Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Biological Psychiatry

Commentary

COVID-19 Infection and Risk for Neuropsychiatric Symptoms

Kristin L. Bigos and Andrea M. Goldensohn

In the current issue of *Biological Psychiatry*, Gillespie *et al.* (1) show a notable association between the use of statins and cognitive markers that indicate a decreased psychological vulnerability to depression, including affective bias and reward processing. In this study, use of statins was associated with reduced recognition of angry and fearful faces, and reduced learning about stimuli associated with loss. Further, these indicators of reduced negative bias were not found in patients taking antihypertensive medications, without statins. Future prospective, controlled, randomized, clinical studies should be conducted to determine the potential use of statins as prophylactic treatment for depression. Statins are among the most commonly prescribed classes of medications, and their use has been associated with a lower risk of all-cause mortality, with an even greater effect in patients with dementia (2). These new data suggest a potential role for statins in the prevention and treatment of depression, especially in older adults, which may contribute to their effects on lifespan by promoting psychological resilience. Safe and effective use of medications for the prevention and/or treatment of mood symptoms is even more important during the COVID-19 pandemic.

The environment created by the pandemic has presented significant mental health challenges independent of the effects of infection by the SARS-CoV-2 virus. Stability has been undermined as routines, activities, relationships, and social opportunities have been upended. Added stressors have presented mental health challenges. Many populations were uniquely vulnerable; among them, essential workers forced to expose themselves to the virus while others isolated; health care workers facing danger, heartache, and physical stress; older adults cut off from their networks; immunocompromised people and families of small children unable to return to a more normal life when others could; students missing classrooms, resources, and social contact. In response to these challenges, vulnerabilities in individuals and communities have become more apparent. Not surprisingly, there have been widespread reports of depression, anxiety, suicidal ideation and suicide, substance abuse, domestic abuse, and interpersonal conflict.

In addition to the mental health impacts created by the pandemic, there are neuropsychiatric consequences of infection with SARS-CoV-2. The acute mood and cognitive symptoms of COVID-19 infection vary considerably, and the longer-term outcomes are largely unknown. The effects of the virus on the human central nervous system, combined with the subsequent host immunologic response, result in variable outcomes in individuals and populations. The introduction of different viral strains, along with many different available vaccines and boosters, and varying vaccination rates across populations, has also led to vastly different outcomes. Some patients experience significant neurological and psychological symptoms during acute COVID-19 infection, including depression, anxiety, and cognitive deficits. Many patients describe their cognitive symptoms as "brain fog," which is characterized by poor attention, problem solving, executive functioning, and decision making. Acute infection can also cause delirium and, in some older adults, can be the first sign of infection, even before fever or cough. Unrecognized hypoxia can result in mood dysregulation, confusion, and psychosis (3) in patients without prior psychiatric history. Anecdotal reports from major hospital systems have found the need for higher than average requirements for both benzodiazepines and opioids related to delirium and agitation in patients requiring mechanical ventilation due to COVID-19 acute respiratory distress syndrome compared with other causes of acute respiratory distress syndrome. Interestingly, early treatment with the antidepressant fluvoxamine improved outcomes in high-risk patients with COVID-19 infection (4), replicating prior retrospective studies of antidepressants and COVID-19 outcomes. While most children experience mild infection symptoms, a small percentage develop multisystem inflammatory syndrome in children associated with COVID-19. One third of children who are diagnosed with multisystem inflammatory syndrome in children have symptoms of meningitis or encephalitis, and the long-term neurologic and psychiatric consequences of this severe brain inflammation due to COVID-19 are unknown.

In addition to the acute effects of the virus, some patients experience longer-term symptoms after COVID-19 infection, termed post-acute sequelae of SARS-CoV-2 infection (PASC), and also known as long COVID. Neuropsychological symptoms of PASC include depression, anxiety, cognitive impairment, sleep dysfunction, chronic fatigue, headache, and sensorimotor symptoms. Most studies of neuropsychiatric symptoms related to PASC have been conducted in adults, but there are case reports of children with similar neuropsychiatric manifestations. One study found that 15% of adult patients reported posttraumatic stress symptoms 1 month post-discharge from their COVID-19 hospitalization (5). Another study followed up with patients 3 months postdischarge and found that 15% of patients met the criteria for a diagnosis of depression based on their responses on the Patient Health Questionnaire-9, and 6% of patients experienced suicidality (6). In this study, the greatest predictors of the development of depression were history of a prior psychiatric disorder, female sex, and chronic pulmonary conditions (6), suggesting that those individuals should be most closely monitored for

SEE CORRESPONDING ARTICLE ON PAGE 543

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psychiatric symptoms after hospitalization for COVID-19. A separate study recruited patients with no prior psychiatric history and found that subjects who were previously diagnosed with COVID-19 had significantly higher scores of depression (Beck Depression Inventory-II), anxiety (Mood and Anxiety Symptom Questionnaire), and anhedonia (Snaith-Hamilton Pleasure Scale) than those who did not have a COVID-19 infection (7). The scores were highest during the acute phase (14–30 days postdiagnosis) and PASC phase (1–4 months postdiagnosis) compared with more than 4 months postdiagnosis (7). In addition, the subjects with a prior COVID-19 infection had a selective impairment in executive functioning, while alerting and orienting abilities remained intact (7). These case-control studies have become harder to conduct because vaccines have become less effective at preventing infection, and therefore a greater percentage of the population has become infected. However, future research could correlate infection duration and severity with acute and longer-term neuropsychiatric symptoms and structural and functional brain changes, such as task-based functional magnetic resonance imaging (MRI).

There is emerging evidence of structural, functional, and biochemical changes in the human brain after COVID-19 infection. A longitudinal study using structural MRI data from the UK Biobank (n = 755, ages 51–81 years) included 401 subjects who tested positive for infection with SARS-CoV-2 between their two MRI scans and 384 control subjects (8). Subjects who had a prior infection showed a greater cognitive decline between their first and second scans, with an average of 4.5 months between reported diagnosis and the second scan. They found structural brain changes in patients after even mild COVID-19 infection, including a greater reduction in global brain size, a greater reduction in gray matter in the orbitofrontal cortex and parahippocampal gyrus, and greater changes in markers of tissue damage in regions connected to the primary olfactory cortex (8). Concerningly, there are also reports of MRI evidence of brain inflammation in children with mild or even asymptomatic COVID-19 infection. A postmortem study found tau hyperphosphorylation in brain lysate from deceased COVID-19 patients (9), which is pathology found in patients with Alzheimer's disease and associated with neurodegeneration and Alzheimer's disease progression. The same postmortem study found increased glutamate carboxypeptidase II (GCPII) (9), which is known to be increased with inflammation, aging, and several neuropsychiatric disorders. GCPII is the primary regulator of *N*-acetylaspartyl glutamate (NAAG), the endogenous ligand for the metabotropic glutamate receptor 3, and increases in GCPII are associated with lower NAAG and cognitive deficits (10). The increased incidence of neuropsychiatric and cognitive symptoms after COVID-19 infection may be related to these signs of brain inflammation and structural damage to key brain regions and circuitries.

Consequently, there is an urgent need to identify and/or develop tools for the prevention or treatment of the neuropsychiatric and cognitive symptoms associated with COVID-19 infection. Repurposing medications could provide much-needed treatment options to promote psychological resilience. Neuropsychiatric symptoms are most likely to emerge or worsen in older adults with and without dementia and appear to be the consequence of both COVID-19 infection and prolonged social isolation. Preventive treatment options may be most important for young children, whose brains are still developing and changing at the highest rate and therefore are most vulnerable to viral and immunological insults. Further research is also required to understand the indirect effect of the pandemic on mental health in order to improve prevention, treatment, and planning for increased availability of mental health care services during COVID-19, as well as potential future pandemics.

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Article Information

From the Department of Medicine, Division of Clinical Pharmacology (KLB), the Department of Psychiatry and Behavioral Sciences (KLB), and the Department of Pharmacology and Molecular Sciences (KLB), Johns Hopkins School of Medicine, Baltimore, Maryland, and Private Practice (AMG), Rockville, Maryland.

Address correspondence to Kristin Bigos, Ph.D., at kbigos1@jhu.edu.

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References

1. Gillespie AL, Wigg C, Van Assche I, Murphy SE, Harmer CJ (2022): Associations between statin use and negative affective bias during COVID-19: An observational, longitudinal UK study investigating depression vulnerability. Biol Psychiatry 92:543–551.
2. Orkaby AR, Driver JA, Ho Y-L, Lu B, Costa L, Honerlaw J, *et al.* (2020): Association of statin use with all-cause and cardiovascular mortality in US veterans 75 years and older. JAMA 324:68–78.
3. Kazi SE, Akhter S, Periasamy D, Faruki F, Tahir R (2021): Acute psychosis and COVID-19 infection: Psychiatric symptoms in hospitalized patients. Cureus 13:e18121.
4. Reis G, dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, *et al.* (2022): Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: The TOGETHER randomised, platform clinical trial. Lancet Glob Health 10:e42–e51.
5. Matalon N, Dorman-Ilan S, Hasson-Ohayon I, Hertz-Palmor N, Shani S, Basel D, *et al.* (2021): Trajectories of post-traumatic stress symptoms, anxiety, and depression in hospitalized COVID-19 patients: A one-month follow-up. J Psychosom Res 143:110399.
6. Vassalini P, Serra R, Tarsitani L, Koukopoulos AE, Borrazzo C, Alessi F, *et al.* (2021): Depressive symptoms among individuals hospitalized with COVID-19: Three-month follow-up. Brain Sci 11:1175.
7. Lamontagne SJ, Winters MF, Pizzagalli DA, Olmstead MC (2021): Post-acute sequelae of COVID-19: Evidence of mood & cognitive impairment. Brain Behav Immun Health 17:100347.
8. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, *et al.* (2022): SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature 604:697–707.
9. Reiken S, Sittenfeld L, Dridi H, Liu Y, Liu X, Marks AR (2022): Alzheimer's-like signaling in brains of COVID-19 patients. Alzheimers Dement 18:955–965.
10. Zink CF, Barker PB, Sawa A, Weinberger DR, Wang M, Quillian H, *et al.* (2020): Association of missense mutation in FOLH1 with decreased NAAG levels and impaired working memory circuitry and cognition. Am J Psychiatry 177:1129–1139.