Chapter

New Use of the SSRI Fluvoxamine in the Treatment of COVID-19 Symptoms

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Abstract

From the perspective of repurposing medication, recent evidence suggests that the use of selective serotonin reuptake inhibitor antidepressants (SSRIs) can help reduce the severity of symptoms and death associated with SARS-CoV-2 infection. To focus more, COVID-19 is a viral disease with potentially high risk of symptoms. There is presently no cure. However, there are specific treatments that may help manage the condition. Since the SSRI fluvoxamine has a unique mechanism of action in reducing cytokine production, researchers have started to relate the antiviral effects via modulation of sigma-1 receptors with the vision of treatment options for COVID-19 patients. The scope of this chapter is to examine different mechanisms of fluvoxamine in relation to immune response, including both the serotonin and the sigma-1 receptor-related mechanisms. Addressing the impact of fluvoxamine in minimizing possible complications during COVID-19 infection.

Keywords: fluvoxamine, anti-inflammatory, coronavirus disease 2019, sigma-1 receptor, clinical studies, preclinical studies

1. Introduction- COVID-19 options for treatment

The coronavirus disease 2019 (COVID-19) is an acute respiratory infection related to the new RNA virus coronavirus 2, that produces severe acute respiratory syndrome (SARS-CoV-2) [1]. Since the first SARS-CoV-2-infected patients were reported in Wuhan, China, in December 2019, the number of individuals infected with COVID-19 has risen significantly around the world [2]. In January 2020, the World Health Organization (WHO) announced that COVID-19 had been labeled as a public health pandemic disease worldwide [3]. Likewise, during the last three years, individuals worldwide face a large wave of COVID-19 produced by SARS-CoV-2 variants (i.e., delta, lambda, mu, and omicron) on a widespread globe. In January 2022, the World Health Organization (WHO) published an updated report about enhancing the response to the new mutation called Omicron SARS-CoV-2 variant [4]. To focus more on COVID-19 symptoms, after the incubation period (2–14 days), three phases of COVID-19 symptoms appeared [1]. The first stage, known as the acute COVID-19 stage (stage I) characterized by mild to moderate symptoms including fever or chills,

cough, shortness of breath fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or running nose, nausea, and diarrhea [2]. The prevalence of mild to moderate symptoms is significant in SARS-CoV-2-infected individuals [5]. Post-acute viral syndromes are acknowledged as prolonged and multi-organ effects [6]. The second stage (stage II) is less common and characterized by severe clinical stages such as dyspnea accompanied by hypoxemia [7, 8]. As a consequence of severe clinical symptoms, stage III can occur, including serious difficulties such as arrhythmias, septic shock, and multi-organ failures, ultimately resulting in intubation or death [2]. A high proportion of COVID-19 non survivors had pre-existing cardiovascular illness and multi organ dysfunction [9].

SARS-CoV-2 infection appears to have harmful effects on the central nervous system (CNS), leading to psychiatric and neurological symptoms [10]. Brain-related manifestations were reported in individuals with and without neuropsychiatric diseases [11]. Existing in vitro and in vivo studies support the notion of SARS-CoV-2-related neuroinvasive risks. These risks were transported mainly through olfaction and the trigeminal pathways [12]. According to national longitudinal research in China, depression, anxiety, and insomnia were the most common psychiatric disorders associated with the COVID-19 pandemic [13]. Another study indicated that the prevalence of neurological manifestations was reasonably noted, including encephalopathy, delirium, seizures, Guillain-Barré-syndrome, and motor dysfunctions [14]. Another review reported that the emergence of psychiatric disorders occurs within three months in COVID-19 survivors [6].

COVID-19 outbreaks present challenges for therapeutic and drug management in clinical conditions and complications. Recently, several researchers emphasized medication repurposing as an approaching method to establish a fast-track line for discovering therapeutic treatments for COVID-19 patients worldwide [15–18]. Drug repurposing, also known as drug reuse, is defined as exploring new indications for existing drugs. This approach limits the cost of both research and development significantly [19]. Serendipitously revealed a substantial number of current identified repurposed drugs [20]. The repurposing strategy provided promising treatment candidates in other viral pandemics outbreaks, including ZIKA, Ebola, and dengue [21].

Zhang et al summarized the current potential therapeutic approaches for diseases related to COVID-19 infection and explain their mechanisms of action, safety, and effectiveness such as antiviral drugs, convalescent plasma, spike Protein-Angiotensin-Converting enzyme 2 blockers, chloroquine, hydroxychloroquine, human monoclonal antibody, mesenchymal stem cells, inhaled nitric oxide (iNO), and corticosteroids [22]. Another review highlighted alternative treatment approaches such as mesenchymal stem cells, human monoclonal antibodies, and complementary Chinese medicine [20].

A comprehensive and systematic research about the repurposing of drugs in COVID-19 was conducted by Srivastava and Singh (2021), the results revealed that no drugs passed clinical trials or were approved by the FDA for COVID-19 [23]. In fact, various reports that clinical trials regarding the potential therapeutic possibilities, such as hydroxychloroquine, lopinavir-ritonavir, and ivermectin, showed that choices were unsuccessful in the treatment of COVID-19 patients [24–27]. Although COVID-19 vaccines were successfully developed and massively distributed, there is a lack of effective treatment [28].

Most significantly, there are cumulative clinical data linked with the use of antidepressants, including the selective serotonin reuptake inhibitor (SSRI) and the serotonin-norepinephrine reuptake inhibitor (SNRI) with a reduced risk of clinical complications in SARS-CoV-2-infected patients [18]. In line with this, a randomized

controlled trial showed that patients who received fluvoxamine had a decreased risk of clinical deterioration compared to those who received placebo during the early period of infection [29]. Following that, an observational study done by Hoertel et al. discovered that the antidepressants, such as SSRIs and SNRIs, may be associated with a lower risk of intubation or death in SARS-CoV-2-infected hospitalized patients [30]. This advantage was not reported with other antipsychotics. For example, a multicenter observational study indicated that administration of haloperidol was not associated with a reduced risk of intubation or death in hospitalized COVID-19 patients [31].

Fluvoxamine has advantages over other repurposing drugs such as positive safety profiles, widespread availability, inexpensive, accessible mode of administration as immediate-release tablets and controlled-release capsules, and use for children and adolescents [32, 33]. The available dosage form of fluvoxamine is both immediate-release tablets and controlled-release capsules. The main therapeutic indication of fluvoxamine is to treat patients with obsessive-compulsive disorder (OCD). The pharmacokinetic properties of fluvoxamine include long half-life of about 9–28 hours according to its dosage form. The clinical guideline recommended the therapeutic dose of fluvoxamine between 100–300 mg/day [34]. Fluvoxamine indication is related to COVID-19 was clarified on the US National Institutes of Health (NIH) COVID-19 Guidelines Panel on April 23, 2021, despite the fact that evidence for fluvoxamine effectiveness was lacking. Recently, a retrospective cohort study of COVID-19 patients treated with SSRIs using electronic health records of 87 health care centers across the US was done in November 2021 by Oskotsky et al. [35]. The study participants were COVID-19 patients receiving fluoxetine only (n = 470), COVID-19 patients receiving fluoxetine or fluvoxamine (n = 481), and COVID-19 patients receiving other SSRIs (n = 2898) compared with matched untreated control COVID-19 patients. The results showed that the patients who received any SSRI had a lower risk of death. In contrast, there was no significant relationship between SSRIs other than fluoxetine or fluvoxamine and the risk of mortality [35]. Finally, fluvoxamine might be used as a preventive medication for patients infected with SARS-CoV-2 in the early stages [16, 36]. In this chapter, we review the fluvoxamine mechanisms of action in COVID-19 and discuss the studies that focus on the impact of the use of fluvoxamine in minimizing the possible complication during COVID-19 infection. Here, we review two main mechanisms mediated by fluvoxamine, the serotonin and the sigma-1 receptor-related mechanisms.

2. Mechanism of fluvoxamine

2.1 Inhibition of serotonin transporter

The main mechanism of action for fluvoxamine, as a selective serotonin-reuptake inhibitor (SSRIs), in the brain is to inhibit the serotonin transporter (SERT) on the 5-HT neuron in the synaptic cleft leading to an increase in the level of the neurotransmitter serotonin [33, 37].

The serotonin transporter is also located on the platelet membranes [38] and in the gut. The serotonin plasma-platelet regulation is a complex biphasic mechanism. Specifically, an elevation in plasma serotonin is associated with reducing platelet SERT surface expression [39]. As a consequence of serotonin transporter inhibition in the platelets by fluvoxamine, this could reduce platelet aggregation [40]. In support of

this, elevated circulating serotonin was reported in hypertensive patients [41]. In fact, previously proven that fluvoxamine should be used with caution in patients receiving NSAIDs, aspirin, or other drugs that may impair coagulation and peptic ulcer patients due to the antiplatelet activity mechanism SSRIs that can increase the risk of bleeding [42, 43]. Interestingly, a previous report indicated that transgenic mice harboring SERT construct mutation exhibited altered platelet aggregation [44]. Overall, the physiological role of SERT in Platelets includes maintaining system homeostasis, regulation of drugs' concentration, and function [39, 45].

Besides, the antiplatelet activity mechanism of fluvoxamine has a protective effect against myocardial infarction (MI) and a promising role for patients with thrombotic risk [46]. Clearly, fluvoxamine has anti-inflammatory properties in several animal and clinical studies through the mechanism of serotonin transporter inhibition [47, 48]. For instance, in a Parkinson's disease model, fluvoxamine has been shown to reduce inflammation in injured striatal neurons by elevating anti-inflammatory cytokines and lowering inflammatory cytokines and lipid peroxidation in a 6-hydroxydopamine (6-OHDA) lesion-induced rat model [49]. In line with this, chronic administration of fluvoxamine to the 6-OHDA Parkinsonism model improves the Parkinson's-like symptoms, including a reduction in the dopaminergic neuronal degeneration, improvement in motor dysfunction, and normalization of corticosterone levels in the circuitry [50]. Another preclinical setting utilized the same model, the 6-OHDA Parkinsonism model, which indicated that chronic fluvoxamine treatment alters inflammatory hallmarks of Parkinsonism centrally using both the mRNA and the protein level analysis. The level of IL-1β, IL-6, and TNF-α was reduced following one month of Fluvoxamine treatment [49]. Highlighting the fluvoxamine-mediated pharmacological link between serotonin – anti-inflammatory mechanisms at central and peripheral levels.

Likewise, another study revealed that fluvoxamine inhibits inflammation genes in *in vitro* settings [32]. In multiple sclerosis, fluvoxamine reduced the lymphocyte infiltration and the circulating IFN-γ in experimental autoimmune encephalomyelitis. It further affects the pathological demyelination of lumbar spinal cord in multiple sclerosis animal models [51]. In the context of dementia, a previous review highlighted the anti-inflammatory effects of SSRIs, and the evidence provided indicated that introducing SSRIs in neurodegenerative dementias has beneficial effects [52]. Previous studies have proven that fluvoxamine has potent anti-inflammatory properties in vitro and in vivo models. Besides being an effective anti-inflammatory agent, fluvoxamine was found to have antioxidant effects. In a rat model of ulcers, the stress-induced peptic ulcer model, compared to the control group, the fluvoxamine-treated group exhibited reduced biochemical measurements representing oxidative stress [53]. Most significantly, the serotonin transporter in rodents and humans is highly expressed by the lung, demonstrating that the serotonin transporter in lung endothelium controls the bioavailability of the potent vasoconstrictor serotonin[54, 55]. It was reported that inhibiting gut- and lung-serotonin modulates pulmonary hypertension [56]. Additionally, fluvoxamine can positively improve the lung function of chronic obstructive pulmonary disease (COPD) [57]. For depressed COPD patients, SSRIs are the first-line treatment [58]. However, there is a need for a further clinical study to clarify more about the role of fluvoxamine in the treatment of COVID-19 patients. Although other antidepressants can act on serotonin transporter as an inhibitor, they did not have the same favorable impact on COVID-19 patients [57]. As a result, it is unclear whether fluvoxamine's blockage of serotonin transporters plays a substantial role in its positive benefits for COVID-19 patients. The anti-inflammatory

effects of serotonin transporter inhibition, on the other hand, may play a role in its positive benefits [55]. To support the potential use of SSRIs in the treatment of post-COVID-19 depression, a recent observational study showed that treatment with different SSRIs antidepressants has positive effects in patients with post-COVID-19 depression [59]. In support of this, another report highlighted that SSRIs might decrease the rate of mortality in COVID-19 patients [35]. However, different mechanism of action needs to be clarified more about the role of fluvoxamine in the treatment of COVID-19 patients. These mechanisms might be acid sphingomyelinase mediated [60], or melatonin receptor-mediated [61].

2.2 The Sigma-1 receptor-mediated mechanism

Several studies established the role of the sigma-1 receptor in the replication of SARS-CoV-2. Initially, it was recognized by its action as a cellular factor known as endoplasmic reticulum (ER) protein sigma-1 receptor that mediates the early steps of viral RNA replication but not the persistent hepatitis C virus (HCV) RNA replication [62]. The ER chaperones are required to control the production of glycosylated proteins in the cell, including those required for viral infection phases and those involved in immune escape [63]. Therefore, they play various important roles at various stages of the infectious cycle. A recent study recognized protein-protein interactions between SARS-CoV-2 and human proteins including the sigma-1 and sigma-2 receptors [64]. In line with this, a recent report linked this molecular pathway and SARS-CoV-2 replication [65]. Moreover, sigma-1 receptor agonists may protect against mitochondrial damage and ER stress in response to SARS-CoV-2 infection [66]. For that reason, the use of drugs with sigma-1 receptor ligand properties may enhance additive value in early intervention for COVID-19 patients [67].

Previous reports have linked sigma-1 receptor and psychiatric disorders, including anxiety [68], depression [69], and schizophrenia [70].

Cognitive deficit is a core feature of psychiatric disorders, including depression. Reports highlighted the role of the sigma-1 receptor in the fluvoxamine antidepressant mediated mechanism [71]. First, Sigma-1 receptors are expressed abundantly in cortical and motor brain regions [72], indicating functional involvement in the pathology of depression. Additionally, electrophysiological studies indicated that sigma-1 receptor modulated glutamatergic transmission in primary hippocampal neurons. Besides, they were found to be highly expressed in the olfactory bulb [72], a brain region involved in adult neurogenesis. Adult neurogenesis is involved in modulating synaptic plasticity [73] and disrupted in preclinical models of depression [74]. A previous study reported sigma-1 receptor's functional involvement in modulating adult neurogenesis [75]. In a model of Alzheimer's with cognitive impairment, sigma-1 receptors were found to promote spines' maintenance and maturation [76]. Recent studies highlight the role of spine modulation in promoting fast-acting antidepressant effects [77], signifying the role of Sigma-1 receptors in tacking pathological mechanisms of depression.

Besides, sigma-1 receptors were reported to modulate protein kinase signaling (pERK) molecularly in a neuropathic pain animal model [78], and this kinase pathway was found to be involved in depression [79].

In addition, a recent review found that the significant potentiation of the nerve growth factor (NGF) by SSRIs including fluvoxamine leading to induced neurite outgrowth in cell culture and brain plasticity via selective sigma-1 receptor agonistic activity [80]. In clinical settings, NGF was reported to be reduced in depressed patients

[81], this reduction was correlated with suicidal tendencies [82]. Moreover, preclinical studies in animal models of depression reported reduced NGF levels [83–85].

Additionally, modulation of the sigma-1 receptor pathway positively impacted inflammatory pathways such as IL-6 tumor necrosis factor-α (TNFα) [86]. In line with this, sigma-1 receptor agonist (the pRE-084) presented neuroprotective effects measured by a decreased infarct volume in an embolic stroke model. This was mostly regraded y a reduction in inflammatory cytokines, including TNF-alpha and multiple isoforms of IL in cortical tissues [87]. In another study utilizing a stroke model in rats, the sigma-1 receptor was reported to exert neuroprotective effects, and these modulations were mediated via targeting glutamate-induced excitotoxicity [88]. Also, in a rat model of renal ischemia, the fluvoxamine mediated sigma-1 receptor mechanism was reported to enhance the survival rate, renal function, and histological characteristics [89]. All these evidence suggest that molecular modulation of the sigma-1 receptor has beneficial effects. It further confirms that the neuroprotective effects of fluvoxamine render it to be considered a prophylactic therapeutic candidate to prevent COVID-19 risks. However, further studies are required to answer whether the anti-inflammatory and other fluvoxamine neuroprotective effects of fluvoxamine are clinically relevant for COVID-19 patients.

Antidepressants	**Affinity to sigma 1 receptor**	**Action at sigma receptor**	**Anti-inflammatory effect**	**Reference**
Fluvoxamine (SSRI)	Potent	Agonist	Beneficial effect in both preclinical and clinical models of inflammation.	[40, 62, 86, 90]
Sertraline (SSRI)	High to moderate	Antagonist	Strong anti-inflammatory effects by lowering and controlling pro-inflammatory cytokines.	[18, 71]
Fluoxetine (SSRI)	High to moderate	Agonist	Anti-inflammatory effects of fluoxetine in lipopolysaccharide (LPS)-stimulated microglial cells.	[91, 92]
Escitalopram (SSRI)	High to moderate	Agonist	Beneficial effect as an anti-inflammatory in the preclinical module.	[66, 93]
Citalopram(SSRI)	High to moderate	Agonist	Beneficial effect in both preclinical and clinical models of inflammation.	[48, 92]
Paroxetine (SSRI)	Very weak		Partial anti-inflammatory effect.	[48]
Imipramine (TCA)	Very weak	Agonist	Weak inflammatory effect.	[48, 94]
Venlafaxine (SNRI)	Very weak		Weak inflammatory effect.	[94]
Mirtazapine (NaSSA)	Very weak		No sufficient evidence in clinical studies.	[95]

TCA: Tricyclic antidepressants; SSRI: Selective serotonin reuptake inhibitor; SNRI: Serotonin norepinephrine reuptake inhibitor; NaSSA: Noradrenaline specific serotonergic antidepressant. The measure for sigma affinity indicates that potent = 17 nM, high to moderate = 30–400 nM, very week > 10,000 nM.

Table 1.
Affinity of the antidepressants for sigma-1 receptor.

For the most important part, which is the relation between the use of antidepressants and sigma-1 receptor, a study examined in an animal model the SSRIs binding affinity to the sigma-1 receptor [71]. As a result, the study revealed that different SSRIs, including sertraline, fluoxetine, citalopram, and fluvoxamine, have a significant functional impact ranging from high to moderate affinity for sigma-1 receptors in the rat brain (**Table 1**).

3. Conclusion

In this chapter, we reviewed the mechanisms of action of fluvoxamine, including the serotonergic and the sigma-1 mediated mechanisms with regard to COVID-19 infection. Fluvoxamine is not FDA-approved for the treatment of any infection-related disorder. However, accumulated evidence highlighted potential beneficial effects.

To sum up, fluvoxamine could help to improve the clinical deterioration associated with COVID-19 symptoms. However, it is for future studies to mechanistically examine the potential mechanisms and profile consequences related to preventive measures of fluvoxamine in treating COVID-19 patients.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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