Growing Evidence for Potential Use of Antidepressants for Long COVID

To the Editor: Long COVID, the postacute sequelae of COVID-19, refers to a condition presenting with a wide range of cognitive, somatic, and behavioral symptoms. It continues to represent a health care crisis that afflicts approximately 6.0% of the overall US adult population and results in significant activity limitation for 26.4% of these individuals.[1] To date, no treatment has been approved for long COVID. The possibility of repurposing antidepressants as a potential treatment for long COVID[2] first emerged following observations that antidepressants might reduce morbidity and mortality when administered during acute COVID.[3–5] In a comprehensive review exploring the purported anti-inflammatory and antiviral activity demonstrated by various antidepressants, several discrete mechanisms—including decreased production of proinflammatory cytokines, agonism of the sigma-1 receptor (an essential inhibitor of cytokine production and a mediator of viral replication), and disruption of the acid sphingomyelinase/ceramide system—were all identified.[2] Given the increased elucidation of the pathophysiology underlying residual COVID phenomena, this pharmacodynamic activity may be particularly relevant amidst growing suspicion that persistent inflammation and ongoing viral replication may be present in long COVID.

Biological and empirical data are gradually amassing that support the use of antidepressants, specifically the selective serotonin reuptake inhibitors (SSRIs), for long COVID. Several studies have noted attenuation of some long COVID symptoms, particularly fatigue, brain fog, and post-COVID dysphoria,[6–8] with the SSRIs. More recently, Wong and colleagues[9] performed a metabolomics investigation intended to identify metabolic signatures associated with long COVID and identified a set of molecules whose levels were depleted in both acute and postacute COVID-19, the most significant of which was serotonin. Integrating data from a combination of human cohort studies, animal models of viral infection, and organoid cultures, they determined that the presence of viral RNA and downstream interferon responses resulted in a decrease in serotonin. Furthermore, these investigators found that in the postacute state of infection, serotonin levels were predictive of whether a patient fully recovered from COVID-19 or would go on to manifest long-term sequelae, prompting them to call for greater assessment of targeting serotonin signaling for the prevention and treatment of symptoms associated with long COVID.[9]

Pending identification and approval of novel compounds that may improve outcome in residual COVID-19, an alternate and parallel strategy is to repurpose or reposition drugs that have been approved for other conditions and subsequently assess their safety and efficacy when applied to COVID-19.[10] While there is clear consensus in the field that randomized controlled trials are needed to determine whether the SSRIs represent a realistic treatment option for long COVID, these antidepressants are well tolerated, widely available, and come with decades of experience in their clinical application for other disorders. Given the ongoing understanding of the pathophysiology of long COVID, results from limited SSRI studies that have been conducted to date, and the prevalence and functional limitations associated with long COVID, these antidepressants may represent an available therapeutic approach in helping to manage those struggling with this syndrome. Among the SSRIs, those with highest affinity for sigma-1 receptor agonism—primarily, fluvoxamine, fluoxetine, escitalopram, and citalopram—may be of greatest benefit.[11] As noted above, preliminary data suggest that certain long COVID symptoms (eg, fatigue, brain fog, and post-COVID dysphoria[6–8]) may be most responsive to SSRIs, although more research is needed to better characterize specific response rates. We encourage practitioners to actively assess the symptom profile of individuals presenting with long COVID to determine if an empirical trial of an SSRI antidepressant is appropriate.

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