APA Resource Document

Resource Document on the Neuropsychiatric Symptoms of Subacute and Chronic Long COVID

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Prepared by the Council on Consultation-Liaison Psychiatry
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I. Introduction

Since the declaration of the global COVID-19 pandemic on March 11, 2020, by the World Health Organization (WHO), there have been insurmountable long-term challenges facing the healthcare landscape (Wang and Han, 2021). In the United States, the economic sector decreased by an annual rate of 32.9% in the second quarter of 2020 alone, which was the largest drop since 1945 (Chen et al, 2021).

Following the pandemic's initial onset came emerging recognition of a novel clinical syndrome—long COVID. Interestingly, initial research efforts into long COVID began via preliminary studies in Italian patients and various patient advocacy platforms including grassroots online patient surveys, all of which depicted "long haulers" with persistent symptoms and ensuing morbidity following initial COVID-19 infection; since then, research has been and continues to be ongoing to better understand the phenomenon of long COVID (Rubin, 2020) (Ceban et al, 2022). Worldwide, there are an estimated 65 million individuals, at a minimum, with long COVID, which represents approximately 10% of all patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The occurrence may be even higher than this estimate due to the percentage of undocumented or undiagnosed cases (Ballering et al, 2022). The incidence of those with long COVID is estimated as 10%-12% of vaccinated patients and 50%-80% of cases that were hospitalized (Ceban et al, 2022) (Bull-Otterson, 2022). This section of the resource document provides a scoping review of current literature on long COVID as pertinent to the general psychiatrist, as they are uniquely poised to care for affected patients given the high degree of neuropsychiatric symptomatology. Here, we specifically describe the clinical picture of long COVID, considerations in the evaluation of patients, and potential role for interventions.

II. Terminology of Long COVID

In general, prolonged symptoms following initial COVID-19 infection, often extending past the clearance of the SARS-CoV-2 virus, are referred to as long COVID. However, adding to the complexity of the discussion is the varying terminology and clinical criteria put forth by medical organizations and used in current literature to describe this clinical entity. As a result, we have outlined key vocabulary relating to this topic. Specifically, long COVID may also be referred to as post-COVID-19 conditions, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS-CoV-2 infection, long-term effects of COVID, and chronic COVID, all of which are synonymous, referring to the same clinical phenomena and etiology. For the sake of clarity, we will refer to this clinical entity as long COVID throughout our text. According to the World Health Organization (WHO), long COVID is defined as the continuation of symptoms, or development of new symptoms, 3 months after initial COVID-19 infection, whereby these symptoms are persistent for at least two months in patients with confirmed or probable SARS-CoV-2 infections (World Health Organization, 2022). Meanwhile, the Centers for Disease Control and Prevention (CDC) states that the diagnosis of long COVID begins at least four weeks after initial infection with SARS-CoV-2 and can occur in patients even if the initial COVID-19 infection was asymptomatic or mild (Centers for Disease Control and Prevention, 2022). The National Institute for Health Care and Excellence (NICE) requires cases of long

COVID to have had symptoms continuing for more than 12 weeks and to not be explained by an alternative diagnosis (National Institute for Health and Care Excellence, 2022).

III. Risk Factors for Long COVID

Facilitating timely recognition of individuals at risk of long COVID may result in earlier connection to care and treatment. Associated risk factors with the development of long COVID include a gradient increase with age and Body Mass Index (BMI), in addition to female sex, belonging to an ethnic minority, a history of COVID-19 infections that required hospital or intensive care unit (ICU) admission with need for supplemental oxygenation, and high symptom burden of initial infection (such as dyspnea and chest pain) (Sudre et al, 2021) (Subramanian et al, 2022) (Davis et al, 2023). A history of preexisting comorbidities has also been associated with the incidence of long COVID, such as a prior psychiatric disorder, hypertension, chronic pulmonary disorders, diabetes mellitus, and in general any chronic illness (Poyraz et al, 2021) (Galal et al, 2021). Laboratory testing indicative of an increased systemic inflammatory state, such as elevated D-dimer, C-reactive protein (CRP), and lymphocyte levels, has also been associated with the onset of long COVID. While a range of risk factors have been provided here, this list is by no means exhaustive; in fact, the recent NICE guidelines have identified this area as a current research priority to promote improved recognition of factors that may predispose individuals to develop long COVID.

IV. Long COVID Pathophysiology

Various hypotheses have been put forth to potentially explain the neuropsychiatric manifestations of long COVID. While this research is ongoing and generally exists in early stages, it builds upon prior research from post-viral illnesses (Yong, 2021) (Monje and Iwasaki, 2022). A large body of research focuses on COVID-related neuroinflammation, which has been shown to contribute to the dysregulation of glial and neuronal cells and can lead to neural circuit dysfunction that impairs both cognitive and neuropsychiatric processes following COVID-19 infection (Wright-Jin and Gutmann, 2019). This phenomenon is not unique to the SARS-CoV-2 virus; in fact, many other viral infections are associated with post-acute infection syndromes (PAISs) that result in neurocognitive impairment (Choutka et al, 2022). It is hypothesized that with the SARS-CoV-2 virus, the immune response may cause neuroinflammation, in which there is a direct increase in cytokines, chemokines, and immune cell trafficking in the brain that induces reactive states for nearby immune cells and microglia (Monje and Iwasaki, 2022). Other projected mechanisms for long COVID include autoimmunity, where immune cells are primed for molecular mimicry, excessive activation of neuronal pathways that promote synaptic pruning and neuron depletion, excitotoxicity of glutamate/N-methyl-D-aspartate pathways, dysfunctional brain stem signaling, endothelial and microvascular abnormalities, and a functioning reservoir of SARS-CoV-2, marked by the persistence of viral levels in patients with long COVID (Davis et al, 2023) (Swank et al, 2023) (Proal and VanElzakker, 2021) (Boldrini et al, 2021).

V. Long COVID Neuropsychiatric and Mental Health Sequelae

a. Hospitalized Patients

The development of long-term neuropsychiatric symptoms has been found to be increased in patients hospitalized for COVID-19, and even more so in those that required ICU admission or developed encephalopathy (Taquet et al, 2021). The most common symptoms included fatigue, headache, and neurocognitive changes such as attention deficit (Yaksi et al, 2022). Compared to patients with other respiratory infections, patients diagnosed with COVID-19 were at increased risk of having any first neurological or psychiatric diagnosis at the 6-month mark following diagnosis—specifically anxiety disorders, mood disorders, psychotic disorders, insomnia, cognitive deficits, and dementia (Taquet et al, 2022). In particular, the risk of cognitive deficits, dementia, and psychotic disorders remained elevated 2 years following COVID-19 diagnosis; however, the risk of anxiety and mood disorders began to decrease starting at the 6-month mark (Taquet et al, 2021) (Taquet et al, 2022). Regardless, due to the impact of mental health on physical health, it remains imperative to screen for anxiety and mood disorders on post-discharge visits even beyond the 6-month mark. This is highlighted in a study by Yaksi et al (2022), which noted that the duration of long COVID was increased as the depression score of the patients increased. Substance use disorders and insomnia were also more common in COVID-19 survivors than in those who had influenza or other respiratory tract infections. The risk of neuropsychiatric diagnoses was greater with the emergence of the delta variant; however, it remained unchanged with the emergence of the omicron variant (Taquet et al, 2022).

b. Outpatients

The risk of developing neuropsychiatric symptoms is also elevated in patients with COVID-19 who did not require hospitalization for their symptoms; however, it is lower than that of those hospitalized and placed in the ICU or those with an encephalopathy diagnosis while hospitalized. Regardless, the risk of developing mood disorders, anxiety disorders, psychotic disorders, or substance use disorders for the first time in the months following a COVID-19 diagnosis remained elevated (Taquet et al, 2022). There is also evidence to indicate that patients with a history of mental health issues may be at higher risk of presenting persistent psychiatric symptoms (Efstathiou et al, 2022). These diagnoses were found to be elevated even in comparison to sequelae of influenza or other respiratory tract infections (Taquet et al, 2021). Due to this elevated risk of psychiatric syndromes, patients should be screened for previous COVID-19 infection during outpatient visits with subsequent screenings for mood disorders, bipolar disorders, psychotic disorders, anxiety disorders, post-traumatic stress disorder (PTSD), and substance use disorders.

Long COVID must be differentiated from the well-documented exacerbation of psychiatric conditions due to the general effects of the pandemic. Responses from 12 featured countries indicated self-reported worsening of psychiatric conditions in two-thirds of the participating patients, determined by their significantly higher scores on scales for general psychological disturbance, PTSD, and depression since the beginning of the pandemic (Gobbi et al, 2020). Other studies showed an increase in psychotic features in the noninfected population as well, indicating that the pandemic had a major psychological impact on the general population (Loch et al, 2022).

c. Post-traumatic Stress Disorder

Previous coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), have been associated with significantly elevated rates of

PTSD in survivors—even several months after diagnosis (Efstathiou et al, 2022). PTSD also seems common in patients following COVID-19 diagnosis (Badenoch et al, 2021). It remains unclear if setting of care or disease severity impacts the incidence of PTSD diagnosis, as it does other psychiatric conditions; however, some studies have found PTSD in 30% of COVID-19 patients who required hospitalization (Nalbseandian et al, 2021). Preexisting mental health problems have been found to increase the risk of post-infection PTSD (Badenoch et al, 2021). Women, the elderly, children, less educated, low-income groups are more vulnerable to PTSD, while comorbidity of chronic mental and somatic disorders and a lack of social connection and social support are possible risk factors (Xiao et al, 2020). Outpatient screening for previous COVID-19 infection and subsequent need for hospitalization should be added to behavioral health interviews, as well as utilization of PTSD screens such as the PCL-5—even in patients that did not previously screen positive for trauma.

d. Cognitive Symptoms

Primary cognitive symptoms include deficits in reasoning, problem-solving, spatial planning, working memory, word retrieval, and attention (Fine et al, 2022). This impairment is more prominent in severe COVID-19 infections and may have delayed onset from, fluctuate, or be continually present from the acute infection phase. A multidisciplinary approach to treatment is ideal, and referrals to neuropsychology, speech/language pathology, and occupational therapists may be helpful in treatment.

Patients should be screened for signs of cognitive symptoms using validated tools and instruments, such as the Montreal Cognitive Assessment (MOCA), the Mini Mental State Examination (MMSE), the Saint Louis University Mental Status, the Short Test of Mental Status, or the Mini-Cog©. They should also undergo thorough neurological examination to identify focal neurological deficits, and neuroimaging should be considered in patients with findings of new or worsening focal neurological deficits or cognitive symptoms. Basic labs should also be ordered to screen for reversible factors contributing to cognitive symptoms, including complete blood count (CBC), vitamin B12, thiamine, folate, homocysteine, 1,25-dihydroxy vitamin D, magnesium, liver function tests, comprehensive metabolic panel (CMP), thyroid function tests (TFT) (thyroid-stimulating hormone, free T3, free T4). In high-risk patients, one may consider syphilis rapid plasma reagin and human immunodeficiency virus testing. Polypharmacy should also be addressed, and patients encouraged to limit use of antihistamine, anticholinergic, and antidepressant/anxiolytic medications that can contribute to cognitive symptoms. Clinicians should assess the impact of cognitive symptoms using standardized patient-reported assessments, including activities of daily living; instrumental activities of daily living; school, work, and avocational (ie, hobbies); and quality of life.

e. Somatic Symptom Disorder and Long COVID

Of increasing interest is the overlap between long COVID and illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome and somatic symptom disorder (Komaroff and Lipkin, 2023) (Horn et al, 2023). This correlation is of particular concern in patients who experienced only mild bouts of COVID-19 and whose long COVID symptoms often remain medically unexplained (Kachaner et al, 2022). Somatic symptom disorder is estimated to be 5%-

7% of the general population with resulting decrease in functioning and quality of life (D'Souza and Hooten, 2023), with some recent studies demonstrating higher rates up to 64% in patients with persistent COVID-19 symptoms (Horn et al, 2023) (Kachaner et al, 2022). These same studies have noted possible associations with mood-anxiety disorders, age, sex, prior diagnoses of somatic symptom disorders, history of trauma/PTSD, alexithymia, and perfectionism. Incidence of functional neurological disorders (FND) in long COVID patients remains complicated and controversial, with some papers citing inadequate characterization of neurological symptoms and lack of overt evaluation of "positive" features of FND, while others note the negative impact and loss of appropriate medical services to long COVID patients who receive an FND diagnosis (Alonso-Canovas et al, 2023) (Teodoro, 2023) (Van der Feltz-Cornelis et al, 2023). Given the increasing concern of this overlap, the wide-ranging definition of long COVID, and the known subsequent risk of disability, it is of vital importance to include assessment of somatization and functional neurological symptoms in long COVID evaluations. Evaluations must be done objectively and thoroughly and take into consideration the broad nature of long COVID symptoms and poorly understood mechanism of the syndrome, as in the early waves of the pandemic, many patients' long COVID symptoms were inappropriately labeled as psychological in origin before long COVID has been identified (Van der Feltz-Cornelis et al, 2023).

Table 1: Screeners for Outpatient Assessment of Long COVID (Fine et al, 2022) (Herrera et al, 2021) (Sevin et al, 2018)

Cognition	• Montreal Cognitive Assessment • Trails A and B • Mini Mental State Examination
Depression	• Hospital and Anxiety Depression Scale • Patient Health Questionnaire-9
Anxiety and trauma	• General Anxiety Disorder-7 • Post-Traumatic Stress Disorder Checklist • Hospital and Anxiety Depression Scale
Fatigue	• Fatigue Severity Scale • Modified Fatigue Impact Scale • Patient-Reported Outcomes Measurement Information System Fatigue.
Somatic symptom disorder	• The Somatic Symptom Disorder-B Criteria Scale (SSD-12) • PHQ-15
Quality of life	• EuroQol Five-Dimension (EQ-5D)

	• CDC Health-Related Quality of Life "Healthy Days Measure" (CDC HRQOL-14)

Table 2: Long COVID Mental Health Outpatient Assessment Recommendations (Fine et al, 2022) (Herrera et al, 2021)

1. Screen patient for psychiatric symptoms and determine timeline of psychiatric symptoms in context of COVID-19 infection using validated tools and instruments and clinical diagnostic interview (see Table 1)
    a. Mood disorders such as depressive or bipolar disorders or symptoms
    b. Anxiety disorders and symptoms
    c. Trauma and stressor-related disorders and symptoms
    d. Psychosis
    e. Somatic symptom disorder
    f. Functional neurological disorder
2. Screen patient for cognitive concerns using validated tools and instruments (see Table 1)
    a. Attention and concentration impairment
    b. Short- and long-term memory impairment
    c. Executive dysfunction
    d. Mental fatigue
    e. Processing speed
3. Determine need for ancillary services such as occupational, speech, or physical therapy for cognitive and/or physical rehabilitation
4. Determine need for more in-depth neuropsychological testing for more debilitating symptoms of cognitive impairment
5. Determine need for neurological, cardiology, sleep, physical medicine, and rehabilitation or pulmonology evaluations through physical exam and comprehensive history and medical review of systems
6. Perform comprehensive medication and supplement review for those that may be contributing to psychiatric, fatigue, or cognitive symptoms

VI. Other Long COVID-Related Symptoms/Disorders

a. Post-ICU Syndrome

The post-ICU population is of particular note when monitoring for symptoms of long COVID. Up to 20% of hospitalized patients infected with SARS-CoV-2 require admission into the ICU, out of which more than 88% require endotracheal intubation and invasive mechanical ventilation (Nanwani-Nanwani et al, 2022). Moreover, COVID-19 patients usually require longer periods of mechanical ventilation and sedation than do non-COVID-19 critically ill patients, which when added to steroid therapy, favors a predisposition to the development of delirium and subsequent

mental health disorders as well as increases physical and respiratory sequelae (Nanwani-Nanwani et al, 2022).

For these reasons, patients with COVID-19 who require ICU admission are at increased risk of post-ICU syndrome (PICS) (Ramnarain et al, 2021). This syndrome encompasses a constellation of symptoms, including but not limited to cognitive impairment, anxiety, depression, and PTSD (Sevin et al, 2018). These diagnoses overlap with those noted in long COVID, which may imply that PICS plays a role in the development of these symptoms in ICU patients. About 3 out of 4 patients in general are found to meet PICS criteria post-ICU discharge. Symptoms of psychiatric disorders, including cognitive disorders, were found in 32% and 31% of patients, respectively (Nanwani-Nanwani et al, 2022). Patients who suffered from septic shock, lung injury requiring mechanical ventilation, and delirium were at increased risk of PICS. Additionally, patients who are younger, of the female sex, have poor recall of their ICU stay, or have longer duration of ICU sedation are at elevated risk of PICS (Biehl and Sese, 2020). Steroid therapy also puts patients at increased risk of PICS (Nanwani-Nanwani et al, 2022). Prior to COVID-19, patients with PICS could see impairments persisting for as long as 5 to 15 years (Biehl and Sese, 2020). As COVID-19 patients have been requiring mechanical ventilation and sedation at higher rates than non-COVID-19 ICU patients, monitoring for PICS and residual sequelae will be imperative in an outpatient setting.

The first outpatient visit following discharge should be scheduled 2-4 weeks after patients have been discharged home. The visit should consist of medication reconciliation, counseling, and screenings for insomnia, depression, anxiety, PTSD, and cognitive deficits. Tools used may include the MOCA, the Hospital Anxiety and Depression Scale, the Post-Traumatic Stress Disorder checklist, Trails A and B, and the MMSE (Sevin et al, 2018). European Quality-of-Life Five Domains for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression may also be useful in assessment (Biehl and Sese, 2020). Treatment will depend on findings and includes pharmacotherapy and psychotherapy, as well as providing the family with education (Sevin et al, 2018).

Table 3: Visit Components and Screening Recommendations at First Post-ICU Outpatient Appointment (Sevin et al, 2018)

Visit components	• Medication reconciliation and counseling • Screening of insomnia, depression, anxiety, PTSD, and cognitive changes
Potential screening tools	• Montreal Cognitive Assessment (MOCA) • Hospital and Anxiety Depression Scale • Post-Traumatic Stress Disorder checklist • Trails A and B • Mini Mental State Examination (MMSE) • EuroQol Five-Dimension

Several studies have recommended the development of ICU recovery centers in order to facilitate the multidisciplinary care these patients will need. Post-COVID-19 ICU clinics bring together specialists in pulmonology, cardiology, pulmonary rehabilitation, physical and occupational therapy, and behavioral health (Neff, 2020). Scheduled patients should be those thought to be at highest risk for post-ICU complications, with risk factors of septic shock and lung injury, especially when treated with mechanical ventilation, and delirium (Sevin et al, 2018). Development of these clinics would allow for better coordination of care, leading to overall improved outcomes for this patient population.

b. Sleep Disorders

Insomnia remains a prominent manifestation of long COVID as well, with duration of hospitalization increasing the risk of developing a sleep dysfunction (Pataka et al, 2021). One study found sleep problems were present in 57% of COVID-19 patients compared to 31% in healthcare providers and 18% in the general population. Another study confirmed that the group most affected by sleep problems during the pandemic was patients with COVID-19, with a pooled prevalence rate of 74.8%, followed by healthcare providers (36.0%) and then by the general population (32.3%.) After 6 months following diagnosis, two-thirds of patients reported continued sleep issues and fatigue (Pataka et al, 2021).

Several diagnostic measures of sleep dysfunctions may be utilized in an outpatient setting, with the most commonly used being the Pittsburgh Sleep Quality Index for many sleep disorders or the Insomnia Severity Index to screen for insomnia alone (Pataka et al, 2021). Management should include sleep hygiene; identification of various risk factors at individual, interpersonal, institutional, and community levels; and early and accurate recognition of sleep dysfunction and psychological distress. Additional treatments may include cognitive behavioral therapy (CBT) and counseling on progressive muscular relaxation (Pataka et al, 2021). Behavioral sleep hygiene strategies include avoiding caffeine, avoiding screen time, avoiding liquids before bed to prevent interruption of sleep with the need to urinate, engaging in relaxation activities, and maintaining a consistent sleep/wake schedule (Fine et al, 2022). Nutritional supplements may have benefits, as subjective sleep quality can be improved by the use of amino acids, melatonin, and vitamin D (Fine et al, 2022). Sleep disorders in long COVID may also represent untreated or inadequately treated mood, anxiety, or trauma disorders.

c. Autonomic Dysfunctions

Patients with long COVID are also at increased risk of autonomic dysfunction, with symptoms including orthostatic intolerance, palpitations, tachycardia, syncope, orthostatic hypertension, labile blood pressures, dizziness, fatigue, and exercise intolerance. The most common autonomic diagnoses associated with long COVID are orthostatic intolerance and postural orthostatic tachycardia syndrome, which often follow a viral infection (Blitsteyn et al, 2022). In evaluation (particularly behavioral health evaluation), it is important to rule out anxiety-related disorders as an etiology of these symptoms prior to diagnosing an autonomic dysfunction. To evaluate for autonomic dysfunction, clinicians should perform a 10-minute stand test recording heart rate and blood pressure while supine and after standing 3 minutes, 5 minutes, 7 minutes, and 10 minutes. Consider obtaining a tilt table test in symptomatic individuals with a negative 10-minute stand test.

Recommended initial laboratory tests in individuals with suspected autonomic dysfunction include CBC, CMP, TFT, vitamin B12, ferritin, morning cortisol, antinuclear antibody panel, erythrocyte sedimentation rate, and CRP. Pulse oximetry to rule out persistent hypoxemia and an electrocardiogram to assess for palpitations and tachycardia are also useful. Ultimately, referral to cardiology or an autonomic specialist is warranted if any positive findings have been noted on a preliminary assessment.

d. Fatigue

Of nonhospitalized COVID+ patients who followed up 1-6 months after diagnosis, two-thirds received a new primary diagnosis, with fatigue being the most common (Herrera et al, 2022). In an outpatient screening setting, it is important to differentiate general or exertional fatigue from mental or cognitive fatigue. Mental fatigue is defined as a progressive decrease in cognitive resources over time when participating in cognitive tasks requiring sustained attention and executive function, independent of deficits from diminished sleep hygiene (daytime sleepiness) or motivation. Several screeners that may be useful for this distinction include the Fatigue Severity Scale, Modified Fatigue Impact Scale, and the Patient-Reported Outcomes Measurement Information System Fatigue (Fine et al, 2022). Clinicians should assess for changes in activities of daily living, independent activities of daily living, school, work, and avocational (Herrera et al, 2022). Patients should also be evaluated for conditions that may exacerbate fatigue symptoms and warrant further testing and potential subspecialty referral, including sleep dysfunctions and mood disorders including anxiety, depression, and PTSD. A medication review should be conducted to investigate medications that may be contributing to fatigue, particularly antihistamine, anticholinergic, and antidepressant/anxiolytic medications that can contribute to fatigue in patients with long COVID. Treatment includes a titrated return to activity program, discussing energy conservation strategies, encouraging healthy diets and hydration, and treating underlying sleep or mood disorders that may be contributing (Herrera et al, 2022).

VII. Subacute COVID-19:

Currently, the literature does make a distinction between long COVID and subacute COVID-19. Subacute COVID-19 is defined as symptoms present between 4 to 12 weeks from initial infection, whereby long COVID is characterized by symptoms persisting or present beyond 12 weeks from initial infection (Nalbandian et al, 2021). In addition to having limited research focused specifically on it, subacute COVID-19's categorization as a clinical entity distinct from long COVID creates numerous challenges ranging from diagnosis to management.

Research does show that patients with subacute COVID-19 may demonstrate significant impairments in cognition, specifically in executive function and attention/processing speed. Specific care should be paid to elderly patients, as research has demonstrated that severity in subacute phase cognitive impairments increases with increased age (Chang et al, 2022). There is limited evidence to assess the likelihood of patients with subacute COVID-19 progressing to long COVID; however, clinically, these patients should be monitored and potentially treated, if applicable, throughout a possible transition point to long COVID.

VIII. Medications And Supplements of Special Interest

a. Low-Dose Naltrexone

Given the lack of consistently effective pharmacotherapy in long COVID, many clinicians and long COVID centers have turned to alternative interventions such as low-dose naltrexone (LDN). The basis for its use stems from proposed long COVID mechanisms, including immune activation, endothelial damage, thromboses, and neuroinflammation (O'Kelly et al, 2022). Mainly known as an opioid receptor agonist frequently used for alcohol use disorder, at lower doses (< 4.5 mg per day), LDN appears to have immune modulation activity and has been shown to be helpful in diseases such as chronic fatigue syndrome, fibromyalgia, complex regional pain syndrome, multiple sclerosis, and some forms of arthritis (O'Kelly et al, 2022). At this time, LDN largely requires out-of-pocket payments and compounding pharmacies and is currently being studied in clinical trials for long COVID (University of British Columbia, 2023).

b. Aripiprazole

Interest has also been increasing in aripiprazole, an atypical antipsychotic with partial D2 agonism (Gettu and Saadabadi, 2023). This stems from the potential benefit seen with myalgic encephalomyelitis/chronic fatigue syndrome, which is thought to have mechanistic overlap with long COVID (Crosby et al, 2021), prior identification of the modulating effects of antipsychotics on inflammatory cytokines and inducible enzymes, and the overlap of gene expression altered by both aripiprazole and COVID-19 infection (Crespo-Facorro et al, 2021). Efficacy in long COVID remains unproven at this time.

c. Antidepressants

Early in the pandemic, selective serotonin reuptake inhibitors (SSRI) were linked to decreased risk of intubation or death in patients with COVID-19 (Hoertel et al, 2021). This was attributed to increased plasma levels of inflammatory mediators such as cytokines and chemokines in COVID-19 and the association of antidepressants with plasma levels of several inflammatory mediators and prevention of infection of epithelial cells (Hoertel et al, 2021). Antidepressants included fluoxetine (also identified to have antiviral effects), paroxetine, escitalopram, mirtazapine, venlafaxine, and fluvoxamine (Hoertel et al, 2021) (Lenze et al, 2020). Recent studies have linked decreased serotonin levels with the development of long COVID due to traces of SARS-CoV-2 lingering in the gut biome of long COVID patients and causing inflammation, platelet hyperactivation, thrombocytopenia, and "enhanced MAO-mediated serotonin turnover" (Wong et al, 2023). This may further support the use of antidepressant therapy in long COVID patients presenting with symptoms such as anxiety, mood changes, and trauma-related symptoms (Fenton and Lee, 2023) (Rus et al, 2023).

d. Psychostimulants

Many long COVID patients report persistence of fatigue and brain fog following their acute infection, which has resulted in many clinicians looking toward psychostimulants such as methylphenidate, amphetamine/dextroamphetamine, lisdexamfetamine, and modafinil (Lopez-Leon et al, 2021) (Pliszka, 2022). Some studies have identified hypometabolism in relevant cerebral networks (frontal cortex, anterior cingulate, insula, caudate nucleus) and persistent central nervous system inflammation, mitochondrial toxicity, and microglial activation, which

further support the therapeutic potential in psychostimulants in long COVID. At this time efficacy remains unclear, though clinical trials are underway looking at the utility of psychostimulants in long COVID symptoms (Szigethy, 2023) (Johnson and Goldstein, 2023).

IX. Conclusions

With the rising prevalence of long COVID and ongoing waves of new COVID-19 infections, it is essential that psychiatrists in various settings and subspecialties become more comfortable with and competent in the evaluation and management of neuropsychiatric sequelae of COVID-19. Evaluation of psychiatric and medical comorbidities, collaboration with other medical specialties and disciplines, and comprehensive treatment planning remain the foundation of long COVID treatment. Though further investigation into underlying mechanisms and potential treatment is needed, psychiatrists are inherently well-suited to participate in long COVID evaluations and provide supportive and targeted treatment to many of the neuropsychiatric and psychological symptoms utilizing existing interventions and medications. Given the delay in the identification of this syndrome, and the initial stigmatization and dismissal of early COVID-19 patients, special care must be taken when evaluating for disorders such as somatic symptoms or FNDs.

Table 4: Long COVID Mental Health Outpatient Treatment Recommendations (Fine et al, 2022) (Herrera et al, 2021) (Sevin et al, 2018) (Moccia et al, 2023) (Parra et al, 2020)

1. For patients with symptoms of mood, anxiety, trauma, somatization, or FND: a. Treat concurrent conditions such as mood, anxiety, stressor-related, or trauma with appropriate psychotherapeutic interventions such as CBT,* biofeedback, EMDR,** and group therapy, and with pharmacological treatments such as antidepressants, anxiolytics, and alpha-agonists 2. For patients with symptoms of cognitive impairment: a. Refer to specialists such as neuropsychologists, occupational therapists, or speech-language pathologists for cognitive rehabilitation b. In collaboration with appropriate specialties, wean or minimize contributory prescription medications, over-the-counter medications, and supplements c. Treat contributory conditions such as mood, anxiety, and insomnia with appropriate psychotherapeutic and pharmacological interventions as above 3. For patients with symptoms of sleep disruption a. Consider referral to sleep medicine if concern for sleep disorder such as obstructive sleep apnea b. Reinforce proper sleep hygiene techniques and behaviors as first-line intervention c. Consider sleep medications such as antihistamines, antidepressants, or sedative-hypnotics d. Treat contributory conditions such as mood, anxiety, or trauma with appropriate psychotherapeutic and pharmacological interventions as above 4. For patients with symptoms of psychosis: a. In collaboration with relevant specialties, rule out neurological conditions such as encephalitis b. Consider pharmacological interventions such as antipsychotics
CBT*: Cognitive behavioral therapy EMDR**: Eye movement desensitization and reprocessing

X. References:

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