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Long Covid & Antidepressants

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Abstract

Three years into this historic pandemic, the scientific and healthcare communities continue to learn a great deal regarding COVID-19, the disease that is produced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The most urgent and immediate focus has been on vaccine development for disease prevention/mitigation and on identification of effective therapeutic interventions for acute phase of illness. However, attention is increasingly being placed on formulating treatment strategies for individuals who are post-COVID-19 and experiencing a syndrome of persistent cognitive, somatic and behavioral symptoms that is being referred to as long COVID. In addition to identifying novel compounds that may improve outcome in either acute or residual COVID-19, an alternate and parallel strategy is to repurpose or reposition drugs which have been approved for other conditions and subsequently assess their safety and efficacy when applied to COVID-19. In this light, antidepressant medications, particularly serotonin reuptake inhibitors, have garnered attention amidst evidence supporting their anti-inflammatory and anti-viral properties. Results from several preliminary studies suggest that early administration of antidepressants may prevent clinical deterioration and even death in patients with acute COVID-19. In this article, we present purported anti-inflammatory mechanisms of the antidepressants, review results from studies that have appeared in the literature to date regarding antidepressants and acute COVID-19, and discuss the possible utility of antidepressants as a potential therapeutic resource for long COVID.

Introduction

Three years into this historic pandemic, the scientific and healthcare communities continue to learn a great deal regarding COVID-19, the disease that is produced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, an estimated 650 million cases of COVID-19 have been confirmed worldwide, including more than 6 million deaths [1]. The disease manifests a broad range of clinical variability, from individuals who are asymptomatic following exposure to SARS-CoV-2 to those who develop severe and critical illness that may ultimately prove fatal.

The most urgent and immediate focus has been on vaccine development for disease prevention/mitigation and on identification of effective therapeutic interventions for acute phase of illness. However, recent attention has increasingly been cast on formulating treatment strategies for individuals who are post-COVID-19 and experiencing residual cognitive, somatic and behavioral symptoms. This protracted syndrome is being referred to as "long COVID," and individuals manifesting this persistent state have been designated as "long haulers." In addition to identifying novel compounds that may improve outcome in either acute or residual COVID-19, an alternate and parallel

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strategy is to repurpose or reposition drugs which have been approved for other conditions and subsequently assess their safety and efficacy when applied to COVID-19. In this light, antidepressant medications, particularly serotonin reuptake inhibitors (SRIs), have garnered attention amidst a substantial body of evidence supporting their anti-inflammatory properties. The objectives of this paper are to review the purported anti-inflammatory and anti-viral mechanisms of the antidepressants, present results from studies that have appeared in the literature to date regarding antidepressants and acute COVID-19, and to encourage discussion and investigation of antidepressants as a potential therapeutic resource for long COVID.

Cytokine storm

The morbidity and mortality associated with COVID-19 has been linked to SARS-CoV-2-initiated immune system dysregulation, referred to as cytokine storm, involving elevated levels of cytokines and immune-cell hyperactivation. Cytokine storm is an umbrella term encompassing various syndromes mediated by immune dysregulation and characterized by systemic inflammation, constitutional symptoms and potentially multi-organ dysfunction [2]. Accumulating evidence suggests that the severity of COVID-19 is associated with increased levels of inflammatory mediators in blood following SARS-CoV-2 infection, including cytokines and chemokines such as interleukin (IL)-2, IL-6, IL-7, IL-10, tumor necrosis factor (TNF), CXC-chemokine ligand 10 (CXCL10), C-reactive protein (CRP), ferritin, and D-dimers [3]. Among the elevated inflammatory mediators, blood IL-6 level is highly correlated with the disease mortality when COVID-19 survivors and non-survivors are compared, suggesting that IL-6 may be an early predictive marker of severe illness as well as a potential mechanism of therapeutic intervention [4].

Proposed biological mechanisms of antidepressants: beyond serotonin

For nearly three decades, there has been a growing literature supporting the notion that antidepressants may modulate the inflammatory response by suppressing the production of pro-inflammatory cytokines and restoring pro- and anti-inflammatory cytokine balance [5,6]. In 1996, Xia and colleagues [7]. Demonstrated that clomipramine, imipramine, and citalopram significantly suppressed the secretion of IL-2 by stimulated T lymphocytes and of IL-1β and TNF-α by stimulated monocytes. Since that time, multiple meta-analyses have confirmed that antidepressants, particularly those with serotonin activity, decrease several markers of peripheral inflammation, most consistently for IL-6 and TNF [8,9]. SRIs enhance serotonergic transmission by blocking the serotonin transporter (SERT) from reabsorbing serotonin following its cellular release, thereby increasing intercellular levels of serotonin. In addition to its role as a critical neurotransmitter in the central nervous system, it is known that serotonin has immunomodulatory properties [10] and both pro- and anti-inflammatory characteristics of peripheral serotonin signaling have been described [11]. Peripheral serotonin is produced in enterochromaffin cells in the gut and released into the bloodstream, where it is sequestered by circulating platelets via SERT that is present on platelet plasma membranes. Serotonin is then stored in dense granules and released upon platelet activation. Several immune cells (e.g., macrophages, T-cells, dendritic cells, B cells) also express SERT and serotonin receptors [12], which are impacted by platelet-released serotonin during the inflammatory response. SRIs directly influence this cycle [13], thereby representing a potential mechanism of action by which these antidepressants modulate immune cell activation and regulation.

In addition to sertonergic-associated anti-inflammatory activity, several antidepressants have demonstrated affinity for the sigma-1 receptor (S1R), one of two sigma receptor subtypes that are encoded by the *SIGMAR*1 gene. S1R is a ligand-operated, membrane-bound chaperone protein expressed at the endoplasmic reticulum (ER) that modulates calcium signaling and ultimately ER stress. CoV replication is structurally and functionally associated with the ER, and CoV infection is well known to activate pathways to facilitate adaptation of ER stress to viral needs [14]. A leading theory is that SARS-CoV-2 replicates in an intermediate compartment between the ER and Golgi complex, inducing ER stress and increased cytokine production which subsequently results in exaggerated inflammation [15].

Therefore, modulation of the ER stress response by targeting S1R might be pivotal in elucidating CoV-host interactions and might provide the rationale for new therapeutic approaches [16]. Mechanistically, S1R is an essential inhibitor of cytokine production [17], and is involved in cellular stress pathways which are used by viruses to promote viral replication [18]. Various S1R ligands have been shown to inhibit infection of B lymphocytes by the human herpesvirus, Epstein-Barr virus [19]; consequently, drugs which act as S1R ligands may hold promise as anti-viral compounds against CoVs. Several psychotropic compounds, including phenothiazines (e.g.,chlorpromazine), butyrophenone (e.g., haloperidol), tricyclics (e.g., amitriptyline, clomipramine) and SRIs (e.g.,fluvoxamine, fluoxetine) have all demonstrated affinity for S1R [16]. Among the SRIs, fluvoxamine has consistently been ranked as one of the most potent S1R agonists clinically available. In animal models, fluvoxamine has been found to exert anti-inflammatory effect by binding to S1R, lowering cytokine production and improving survival from septic shock [17].

Another pharmacodynamic characteristic of antidepressants has also received attention in the context of potential utility for treating acute COVID-19. Several antidepressants (e.g., fluvoxamine, fluoxetine, escitalopram, amitriptyline) have been found to be functional inhibitors of the acid sphingomyelinase/ceramide system, which plays an important role in viral receptor signaling and infection biology [20]. Acid sphingomyelinase (ASM) is a glycoprotein enzyme that catalyzes the degradation of sphingomyelinase into ceramide and phosphorylcholine. ASM is activated by viral infection and triggers a release of ceramide on the cell surface, the presence of which facilitates viral entry into the cell and subsequent viral replication. Compounds which disrupt the ASM/ceramide system subsequently inhibit viral infection. Carpinteiro and colleagues [21] demonstrated that ASM is activated 20 to 30 minutes after exposure to the SARS-CoV-2 spike protein. Infection of freshly isolated nasal epithelial cells from healthy volunteers who had been treated with a single dose of the functional ASM inhibitor amitriptyline showed almost complete inhibition of cellular infection with SARS-CoV-2 spike particles, an inhibitory effect which lasted 24 hours. This effect was replicated with several other antidepressants, including fluoxetine, sertraline and escitalopram.

Taken together, data indicating that antidepressants regulate gene expression and inflammatory cytokine activity that may dampen cytokine storm, as well as inhibit SARS-CoV-2 cellular penetration and subsequent replication, has clear implications for therapeutic intervention of COVID-19 [16,20,22].

Antidepressants and acute covid-19

Based on observations noted above that fluvoxamine demonstrated anti-inflammatory effects by lowering cytokine production and improved survival from septic shock in animal models, Lenze and colleagues [23], assessed whether this antidepressant could mitigate clinical deterioration in recently infected adults with mild to moderate illness (all maintaining oxygen saturation of 92% or greater). They randomly assigned 152 non-hospitalized adults to either fluvoxamine (n = 80) or placebo (n = 72) within 7 days of manifesting symptoms of COVID-19. Primary outcome was clinical deterioration within 15 days of randomization as defined by dyspnea, hospitalization for pneumonia or shortness of breath, or decrease in oxygen saturation (<92%). Participants received either placebo or 100 mg of fluvoxamine three times daily for 15 days. Results indicated that none of the 80 patients in the fluvoxamine group demonstrated clinical deterioration (as defined above) versus 6 of the 72 patients (8.3%) in the placebo group (survival analysis of log-rank $\chi^2 = 6.8$ and $p = .009$).

Given results from this small outpatient trial, Hoertel and colleagues [24], conducted a multicenter observational retrospective study examining the association between antidepressant use and risk of intubation or death among adult patients who had been admitted to the hospital with more severe COVID-19. They reviewed electronic health records (EHR) of 7230 adults who had been consecutively admitted to any of 39 Greater Paris University hospitals for COVID-19, and identified 345 (4.8%) patients who had received antidepressants within the first 48 hours of hospitalization. They found a significant association between initiation of escitalopram, fluoxetine, paroxetine, venlafaxine or mirtazapine and reduced risk of intubation or death (HR, 0.56; 95% CI, 0.43–0.73, $p < 0.001$). A subsequent retrospective EHR review of 83,584 patients diagnosed with COVID-19 during an 8-month period across 87 US health care centers identified 3401 adult patients that had been prescribed SRIs. When compared with matched untreated control patients, relative risk of mortality was reduced among patients prescribed any SRI (RR, 0.72; 95% CI, 0.54–0.97, $p < 0.03$), with a trend identified that seemed to favor fluoxetine and fluvoxamine [25].

Reis and colleagues [26], subsequently designed and conducted a prospective randomized, placebo-controlled trial in Brazil to determine whether initiation of fluvoxamine could reduce risk of disease progression as defined by need for hospitalization. The study team recruited 1497 unvaccinated subjects presenting to 11 outpatient clinics for acute COVID-19 symptoms. Patients were randomly assigned to either fluvoxamine (100 mg twice daily for 10 days) or placebo. Primary outcome was progression to disease severity defined by need for either hospitalization or emergency room treatment greater than six hours. Results indicated that disease progression was lower for the fluvoxamine group

(79 [11%] of 741 participants) versus the placebo group (119 [16%] of 756 participants; RR 0·68; 95% Bayesian credible interval [BCI] 0·52–0·88).

In addition to preventing clinical deterioration in recently diagnosed COVID-19, antidepressants may confer a protective effect for individuals taking these medications while exposed to SARS-CoV-2, which would be in keeping with observations made by Carpinteiro and colleagues [21] regarding the capacity for these compounds to inhibit viral entry into epithelial cells. A retrospective study of 165 individuals who were inpatients in a New York psychiatric facility during the initial pandemic wave (January to June 2020) indicated a significant protective association between antidepressant use and COVID-19 (odds ratio [OR] = 0.33, 95% CI, 0.15–0.70, $p < 0.05$), with the lowest risk of infection in this sample being observed with fluoxetine and trazodone [27].

Taken together, these findings represent strong preliminary evidence for initiating prospective controlled trials that would generate systematic data to better characterize the effectiveness of antidepressants in mitigating clinical deterioration following acute exposure to SARS-CoV-2.

Long covid: Is there a role for antidepressants?

To date, most of the focus in developing novel compounds or repurposing existing medications has been placed on mitigating or preventing clinical deterioration during acute COVID-19. However, increased awareness is now beginning to encompass a postacute syndrome which some individuals will go on to manifest following resolution of COVID-19+ status. To be clear, most individuals who develop symptomatic COVID-19 will return to their baseline, with the average recovery time being 2–3 weeks, depending on symptom severity during acute phase. However, 1 in 5 people, regardless of the severity of their acute infection, may exhibit symptoms for 5 weeks or more, while 1 in 10 may have symptoms lasting 12 weeks or more [28,29]. Those who are most at risk for residual symptoms are individuals who met criteria for severe or critical illness during acute COVID-19 and experienced CNS insult secondary to various pathological mechanisms (e.g., hypoxic/ischemic injury, encephalitis, cerebrovascular accident). The more puzzling phenomena centers around individuals who have had milder forms of acute COVID-19. One of the first accounts of "frightening and long" symptom persistence appeared in the literature on May 5, 2020 from Dr. Paul Garner, a British infectious disease professor who developed mild symptoms that did not require hospitalization. Written seven weeks following initial symptom onset, Dr. Garner described "a roller coaster of ill health, extreme emotions, and utter exhaustion" that involved not only symptom persistence, but waves of abating and resurging symptoms [30]. He characterized this condition as the "long tail" of the disease; soon after other terms such as "long COVID" began appearing in the literature. The precise term "long hauler" was borne out of and popularized by the collective experience of individuals who were struggling with persistent post-COVID-19. The term was originally championed by Amy Watson, who was wearing a trucker hat when she initially tested positive for SARS-CoV-2 and who went on to establish Long Haul COVID Fighters, a web-based platform providing support for those with long COVID and serving as an advocacy mechanism for medical, psychological and social needs of long haul COVID survivors. The Center for Disease Control and Prevention has officially designated long COVID as "post-acute sequelae of SARS-CoV-2 (PASC) for research purposes; in December 2020, the United States Congress appropriated 1.15 billion in funding over four years to the National Institute of Health to support research into the prolonged health consequences associated with long COVID.

Although no precise definition exists, long COVID is typically characterized as cognitive, somatic and behavioral symptoms persisting four weeks after initial infection [31]. Across various studies, the most common long COVID symptoms are fatigue, shortness of breath, myalgia (muscle pain), headache, decreased sense of smell and/or taste, post-exertional malaise,

inability to return to exercise or normal activity levels, depression, apathy and anxiety [28,32-35]. Complaints of "brain fog" have also become quite characteristic of long haul phenomena. Although there is not yet consensus as to how to define this term, decreased cognitive acuity, memory deficits, poor focus, reduced concentration, increased word-finding latency, difficulty tracking complex information, and reduced ability for multitasking have all been associated with the term. Lamontagne and colleagues [36], assessed mood and cognitive symptoms in 50 healthy individuals (with no prior history of COVID-19 infection) versus 50 post-COVID-19 individuals. The two groups did not differ with respect to age, gender, education, race/ethnicity or pandemic stress experiences. Participants completed self-report measures of stress and depression and were administered a brief cognitive battery to assess attention, orienting and executive functions. Results indicated significantly higher levels of depression, anhedonia, inattention and executive dysfunction in the post-COVID-19 group, with the most pronounced effects being noted in individuals who were 1 to 4 months post-acute phase [36].

The exact prevalence of long COVID has been difficult to specify, partly due to differences in follow-up examination intervals, as well as lack of consensus on the number of symptoms required to meet criteria for long COVID [37]. Female gender and severity of illness during acute COVID-19 (as defined by >5 symptoms) are associated with increased likelihood of reporting long COVID [28]. Taquet and colleagues[35], conducted a retrospective review of

236,379 EHRs of COVID-19 recovered patients, 80% (190,077) of which had mild illness. At six-month follow-up, 57% of their sample had at least one or more long COVID symptoms. Other studies have reported rates of residual symptoms of 87% at two months, 96% at three months, and 76 % at six months [32,38,39]. Logue and colleagues [34] reported on a prospective nine-month follow-up study with 177 post-COVID-19 individuals, 161 (91%) of which had had mild acute illness. At follow-up, 30% of their sample reported persistent symptoms, the most common of which was fatigue. Groff and colleagues [40] recently completed a systematic review of 57 studies with more than 250,000 COVID-19 survivors and found that more than half were demonstrating at least one long COVID symptom six months after SARS-CoV-2 exposure.

A "symptom lag" has been described in a subset of patients who go on to manifest long COVID [34]. These individuals were either asymptomatic or very mild (reporting only minimal respiratory symptoms) during COVID-19+ phase, and then began experiencing new-onset cognitive, somatic or behavioral symptoms after an interval of having tested negative. Huang and colleagues [41] reviewed records of 1407 post-COVID-19+individuals for presence of symptoms $\geq$60 days following initial PCR+ testing and found that 32% of individuals reporting symptoms after a period of a least two months were asymptomatic during the acute phase. In keeping with the description originally provided by Dr. Garner[30], some long haulers also report that their symptoms come in waves. Individuals in this subgroup state that their initial symptoms, which may have been respiratory or cardiac in nature, dissipated during initial recovery, only to be followed a brief time later by a second (and possibly a third) wave of other long haul symptoms [32,33].

The underlying mechanism of long COVID is not yet fully understood. The persistence of symptoms long after individuals have tested negative for COVID-19, coupled by observations of symptom lag and symptom waves, has drawn speculation as to whether the body's immune response becomes aberrantly and intermittently activated even after there is no longer detectable virus in the body [39]. Within the cardiac literature, there have been findings of persistent myocardial inflammation and cardiac dysfunction (demonstrated by elevated cardiac enzymes and lower ejection fraction) up to 3 months following recovery from COVID-19+ status [42]. Is it possible that analogous inflammation-associated dysregulation is taking place within the CNS and resulting in the neurobehavioral symptoms manifested by the long haulers [43]? Evidence supporting this hypothesis is provided by Patterson and colleagues [44], who found persistently elevated levels of intermediate and non-classical monocytes in patients with long COVID versus normal controls up to 15 months post infection. Moreover, the profile of particular cytokine elevations, in addition to prolonged nature of the elevations, may be a signature element specific to PASC [45]. More recently, Apple and colleagues [46] analyzed cerebrospinal fluid (CSF) in a small series of post-COVID patients (N =17), 13 of which were reporting cognitive symptoms. Lumbar punctures were performed a median of 9.7 months following initial COVID+ presentation. CSF abnormalities were found in 77% (10/13) of participants reporting cognitive long haul symptoms versus 0% (0/4) in post-COVID individuals manifesting no cognitive sequela.

It is known that infectious diseases can produce a syndrome of cognitive, somatic and behavioral symptoms described in the literature as "sickness behaviors," which include fatigue, malaise, dysphoria, sleep disturbance, cognitive deficits and decreased participation in psychosocial activities [47,48]. Furthermore, comparisons are being drawn between long COVID and other conditions such as fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome, which can be initiated by viral infection and mediated by pro-inflammatory cytokines [49,50]. It is also interesting to note the substantial evidence supporting the notion that major depression is associated with a chronic low-grade inflammatory response and activation of the compensatory anti-inflammatory system [5,6]. Mulitple meta-analyses have confirmed the findings that pro-inflammatory cytokines and acute-phase proteins are increased in patients with major depression, with the strongest evidence supporting elevations of IL-6, TNF and CRP [51]. Pitharouli and colleagues [52], recently conducted a case-controlled study of 26,894 participants with major depression versus 59,001 non-depressed controls. They found that the depressed group demonstrated low-grade inflammation relative to non-depressed controls, manifested by significantly higher levels of CRP. Results from autopsy studies have shown up-regulation in the expression of pro-inflammatory cytokines in the frontal cortex of patients meeting criteria for major depression [53]. Furthermore, experimental administration of pro-inflammatory cytokines can produce depressive-like effects, including fatigue, anxiety and hypersomnolence [8]. Reichenberg and colleagues [54], induced elevated levels of IL-6 and TNF in a sample of healthy volunteer subjects by administering the *Salmonella abortus equi* endotoxin, and found a significant positive correlation between increased cytokine release and anxiety, anergia and depressed mood.

If persistent inflammation is an underlying factor in long COVID, there may be a role for antidepressants given their suspected anti-inflammatory mechanism. Based upon reports noted above of antidepressants administered during acute COVID-19, Mazza and colleagues [55] identified 60 individuals who

had developed depression within six months of recovery from COVID-19 and initiated treatment with an SRI. After four weeks of treatment, 55 (92%) of patients had demonstrated a clinical response, as defined as a 50% reduction in depression scores. The rapidity of response in this sample prompted the authors to speculate that an anti-inflammatory mechanism of action inherent in these antidepressants may have mediated their favorable clinical outcome. Although preliminary, these findings are encouraging and warrant further investigation regarding the efficacy of antidepressants in long COVID. At the present time, there are two double-blind, placebo-controlled studies underway, one assessing whether fluvoxamine as monotherapy or in combination with another agent (metformin or ivermectin) is superior to placebo in improving viral load and serologic markers associated with COVID-19, as well as reducing risk of developing long COVID [56], and another to determine whether the serotonergic antidepressant vortioxetine is superior to placebo in improving cognitive deficits following COVID-19 [57].

Conclusions

As our knowledge base regarding the infection biology of SARS-CoV-2 and the clinical course of COVID-19 continues to expand, we anticipate ongoing development and identification of interventions that are effective in reducing the morbidity and mortality associated with exposure to this novel CoV. Expanded insights into the biologic effects of the antidepressants with regard to anti-inflammatory and anti-viral properties make them ideal as a repurposed drug class in COVID. The point has well been made that SRIs are versatile, economical, readily available, and demonstrate a well-established safety profile [13,20]. Although most studies to date that involve the application of antidepressants to COVID-19 have been in the setting of acute phase illness, we believe that long COVID represents a therapeutic opportunity for the SRIs. This paper sought to encourage and advance this position by reviewing the current literature implying that persistent inflammation may very well underlie long COVID phenomena, and connect that hypothesis with existing and emerging data regarding mechanisms by which SRIs may exert anti-inflammatory activity. In our opinion, antidepressants are leading candidates for rigorous investigation to establish efficacy in treatment of long COVID.

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