

# Mood Disorders in Times of COVID-19: Challenges and Opportunities

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*Introduction: Less than a year after it began in Wuhan, the SARS-CoV-2 coronavirus infection has had profound repercussions worldwide. The health manifestations are varied, as are the psychological aspects involved.*

*Method: A bibliographic search was conducted through PubMed; articles related to mental health topics, neuropsychiatry, mood disorders, and COVID-19 were included.*

*Results: COVID-19 has generated mental health manifestations that are believed could persist over time, with anxiety and depression being the most significant ones reported. The virus has the ability to enter the central nervous system, causing neuropsychiatric manifestations. Patients with mood disorders, as well as health professionals and survivors of COVID-19, are presented as a risk group. Regarding treatment, special care must be taken in terms of drug interactions and possible severe adverse reactions. Lithium carbonate has properties that could be of interest as a potential coronavirus treatment.*

*Conclusions: The traditional working modalities of mental health teams should be changed. In mood disorders, consider aspects proper to the viral infection, as well as the psychosocial determinants. Propose suicide prevention strategies, where remote interventions become critical. In addition to the challenges, this period can be considered an opportunity to modify care paradigms and generate new research lines.*

**Keywords:** “COVID-19”, “coronavirus”, “psychiatry”, “mental health”, “mood disorder”, “depression”, “bipolar disorder”, “psychopharmacology”.

## INTRODUCTION

Only seven months have passed since the first cases of infection by the then called “new coronavirus of 2019”, detected in the city of Wuhan, China. In February 2020, the WHO named the illness “coronavirus disease” (COVID-19) and the causative pathogen, “type 2 coronavirus causing severe acute respiratory syndrome” (SARS-CoV-2).

When we talk about dates, considering the global impact that this pandemic has had, it seems like a recent event. From this side of the world, society watched what was happening with the distance of a spectator. While thousands died in Asia and Europe, Chile, still in summer, was shocked by the repercussions of the social outbreak. However, the potential impact of the pandemic did not appear to be felt until

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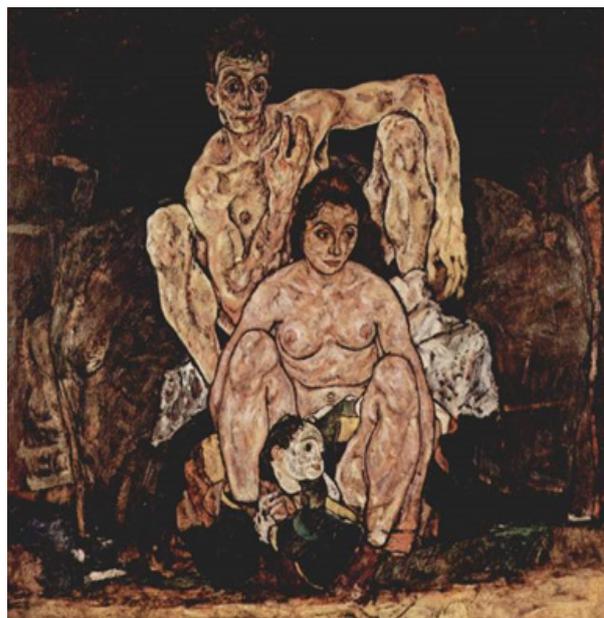
However, not only local challenges and processes favored the feeling of distance from risk. Throughout history, humanity, plagued by various pandemics, seems to need historical texts to recall the notion of “biological vulnerability.” The Spanish Flu—a relatively recent historical event as only one hundred years have passed since it began—was a disease that was responsible for the loss of 50 million people worldwide in less than a year and whose multiple health, economic, and historical consequences may have been overshadowed by the aftermath of humanity already struck by the ravages of war<sup>(1)</sup>. Nevertheless, there are records of survivors which account for the harsh reality of the pandemic—in a period where the immediate capacity for recording and broadcasting that we have today was not possible, with the benefits and harms that this implies. Among the tragic outcomes of the pandemic is the story of the painter Egon Schiele, known for his position as an intellectual and cultural elite, who lost his wife and unborn child to the virus, and died a few days later from the same illness. His mentor, the famous Gustav Klimt, also succumbed to the illness eight months before Schiele himself. One of the young painter’s most famous works was developed the same year of his death, remaining unfinished (*Figure 1*).

### **Mental Health and COVID-19**

The scope of the pandemic involves diverse global aspects; thus, the entire population is affected directly or indirectly. However, there are groups that evidently present a higher degree of vulnerability, whether due to biological, economic, social, professional determinants or a combination of all of the above.

The Severe Acute Respiratory Syndrome (SARS) disease caused by SARS-associated coronavirus (SARS-

**Figure 1.** Egon Schiele, *The Family*, 1918.



CoV) in 2003 generated mental health consequences in patients and families that lingered after recovery; the biological aspects (of the virus, hospitalization, medication) and psychosocial<sup>(2)</sup> were considered relevant. Psychological distress remained high for one year after infection in that SARS epidemic, while healthcare personnel had higher rates of depression, anxiety, and post-traumatic stress disorder each year<sup>(3)</sup>. Completed suicide rose, specifically in the geriatric female population, the year of the Hong Kong pandemic<sup>(4)</sup>.

Experts propose four groups of particular interest due to their higher-risk potential: (I) people who have been in direct contact with the virus and the disease, (II) people with previous psychosocial and biological vulnerability (including those patients with already diagnosed psychiatric illnesses), (III) healthcare professionals, and (IV) people who follow multiple channels of information regarding the pandemic<sup>(5)</sup>. This last point opens an interesting discussion regarding the role of the media and how

the globalized immediacy of information can influence health outcomes, differing in certain areas from the course of previous global pandemics, such as the Spanish Flu.

Research in relation to the impact on mental health during the COVID-19 pandemic is still a subject in full development. The most substantive data comes from the Chinese population, with some longitudinal and case-control studies. In the general population, the levels of anxiety, depression, and stress lingered one month after the peak of new cases, and the group of adolescents and young students is proposed as the most vulnerable group<sup>(6)</sup> which is not replicated in other studies. It is suggested that the population with psychiatric pathology would suffer a greater impact than that of the general population during the COVID-19 pandemic, quantified through anxiety and depression scales<sup>(7)</sup>. Although studies are still scarce, the multiplicity of adverse factors at play make this a theoretical population at risk due to inadequate coping strategies in the face of stress, previous psychosocial problems, lack of access to timely controls during the pandemic, and difficulties in the access to regular medication, among others. The increase in depression figures could be associated with lower income, interpersonal conflicts, frequent use of the media, and less social support, and it is higher in females<sup>(8)</sup>.

The call to social isolation as a measure of physical protection can be detrimental to mental health, which is why the term "physical distancing" has been preferred to "social distancing"<sup>(9)</sup>. Although they may seem like subtleties of language, it becomes relevant when considering other effective communication channels to sustain the experience of emotional containment in times of crisis, making a virtuous use of technology to maintain contact with meaningful relationships, and access to healthcare in a timely manner. In China,

it has been observed that the quarantined population presents significantly higher levels of anxiety and depression than the population without mobility restriction<sup>(10)</sup>. In the particular case of Chile, a country where the issue of inequality has been at the fore in the past year, and with a large vulnerable and marginalized population, isolation also carries the stressor of a scarcity of basic goods<sup>(11)</sup>.

A group of particular interest corresponds to that of healthcare professionals. The degree of exposure and risk, the experience of work overload and sleep deprivation, the making of ethically complex decisions on a daily basis, and distancing oneself from the primary support group to avoid contagion are some of the influencing factors. The prevalence of anxiety, depression, and insomnia as isolated symptoms in healthcare professionals during the COVID-19 pandemic reaches 23.2%, 22.8% and 38.9%, respectively; the figures being higher specifically in the female population and the nursing profession<sup>(12)</sup>.

Considering the various mental health issues faced due to the pandemic and defining the main research priorities, The Lancet published a position paper in April with a complete bio-psychosocial approach, understanding the scopes of multiple determinants<sup>(13)</sup>. In it, they establish as immediate research priorities: (I) obtaining data on rates of anxiety, depression, and suicidality; (II) investigating support strategies for particular risk groups (pre-existing severe mental or physical illness, individuals recovered from COVID-19 infection, and people who report new psychiatric/psychological symptoms during the pandemic); and (III) develop a neuropsychological database of COVID-19 patients that allows generating standardized studies to understand the neuropsychiatric effects of the virus better.

### **Neurobiological Aspects: SARS-CoV-2 and the Nervous System**

SARS-CoV-2 is an RNA virus, which in addition to respiratory manifestations, presents extrapulmonary manifestations, including those in the nervous system, generating neuropsychiatric conditions already documented<sup>(14)</sup>, such as encephalitis, meningitis, vascular events, cognitive alterations (specifically a dysexecutive syndrome), neuro-ophthalmological alterations, and Guillain-Barré syndrome, among others. It is even suspected that a neuroinvasion at the brainstem level could be partly responsible for the great respiratory failure in these patients<sup>(15)</sup>. Regarding delirium in critical patients due to COVID-19, some authors propose underdiagnosis as a potential problem, but it is posed as a daily clinical reality<sup>(16)</sup>. Among the factors inducing delirium, the direct effect of the virus on the central nervous system and the inflammatory cascade is considered as two influential components, in addition to those inherent to any critical patient<sup>(17)</sup>, which forces us to ask questions about the neurotropic mechanisms of this virus.

Past epidemics such as SARS and the Middle East Respiratory Syndrome (MERS) generated studies on coronavirus neurotropism (CoVs) in animal models; one of the consistent findings was that they all require angiotensin-converting enzyme 2 (ACE-2) as a neuronal gateway<sup>(18)</sup>. ACE-2 is expressed in multiple organs, including the brain, specifically in neurons and glia. SARS-CoV-2 uses the S1 “spike” glycoprotein that binds to ACE-2, entering the cell, and it has been seen that the affinity of SARS-CoV-2 for this receptor is greater than for other coronaviruses<sup>(19)</sup>. One line of research regarding neuroinvasion is entry through the olfactory nerve, with ECA-2 being widely distributed at the level of this sensitive epithelium, and it is known that SARS-CoV-2 generates anosmia and

ageusia as a frequent symptom<sup>(20)</sup>.

In sum, the mechanisms of SARS-CoV-2 in injuring the nervous system may include entry through systemic circulation, direct neuronal pathway, damage from neuroinflammation, and damage from hypoxia and vascular events, among others, having at least been clarified up to the important role of ACE-2 in cell admission<sup>(21)</sup>.

### **Mood Disorders and COVID-19**

Data on depression, bipolar disorder, and COVID-19 are still scarce, but it is suspected that there is likely to be an increase in the figures considering what happened with the SARS pandemic. Up to 36% of the patients had a low mood during the acute recovery phase, with the severity of SARS and the use of corticosteroids being associated with higher levels of anxiety and depression<sup>(22)</sup>. Long-term follow-up of survivors, even over three years, showed that 39% met the criteria for depression<sup>(23)</sup>. In the past, interest has been generated in the possible relationship between respiratory virus infections and the triggering of mood disorders, finding that seropositivity for influenza A, influenza B, and coronavirus is associated with mood disorders, without demonstrating specificity for unipolar depression or bipolar disorder<sup>(24)</sup>. It is believed that carriers of a mood disorder could eventually have a more lasting inflammatory response in viral infections due to the increase in pro-inflammatory cytokines, which is characteristic of the pathophysiology of the mood<sup>(25)</sup>.

In a prospective study on COVID-19, it was seen that the severity of anosmia and ageusia was associated with higher levels of anxiety and depression<sup>(26)</sup>, which again suggests the potential compromise of the central nervous system by the coronavirus.

In a study comparing current mental health repercussions in patients with previous mood disorders (either depression

or bipolar disorder) versus the general population, indicators of depression and anxiety were higher in the former group and even more so in bipolar disorder compared to unipolar depression, with bipolar men being the most affected<sup>(27)</sup>.

Regarding the risk of suicide, it is presumed that the rates could increase if we consider the precedent of an increase in suicide deaths in the United States during the Spanish Flu and among older adults during the SARS epidemic<sup>(28)</sup>. So far, several cases of suicides related to COVID-19 have been reported both in the press and in scientific publications in the United States, Italy, Great Britain, India, among other countries; therefore, it is proposed that the role of the psychiatrist and mental health teams should be more active than usual in patients who are deemed to be at higher risk, such as those with a history of previous attempts, patients with active psychiatric conditions, especially if they are older adults, and health professionals<sup>(29)</sup>. In anticipation of the potential increase in suicidal phenomena, and in addition to quarantine prolongations and the psychosocial consequences that this implies, some efforts have already been proposed to conduct brief and structured interventions that specifically aim at reducing suicide risk, such as the Collaborative Assessment and Management of Suicidality (the acronym CAMS is frequently used in English) through a telepsychology protocol<sup>(30)</sup>. Psychiatry and psychology experts, therefore, support the idea of having an active approach to suicide prevention in risk populations, and, in this sense, remote interventions should have a preponderant place.

Regarding psychopharmacological aspects, greater rigor is required when prescribing and monitoring patients with mood disorders during the course of SARS-CoV-2 infection, especially considering three aspects: (I) the risks of the use of

drugs common in psychiatry in critical patients, with complications in various systems; (II) the multiple pharmacological interactions existing between experimental treatment protocols and the use of certain psychoactive drugs; and (III) the potentially adverse neuropsychiatric reactions to drugs used to combat SARS-CoV-2 infection.

Given the multisystemic alterations in severe patients due to COVID-19, it is relevant to consider pharmacokinetic and pharmacodynamic aspects when prescribing and dosing. In the case of antipsychotics, special caution should be exercised in patients with cardiological alterations in the critical patient context due to the risk of QTc prolongation, and in patients with transaminase alterations due to systemic inflammation; antipsychotics with risk of hepatotoxicity should be avoided<sup>(31)</sup>. Furthermore, COVID-19 has been associated with leukopenia and lymphopenia, so starting a prescription of drugs such as clozapine or carbamazepine should be carefully considered, balancing risks and benefits<sup>(31)</sup>. Concomitantly, the use of clozapine has been associated with an increased risk of systemic inflammation and pneumonia<sup>(32)</sup>.

Regarding the follow-up protocols in patients with pharmacotherapy already installed, due to the problems of access to the laboratory and the risks of contagion, it has been proposed for some drugs to postpone laboratory controls. Experts have recommended reducing the frequency of hematological monitoring with the use of clozapine every three months in patients who have been using it for more than a year and have stable white blood cell and neutrophil counts in that period<sup>(33)</sup>.

Among the “off-label” uses of therapies for COVID-19, various drugs can be found, including chloroquine, hydroxychloroquine, azithromycin, lopinavir-ritonavir, favipiravir, remdesivir, ribavirin, and interferon, among others. Some of them present potentially

serious adverse reactions such as QTc prolongation, hepatitis, pancreatitis, neutropenia, and anaphylaxis<sup>(34)</sup>. In this scenario, the psychiatrist liaison must take special care to review possible drug interactions and choose a safe scheme within the possibilities.

In the subgroup of patients with a greater systemic inflammatory component, such as cytokine storm, the use of immunomodulatory drugs such as corticosteroids, immunoglobulin, and selective cytokine blocking such as tocilizumab<sup>(35)</sup> has been proposed, with known psychiatric adverse reactions, especially from corticosteroids and interferon, such as depression, mania, agitation, and suicidal reactions, among others<sup>(31)</sup>.

Regarding lithium carbonate, which continues to be one of the cornerstones of treatment in mood disorders, there are specific concerns but also promising aspects regarding its use during the pandemic. There are already documented cases of patients with lithium intoxication and hospitalizations for SARS-CoV-2<sup>(36)</sup>, which warns about the complications that may occur due to low fluid intake or kidney failure as part of the severity of their evolution; thus, timely control of lymphoma in patients who acquire the infection is highly relevant, adjusting doses as needed. Nevertheless, lithium has certain potential benefits worthy of consideration; it is a drug that has been shown to slow down the replication of coronavirus in animals in vitro through the inhibition of an enzyme called glycogen-synthetase kinase 3, involved in the phosphorylation of cofactors necessary for RNA polymerase<sup>(37)</sup>. Some have proposed studying lithium in microdoses for its protective effects, preventing inflammation associated with a senescent phenotype<sup>(38)</sup>. In this way, new fields of research are opened regarding the use of lithium and viral infections.

## **Challenges**

The challenges for psychiatry during this pandemic are several. On the one hand, the need to anticipate and prepare for the increased demand for care due to the immediate and long-term mental health repercussions. In this sense, implementing an effective and efficient telepsychiatry system is presented as a highly relevant challenge<sup>(39)</sup>. Perhaps in more global terms, the challenge has to do with modifying the clinical and research work modality of mental health teams<sup>(40)</sup> from all their intervention spaces. The need to implement telepsychiatry and telepsychology platforms early and effectively, create an efficient process of dispensing and withdrawing medication to ensure continuity of treatment, intensify isolation measures in psychiatric hospitalization units, and conduct virtual psychiatric interventions<sup>(41, 42)</sup>.

Another challenge is implementing multidisciplinary mental health interventions in two specific groups: healthcare personnel and patients and relatives affected by COVID-19<sup>(43)</sup>. Therefore, needs arise beyond the usual task, which will be particularly complex for psychiatry teams.

Leaving the clinical field, a pending challenge for psychiatry and scientific societies is that of broadcasting and education of the media, so that the type of information and its modes of transmission do not detract from the mental health of the population. This is a preventive strategy<sup>(44)</sup>.

## **CONCLUSIONS**

COVID-19 has come to revolutionize various aspects of daily life. For mental health teams, this implies a need to adapt at a rate seldom seen before, in order to meet the new requirements for the population and especially for groups at risk of presenting psychopathology.

Current information indicates that SARS-CoV-2 is a virus that has the ability to enter

the central nervous system and present numerous neuropsychiatric manifestations, this being a field in full development. In mood disorders, aspects of the viral infection must be taken into consideration and the psychosocial determinants involved. In psychopharmacology, special care must be taken when evaluating drug interactions and possible neuropsychiatric repercussions of new treatments for COVID-19. On the other hand, lithium carbonate has properties that could be of interest as a potential treatment for coronaviruses.

Considering this a period of crisis from multiple angles, it is also an opportunity for growth and to modify our usual paradigms of functioning, both in psychiatry and in other areas. As an example, the creation of a virtual art gallery, The Covid Art Museum, specifically dedicated to publishing works related to the pandemic. This is how creative spaces arise, which also, in part, can be considered a strategy of expression and coping during such complex times (Figure 2).

**Figure 2.** Virtual work published in the Covid Art Museum, artist @anindianminiaturist



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