The Relationship Between COVID-19 and the Development of Depression: Implications on Mental Health

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Padmashri A Shetty[1], Lena Ayari[2], Jessica Madry[2], Colton Betts[2], Diana M Robinson[3] and Batool F Kirmani[2,4]

[1]Institute for Regenerative Medicine, Department of Cell Biology and Genetics, Texas A&M University School of Medicine, College Station, TX, USA. [2]School of Medicine, Texas A&M Health Science Center, Bryan, TX, USA. [3]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA. [4]Department of Neurology, CHI St. Joseph Health, Bryan, TX, USA.

ABSTRACT: Initially, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease-2019 (COVID-19), was predominantly considered to primarily affect the respiratory system. However, later studies revealed that it also affects brain function through its ability to bind to the angiotensin-converting enzyme type 2 (ACE2) receptors expressed on neural cells. Our study involved a comprehensive review of literature aiming to investigate the relationship between COVID-19 and the development of depression. Our analysis shows a connection between these 2 conditions, as a consequence of the inflammatory response in the nervous system to the COVID-19 virus and the psychophysiological effects of the pandemic. In COVID-19 patients, depression can arise either due to the direct viral infection of the brain or as a result of an indirect immune response triggering neuroinflammation after a cytokine storm. The resulting depression can be treated with non-pharmacological therapies such as psychotherapy, antidepressant medications, or a combination of these treatments depending on the severity of the symptoms.

KEYWORDS: Depression, COVID-19, antidepressants, neuroinflammation, cytokine storm

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CORRESPONDING AUTHOR: Colton Betts, Department of Clinical Education, Texas A&M University School of Medicine, 8441 Riverside Parkway, Bryan, TX 77807-3234, USA. Email: rcbetts@tamu.edu.

Introduction

In 2019, COVID-19, which stems from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially emerged in Wuhan, China. After the worldwide tally of reported cases exceeded 7 million, the World Health Organization designated it as a pandemic. Initially classified as a respiratory illness, COVID-19 primarily manifests acute symptoms associated with lung infection and/or inflammation. However, later studies demonstrated the tremendous invasive potential of SARS-CoV-2 to other organ systems of the human body, including the central nervous system (CNS), causing severe complications.[1]

Numerous studies denote that coronaviruses have many neurotropic strains, such as the Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV.[2] These CNS manifestations are also observed following SARS-CoV-2 infection. One of the mechanisms by which it affects other organs is its capability to attach to the ACE2 receptors (type 2 angiotensin-converting enzyme), which is present in various tissues, most importantly the CNS. The binding of the spike glycoprotein to the ACE2 receptor that is distributed throughout the body mediates the host cell infection (Figure 1).[2] These neurotrophic pathogens can access the CNS by passing through a disrupted blood-brain barrier or retrograde axonal transport. Within the CNS, SARS-CoV-2 can cause demyelination, neurodegeneration, and cellular senescence. These may result in increased brain aging, possibly causing or worsening depressive symptoms.[2] Neural impairments can co-occur with respiratory symptoms or after patient recovery because of SARS-CoV-2 infection of different neural cell types in the brain or due to side effects of the cytokine storm at the systemic level.[1] Another mechanism through which the virus may affect the nervous system is by retrograde olfactory bulb transport. There have been reports of Parkinsonism after infection with SARS-CoV-2, which is thought to develop when the virus uses the olfactory pathway to reach and attack the substantia nigra via a direct nigro-olfactory connection.[3]

The initial focus has been on treating the pathophysiological effects of SARS-CoV-2 to save lives and prevent significant damage to different organ systems. Acute neuropsychiatric manifestations of COVID-19 can include stroke, seizure, agitation, psychosis, mania, depression, insomnia, delirium, catatonia, and akinetic mutism. However, an increasing number of studies are now considering the acute psychological effects of the virus in infected patients and may continue chronically in recovered patients.[4] This is because following recovery from the primary infection or complications, a significant proportion of patients display persistent neurological or psychiatric symptoms.

In previous SARS and MERS outbreaks, symptoms of depression were evaluated due to the isolation that occurs

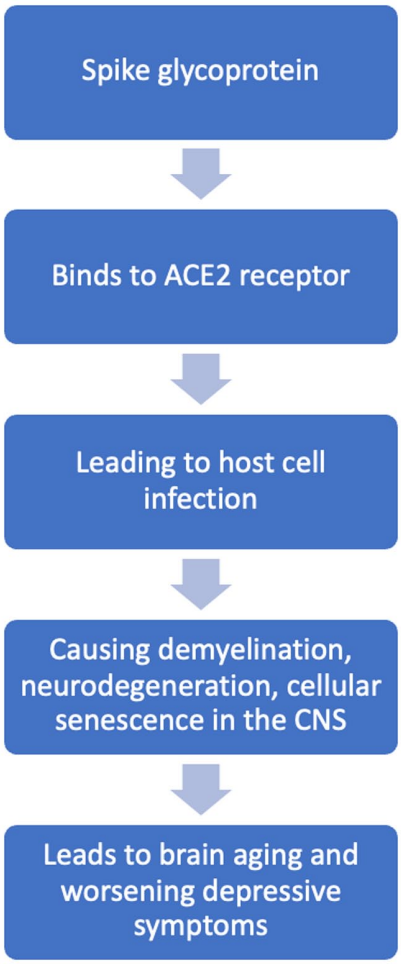

Figure 1. Mechanism of action of action of SARS-CoV-2 in the central nervous system.

because of the viral infection.[5] The COVID-19 pandemic has a significantly greater psychological impact due to its massive scale, shortage of critical supplies such as ventilators, prolonged social isolation, and increased concerns about infecting others.[6] Research findings indicate a higher incidence of depression among patients necessitating hospitalization and even more evident among those requiring ICU admission.[1,7]

This review discusses psychiatric symptoms associated with SARS-CoV-2 infection and depression after recovery from infection. Depression arising from an inflammatory response in the brain and the pandemic's psychophysiological effects are considered.

Depression in the Setting of Acute Infection With COVID-19

Studies have shown increased rates of psychiatric conditions during infection with COVID-19.[8] The most common of these disorders include major depressive disorder (MDD) and anxiety disorders. A systematic review and meta-analysis demonstrate that the prevalence of depression during the COVID-19 pandemic was 33.7% in a sample of 44 531 people.[9] Epidemiological data indicates that women seem to be more likely to develop depression, and the incidence was highest in the 21 to 40 years age group.[9]

A study from 2019 showed that among 44 adult patients who were recently hospitalized with COVID-19 less than 96 hours prior, 36% had symptoms of anxiety and 29% had symptoms of depression.[10] At the 2-week follow-up, there was a decrease in the anxiety symptoms while the depression symptoms remained constant, with 9% having anxiety symptoms and 20% having depression symptoms. They also found that 25% of the subjects had signs of acute stress disorder. These findings are concordant with the psychiatric symptoms of other coronavirus infections such as MERS-CoV and SARS-CoV.

In addition to psychosocial stressors, depression in COVID-19 positive patients may be due to direct viral infection of the brain or through an indirect immune response that triggers neuroinflammation via a "cytokine storm".[11] This cytokine storm involves the substantial production of interleukin 1 β (IL-1β) and interleukin 6 (IL-6).[12] Other biomarkers which have been found to be frequently increased in COVID-19 patients include tumor necrosis factor α (TNF-α), interferon gamma (IFN-γ), interleukin 10 (IL-10), interleukin 2 (IL-2), soluble interleukin 2 receptor (sIL-2R), C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP-1), and serum amyloid A (SAA1)[8] (Figure 2).

Cytokines influence the brain in several ways that can lead to the development of depression. This includes hyper-activation of the hypothalamic-pituitary-adrenal axis, which sets off a cascade of events resulting in neurotoxicity and neurodegeneration as well as disruption of synaptic plasticity, all of which are associated with an increased risk of MDD.[8]

Depression as a Result of Post-COVID-19 Syndrome

The post-acute sequelae of COVID-19 (PASC) indicates the long-term symptoms which remain after infection with COVID-19. Some of the most common PASC symptoms include depression, anxiety, fatigue, and cognitive impairments.[13]

A meta-analysis of 51 studies included 18,917 patients with COVID-19 found that the most common neuropsychiatric PASC symptoms were insomnia (27%), fatigue (24%), cognitive deterioration (20%), anxiety (19%), post-traumatic stress disorder (PTSD; 15%), and depression (12.9%). A similar symptom prevalence was seen across different severities between patients requiring community treatment, hospitalization, and intensive care unit (ICU) admission.[14] Being female and illness severity were risk factors for continuing psychiatric symptoms. Another study in the U.S. covering 62 354 patients revealed that the most common psychiatric diagnosis after infection with COVID-19 was anxiety disorder (12.8%), with mood disorders being the next most common (9.9%).[13] Findings show that the prevalence of depression in the U.S. increased over threefold during the pandemic compared to before.[15]

A 2022 multicenter study looking into the trajectory curve of post-COVID anxiety and depression symptoms, as well as

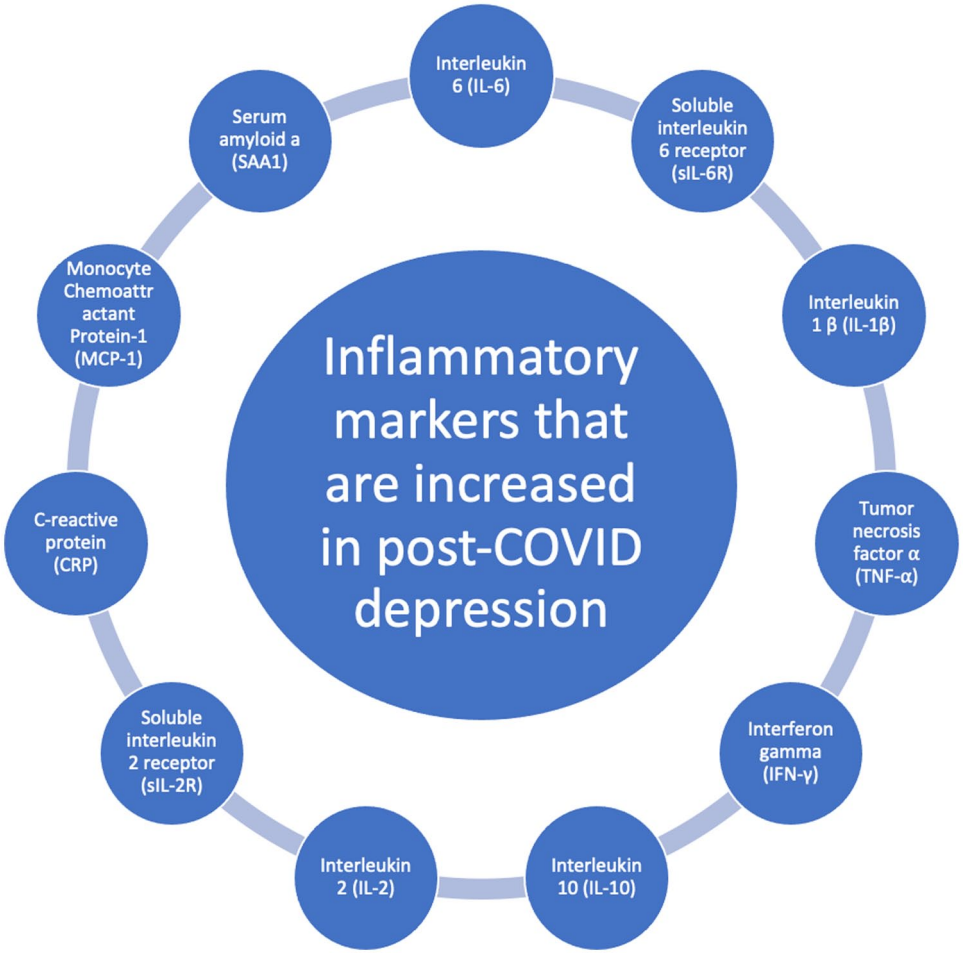

Figure 2. Role of inflammatory markers in post-COVID depression.

quality of sleep, assessed 1,593 COVID-19 patients after hospital discharge at 2 follow-up periods with 5 months in between.[16] The mean time for the first follow-up was 8.4 and 13.2 months for the second follow-up. The findings showed that the prevalence of anxiety symptoms was reduced from 16% at the first follow-up to 15.1% at the second follow-up. The prevalence of depressive symptoms went from 18% at the first follow-up to 13.2% at the second follow-up. Poor sleep quality decreased from 33.2% at the first follow-up to 27.7% at the second follow-up. Although the prevalence of the symptoms decreased over time, the trajectory was not as marked as expected, indicating that increased anxiety, depression, and poor sleep quality may be chronic COVID-19 sequelae.

The long-term prevalence of depressive symptoms in COVID-19 survivors may be due to the prolonged state of high inflammatory marker levels.[8] The patients who are most vulnerable to post-COVID depression are those who had a severe disease course, since they had the highest levels of the inflammatory factors. A 2021 study suggests that the administration of cytokine-blocking agents during COVID-19 infection may have a preventive role against the onset of depression later on.[12] Patients were treated with either high-dose anakinra (IL-1β receptor antagonist) or tocilizumab (IL-6 receptor antibody). A follow-up at 3 months showed significant protective effects of these agents against depression, with no significant difference between the 2 agents.

Depression Due to PASC Workup

The evaluation of depression and PASC begins with a thorough medical history including the history of COVID-19 with symptoms, trajectory, hospitalization, ventilation, treatments (steroids, antivirals, antibodies, prescriptions, and over the counter [OTCs]), vaccination, and reinfections. A complete review of systems, past medical history, past psychiatric history, past substance history, and physical exam should be performed. Judicious use of consultation and diagnostics to address ongoing physical symptoms (eg, hypoxemia and orthostasis) should be considered. Vance et al. included the following medical workup as part of the RECOVER protocol dictated by the patient's particular needs (comprehensive metabolic panel with cystatin-C, complete blood count with differential, lipid panel, hemoglobin A1c, coagulation panel, d-dimer, troponin, N-terminal pro b-type natriuretic peptide, thyroid panel, 25-hydroxy vitamin D, urinalysis, urine microalbumin and creatinine, antinuclear antibody, anti-cyclic citrullinated peptide, rheumatoid factor, high-sensitivity C-reactive protein

[hs-CRP], Epstein-Barr virus DNA polymerase chain reaction [PCR], SARS-CoV-2 antibodies and nucleic acid amplification test).[17] Next address identifiable disorders including PTSD, depression, and anxiety. The diagnosis of PTSD requires the exposure to death, threat of death, or serious injury with intrusion symptoms (eg, nightmares and flashbacks), avoidance, negative cognitions/emotions (eg, dissociation and loss of interests), and alterations in arousal (eg, hypervigilance and startle), with symptoms lasting >1 month duration.[18] The diagnosis of MDD requires either low mood or anhedonia lasting at least 2 weeks as well as at least 4 of 8 neurovegetative symptoms (poor sleep, lack of interests, excessive guilt, low energy, poor focus, change in appetite, motor slowing, and suicidal ideation). Diagnosis of generalized anxiety disorder requires at least 6 months of persistent feeling of anxiety or dread as well as 3 or more of the following symptoms: restlessness, fatigue, poor focus, irritability, muscle tension, and poor sleep. Consider adding evidence based scales and cognitive testing including the PTSD Checklist 5 (PCL-5), Patient Health Questionnaire 9 (PHQ-9), Generalized Anxiety Disorder Questionnaire 7 (GAD-7), and Montreal Cognitive Assessment (MoCA).

Depression as a Result of Psychophysiological Effects of the Pandemic

Impact on healthcare workers

Healthcare workers (HCWs) have shown milder symptoms of both depression and anxiety and have been less likely to show severe symptoms compared to the general population. The prevalence of depression was 31% and anxiety symptoms were 30%, with substantial heterogeneity in the pooled group.[19] Other studies found that there is a higher prevalence of behavioral disorders in hospital staff caring for the COVID-19 patients compared to other groups and that the prevalence of depression in physicians was higher than in other hospital staff.[20] Some of the aspects contributing to this include: high workload and pressure in the workplace, uncertainty about the impacts and deadliness of COVID-19, healthcare working conditions that provided fast adaptations, critical care situations, shorter time for interactions with patients, observing deaths, and family visit bans.[19] Physicians in many countries found ways to cope with their mental health with physical exercise or psychotherapy. Even so, mental health problems experienced by HCWs decrease productivity.[19]

Stress is a contributor to many mental health disorders and is possibly one of the most common issues in society.[20] The prevalence of stress in the workplace for hospital staff excluding physicians or nurses was 36.4% and a prevalence in physicians specifically was 93.7%.[20] Two studies showed a prevalence of depression in physicians of 25.4% and 40.4% respectively.[20,21] Lifestyle factors, stress mitigation at work, and being more attentive to the symptoms of depression and recognizing them early can help in decreasing depression and burn out.[20]

Impact on children and adolescents

The COVID-19 pandemic had affected the emotional and behavioral experiences of children and adolescents significantly.[22] There are many lifestyle transformations during this time such as school closure, quarantine, physical distance between individuals, and the threat of infection, which are associated with depression and anxiety disorders among children and adolescents.[22] Children that quarantined during the pandemic more commonly showed fear, helplessness, worry, insomnia that related to anxiety, feelings of isolation, boredom, and sadness.[22] Being left at home on weekdays without someone to spend time with could be one of the many factors contributing to this.[23] Many studies have shown that female adolescents were at a higher risk of depression and anxiety during the peak of COVID-19 compared to their counterparts.[24] Older adolescents were more depressed than younger ones during this time. Many contributory aspects to this included the lack of positive coping skills among adolescents, which include resilience and having good mental health when there are periods of adjustments. Adolescents perceived having less social support during the pandemic, which contributed to increases in anxiety and depression.[24] This may have been a contributing factor to addiction and the increasing use of alcohol and cannabis during the pandemic with about 49% engaging in drug use.[24] A tactic that had protective effects on adolescent mental health was physical exercise.[23] While many of the children and adolescents had an increase in mental health conditions, their caregivers and adults alike were also impacted.

Impact on adults/caregivers

Even early on in the pandemic children and their caregivers were impacted. The parents of children who were admitted to the hospital during the COVID-19 epidemic appeared to have more severe anxiety and depressive symptoms relative to the non-epidemic period.[25] One study showed significant depression (42%) and anxiety (48%) in such parents during the period of the pandemic.[25] Additionally, around 90% of caregivers demonstrated feelings of worry and nervousness, showing that parents feared the risk of infection to their child and themselves.[25]

Many populations of individuals such as caregivers of children with special needs were also impacted. There was a high prevalence of depressive symptoms at about 62% among caregivers. Caregivers of children with special needs showed that between 20% and 36% had anxiety and stress symptoms.[26] Access to mental health resources and tele-rehabilitation during this time may have been limited and contributed to these findings. Caregivers who did not continue tele-rehabilitation during the lockdown periods were associated with having higher anxiety.[26] Other methods, such as lack of in-home therapy, were associated with depression in caregivers. In those that held the perception that in-home therapy was moderate to difficult for their child, there was an association with stress symptoms.[26] Overall, the COVID-19 pandemic showed a high

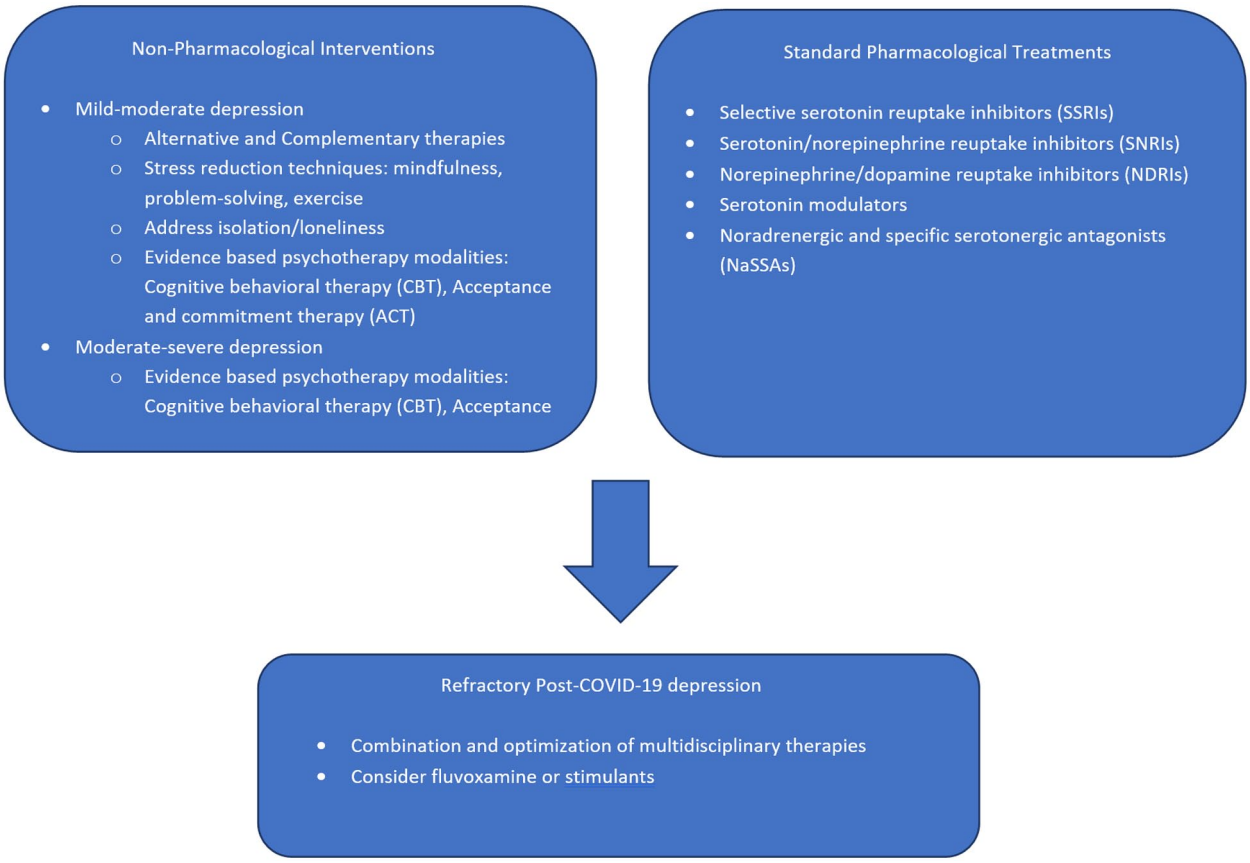

Figure 3. Management of depression.

prevalence of depressive symptoms among caregivers taking care of children with special needs.[26]

Caregivers in other populations, such as those caring for individuals with dementia were shown to be at a greater risk of depression, anxiety, and caregiver burnout.[27] In many aspects, caregivers with higher resilience were found to have an increased level of anxiety during the lockdowns of the COVID-19 pandemic.[27] In comparison, caregivers with low resilience had no significant increase in anxiety levels.[27]

Treatment of Depression and the Psychosocial Impacts of COVID-19

In the United States (US), depression has a prevalence that ranges from 5% to 10%, usually,[28] with numbers as high as 33.7% being reported during the pandemic.[9] The first line treatment for milder forms of depression can include non-pharmacological therapies such as complementary, alternative, or exercise-based treatments but close follow-up is required due to the limited research on these modalities.[28] In more severe cases of depression, such as in MDD, psychotherapy, antidepressant medication, or a combination of both should be used (Figure 3).[28]

The COVID-19 pandemic brought about substantial psychosocial impact in the form of shelter-in-place orders, economic instability, and social distress. For the people who began experiencing mild depression or depressive symptoms, a non-pharmacological approach is preferred as a first line therapy. The extenuating circumstances of the pandemic provide targets for these interventions. For example, online-based mindfulness programs were found to be effective in reducing anxious, depressive, and stressful symptoms in both healthy and those infected with COVID-19.[29] Physical activity was also correlated to improvements in mental health during the first year of the pandemic.[30] Interventions such as these may increase resilience to the social turmoil surrounding the pandemic and alleviate the negative effects of the stay-at-home orders.

For patients with existing depression, or those requiring pharmacological intervention, a very important consideration is the availability of specialist care. An analysis of the Veteran Health Administration mental health services showed a decrease in the counts of patients receiving mental health treatments and psychotropic prescriptions during the first months of the pandemic.[31] Continued access to care and prescriptions is imperative in the long-term treatment of depression. Telehealth was shown to be effective in improving mental health problems in a systematic review.[32] This study did not, however, compare telehealth to in-person visits, nor did it determine the most effective method of delivering telehealth services. Regardless, in times where infection control is the priority, telehealth provides a viable alternative to maintain the mental health of patients undergoing treatment. Cognitive behavioral therapy (CBT) is psychotherapy that may be used in MDD with or without medication. A systematic review showed that technology-based

Table 1. Commonly used treatments for depression during the COVID-19 pandemic.

NAME	DOSE (STARTING-MAXIMUM)	MECHANISM	COMMON SIDE EFFECTS
Citalopram	20-40 mg 20 mg maximum in patients over age 60 years	Selective serotonin reuptake inhibitor	• Nausea • Xerostomia • Somnolence • Insomnia
Escitalopram	10-20 mg	Selective serotonin reuptake inhibitor	• Headache • Nausea • Ejaculatory dysfunction • Somnolence
Fluoxetine	20-80 mg	Selective serotonin reuptake inhibitor	• Insomnia • Nausea • Headache • Asthenia
Fluvoxamine	100-200 mg	Selective serotonin reuptake inhibitor; anti-viral activity; sigma 1 agonism	• Sexual dysfunction • Nausea • Diarrhea • Sedation
Paroxetine	20-50 mg	Selective serotonin reuptake inhibitor	• Nausea • Sexual dysfunction • Somnolence • Insomnia
Sertraline	50-200 mg	Selective serotonin reuptake inhibitor	• Nausea • Diarrhea • Insomnia • Xerostomia
Duloxetine	40-60 mg	SNRI	• Headache • Nausea • Diarrhea • Insomnia
Venlafaxine	75-225 mg	SNRI	• Headache • Nausea • Diarrhea • Insomnia
Vilazodone	20-40 mg	Serotonin receptor modulator; serotonin partial agonist reuptake inhibitor	• Nausea • Diarrhea • Insomnia • Dizziness
Vortioxetine	5-20 mg	Serotonin receptor modulator	• Nausea • Vomiting • Constipation
Bupropion	150-450 mg	Norepinephrine and dopamine reuptake inhibitor	• Insomnia • Anorexia • Weight loss • Xerostomia
Mirtazapine	15-45 mg nightly	Noradrenergic and specific serotonergic antidepressant; Alpha 2 antagonist	• Sedation • Hunger • Weight gain • Anti-emetic

CBT platforms were non-inferior to in-person administered CBT.[33] Telehealth can provide efficacious mental health care and should be considered for patients who are at a higher risk from infection with COVID-19.

Treatment of Post COVID-19 Depression

Depression that arises after an infection with COVID-19 can be due to a variety of etiologies including post ICU syndrome (PICS)[34] and PASC.[35] These different syndromes entail that depression can follow both severe and mild courses of the disease. Antidepressants in various classes including selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), norepinephrine/dopamine reuptake inhibitors (NDRIs), serotonin modulators, and noradrenergic and specific serotonergic antagonists (NaSSAs) have been shown to benefit for patients with post-COVID depression (Table 1).[36] Additionally, patients with the PASC syndrome have been treated with physical therapy, occupational therapy, or

brain rehabilitation.[35] Antidepressants with antiviral and sigma-1 receptor agonist activity like fluvoxamine have been investigated to see if they reduce the risk of COVID complications, showing mixed results. The STOP-COVID trial enrolled 152 COVID positive outpatients to receive fluvoxamine 100 mg 3 times daily for 15 days. A total of 80 patients had lower rates of deterioration compared to placebo (N = 72).[37] The Phase 3 trial of STOP-COVID-2 stopped due to futility with >700 patients per arm.[38] The TOGETHER trial investigated COVID positive outpatients receiving fluvoxamine 100mg twice daily for 10 days and found that (N = 741) had fewer ED/hospital admissions (11%) compared to placebo (N = 756; 16%).[39] Additionally, preliminary results from a retrospective study of pooled patient data from multiple treatment centers showed a potential benefit in patients that were already taking fluvoxamine or other SSRI's at the time of their COVID-19 illness.[40]

Stimulants have been explored for the treatment of PASC fatigue, brain fog, with or without depression. The Rochester Center for Behavioral Medicine conducted a small open label trial of lisdexamfetamine for PASC with success in reducing COVID related fatigue (N = 30).[41] Modafanil was used in 14 patients with PASC and reduced fatigue.[42] There are currently ongoing trials for the treatment of PASC of antivirals nirmaltrevir/ritonavir, molnupravir as well as other pharmacological interventions including antidepressants (vortioxetine), anti-inflammatories (colchicine), anti-histiminics (famotidine, loratadine), and antithrombotics (rivaroxaban). In patients with a refractory post-COVID syndrome, case reports of experimental therapies including perispinal etanercept[43] and pulsed electromagnetic fields[44] have been reported to successfully treat the syndrome and associated depression. Furthermore, intravenous infusion of cytoflavin was successful in improving somatic and mental health symptoms in a cohort of patients with PASC.[45]

While neuropsychiatric PASC are common, significant, and can be debilitating, they often stem from multiple pathophysiologies. There are currently no validated treatments for PASC; treatment is symptom-driven and multimodal, with a priority on addressing diagnosable co-occuring conditions such as depression, anxiety, and PTSD, and a careful risk-benefit analysis is necessary for off-label or unproven therapies. Continued research and high quality clinical trials are necessary to optimize the treatment of post-COVID syndromes because of the global spread of disease and the high morbidity of PASC.

Conclusion

Depression remains a common psychiatric outcome encountered by COVID-19 patients or as a result of the psychophysiological effects of the pandemic. Additional consideration should be given to the coronavirus's neurological effects as well as the more commonly observed respiratory symptoms. Depressive symptoms can be treated with non-pharmacological therapies such as psychotherapy, antidepressant medications, or a combination of these treatments depending on the severity. Continued access to mental health care is imperative in the treatment of depression. Telehealth is a viable option for those who lack access to in-person mental health services due to mobility or transportation barriers, have lower function due to medical illness, or who are at higher risk of COVID infection. Depression that arises from post-COVID syndrome can be treated with antidepressants; however, continued research and clinical trials are required to optimize the treatment in these patients due to the high morbidity of PASC.

Author Contributions

All authors contributed to the planning, writing, and editing of this manuscript.

ORCID iDs

Lena Ayari https://orcid.org/0000-0003-3352-9405
Jessica Madry https://orcid.org/0000-0002-4040-1090
Colton Betts https://orcid.org/0000-0001-6649-761X

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