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ANTI-DEPRESSANTS AND COVID-19: A NEW RAY OF HOPE

Erum Khan[1], Ishan Jani[1], Mainak Bardhan[2,3] & Mohammad Mehedi Hasan[4,5]

[1]*B.J. Medical College and Civil Hospital, Ahmedabad, India*
[2]*Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India*
[3]*ICMR- National Institute of Cholera and Enteric Diseases (NICED), Kolkata India*
[4]*Department of Biochemistry and Molecular Biology, Faculty of Life Science, Mawlana Bhashani Science and Technology University, Tangail, Bangladesh*
[5]*Division of Infectious Diseases, The Red-Green Research Centre, BICCB, Dhaka, Bangladesh*

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SUMMARY

The coronavirus disease pandemic has grown worldwide. As we understand the exact pathophysiology of the disease and how it affects the systems in the human body, we are in the process of discovering and repositioning drugs potentially effective in these regards. A few targets of these drugs are excessive inflammation following SARS-CoV-2 infection and sigma-1 receptor ER chaperone protein, which plays a role in replication. The recent discovery of antidepressants like fluvoxamine and clomipramine acting through these targets may provide a new ray of hope to decrease mortality and morbidity in severe COVID patients.

Key words: *antidepressants - COVID-19 pandemic - drug repositioning - SSRI - SNRI*

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INTRODUCTION

The Coronavirus disease-2019 (COVID-19) originated in Wuhan, China, in December 2019, and has spread rapidly worldwide. The exact pathophysiology of the disease and how it affects nearly all the systems in the human body is in the process of being figured out. Majority of the people affected are asymptomatic, or present with mild symptoms. However about 20% of the patients present with severe symptoms with high mortality (Grant et al. 2020). The lack of a specific treatment to the disease has led the world into a race against time to discover one, and during times like these, drug repositioning seems to be the fastest way to efficient treatments.

Currently, many trials are underway that target various features of the disease physiopathology, the main target being excessive inflammation following SARS-CoV-2 infection. Severe COVID-19 is associated with an increase in plasma level of inflammatory mediators including cytokines and chemokines such as interleukins IL-2, IL-6, IL-7, IL-10, tumor necrosis factor alpha (TNF-α), monocyte chemo-attractant protein-1 (MCP1; also known as CCL2), macrophage inflammatory protein-1 alpha (MIP1α; also known as CCL3), C-reactive protein, ferritin, and D-dimer (Creeden et al. 2021).

SUBJECTS AND METHODS

The discovery of sigma-1 receptor ER chaperone protein playing an important role in replication of SARS-CoV-2, led to the hypothesis of it being a potential therapeutic target. Hashimoto et al. (2021) discovered the role of antidepressants that act on sigma-1 receptors as agonists, in preventing the cytokine storm in severe COVID-19 (Hashimoto 2021). Increased IL-6 signal transduction causes cytokine storm which is associated with increased morbidity and mortality in COVID-19 patients. NF- kappaB is known to play a pivotal role in cytokine storms through activation of the pro-inflammatory cytokines IL6 and IL6ST. Creeden et al. (2021) provides evidence supporting the use of fluoxetine to decrease NF-kappaB signaling and thereby decrease the IL6ST signal transduction pathway (Creeden et al. 2021).

Activity of antidepressants as S1R agonists prompted one observational study (Hoertel et al. 2021) and a Randomized Controlled Trial (Lenze et al. 2020). The other observational study uses anti-inflammatory effects of fluoxetine through disruption of NF-kappaB pathway as a basis to form hypothesis (El-Ashmawy et al. 2021).

RESULTS

Three of them have published their results, and one RCT is still underway, the details of which are provided in Table 1.

DISCUSSION

Both the observational studies and one RCT published, have shown significant association of fluvoxamine with reduced clinical deterioration in patients affected with COVID-19. For instance, Hoertel et al (2021) reported that 35 patients on standard fluoxetine dose had a lower risk of intubation and death when they were hospitalized for COVID-19 (Hoertel et al. 2021). Ejder Bora et al (2021) reported lower mortality

Table 1. Summary of studies from literature review

Authors	Study type	Endpoint	Conclusion
Hoertel et al. (2021)	Multicenter observational retrospective study	Intubation or death	Significant association between antidepressant use and reduced risk of intubation or death.
Ejder et al. (2021)	Observational retrospective study	Death	Significantly decreased mortality in COVID-19 patients using antidepressants.
Lenze et al. (2020)	Randomized Controlled trial	Not applicable	Patients treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days.

in the 108 patients on antidepressant use compared to 943 not using antidepressants (Ejder et al. 2021). The results entailing these studies can be attributed to various pathophysiology. As mentioned above, the primary hypothesis that prompted these studies was a recent study indicating Sigma-1 receptor (S1R) agonists can be repurposed for treatment of COVID-19 patients. S1R plays an important part in replication of SARS-CoV-2, and several antidepressant drugs (i.e., fluvoxamine, donepezil, ifenprodil) have a high affinity for S1R. Moreover, this is not the only reason which might explain the efficacy of antidepressants against SARS-CoV-2. A recent study suggests that functional inhibitors of acid sphingomyelinase activity (FIASMA), including several SSRI and non-SSRI antidepressants, may prevent the infection of epithelial cells with SARS-CoV-2 (Carpinteiro et al. 2020).

Molecules like clomipramine have also been implicated as good candidates as it has anti-inflammatory properties and potential to prevent brain damage by direct effect of viral infection and indirect effect of excessive inflammatory response. As evidenced earlier, clomipramine has also significantly inhibited replication of Ebola virus (RNA virus), SARS-CoV, and MERS-CoV (Kouznetsova et al. 2014, Dyall et al. 2017). It was hypothesized that clomipramine's chemical structure i.e., a cationic amphiphilic drug, allows it to accumulate in lysosomes and increase its pH thereby inhibiting viral protease activity (Vater et al. 2017).

In addition, SSRIs also inhibit platelet activation, as indicated by Schlienger et al (2003) (Schlienger & Meier 2003). Thromboembolic conditions causing a significant morbidity in COVID-19 patients, this might explain decreased clinical deterioration in patients on antidepressant therapy.

The similar findings in the studies complement each other, and can be considered novel in the present context of the COVID-19 pandemic. Study analyses suggest SSRI and non-SSRI antidepressants, specifically the SSRIs escitalopram, fluoxetine, and paroxetine, and the SNRI venlafaxine, to be significantly associated with reduced risk of intubation or death. The advantages SSRIs hold over other classes of drugs used in management of the disease are that of easy availability, lower costs, and c oral administration. These drugs have no direct antiviral effects proved in vivo, but their administration may decrease the likelihood of clinical deterioration in patients of COVID-19.

CONCLUSION

Nevertheless, the published studies are not without limitations. All these studies have been conducted in a single geographical area, with a homogenous study population, cautioning the interpretation of results as hypothesis generating. Moreover, since these studies were conducted on severely ill patients, no effects on mild to moderate cases can be commented upon. Larger cohorts comparable to the world-wide usage of fluoxetine and other antidepressants should be conducted to elucidate the potential of these molecules in combating SARS-CoV-2 infections. Since the current literature emphasizes the importance of treating the acute phase of illness at the same time keeping in mind the long-term sequelae in survivors, these molecules should be heavily investigated. Such an investigation calls for collaborative studies between psychiatrists, immunologists, virologists and intensive care specialists.

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Contribution of individual authors:

Erum Khan & Ishan Jani: writing original draft;
Mainak Bardhan: conceptualization, writing review and editing, project administration;
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Correspondence:
Mainak Bardhan, MD
Department of Neurology,
National Institute of Mental Health and Neurosciences (NIMHANS)
560029 Bengaluru, India
E-mail: bardhan.mainak@gmail.com