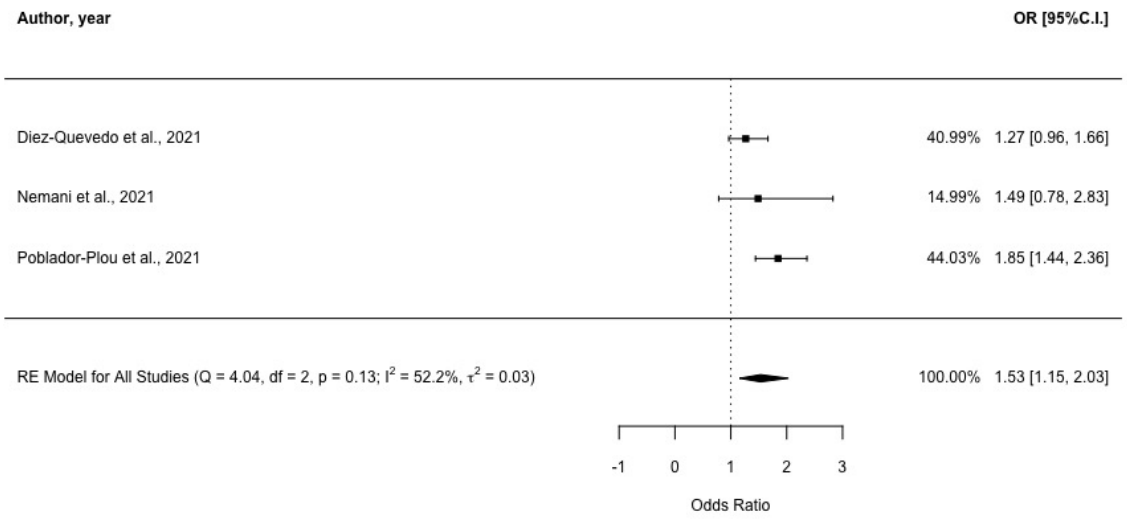


**Figure 6. Meta-analysis of the association between treatment with antipsychotics and mortality in patients with COVID-19.** *COVID-19 mortality is expressed as Odds Ratio (OR), unadjusted. The diamond represents the pooled OR and corresponding 95 % CI.*



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Contributors: GF, AM and MM designed the study and wrote the protocol. GF and UI managed the literature searches and analyses. Authors GF, VO and MDP undertook the statistical analysis, and author GF wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interests**:** GF has received CME-related honoraria, or consulting fees from Angelini, Janssen-Cilag and Lundbeck. MSV has received financial support for CME activities or travel funds from Janssen-Cilag and Lundbeck, and has served as a speaker for Casen Recordati. She reports no financial or other relationship relevant to the subject of this article. IG has received grants and served as consultant, advisor or CME speaker for the following identities: Angelini, Casen Recordati, Ferrer, Janssen Cilag, and Lundbeck, Lundbeck-Otsuka, Luye, SEI Healthcare outside the submitted work. MGR has received funding unrelated to the present work for research projects and/or honoraria as a consultant or speaker from the following entities: Angelini, Janssen, Lundbeck, Otsuka, Sanofi-Aventis and Spanish Ministry of Science and Innovation- Instituto de Salud Carlos III. EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Boehringer-Ingelheim, Celon, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Novartis, Organon, Otsuka, Sanofi-Aventis, Sunovion, and Takeda, outside the submitted work.

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