Neuropsychiatric Drugs Against COVID-19: What is the Clinical Evidence?

Authors
Juliane K. Mueller[1], Peter Riederer[2, 3], Walter E. Müller[4]

Affiliations
1 Department of Psychiatry, Psychosomatic Medicine, and Psychotherapy, University Hospital Frankfurt, Frankfurt/M, Germany
2 Clinic and Policlinic for Psychiatry, Psychosomatics and Psychotherapy, University Hospital Würzburg, Würzburg, Germany
3 University of Southern Denmark Odense, J.B. Winslows Vey Odense, Denmark
4 Department of Pharmacology und Clinical Pharmacy, University Frankfurt, Frankfurt/M, Germany

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Walter E. Mueller, PhD
Department of Pharmacology and Clinical Pharmacy
Goethe University Biocenter
Max von Laue Str. 9
60438 Frankfurt/M.
Germany
w.e.mueller@em.uni-frankfurt.de

ABSTRACT

Since the beginning of the coronavirus disease (COVID)-19 pandemic, the need for effective treatments for COVID-19 led to the idea of "repurposing" drugs for antiviral treatment. Several antipsychotics and antidepressants have been tested for in vitro activity against the severe acute respiratory syndrome coronavirus 2. Chlorpromazine, other phenothiazine antipsychotics, and the antidepressant fluoxetine were found to be rather potent in these studies. However, whether effective plasma concentrations can be obtained with clinically accepted doses of these drugs is not clear. Data of COVID-19 patients are not yet available but several clinical studies are currently underway.

The specific serotonin reuptake inhibitor fluvoxamine is a potent Sigma-1 receptor agonist and reduces inflammation in animal models of cytokine-stress. Accordingly, fluvoxamine treatment was superior to placebo in reducing impaired respiratory function and other symptoms of inflammation in COVID-19 patients in a placebo-controlled clinical study and another open clinical trial. The beneficial effects of fluvoxamine on the course of COVID-19 were recently confirmed in a large placebo-controlled double-blind trial with several hundred patients.

Inflammation represents a major risk factor for many psychiatric disorders which explains the high susceptibilitiy of COVID-19 patients for psychiatric diseases. Many antidepressants and antipsychotics possess anti-inflammatory properties independent of sigma-1 activity which might be important to reduce psychiatric symptoms of COVID-19 patients and to improve respiratory dysfunction and other consequences of inflammation. This might explain the rather unspecific benefit which has been reported for several cohorts of COVID-19 patients treated with different psychotropic drugs.

Introduction

Repurposing licensed drugs to treat COVID-19

The World Health Organization (WHO) declared COVID-19 a pandemic by March 2020 after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in China by the end of 2019 and until now has led to massive challenges for people and healthcare systems worldwide.

The fast outbreak of the COVID-19 pandemic required a rapid development of effective drugs to prevent the infection, ideally to reduce the virus load and even more important to treat the severe consequences of the virus-induced inflammation. While the fast development of several effective vaccinations represents a remark-

able story of success, research has been less successful in developing drugs against COVID-19. The mainly used drugs to treat COVID-19 are still corticosteroids like dexamethasone or budesonide [1].

To save time and money especially in the preclinical phases of drug development, many known drugs were tested for "anti-COVID" activity. This approach to "repurpose" old drugs has been quite successful [2–4] and many substances with "anti-COVID" activity in vitro could be identified [4, 5]. However, there is only limited clinical data, as only very few of those drugs have been tested yet in COVID-19 patients.

During the course of these studies, many antidepressants and antipsychotic drugs were reported to be active against the SARS-CoV-2 virus in vitro confirming older studies indicating in vitro activity against several other viruses [5–10]. In some cases, the results appeared quite promising and led to further studies about their possible clinical use to treat COVID-19. Accordingly, we addressed this point in the present manuscript by reviewing specifically all psychotropic drugs for which at least some initial clinical data in patients has been published.

Chlorpromazine and other antipsychotics

Antiviral activities of chlorpromazine and other phenothiazine antipsychotics against various coronavirus species are known for many years and have been confirmed for SARS-CoV-2. But since the effective concentrations are rather high (between 5 and 10 µmol/L), the effect was not considered relevant for a possible therapeutic application [6, 8].

The possible clinical use of chlorpromazine as an antiviral drug was reconsidered following the report by Plaze et al. [11, 12] of a very low prevalence of COVID-19 infections in psychiatric inpatients relative to the clinical staff which was explained by the authors as a consequence of possible antiviral effects of the psychiatric treatment. Since most of the patients received phenothiazine antipsychotics as part of their therapy, the authors speculated about a protective effect of these drugs due to their antiviral activity against SARS-CoV-2 [12]. However, their potency as antiviral drugs was rather low. Nevertheless, the concept of repurposing chlorpromazine or other antipsychotics to treat COVID-19 was seen rather enthusiastically [13].

Based on these in vitro findings, two clinical studies about the efficacy of chlorpromazine for the treatment of COVID-19 have already been approved several months ago but apparently have not yet started to recruit (▶ **Table 1**). Other clinical data is not available except for some results from a large observational study in Paris [14]. In this study, the outcome (death) was not different for the 55 COVID-19 patients treated with chlorpromazine (on the average 71 mg/day for 14 days) when compared to a matched control group of COVID-19 patients without chlorpromazine treatment [15]. Furthermore, specific concern was raised in respect to the well-known side effects of chlorpromazine and the rather high concentrations needed for antiviral effects as outlined by Girgis and Lieberman [16]. Therapeutic plasma levels of chlorpromazine range up to about 1 µmol/l and may overlap with the critical or already toxic plasma levels which start around 2–3 µmol/l [17].

Similar to chlorpromazine, several older antipsychotics have in vitro activity against SARS-CoV-2 but offer no advantage while the second-generation antipsychotics (SGA) are generally much less active with the possible exception of lurasidone [18]. Nevertheless, clinical data is still missing. Haloperidol has been suggested as a possible treatment against COVID-19 but was not effective to prevent death at an average daily dose of 4.5 mg per day in an observational study [19].

On the other hand, a retrospective observational study [20] reported a substantially better outcome of COVID-19 in schizophrenic patients treated with long-acting antipsychotics relative to a control group. Outcome criteria included infection rates, hospitalization rates, ICU admission, and deaths. The antipsychotics aripiprazole and risperidone/paliperidone which made up about 90 % of the antipsychotics used in this study showed well-defined anti-inflammatory properties [21]. Other clinical data about the possible therapeutic effects of SGA against COVID-19 have not yet been published. The use of clozapine in COVID-19 patients is not recommended because of its side effects [22]. For the treatment of therapy-resistant schizophrenic symptoms in COVID-19 patients, ursodeoxycholic acid has been proposed as an option but clinical data is still missing [23].

Antidepressant drugs

Fluoxetine

Antiviral properties in vitro have been known for many but not all antidepressant drugs in the past years and could be confirmed in many cases for SARS-CoV-2 with effective concentrations in the micromolar range [4, 5, 9]. Fluoxetine turned out to be one of the more potent molecules but its half-maximal inhibitory concentration was never lower than about 1 to 2 µmol/L. As lipophilic molecules with a cationic structure (secondary or tertiary amine), these compounds are easily taken up into acidic cell organelles (e.g. lysosomes) (lysosomotropic properties). Once inside the lysosome, they are trapped and can interfere with the release of the virus from the lysosome probably by reducing the concentration of ceramide [24, 25].

For some antidepressants, antiviral properties could be linked to the enzyme acid sphingomyelinase (ASM) which is widely expressed in lysosomes [26]. ASM releases ceramide from sphingomyelin. Its inhibition by fluoxetine and a few other antidepressants including amitriptyline has been shown to reduce ceramide levels in the brain causing antidepressant-like effects at the behavior and biochemical level [26]. Because of the important role of ceramide in the processing of different virus species in the lysosome the antivirus activity of fluoxetine has been explained by its inhibitory effect on ASM and the reduction of ceramide [27–29]. The antiviral activity of fluoxetine has recently been shown to be additive to the antiviral effects of the RNA-dependent RMA polymerase inhibitor remdesivir [30].

While these data appear quite interesting it should be realized that fluoxetine was always active in the low micromolar range only with IC50 values at best around 1 µmol/l [28]. Considering the recommended therapeutic plasma levels for the treatment of depression (about 0.5 to 1.0 µmol/l) [17] further studies are needed to show if these concentrations are sufficient to achieve antiviral

▶ **Table 1** The efficacy of antipsychotics and antidepressants for the treatment of COVID-19.

Title	Design	Intervention	Location	Status
Repurposing of Chlorpromazine in COVID-19 Treatment (reCoVery)	open	Chlorpromazine (CPZ) Combination Product: Standard of Care (SOC)	Centre Hospitalier St Anne Paris, France	Not yet recruiting
Administration of Chlorpromazine as a Treatment for COVID-19	open	Chlorpromazine	Cairo University Cairo, Egypt	Not yet recruiting
Fluoxetine to Reduce Intubation and Death After COVID19 Infection	open	Fluoxetine	University of Toledo Health Science Campus Toledo (USA)	Recruiting
TDCS in Pediatric and Teenage Patients With Major Depressive Disorder During COVID-19 Pandemic	double-blind	Transcranial Direct Current Stimulation Fluoxetine	Mexico	Recruiting
Fluvoxamine for Early Treatment of COVID-19 (Stop COVID 2)	double-blind	Fluvoxamine Placebo	Washington University School of Medicine. Chicago, USA	Active, not recruiting
Fluvoxamine Administration in Moderate SARS-CoV-2 (COVID-19) Infected Patients	double-blind	Placebo Fluvoxamine	Budapest, Hungary,	Recruiting
ACTIV-6: COVID-19 Study of Repurposed Medications	double-blind	Ivermectin Fluvoxamine Fluticasone Placebo	USA	Recruiting
Outpatient Treatment of SARS-CoV-2 With Ivermectin, Fluvoxamine, and Metformin (COVID-19)	double-blind	Metformin Placebo Fluvoxamine Ivermectin	University of Minnesota Minneapolis, USA	Recruiting
Repurposed Approved and Under Development Therapies for Patients With Early-Onset COVID-19 and Mild Symptoms	double-blind	Fluvoxamine Doxazosin Ivermectin Placebo Peginterferon Lambda-1a Peginterferon Beta-1A	Brazil	Recruiting
Valproate Alone or in Combination With Quetiapine for Severe COVID-19 Pneumonia With Agitated Delirium	double-blind	Valproate Quetiapine Standard of Care	University of Miami Miami, USA	Not yet recruiting
Cannabidiol for COVID-19 patients With Mild to Moderate Symptoms (CANDIDATE)	double-blind	Cannabidiol Placebo	University of Sao Paulo Sao Paulo, Brazil	Active, not recruiting
Cannabidiol Treatment for Severe and Critical Coronavirus (COVID-19) Pulmonary Infection	open	Cannabidiol 150 mg twice daily during 14 days	Rabin Medical Center	Recruiting
Cannabidiol in Patients With COVID-19 and Cardiovascular Disease or Risk Factors	double-blind	Cannabidiol Placebo	USA Sponsor: Cardiol Therapeutics Inc.	Recruiting
Synthetic CBD as a Therapy for COVID-19	double-blind	Cannabidiol Placebo	Sheba Medical Center Tel-Hashomer, Israel	Not yet recruiting

An overview of the approved clinical studies on psychotropic drugs and/or cannabis in Covid-19 patients and their current status. Data are from the US government ClinicalTrials.gov home page by July 30, 2021 [91, 92].

effects in patients. One double-blind study examining the effects of fluoxetine on COVID-19 patients is currently in progress using time of intubation and/or death as endpoints (▶ **Table 1**). Other clinical data about the use of fluoxetine to treat COVID-19 patients has not yet been published except for an observational study in France. Hoertel et al. [14] reported that the concomitant use of fluoxetine in COVID-19 patients was associated with a reduced risk of death or intubation. Still, similar effects were reported in the same study for other SSRIs not showing specific antiviral properties and also for many other antidepressant drugs independent of inhibitory effects on ASM [14]. On the other hand, a recent analysis of the same data set reported a similarly reduced risk of death or intubation for 15 different drugs with inhibitory activity against ASM [31]. Besides fluoxetine, several other antidepressants, but also some antipsychotics, and cardiovascular drugs were included.

Fluvoxamine and the relevance of Sigma-1 binding sites

Sigma-1 binding sites or receptors are chaperone proteins mainly at the level of the endoplasmatic reticulum (ER) [32, 33] and are involved in the regulation of many cellular functions especially in the brain. Many antipsychotic and antidepressant drugs are potent

ligands for sigma-1 sites in addition to their main mechanism of action, but whether this additional property contributes significantly to their pharmacological or therapeutical effects is still a matter of dispute.

During the search for targets of possible anti-COVID drugs, sigma-1 receptors were identified as functional host-dependency factors for SARS-CoV-2 and were initially suggested as a target for drugs to inhibit SARS-CoV-2 replication [34]. Knocking down sigma-1 sites or treatment with several antipsychotics as sigma-1 antagonists caused a reduction of SARS-CoV-2 replication [32]. However, their binding affinity for sigma-1 sites did not correlate with their potency as inhibitors of virus replication and their potency probably was too low to suggest therapeutic usefulness at the recommended dose ranges of those drugs [32].

On the other hand, findings that sigma-1 receptors play a role in the regulation of the massive inflammation and cytokine storm following sepsis are another link suggesting beneficial effects of fluvoxamine in COVID-19 patients [35]. Knocking down sigma-1 sites enhances the release of proinflammatory cytokines [35] and increases depressive-like behavior [36]. On the other hand, Sigma-1 agonists like fluvoxamine and many other antidepressants have been shown to reduce ER stress in several preclinical models of sepsis and inflammation [35] which mirror the massive inflammation and the cytokine storm following SARS-CoV-2 infections [35, 37]. Fluvoxamine also shows specific anti-inflammatory effects in different cell models with relevance for the cytokine activation induced by SARS-CoV-2 [32, 35, 37]. Most importantly, contrary to chlorpromazine and other antipsychotics the therapeutic plasma levels of fluvoxamine are sufficient for similar effects in patients, as a daily fluvoxamine dose of 300 mg leads to complete occupation of sigma-1 sites in the human brain [38].

The hypothesis that the sigma-1 agonist fluvoxamine might be beneficial during the course of the massive inflammation following SARS-CoV-2 infections was confirmed in a double-blind placebo-controlled study by Lenze et al. [39]. Fluvoxamine was given for 15 days at a daily dose of 300 mg, the maximum therapeutic dose. One hundred fifty-two COVID-19 patients with the severe acute respiratory syndrome were included. The primary outcome was clinical deterioration within the 15 days of randomization defined by meeting both criteria of (1) shortness of breath or hospitalization for shortness of breath or pneumonia and (2) oxygen saturation less than 92 % on room air or need for supplemental oxygen to achieve oxygen saturation of 92 % or greater. Clinical deterioration occurred in none of the 80 patients in the fluvoxamine group but in 6 of the 72 patients in the placebo group. The difference was highly significant. This is the first controlled study about the successful use of a psychotropic drug to treat COVID-19 patients. These findings were recently confirmed in a prospective open exploratory study where 50 COVID-19 patients treated with fluvoxamine 100 mg daily for 15 days showed a much better outcome than 35 control patients at the same clinic who received no fluvoxamine treatment [40]. A very recent well-designed placebo-controlled double-blind study in about 1500 COVID-19 patients confirmed the beneficial effects of fluvoxamine again using the need for hospitalization or emergency care as the primary outcome criterium [41]. Taken together, there is substantial evidence for the possible usefulness of fluvoxamine in COVID-19 treatment. Several further prospective studies with fluvoxamine are currently underway intended to replicate these results (▶ **Table 1**).

The concept to reduce the inflammation response in COVID-19 patients [37] by sigma-1 receptors ligands is gaining more and more attention. Another example of this concept is the old antihistaminic drug hydroxyzine which is still used in many European countries not only as an antihistaminic but also as an anxiolytic sedative alternatively to benzodiazepines. Together with some other H_1-antihistaminic drugs, hydroxyzine has been shown to exhibit moderate antiviral properties in vitro but with potencies too low to suggest a therapeutic potential to treat COVID-19 patients [42]. This is in contrast to a recent observational study in France [43] in which 140 patients treated with hydroxyzine showed a significantly lower death rate relative to a control group without hydroxyzine treatment (10.9 vs 16.6 %). Moreover, the patients treated with hydroxyzine showed a significantly larger reduction of several inflammation markers than the control group [43]. Hydroxyzine has a moderate affinity for sigma-1 receptors [42, 44] with IC50 concentrations of about 200 nmol/mL which is probably too low for relevant effects mediated by sigma-1 sites under therapeutic conditions. However, its in vivo interaction with the sigma-1 receptor requires substantially lower doses than one would expect from the in vitro binding affinity. This is probably caused by a metabolite with much higher in vivo activity [44] which would suggest sigma-1 sites as possible targets of hydroxyzine.

A possible protective role of sigma-1 sites for the clinical course of COVID-19 is also suggested by the genetic findings of Lehrer and Rheinstein [45]. Using a UK Biobank cohort the authors investigated the sigma-1 locus on chromosome 9p13.3 in a cohort of COVID-19 patients. The longer alleles are associated with loss of function mutations. Homozygosity of the rs 17775810 minor allele phenotype was strongly associated with the survival of the patients. This was not seen for the patients heterozygotic for the minor allele or homozygotic for the longer alleles.

Other neuropsychiatric drugs

Within the large screening programs initiated at the beginning of the COVID-19 pandemic many other psychotropic drugs have been identified with antiviral activity in vitro (inhibition of the cellular uptake of SARS-CoV-2 or its replication), but in most cases, the concentrations needed for the antiviral effects were too high for considering a possible therapeutic effect [5, 7, 8, 24]. Therefore, only a few other psychotropic drugs have been investigated in COVID-19 patients.

Lithium

Antiviral effects of lithium against several classes of viruses including some coronavirus species are known for several years but require rather high concentrations in vitro [46]. Specific effects on SARS-CoV-2 have not yet been reported. Spuch et al., [47] reported of 6 patients who possibly responded to lithium during COVID-19 and proposed lithium as a possible candidate for COVID-19 treatment. A similar case report was published recently by Sönmez and Hocaogu [48]. However, other data except these 7 case reports have not yet been published.

Moreover, there is some concern about the use of lithium in COVID-19 patients because of its significant side effects and toxicity [10, 46]

Memantine and amantadine

Amantadine has been introduced many years ago as an antiviral drug to treat influenza A2 but has not been widely used. Besides the antiviral activity, it also possesses a broad spectrum of pharmacological properties [49] including anti-inflammatory effects probably related to its activity as a sigma-1 receptor agonist [49]. The structurally related compound memantine is predominantly an NMDA-receptor antagonist and is used clinically as an antidementia drug [50]. Both compounds show in vitro activity against SARS-CoV-2 [51] and have anti-inflammatory properties [52]. A few case reports suggest a possible beneficial effect of amantadine on the clinical course of COVID-19 [53]. An observational study using a national Korean database found no effect of memantine on the course of COVID-19 disease [54]. Further clinical data for either drug in COVID-19 patients is not available.

Cannabis

Cannabis and/or cannabidiol show several properties making it a potential candidate for the treatment of COVID-19 [55]. Cannabis and cannabidiol possess rather potent antiviral activity against SARS-CoV-2 in vitro with IC50 values around 1–2 µmol/L [56–58] and also potent anti-inflammatory properties [56]. Cannabis users seem to have a lower risk for COVID-19 relative to non-users [58]. Thus, several authors proposed cannabis and/or cannabidiol as a candidate for COVID-19 treatment [55, 59] as an antiviral drug but also against different psychiatric symptoms like depression, anxiety, or psychosis related to a SARS-CoV-2 infection [55, 59]. Still, clinical data about the possible use of cannabis and/or cannabidiol to treat COVID-19 patients is not available. However, several studies have been registered so far to investigate the possible effects of cannabidiol on inflammation during the course of COVID-19 (▶ **Table 1**).

Psychotropic drugs as multifactorial protection

Contrary to the concept of specific pharmacological mechanisms explaining the protective effects of individual psychotropic drugs against COVID-19 (see above) several researchers have speculated about a common rather non-specific effect of many different psychotropic drugs against COVID-19. These speculations were based on the many psychotropic drugs used on psychiatric wards where only a few patients got infected with SARS-CoV-2. This preventive effect was not associated with a single specific drug and was also not associated with a specific class of psychotropic drugs [11, 24, 60, 61]. Thus, it appeared that rather common properties of many different drugs or classes of drugs were leading to the improved outcome of SARS-CoV-2 infected patients.

Do effects on catecholamines and serotonin play a role?

Antidepressant drugs have been associated with beneficial effects on the course of COVID-19 [14]. This observation was found for most classes of antidepressants and did not differentiate specific serotonin reuptake inhibitors from noradrenaline reuptake inhibitors [14]. Thus, there is little evidence that the beneficial effects of these drugs in COVID-19 are mediated by the classical effects of antidepressants on catecholaminergic and serotoninergic neurotransmission and that these neurotransmitters are specifically affected by COVID-19 [62–65]. It seems however that a common additional property or properties independent of the primary mechanisms of the psychotropic activities are probably relevant.

Antiviral activity due to cationic amphiphilic activity (cationic amphiphilic drugs, CAD)

Many antidepressants are amphiphilic cationic drugs (CAD) with lysosomotropic properties and can impair lysosomal function. As lysosomes play a major role in virus processing many CAD show antiviral activity in vitro [24, 25]. However, this effect is not specific to antidepressant drugs since CAD like properties are a common feature of many other drugs including antipsychotics, antihistaminics, and others. Several antidepressant drugs with CAD properties have been found to possess comparable antiviral activity against SARS-CoV-2 in vitro including clomipramine, doxepin, amitriptyline, vortioxetine. On the other hand, other drugs with CAD like properties are not showing any antiviral activity against SARS-CoV-2. [24, 25]. Accordingly, further studies are needed to show if CAD-like properties are sufficient for antiviral effects in COVID-19 patients.

Anti-inflammatory effects of psychotropic drugs as a common property

The concept of inflammation as one of the contributing factors to the pathophysiology of neuropsychiatric disorders like schizophrenia and depression is quite old and has received more and more support over the recent years (as are reports that the comedication with certain anti-inflammatory drugs might be of some benefit in addition to therapy with antipsychotic and/or antidepressant drugs) [66–72]. Moreover, therapy with antipsychotics and antidepressants can reduce the elevation of inflammatory markers which is common in both groups of patients [69–71, 73–75]. The mechanism of these anti-inflammatory effects is not yet finally understood but seems to be an intrinsic property of some of the psychotropic drugs independent of their antidepressant or antipsychotic properties [70]. The anti-inflammatory properties of the individual antidepressants and antipsychotics vary considerably in respect to the effects on the immune system and/or the inflammatory markers [70]. The large variability could be a plausible explanation for the broad and rather non-specific effect of psychotropic drug treatment on inflammation in COVID-19 patients and on the outcome of inflammation-induced respiratory complications. This would also match the observation that the effects are variable and of moderate magnitude only. Thus, unless further data is available the use of psychotropic drugs to treat COVID-19 patients except for neuropsychiatric indications cannot be recommended.

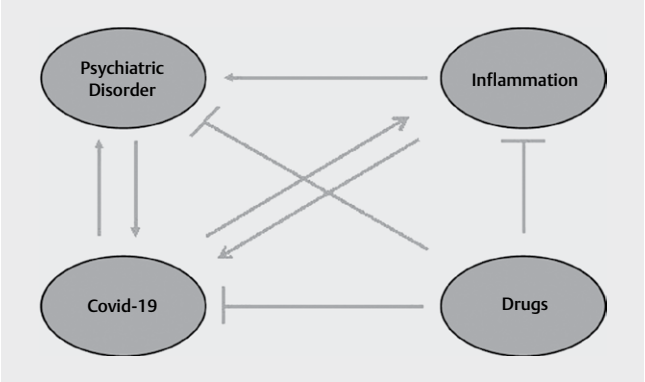
Neuroinflammation and the bidirectional relationship between psychiatric illnesses and a SARS-CoV-2 infection: the specific role of proinflammatory cytokines like interleukin-6 (IL-6)

In line with the important interplay between inflammation and the development of neuropsychiatric disorders the profound neuroinflammation taking place in the brain as a consequence of a SARS-CoV-2 infection was seen as one of the pathophysiological factors [75, 76] underlying depressive and psychotic symptoms in COVID-19 patients [77–80]. Immunological markers of depression seem to be correlated with the severity of depression and anxiety in COVID-19 patients at baseline [81] and at a follow-up three months later [82]. Among the many genes relevant for neuropsychiatric disorders whose expression seems to be altered in COVID-19 patients many markers of inflammation have been identified [64]. Moreover, in a genome-wide association study, a substantial overlap of genes relevant for signaling and inflammation was seen between COVID-19 and psychiatric disorders [83]. A genomic analysis linked inflammatory genes altered by aripiprazole treatment with genes altered in COVID-19 patients [84].

Neuroinflammation seems to be an important link within the bidirectional relationship between psychiatric illness and COVID-19 infection (▶ **Fig. 1**). Neuroinflammation also represents an important trigger for depressive disorders in general and affective symptoms during COVID-19 infection in specific. Therefore, treatment with antidepressant drugs obviously reduces affective symptoms not only by the classical effects on neurotransmitters but also by their direct anti-inflammatory effects [70]. Accordingly, parts of their beneficial effects on the psychiatric symptoms in COVID-19 patients will come from their anti-inflammatory effects. Moreover, symptoms caused by inflammation and impaired pulmonary function in COVID-19 patients might be positively affected by these properties of antidepressants and antipsychotics, explaining the rather beneficial outcome of COVID-19 patients treated with different psychiatric drugs. Whether depressive and/or psychotic symptoms caused by SARS-CoV-2 are specifically sensitive to the anti-inflammatory properties of psychiatric drugs has not yet been demonstrated. In one observational study the positive response to the anxiolytic drug hydroxyzine was associated with a reduction of inflammation markers [43] (see also paragraph 3.2).

Inflammation during COVID-19 is characterized by the release of large amounts of cytokines sometimes even leading to a cytokine storm syndrome (CSS) [85–87]. While many different pro-inflammatory cytokines are part of the COVID-CSS, Interleukin-6 (IL-6) plays a prominent role with elevations more than one hundred-fold over baseline in some patients [85–87] The two first anti-COVID-19 drugs approved recently by the WHO are antagonizing IL-6 function (the IL-6 receptor antagonist Tocilizumab and the IL-6 receptor antibody Sarilumab) [32]. Interestingly, IL-6 also represents the major cytokine elevated in the plasma of depressive and schizophrenic patients [88]. Furthermore, the treatment of patients with antidepressants has a major impact on IL-6 levels [69, 88].

IL-6 also represents the major cytokine released in animal models of cytokine storm where cytokine release is initiated by lipopolysacchaccharide (LPS). LPS induced cytokine release and elevation of IL-6 is regulated by sigma-1 sites leading to elevated IL-6 levels in sigma-1 knockout animals [32, 35]. Both key parameters of the LPS model (depression-like behavior and cytokine release) respond well to sigma-1 ligands like fluvoxamine but also other antidepressants without relevant sigma-1 activity [32, 35]. The reduction of cytokines by many antidepressants with different primary mechanisms of action is paralleled by their activity in several behavioral models of antidepressant activity in mice [89]. Thus, inflammatory cytokine-like IL-6 might represent the link between depression and anxiety of COVID-19 patients with beneficial effects of antidepressant drugs not only on the psychiatric symptoms but also on the systemic inflammation of the patients. This interplay is also supported by the observations of Benedetti et al., [90] that COVID-19 patients who had been treated during hospitalization with anti-cytokine drugs including the IL-6 antagonist tocilicumab complained less of depressive symptoms three months after discharge than patients without anti-cytokine drugs.



▶ **Fig. 1** The bidirectional relationship between COVID-19, psychiatric disorders, inflammation, and psychotropic drugs. For further details see text.

Conclusions

In conclusion, the most likely concept to explain the rather unspecific positive effect of antidepressants and antipsychotics on the course of COVID-19 seems to be the underlying inflammation in COVID-19 as the causative factor not only for the clinical course of COVID-19 including respiratory distress but also for the development of psychiatric symptoms. Thus, the inflammation during COVID-19 may not only represent a therapeutic target of many psychotropic drugs for improving the course of the illness including respiratory impairment but may also contribute to their beneficial effects on psychiatric symptoms, and illness (▶ **Fig. 1**).

Conflict of Interest

The authors declare that they have no conflict of interest.

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