Press Release: European College of Neuropsychopharmacology

Depressed COVID patients respond better than expected to antidepressants

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Type of work: peer-reviewed/observational study/human subjects

The COVID pandemic has led to a significant increase in mental health problems. Now, in some good news, a pilot study has shown that depressed patients who have suffered from COVID respond better to standard antidepressants than do people who have not had COVID.

Around 40% of COVID sufferers report the development of depression within 6 months of infection. The inflammation caused by COVID is believed to be the main reason for the development of depression. Now new research has shown that around 90% of patients who have suffered from COVID respond to SSRIs, significantly more than would be expected.

This work is presented at the ECNP Conference in Lisbon, and has been accepted for publication by the peer-reviewed journal *European Neuropsychopharmacology**. Lead researcher Mario Mazza MD, San Raffaele University, Milano said:

"We know that COVID has led to an epidemic of mental health problems. Post-COVID depression is a serious issue, with around 40% of COVID patients developing depression within 6 months of infection. But this study indicates that patients who have had COVID have a better chance of managing their depression than we thought".

The researchers, from Professor Francesco Benedetti's Laboratory of Psychiatry and Clinical Psychobiology at San Raffaele Hospital in Milano, treated 58 patients who had developed post-COVID depression with SSRIs (Selective Serotonin Reuptake Inhibitors) such as sertraline, paroxetine, fluvoxamine, and citalopram. Normally around a third of patients don't respond to SSRIs, but the team found that that 91% of those with post-COVID depression responded to treatment within 4 weeks (response was measured using the standard Hamilton Depression Rating Scale: a patient was considered to have responded if they showed a 50% reduction in the scale after 4 weeks of treatment).

Dr Mazza continued:

"This is a pilot study, but it does indicate that post-COVID depression is treatable. We would normally have expected around 40 of the 58 patients to have responded positively to treatment, but in fact we found that 53 of the 58 responded. Considering the anti-inflammatory and antiviral properties of SSRI, we hypothesized that post-COVID depression triggered by infection and sustained by infection-related systemic inflammation could particularly benefit from antidepressant treatment. We are now taking this work forward to a larger scale trial. We also want to investigate whether SSRIs can also help with other post-COVID symptoms, such as cognitive impairment and fatigue, and to look at the role of inflammation in post-COVID depression"

Commenting, Dr Livia De Picker MD PhD (University of Antwerp, Belgium) said this study is of particular importance to the large group of patients and clinicians who are currently dealing with long COVID syndromes.

"Long COVID consists of a combination of persistent physical, psychological and neurocognitive symptoms after COVID-19 infection, which may present very different in different individuals. Even if we still do not understand all the causes of long COVID, this study indicates post-COVID depressive symptoms respond very well to serotonergic antidepressants. This does not come as a surprise to me, as recent studies have pointed out such compounds may also protect patients against severe COVID-19 illness and several antidepressants are currently under study as COVID-19 treatment options. I hope the current findings will prompt further research into the mechanisms through which antidepressants can help against both acute and long-term COVID-19 complaints. Most importantly, these findings stress the importance of adequate screening and treatment of mental health symptoms in patients who suffer from persistent health problems after having been exposed to COVID-19."

Dr De Picker was not involved in this work, this is an independent comment.

*The paper is accepted and is in press at *European Neuropsychopharmacology*: "Rapid response to selective serotonin reuptake inhibitors in post-COVID depression", by Mario Mazza, Raffaella Zanardi, Mariagrazia Palladini , Patrizia Rovere-Querini, and Francesco Benedetti. l. A pre-print (not final version) is available from the press officer. *European Neuropsychopharmacology* is the official journal of the ECNP.

This work is presented at the 34th ECNP Annual conference, which takes place in Lisbon and online from 2-5 October, see https://www.ecnp.eu/Congress2021/ECNPcongress . The European College of Neuropsychopharmacology is Europe's main organisation working in applied neuroscience.

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Notes for Editors

Conference Abstract. P.0404 Rapid antidepressant response to first-line selective serotonin reuptake inhibitors in post-COVID-19 depression

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Introduction

Depression was reported in 30–40%25 of patients at one, three, and six months following COVID-19 [1]. The host immune response to SARS-CoV-2 infection and related severe systemic inflammation seems to be the main mechanism contributing to the development of post-COVID depression. Emerging literature suggests anti-inflammatory and antiviral properties of antidepressants in the treatment of SARS-CoV-2 infection [2].

We hypothesized that post-COVID depression, triggered by infection and sustained by systemic inflammation, could particularly benefit from antidepressants. Thus, the present study aims to investigate the efficacy of SSRI in treating post-COVID depression.

Methods

We included 58 adults patients who showed depressive episodes in the six months following COVID-19. We excluded patients if they showed: other psychiatric comorbidities, ongoing treatment with antidepressants or neuroleptics, somatic disease and medications known to affect mood. The severity of depression was rated at baseline and after for four weeks from the start of the treatment on the Hamilton Depression Rating Scale (HDRS) and response was considered when the patients achieved a 50% HDRS reduction after treatment.

Statistical analyses to compare group means and frequencies (Student's;t-test, Pearson χ^2;test) were performed. To investigate changes in HDRS scores over time, repeated measures ANOVAs (according to sex, mood disorder history, and antidepressant molecule) were performed.

Results

We found that 53 (91%) patients showed a clinical response to antidepressant treatment. Age, sex, mood disorder history, and hospitalization for COVID did not affect the response rate.

Patients were treated with sertraline (n=26), citalopram (n=18), paroxetine (n=8), fluvoxamine (n=4), and fluoxetine (n=2). From baseline to follow-up, patients showed a significant decrease over time of HDRS score ($F=618.90$, $p<0.001$), irrespectively of sex (0.28, $p=0.599$), mood disorder history ($F=0.04$, $p=0.834$), and drug used ($F=1.47$, $p=0.239$).

Discussion

Common knowledge highlights that among antidepressant-treated patients, response rates are moderate (40–60%). On the contrary, we observed a rapid response to the first-line antidepressants in more than 90% of patients irrespectively of clinical variables, thus suggesting a higher antidepressant response rate in post-COVID depression.

The pathophysiology of post-COVID neuropsychiatric sequelae mainly entails severe systemic inflammation and subsequent neuroinflammation. In this context, we have previously found that one and three months after COVID-19, the severity of depression was predicted by the baseline systemic immune-inflammation index (SII) [3,4]. Furthermore, we found a protective effect of the IL-1β and IL-6 receptor antagonist against post-COVID depression possibly associated with their effect in dampening SII [5].

Mounting evidence suggests that antidepressants may a) decrease markers of inflammation; b) may inhibit acid sphingomyelinase preventing the infection of epithelial cells with SARS-CoV-2; c) may prevent the COVID-19 related cytokine storm by stimulating the σ-1 receptor; d) may exert antiviral effects via lysosomotropic properties; e) may inhibit platelets activation [2].

In conclusion, we hypothesized that post-COVID depression could particularly benefit from antidepressants since this molecules have anti-inflammatory and antiviral properties, pass the BBB and accumulate in the CNS, thus preventing the neuro-inflammation triggered by SARS-CoV-2 and associated with post-COVID depression.

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