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Case Report

The impact of stress on COVID-19 severity: Exploring antidepressants as a potential intervention

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ABSTRACT

The COVID-19 pandemic has impacted not only our physical health, but also our mental well-being, leaving long-lasting scars that time might heal. Antidepressants are known to alleviate stress, anxiety, and depression by modulating specific neurotransmitters that are associated with these conditions, which aid in communication between brain cells, and each antidepressant acts on these neurotransmitters in slightly different ways, making them a popular treatment choice. We describe in this prospective longitudinal observational study ten COVID-19-positive cases with severe disease symptoms and post-infection mental scars, who were prescribed fluoxetine and paroxetine. These treated cases experienced a progressive reduction of illness severity and anxiety upheaval surrounding this pandemic, which may involve the negative action of stress on COVID-19 patients and the positive action of antidepressants against the viral disease. Effective treatments of COVID-19, especially those that are easy to use, show good tolerability, and have widespread availability at low cost, with their less bothersome effects and non-addictive properties should be widely studied.

KEYWORDS: SARS-CoV-2, COVID-19, antidepressants, fluoxetine, paroxetine.

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INTRODUCTION

The world is still under the threat of the COVID-19 pandemic even with the application of confinement, preventive measures, and the availability of vaccines [1], and as of July 28th, 2022, there are 579,085,353 cases and 6,413,185 deaths worldwide [2].

Stress and anxiety are both emotional responses to a stressor that affect our mental and physical health, and with the COVID-19 pandemic, almost everyone has been touched physically and mentally, whether by the death of a family member, confinement, or all stress from social media, and this has not only impacted all ongoing activities but has led to a tremendous negative effect on people's mental health, like fear of contracting the virus, lack of treatment, increased mortality, and uncertainty about when the virus would be eradicated. In addition to assessing the global prevalence of mental health disorders related to the pandemic, researchers should also examine the impact of social and environmental factors on the development and recovery of these conditions [3].

Some medications may reduce the risk of COVID-19 infection after exposure by preventing SARS-CoV-2 host cell entry, which occurs when the virus binds to the membrane-bound angiotensin-converting enzyme 2 (ACE2) in the nasal passage and lungs. Nonetheless, no effective

treatments have been approved. We present ten cases of COVID-19-positive patients, 70% of whom were males and 30% of whom were females, with Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR), or antigenic test confirmation. These patients experienced severe episodes of high stress and anxiety as a result of the pandemic, on top of being severely infected. After each checkup during the course of taking the medications prescribed, all cases had very positive outcomes.

CASE SERIES

Investigation and diagnosis

This prospective, longitudinal cohort study evaluated the incidence of high stress as an associated risk factor for severe COVID-19 and the relief of that severeness after prescribing two different antidepressants to 10 individuals who were COVID-19 positive, with an age range from 40 to 70 years, mutual chronic diseases and dissimilar weight (Table 1).

Treatment

All patients were prescribed antidepressants, specifically fluoxetine and paroxetine with either 10 mg or 20 mg doses for a period of 3 to 6 months (Table 2). Assessment of stress exposure was done using a combination of self-report measures, behavioral coding, and sleep tracking.

Follow-up and outcomes

In our observational study, all patients that were prescribed antidepressants had amazing relief outcomes with low levels of stress while still being positive for COVID-19 and even post-infection, showing signs of increased mental improvement at every checkup over the periods mentioned earlier. All of them had sleep improvements and better upgraded overall mental health.

DISCUSSION

Several plausible pathophysiological mechanisms could explain the protective effects of the antidepressant medications against COVID-19 infection. Studies in both cell culture systems and *in vivo* models have also revealed the antiviral activity of specific antidepressants, such as fluoxetine, which was discovered to be a potent inhibitor of enterovirus replication, and they can also act as anti-inflammatory agents, lowering levels of pro-inflammatory cytokines [4].

Table 1. Table showing the case description of this study.

Patients	Gender	Age	Weight (kg)	Chronic diseases
Patient n1	Females	41	68	Hypothyroidism
Patient n2		43	70	None
Patient n3		60	100	High blood pressure and depression
Patient n4	Males	48	95	Dyslipidemia
Patient n5		65	85	High blood pressure
Patient n6		55	66	None
Patient n7		44	93	High blood pressure
Patient n8		70	60	Depression
Patient n9		42	85	None
Patient n10		60	70	High blood pressure

Table 2. Table reporting the prescribed medications for the patients treated in this study and their doses.

Patients	Treatment	Dose (mg)	Periode
Patient n1	Paroxetine	10	6 months
Patient n2	Paroxetine	10	6 months
Patient n3	Fluoxetine	20	Unspecified
Patient n4	Paroxetine	20	3 months
Patient n5	Paroxetine	20	3 months
Patient n6	Paroxetine	20	6 months
Patient n7	Paroxetine	20	6 months
Patient n8	Paroxetine	20	Unspecified
Patient n9	Fluoxetine	20	6 months
Patient n10	Paroxetine	20	6 months

Furthermore, fluoxetine has recently been shown in cell cultures to inhibit the entry and propagation of SARS-CoV-2 without causing cytotoxicity. There is also clinical evidence that fluvoxamine can help COVID patients with acute respiratory syndrome, as demonstrated in a 15-day double-blind, randomized, fully remote, placebo-controlled study [5]. Furthermore, a previous multi-center, retrospective, observational study involving COVID-19 patients hospitalized in Paris, France, found that antidepressant use, particularly fluoxetine, was associated with a lower risk of intubation or death [6].

Antidepressants such as fluoxetine, paroxetine, or amitriptyline belong to the class of functional inhibitors of acid sphingomyelinase (FIASMAs), which have many anti-inflammatory properties and play an important role in regulating inflammation by inhibiting cytokine production in COVID-19. The high affinity of certain antidepressants for Sigma-1 receptors to restrict the endonuclease activity of an endoplasmic reticulum (ER) stress sensor called Inositol-Requiring Enzyme1 or the inhibition of ASM in endothelial cells and the immune system may explain these anti-inflammatory effects [7]. COVID-19 severe outcomes have been linked to several pro-inflammatory cytokines, and several studies have shown that selective serotonin re-uptake inhibitors (SSRIs), specifically fluoxetine, can reduce the levels of these cytokines and interleukin 6 signaling activity [8].

Another study found a small, statistically significant 8% reduction in the risk ratio of mortality among COVID-19 patients prescribed SSRI when compared to matched control patients [8]. SSRIs' anti-inflammatory properties may explain their potential anti-COVID-19 action [6]. Another possible explanation is that they inhibit the acid sphingomyelinase/ceramide system, whose activation may be important in SARS-CoV-2 infection because it leads to the formation of ceramide-enriched membrane domains that facilitate viral entry and infection [8].

A group of scientists have discovered that antidepressant use at a mean dose of 21.6 (SD = 14.1) fluoxetine-equivalent milligrams was significantly associated with a lower risk of intubation or death, regardless of patient characteristics, clinical and biological markers of disease severity, or other psychotropic medications [9].

CONCLUSION

In this paper, we report on the positive effect of anti-depressants, specifically the selective serotonin re-uptake inhibitors (SSRIs) fluoxetine and paroxetine in severe COVID-19 patients with episodes of stress and anxiety, where these medications may play a role directly or/and indirectly in reducing stress against the COVID-19 infection which may be the cause of the environmental situation that we are living through. Our study has a lot of limitations, and we hope other studies would back up the concept with larger clinical studies.

Given that the majority of the global population remains unvaccinated and the COVID-19 pandemic is still ongoing, there is a pressing need for effective and accessible treatments for the disease. Specifically, treatments that are easy to administer orally, well-tolerated, widely available at a low cost, and have fewer side effects and non-addictive properties should be recommended, based on more in-depth research and large-scale clinical trials.

AUTHORS CONTRIBUTIONS

LW : Conceptualization, data collection, supervision of the project.
IZ : Literature search, data analysis, manuscript writing, manuscript editing.
LB : Manuscript review, supervision of the project.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article is original and contains unpublished material. The authors declare no ethical issue. Informed consent was obtained from each of the patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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