

# Psychiatric Complications of SARS-CoV-2 Infection during the COVID-19 Pandemic

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## Abstract

The COVID-19 pandemic has been associated with increased reports of psychiatric conditions in patients who were infected with the SARS-CoV-2 and in those who recovered from the infection. It has also caused increased in mental and emotional difficulties in health care providers caring for COVID-19 patients. Some patients with preexisting psychiatric conditions also experienced worsening of their illness due to the COVID-19 pandemic. Furthermore, the pandemic has and continues to have an increased psychological impact on the general population. This review summarizes some of the psychiatric and psychological sequela of the COVID-19 pandemic in patients with pre-existing psychiatric conditions, patients infected and recovering from SARS-CoV-2, the health care providers and the general population.

Keywords: COVID-19 • Psychiatric • Psychological • Mental • Pandemic

## Introduction

Coronavirus disease 2019 (COVID-19) is a novel type of highly contagious infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has several medical complications that keep being observed and addressed on a daily basis as this global pandemic continues to progress worldwide. Most recently several psychiatric complications of COVID-19 have begun to emerge adding to the tremendous burden and human suffering of this devastating illness.

This review summarizes some of the neuropsychiatric manifestations of SARS-CoV-2, the psychiatric complications that could occur during the acute phase of infection and recovery period. The psychological impact of the COVID-19 pandemic on patients with pre-existing psychiatric conditions, its emotional toll on the health care providers and the general population will also be described. It is hoped that this review will provide clinicians, health care providers, and the public with a summary of the recent findings in regard to the psychiatric manifestation of the COVID-19 pandemic.

## SARS-CoV-2 general background classification and evolution

Coronavirus belongs to the family Coronaviridae which contains two genera, Coronavirus and Torovirus, that differ in their nucleocapsid morphology, with Coronavirus being helical and Torovirus being tubular [1]. In 1965, the first human coronavirus was identified and it caused the common cold. Later during that decade, a group of similar human and animal viruses were recognized and named Coronavirus after their crown-like appearance. In 2002, a species known as severe acute respiratory

syndrome coronavirus (SARS) caused a highly contagious respiratory disease that was characterized by fever, cough, muscle ache, and often progressed to breathing difficulty. Although SARS emerged in humans; it is believed that it jumped to humans from an animal reservoir of possibly horseshoe bats [2]. In 2012 another coronavirus capable of causing a severe acute respiratory illness which was later described as Middle East respiratory syndrome (MERS) was discovered in humans. The first case was found in Saudi Arabia, and others were reported within the following year in France, Germany, Jordan, Qatar, Tunisia, the United Arab Emirates, and the United Kingdom. All confirmed cases were directly or indirectly linked to the Middle East. Of all confirmed cases documented by 2019, roughly one-third had ended in death. The novel MERS coronavirus was similar to other coronaviruses known to have originated in bats and was thought to be passed from bats to other animals before being transmitted to humans. Camels were identified as one possible reservoir for the MERS virus [3]. In late 2019 a virus apparently closely related to SARS coronavirus emerged in Wuhan, China. The virus, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused an illness known as COVID-19, which had some similarity with SARS and was being characterized primarily by fever cough, fatigue, shortness of breath, and loss of smell and taste. While most people experienced mild Flu-like symptoms, other developed acute respiratory distress syndrome (ARDS) possibly precipitated by cytokine storm, multi-organ failure, septic shock, and blood clots [4]. It has been concluded that SARS-CoV-2 made the jump to humans at one of Wuhan's open-air "wet markets." Where fresh meat and fish, including animals that are killed on the spot are sold. Some wet markets also sell wild or banned species like cobras, wild boars, and raccoon dogs. Through genetic recombination and variation, coronaviruses can adapt to and infect new hosts. Bats are thought to be the natural reservoir for SARS-CoV-2, but it has been suggested that humans became infected with SARS-CoV-2 via an intermediate host, such as the pangolin, also called scaly anteaters,

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which are sold illegally in some markets in China [5,6]. By early 2020 SARS-CoV-2 had spread throughout many regions of China and reached Europe and the United States and, spread worldwide prompting the World Health Organization on the 11th of March 2020 to declare the COVID-19 outbreak as a global pandemic [7]. As of 20 August 2020, more than 22.5 million cases have been reported across 188 countries and territories, resulting in more than 789,000 deaths with more than 14.3 million people who have recovered [8].

### SARS-CoV-2 General Pathophysiology

Transmission of SARS-CoV-2 occurs primarily via respiratory droplets from face-to-face contact and, to a lesser degree, via contaminated surfaces and aerosol spread with an estimated 48% to 62% of transmission occurring via asymptomatic carriers [9]. Common SARS-CoV-2 symptoms in hospitalized patients include fever, dry cough, shortness of breath, fatigue, myalgia, nausea, vomiting or diarrhea, headache, weakness, and rhinorrhea. Anosmia which is an absence or decreased sense of smell or ageusia which is the loss or impairment of the sense of taste may be the sole presenting symptoms in approximately 3% of individuals with COVID-19 [10]. Complications of COVID-19 include pneumonia, acute respiratory distress syndrome, acute liver injury, cardiac injury, acute heart failure, dysrhythmias, and myocarditis; prothrombotic coagulopathy resulting in venous and arterial thromboembolic events, acute kidney injury, acute cerebrovascular disease and shock [10,11]. Rare complications among critically ill patients with COVID-19 include cytokine storm and macrophage activation syndrome [12]. The development of neuropsychiatric symptoms has been associated with rapid clinical deterioration and worsening of COVID-19 infection poor prognosis, greater hemodynamic instability, worsening clinical conditions and increased mortality. Therefore, the neuropsychiatric status of patients should be as frequently monitored as their respiratory status [13].

### SARS-CoV-2 Neuropsychiatric Pathophysiology

In many patients with SARS-CoV-2 and, in particular those who develop moderate to severe respiratory failure, neuropsychiatric disorders can occur due to different mechanisms that can act concomitantly, such as cerebral hypoxia due to respiratory failure resulting in mental confusion, cytokine storm due to exaggerated immune response leading to apathy, anorexia and muscular pain, and encephalitis precipitating agitation and psychosis [13]. The cytokine storm which occurs in many genetically predisposed patients, is generated by the interaction of the immune system with the virus, which, in addition to the systemic repercussion, primarily affects the nervous system. Cytokine storm is associated with the severity of SARS-CoV-2, and is characterized by an increase in interleukin (IL) -2, IL-7, granulocyte colony-stimulating factor, interferon-inducible protein 10- $\gamma$ , monocyte chemoattractant protein 1, macrophage inflammatory protein 1- $\alpha$  and tumor necrosis factor- $\alpha$  [14]. Brain cytokines produce behavioral changes that are manifested by depressive symptoms such as emotional hyperresponsiveness, apathy, anhedonia, anorexia, weight loss, hypersomnia, alteration of the circadian rhythm, fatigue, chronic pain, psychomotor retardation, loss of motivation, and alteration of higher mental functions including the cortex. These symptoms in addition to the typical SARS-CoV-2 symptoms of fever, cough and dyspnea would precipitate mental confusion, agitation, delirium and psychosis that many patients may experience even in the initial stages of the infection [15]. Even in the absence of central nervous system (CNS) infiltration, peripheral cytokines may elicit neuropsychiatric symptoms by precipitating neuroinflammatory responses and/or compromised blood-brain-interface (BBI) integrity, leading to peripheral immune cell transmigration into the CNS, and disruption of neurotransmission [16].

## SARS-CoV-2 Neuropsychiatric Manifestations

The neuropsychiatric manifestations SARS-CoV-2 infection and in particular its psychiatric complications has become an essential yet less understood clinical manifestation for the word of this disease. There are numerous signs that SARS-CoV-2 not only targets the lungs and the respiratory system, but also other organs on a massive scale including the CNS which could contribute to increasing the mortality rate [13,17].

When treating patients with new onset of neuropsychiatric manifestations, clinicians are behooved to consider SARS-CoV-2 infection as one of the first-line differential diagnosis to avoid misdiagnosis and delayed intervention which could be an essential element in preventing transmission of the infection [13]. The similarities between other coronavirus and SARS-CoV-2 suggest that the following neuropsychiatric complications which have occurred in SARS and MERS could occur in patients infected with SARS-CoV-2.

### SARS-CoV-2 Effects on Central Nervous System

#### Viral encephalitis

Encephalitis is an inflammatory process affecting the brain parenchyma can cause neuronal damage and nerve tissue lesions. It is characterized by a set of acute symptoms of headache, high fever, vomiting, convulsions, fluctuation of consciousness and possible delirium [18]. Recent findings identified the angiotensin 2-converting enzyme (ACE2) as the functional receptor that precipitate neuropsychiatric symptoms. Coronavirus encephalitis has also been confirmed, as in SARS and MERS, through the detection of SARS-CoV nucleic acid in the cerebrospinal fluid in recovering COVID-19 patients and also in brain autopsies of deceased patients [19]. Viral encephalitis symptoms due SARS-CoV-2 could cause patients increased anxiety, depression and even psychosis.

#### Infectious toxic encephalopathy

This Infection, also known as acute toxic encephalitis, although not specific to SARS-CoV-2 could occur due to other viral or bacterial acute infections and is usually caused by several factors such as systemic toxemia, metabolic disorders, and hypoxia. Hypoxic injury to neural and other brain structures could lead to cerebral atrophy thus resulting in psychotic symptoms and long lasting cognitive decline [20]. Toxic encephalopathy could precipitate dysphoria, delirium, disorientation, loss of consciousness, coma, paralysis and new onset of mental disturbances. Although COVID-19 could cause infectious toxic encephalopathy, detailed studies are needed to confirm that this type of encephalopathy is specifically induced by SARS-CoV-2.

#### Peripheral immune cell transmigration

SARS-CoV-2 infects peripheral myeloid cells [21], and can subsequently be recruited or transmigrate to the CNS under conditions which increase blood brain barrier (BBB) permeability, such as inflammation or psychological stress. In the CNS, virus-infected monocytes can propagate neuroinflammation, and therefore neuropsychiatric symptoms, by releasing inflammatory cytokines, and by promoting microglial activation [22]. There is also evidence suggesting that leukocytes can remain persistently infected by SARS-CoV-2 [23]. These peripheral immune reactions lead to the speculation of suggesting that SARS-CoV-2 infected immune cells could remain a source of neuroinflammation that could significantly last longer than the initial acute infection symptoms.

#### Hypercoagulability

Clinical findings of hypercoagulability are frequently being reported and describe blood coagulation abnormality in COVID-19 patients, which increase the risk for blood clots in the circulatory and the cerebrovascular system thus increasing the risk of cerebrovascular accidents and strokes related neuropsychiatric complications [24].

## SARS-CoV-2 infection psychiatric complications

The similarity of the clinical pattern of psychiatric complications between SARS-CoV-2 and other corona virus such as SARS and MERS suggests that knowledge of their psychiatric complications could guide clinicians into the early detection of similar complications in patients infected with SARS-CoV-2. For instance in the acute stage SARS and MERS, confusion occurred in 27.9% of patients, suggesting that delirium was common. Other common psychiatric findings were depression, anxiety, and insomnia. Diagnoses of mania and psychosis did occur in a small minority (0.7%), but could not be confirmed as being a result of the infection or induced by corticosteroid treatment [25]. The common persistence of insomnia, emotional lability, irritability, pressured speech, and euphoria suggested that although a full syndrome of mania was uncommon, subthreshold symptoms might have been precipitated by the infection. In the context of COVID-19, the available information suggests that in the acute stage-as in SARS- and MERS-confusion is a common feature, with delirium being a significant clinical presentation that could be correlated with poorer psychiatric outcomes [26]. Although studies have confirmed the development of psychiatric complications in the terminal phase of SARS-CoV-2, even if the infection is mild, moderate or severe, there are neuropsychiatric symptoms that are manifested in the acute early stage of the disease especially in those who develop strokes [27]. It has been reported that approximately 20% to 40 % of patients could present with symptoms that are consistent with delirium [25]. Delirium clinically present with impaired attention and concentration, confusion and altered consciousness. Anxiety, depression, memory impairment, and insomnia could be also a component of delirium or independent variables in response to several psychosocial stressors such as racial stigma, isolation, fear of death, and disruption of family and social life [28]. Some patients could also experience psychotic symptoms while in the stage of delirium , and some will have psychotic symptoms in the absence of delirium. The psychotic features could be visual or auditory hallucinations and delusional themes [29].

## Psychiatric manifestations in COVID-19 survivors

Although there are still limited data available for COVID-19-related psychiatric symptoms. In SARS and MERS, after recovery from the infection, sleep disorder, frequent recall of traumatic memories, emotional lability, impaired concentration, fatigue, and impaired memory were reported in more than 15% of patients at a follow-up period ranging between 6 weeks and 39 months [25]. Emotional lability, pressured speech, and euphoria were reported after a short follow-up period of 42 days by patients who were prescribed high doses corticosteroids [30]. Similar presentation might occur in COVID-19 survivors who received dexamethasone treatment. Studies based on clinical interviews and self-assessment questionnaires have found that SARS-CoV-2 survivors developed psychiatric disorders following their medical recovery [31]. These newly diagnosed psychiatric disorders represented dramatic increase from the 3% pre-infection prevalence of any psychiatric condition. These studies also showed that women in particular suffered the most from anxiety and depression, even if they had lower infection severity. Although delirium is a well-recognized complication of respiratory illness, in older adults, studies indicate that 20–30% of patients with severe COVID-19 patients will present with or develop delirium or mental status changes during the course of their hospitalization at all ages [13]. Current available clinical findings also suggest the presence of psychotic symptoms without delirium in 4% of patients infected by SARS-CoV-2 who had no previous psychiatric history but were discharged from intensive care units [32]. It is still unclear whether SARS-CoV-2 infection could cause new onset of bipolar disorder [25], however case reports have indicated the possibility of developing COVID-19 stress induced mania [33] and at the writing of this review the percentage of COVID-19 induced bipolar disorder is not yet known. Provided table 1 summarizes the percentage of the various psychiatric disorders that were identified in SARS-CoV-2 survivors [25,34,35].

## The Psychiatric Manifestations in COVID-19 Survivors

In view of the high prevalence of psychiatric disorders, management of SARS-CoV-2 survivors should be expanded beyond the medical treatment of the infection. Clinicians responsible for patients after care and follow-up need to be alerted and educated about the possible long-term psychiatric sequelae, of the illness. Evaluation of the psychiatric complications may require culture sensitive assessments of psychiatric symptoms to prevent preexisting fears of social stigmatization toward mental illness [36]. The similarity of the clinical pattern of psychiatric complications between SARS-CoV-2 and other corona virus such as SARS and MERS suggests that knowledge of previous psychiatric interventions can be applied to the COVID-19 survivors while awaiting further research evidence on the effectiveness of SARS-CoV-2 specialized interventions. Survivors should be referred for psychological and social support counseling before discharge and then be seen in regular follow-up, sometimes helped by regular phone or online check-ins to assess level of distress and progression of psychiatric symptoms [37,38]. Mental health screening exams should be done soon after discharge, with continued psychological and social support and pharmacotherapy as needed. Although the effectiveness of these measures on survivor morale and community perceptions has not been assessed additional psychosocial and social support should be considered for the survivor's family and others in communities. Assessment; and management of delirium especially in older survivors of COVID-19 need to be also implemented using special guidelines which include delirium as a presenting feature, using screening as a standard of care, and non-pharmacological approaches for delirium prevention and management. These guidelines need to be implemented as early and often as possible. Resources to assist healthcare providers should be built into electronic medical records, order sets and protocols. Most importantly, person-centered care needs to be at the heart of our response in this highly vulnerable group [39]. Mental health professionals should be more proactive and given an integral role in the multidisciplinary teams that manage the patients [40]. The psychological effects of the pandemic on other at-risk populations including families and friends and their correlation with patients' psychological health should also be assessed and promptly managed. Longitudinal follow-up studies of SARS survivors should be also conducted to evaluate the course of their CoV-2 psychiatric complications and their prognosis [41].

**Table 1.** Approximate Percentage of Psychiatric conditions in COVID-19 Survivors.

Psychiatric conditions	Percentage
PTSD	54.5%
Depression	32.5%
Anxiety	42%
Panic disorder	32.5%
Insomnia	40%
obsessive-compulsive symptoms	20%.
Delirium	60%

## SARS-CoV-2 effects on pre-existing psychiatric disorders

Since social interactions ,physical activity and avoiding personal isolation are considered important nonpharmacologic interventions in psychiatric treatment, the pandemic has been hindering the efforts to tackle loneliness and combined with social isolation could negatively affect these patients and increasing the risk of worsening of their psychiatric symptoms. The most vulnerable would be patients with

depression, phobias, generalized anxiety, and obsessive-compulsive disorders. Patients with these pre-existing disorders experienced increased fears about danger of contamination, socioeconomic losses, xenophobia, and high level of stress [42]. There have been reports also of increased eating in patients with eating disorders and the development of new onset of anxiety symptoms that were not present prior to the pandemic [43]. Patients with schizophrenia and other psychotic disorders may not be able to reach their scheduled appointments specially those maintained on long-acting antipsychotic injections and could relapse into psychosis manifested by recurrence of hallucinations and paranoid delusion about getting infected with the virus, or believing in conspiracies about other intentions on infecting them [44]. Some psychiatric patients with PTSD could experience triggers and worsening of their symptoms [45]. Psychiatric patients living in close quarter facilities and many already have co-occurring medical conditions, could become at a greater risk of contracting SARS-CoV-2. Furthermore staff and hospitalized psychiatric patients often do not have access to personal protective equipment or testing availability and thus increasing vulnerability for developing and spreading the disease. These factors could contribute to a higher incidence of COVID-19 infection in psychiatric patients and worsening of their underlying psychiatric symptoms during and following their infection recovery [46].

### The effects on health care providers

The disease characteristics of the current COVID-19 pandemic provoked a generalized climate of wariness and uncertainty, particularly among health providers, due to several factors such as the rapid spread of the disease, the severity of symptoms it can cause in a segment of infected individuals, the lack of knowledge of the disease, and deaths among health professionals. Stress may also be caused by organizational factors, such as depletion of personal protection equipment, concerns about not being able to provide competent care if deployed to new area, concerns about rapidly changing information, lack of access to up-to-date information and communication, lack of specific treatments, the shortage of ventilators and intensive care unit beds necessary to care for the surge of critically ill patients, and significant change in daily social and family life. As a result, psychiatric symptoms and disorders can occur in clinicians and health care workers caring for COVID-19 patients [47]. Among various disciplines of health care providers 12%-20% experienced anxiety disorders, 15%-25% developed depression, 8% had insomnia and 35% to 49% had traumatic distress leading to PTSD [48]. Risk factors for the development of psychiatric symptoms in health care providers included increased contact with affected patients, prior history of psychiatric disorders and general medical conditions, spending a prolonged time in quarantine, perceived lack of organizational support, shortage of personal protective equipment, long working hours and fears of contracting the illness and dying and being the cause for passing undiagnosed infection to family members and the ongoing political antagonism directed toward infectious diseases experts [49]. The protective factors that have been identified in preventing adverse psychological effects in health care providers included readily access to personal protective equipment, working with cohesive supportive peers, non-stigmatized access to psychiatric interventions, strong feelings of trust in institutions infection control measures and their clear channels of updated communication about the virus spread and containment, in addition to adequate time off from work and burnout prevention [50].

### Psychological effects on the general population

Isolation and quarantine which is considered an extreme form of social distancing have precipitated depression and anxiety in previous pandemics [51]. Confined people become detached from their loved ones, are deprived of personal liberties, and lose their life's purpose owing to altered routine and human connection. These necessary lifesaving primary prevention measures could contribute to frustration, boredom, depression and anxiety arising from fear of contagion and inadequate clarity around social distancing guidelines, often made worse by less reliable media

sources heightening confusion and politically driven conflicts. In the context of the COVID-19 pandemic, it appears likely that there will be substantial, increases in anxiety and depression, substance use, loneliness, domestic violence child abuse and social unrest [52]. Psychological distress due to loss of employment, physical separation and death of loved ones could lead to depression, hopelessness and PTSD [35]. Feeling overwhelmed or excessively concerned about COVID-19 can affect the ability and resilience of family members of patients and could precipitate traumatic stress manifested by fatigue, fear, personal withdrawal, guilt, feelings of hopelessness vulnerability and learned helplessness [35,46,53]. The long-term consequences, COVID-19 pandemic may include deterioration of social networks and economies, stigma towards survivors of illness, possible higher anger and aggression of frontline workers and the government, possible anger and aggression against children who have been confined to their homes due to school closure and increase mistrust of information provided by political authorities [54]. The conflicting medical advises about prevention and treatment of SARS-CoV-2 infection could lead to medical mistrust and the promotion of conspiracy theories and initiation of dangerous movements such as anti-vaccination trends, and the use of non-recommended perilous and lethal treatment interventions [55].

### The impact of the COVID-19 pandemic on suicide

The COVID-19 pandemic has been associated with distress, anxiety, fear of contagion, depression, insomnia, uncertainty, chronic stress, and economic difficulties. These unprecedented circumstances could lead to the development or exacerbation of depression, anxiety, substance use and other psychiatric disorders in vulnerable populations including individuals with pre-existing psychiatric disorders and people who reside in high COVID-19 prevalence areas. Stress-related psychiatric conditions including mood and substance use disorders are associated with suicidal behavior. COVID-19 survivors may also be at elevated suicide risk. Another alarming aspect of this pandemic is suicide, among front-line workers and health care providers. So it is becoming more apparent that the mental health consequences of the COVID-19 crisis including suicidal behavior are likely to be present for a long time and may continue to peak even after the remission of the pandemic.

## Conclusion

COVID-19 is projected to affect all segments of the population which is unprecedented for a virus with such case fatality and infection rates in modern medicine. The psychiatric burdens of this pandemic are being assessed and evaluated with every passing day of this global health crisis.

This review was an attempt to summarize some of the known psychiatric complications of SARS-CoV-2 including its neuropsychiatric manifestations, its psychiatric sequelae on patients and survivors of the infection, its effects on patients with pre-existing psychiatric conditions, on the health care providers and the general population. Research evaluating the direct psychiatric consequences and the indirect effects of SARS-CoV-2 infection on mental health is highly needed to improve the psychiatric care of the affected individuals and for preventive plans during the current COVID-19 pandemic and potential subsequent pandemics.

It is hoped that this review will provide clinicians, health care providers, and the public with a summary of the recent findings in regard to the psychiatric manifestations of the COVID-19 pandemic which are still not full known, but likely to be highly

significant and important in tackling this rapidly developing global public health crisis.

## Disclaimer

The Views described in this manuscript are those of the author and do not reflect the official policy of the Sacramento VA Medical Center or The Department of Veterans Affairs or UC Davis Health.

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