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Another Outcome of the COVID-19 Pandemic: The Possible Repurposing of Selective Serotonin Reuptake Inhibitors

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Antidepressants are among the most frequently prescribed medications in the United States.[1] Depression, or major depressive disorder, is the most common psychiatric disease in the world and a frequent cause of disability.[2] Diagnosis is primarily based on clinical symptoms and self-report. However, recent research and theory development in the pathophysiology of major depressive disorder has uncovered immune, digestive, endocrine, neurotrophic, and metabolome biomarkers for possible translation to practice.[3] Also emerging is the possible repurposing of the newer-generation antidepressants—selective serotonin reuptake inhibitors (SSRIs)—as a possible future treatment option for COVID-19.

HOW CAN SEROTONIN HELP IN COVID-19?

Serotonin is a neurotransmitter and immunomodulator that improves mood and organizes innate and adaptive immune responses to disease and physiology. Whereas decreases in serotonin levels are a major cause of depression and correlated with increased susceptibility to bacterial infections, emerging science suggests that elevated serotonin levels may play a central part in immunity against viral infections.[4] Some SSRIs seem to have the ability to regulate cytokine and gene expression in both cell and animal models of inflammation and modulate immune responses.[5] Research exploring SSRIs' potential antiviral, modulating, antioxidant, and immunoregulatory effects is emerging worldwide.[4]

The stress and depression associated with coronavirus disease further weaken immune responses, resulting in more severe disease expression. Immune dysregulation related to elevated cortisol and reduction in serotonin may be in part responsible for the progression of COVID-19 infection. Elevations in inflammatory mediator interleukin and tumor necrosis factor α) catecholamines, and histamine concomitant with falling numbers of lymphocytes, monocytes, eosinophils, and basophils further enhance infection progression.[4]

Evidence from small- and low-powered studies suggests that the use of SSRIs, specifically fluoxetine hydrochloride and fluvoxamine (FLV) maleate, may be associated with decreased mortality in COVID-19 via reduction of some proinflammatory cytokines.[6] Selective serotonin reuptake inhibitors may have a broader and more powerful activity in viral infection than previously thought.

RECENT STUDIES AND FINDINGS

In a recent retrospective cohort study using propensity score matching, the relationship of SSRI use and outcomes for patients with COVID-19 was examined with matched controls not receiving SSRIs. The sample of 83,584 patients was diagnosed with COVID-19 during January to September 2020, with a follow-up duration as long as 8 months in 87 healthcare centers in the United States. Three thousand four hundred one adult patients with COVID-19, of whom 2033 were women with a mean age of 62.8 (SD, 18.1), years were receiving SSRIs. When compared with matched untreated controls, relative risk of mortality for all receiving SSRIs was reduced 14.6%, suggesting that SSRIs reduced the severity of infection and mortality.[6]

The South America TOGETHER trial examined the efficacy of FLV versus placebo in preventing hospitalization in high-risk symptomatic confirmed COVID-19 patients. This was a placebo-controlled, randomized, adaptive platform trial in adults from 11 clinical sites in Brazil. This trial is registered at ClinicalTrials.gov (NCT04727424) and is part of the project "Repurposed Approved and Under Development Therapies for Patients With Early-Onset COVID-19

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and Mild Symptoms," which is ongoing at this time.[7] Subjects were randomly assigned (1:1) to either FLV (100 mg twice daily for 10 days) or placebo or other treatment groups. The trial team, site staff, and patients were blind to treatment allocation. Nine thousand eight hundred three persons were screened with 741 patients allocated to FLV and 756 to placebo. The average age of the subjects was 50 years (range, 18-102 years), and 58% were female. There were no significant differences in numbers of treatment adverse events for both groups. For this sample, treatment with FLV (100 mg twice daily for 10 days) among high-risk outpatients with early diagnosed COVID-19 significantly reduced the requirement for hospitalization defined as retention in a COVID-19 emergency setting or transfer to a tertiary hospital. The proportion of patients observed in a COVID-19 emergency setting for more than 6 hours or transferred to a tertiary hospital because COVID-19 was lower for the FLV group compared with placebo (79 [11%] of 741 vs 119 [16%] of 756); relative risk, 0.68; 95% Bayesian credible interval, 0.52-0.88), with a probability of superiority of 99.8% surpassing the prespecified superiority threshold of 97.6% (risk difference, 5.0%).[7]

Two other studies with FLV revealed similar findings. In a double-blind, randomized study, adult outpatients with symptomatic COVID-19 enrolled within 7 days of symptom development; 80 patients were treated with FLV, compared with 72 treated with placebo. None of the FLV-treated patients deteriorated, and 8.3% of patients in the control arm demonstrated clinical deterioration.[8] A prospective study of FLV for early treatment of COVID-19 hospitalization was 0% (0/65) for the FLV arm and 12.5% (6/48) for observation alone. At 14 days, 0% (0/65) of the FLV group experienced residual symptoms compared with 60% (29/48) among people who chose no therapy.[9]

In summary, early evidence suggests that FLV prevents clinical deterioration in COVID-19. Effects include decreased inflammation, inhibited platelet aggregation, decreased mast cell degranulation, and increased melatonin levels. Together, these effects provide significant antiviral effects, regulation of coagulopathy, and allay cytokine storm that occurs in acute COVID-19.[5]

Another interesting study examined the relationship of SSRIs in reducing risk for intubation and death in COVID-19. This observational multicenter retrospective cohort study was conducted at Greater Paris University Hospitals, which examined the usefulness of antidepressants for patients hospitalized for COVID-19 with a primary endpoint of intubation or death. Of 7230 patients admitted for COVID-19, 345 (4.8%) received an antidepressant within 48 hours of admission. Analysis using a multivariate COX model with inverse probability weighting accounted for who did and did not receive the antidepressant, as well as patient characteristics, clinical and biological markers of disease severity, and other medication therapies. Analysis revealed that there was a significant relationship between antidepressant use and reduced risk for intubation or death (hazard ratio, 0.56; 95% confidence interval, 0.43-0.73; $P < .001$), and this association remained significant through multiple sensitivity analyses. Even more interesting, this association was significant for SSRI as well as non-SSRI antidepressants and for fluoxetine, paroxetine, escitalopram, venlafaxine, and mirtazapine (all $P < .05$). These results suggest that antidepressant use may be associated with lower risk of death or intubation in COVID-19. Certainly, double-blind controlled randomized clinical trials of antidepressant medications for COVID-19 are needed to further evaluate these associations.[10]

GOING FORWARD

Strong evidence suggests that SSRIs' antiviral effects, antioxidant properties, and immunoregulatory actions in addition to primary antidepressant effects may have broader applications in practice in the future. The low cost and access to SSRIs are certainly a benefit.[4] In COVID-19 patients, SSRIs seem to hinder cytokine release syndrome that is responsible for aggravating sickness progression and the subsequent increase in TNFα.[11] For repurposing SSRIs going forward, further research is needed to discern SSRIs' roles in symptom management and mortality reduction in COVID-19. Understanding SSRI anti-inflammatory activity, T-cell activation, ability to boost antioxidant status, analgesic properties, and demonstrated anticoagulation effects requires more randomized trials.[4,6]

Small biomarker intensive trials should also be planned to further describe antiviral, immunomodulatory, and antithrombotic effects. Serotonin modulation in the inpatient setting may be common in the future. Perhaps repurposed SSRIs will be prescribed as an antiviral, immune modulator, or part of antiplatelet therapy. Of course, there are concerns with this possible repurposing. Vigilance will be necessary to monitor for emergence of a hyperserotonergic state with similarities to serotonin syndrome.[5]

Some suggest that SSRIs may have a significant role in COVID-19 long-haulers.[12] Although all these possible benefits of SSRIs in COVID-19 provide much needed hope, clinical and prescribing implications in the future must be carefully constructed and research based. Many at-risk COVID-19 patients have multiple comorbidities with polypharmacy, which increases risks for serotonin toxicity and drug-drug interactions that can result in arrhythmia and difficult glycemic control.[13]

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