REVIEW ARTICLE

Sleep disorders and post-COVID-19 syndrome: a narrative review

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ABSTRACT

The COVID-19 pandemic has resulted in both high mortality rates and a decrease in the response of health services worldwide. Many people changed their lifestyles due to the deterioration of their health both during the acute and post-illness stages. Depression, and especially sleep disorders, deserve attention due to their high prevalence within the so-called post-COVID-19 syndrome because they are associated with a deterioration in the quality of life of those affected. Knowing its prevalence and understanding its pathophysiology, clinical spectrum and treatment methods remain matters of research. The objective of this narrative review is to present the latest findings on sleep disorders as manifestations of post-COVID-19 syndrome. For this purpose, scientific literature was consulted using three databases—PubMed, Scopus and SciELO—resulting in a total of 867 articles, which were reviewed by title and abstract. This search was updated twice, resulting in 61 articles, which were included in this narrative review. A prevalence of sleep disorders in post-COVID-19 syndrome ranging from 9.7 % to 50 % has been observed; its cause is identified as being multifactorial, and the systemic inflammatory response may play a fundamental role due to the toxic action of cytokines and the inadequate neuronal response to the reversal of the inflammatory process. Insomnia is the most frequent symptom; being female and suffering from concomitant depressive disorders are prevalent risk factors. There is a possible beneficial effect on symptom control with the use of antidepressants as well as nonpharmacological treatments such as individualized physical therapy and antioxidant nutritional regimens. It is concluded that many gaps remain in the understanding of this pathology and further research is needed to elucidate them.

Keywords: Sleep Initiation and Maintenance Disorders; SARS-CoV-2; COVID-19 (Source: MeSH NLM).

INTRODUCTION

On January 30, 2020, the World Health Organization (WHO) announced the start of the COVID-19 pandemic in the world. Since then, it has rapidly spread worldwide, with a total of 626'337,158 confirmed cases and 6'831,681 deaths reported as of January 2023 [1].

The impact of the pandemic on the population has been significant across the health, social and economic sectors, with many countries potentially facing a deep recession in the short term, exacerbating the health crisis and increasing poverty levels to extreme degrees [2].

The acute symptomatology of COVID-19 is characterized by a clinical presentation that is often asymptomatic or similar to influenza, including fever, cough, general malaise, headache, and loss of taste and smell. Only 10 % to 15 % of cases develop severe disease and 5 % require critical care, with a recovery period of approximately three to four weeks [3].

Prior to the initiation of immunization programs, the COVID-19 fatality rate was notably high, particularly among hospitalized patients and individuals with comorbidities [4,5]. Now vaccines have changed the course of the disease for many individuals, reducing both the risk of death and the hospitalization rate [6,7].

Efforts to combat the disease and its spread are currently challenged by a new condition associated with the sequelae of SARS-CoV-2 infection: the persistence of symptoms beyond 12 weeks, referred to as post-COVID-19 syndrome, chronic COVID or long COVID [8].

Post-COVID-19 syndrome is characterized by a spectrum of symptoms, including pulmonary and extrapulmonary manifestations, with the latter comprising cardiac, renal, endocrine and neuropsychiatric disorders [9]. Among the neuropsychiatric disorders described in the post-COVID-19 syndrome, sleep disorders show a prevalence ranging from 17 % to 30 %, with insomnia being the most common [10].

The impact of sleep disorders during the pandemic has been studied because the prevalence of conditions such as insomnia increased by up to 80 % in the general population [11]. The origin of these disorders may be due to

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multiple reasons, including viral neurotropism, its ability to replication and invade the central nervous system (CNS) and induce a prolonged inflammatory process in brain areas involved in sleep regulation, as well as an erratic process of glia remodeling [12]. The increased frequency of other neuropsychiatric processes such as anxiety, depression and stress during the pandemic also contributed to the onset of sleep disorders [13].

Several risk factors associated with post-COVID-19 syndrome and the presence of sleep disorders have been identified, such as being female, a history of mental disorders and the presence of comorbidities. It is presumed that many of these factors would be reversible over time; however, the long-term effects on sleep quality in affected individuals are not yet fully understood [14].

The objective of this article is to provide an updated review of sleep disorders associated with post-COVID-19 syndrome, focusing on their epidemiology, pathophysiology, clinical manifestations and treatment.

SEARCH STRATEGY

For the development of this narrative review, a literature search was conducted in the PubMed and Scopus databases, and in SciELO for Spanish-language articles, including all publications up to July 17, 2022. The search for terms incorporated the keywords suggested by the controlled vocabulary of Medical Subjects Headings (MeSH) and the Boolean connectors "Post-acute COVID-19 syndrome" [MESH] AND "Sleep Wake Disorders" OR "Sleep Quality." Using the aforementioned criteria, 867 results were obtained, of which 297, 550 and 20 corresponded to PubMed, Scopus and SciELO, respectively. This search was updated twice. The first update was on December 22, 2022, resulting in 261 additional articles, of which 175 were from PubMed and 86 from Scopus. The last update was on June 12, 2023, and 115 more articles were obtained, of which 13 were from PubMed and 102 from Scopus. The Rayyan web tool for systematic reviews [15] was used, and articles containing relevant information on the topic were selected. For this purpose, filters were applied based on title, abstract and full text. As a result of this process, 61 articles were included in the review. Additionally, a manual search of the reference list of eligible papers was conducted to enhance the literature for the review.

Epidemiology and risk factors of sleep disorders in post-COVID-19 syndrome

During the COVID-19 pandemic, most patients developed an upper respiratory illness accompanied by fever, with an average recovery time of two to three weeks, depending on symptom severity. Only 15 % developed severe disease and 5 % a critical condition [9]. However, it has been reported that one in five individuals, regardless of the severity of their acute condition, experiences symptoms lasting five weeks or more, while 1 in 10 may remain symptomatic for 12 weeks [3]. Symptoms that persist beyond this period constitute what is known as post-COVID-19 syndrome or long COVID, which would be associated with processes that are not yet well defined but may include organ damage, autonomic dysfunction, ongoing inflammatory response and coagulation disorders [10].

There are reports on the prevalence of symptoms in the post-COVID-19 period, but the data have not been standardized due to differences in study designs, heterogeneous samples and the diversity of described symptoms [16]. Nevertheless, some authors identify fatigue, dyspnea and sleep disorders as post-COVID-19 manifestations in an early period (i.e., before 12 weeks) and a late period after that. In addition to sleep disorders, depression and poor quality of life are commonly observed. Taking this into consideration, sleep disorders vary by 36 % and 33 %, respectively, and it is likely that the prevalence decreases over time [17].

Sleep disorders in post-COVID-19 syndrome have also been reported in other series, with prevalence rates ranging from 9.7 % to 50 % [18-23]. Even among patients who were hospitalized, reports indicate a prevalence of up to 80 %, a figure much higher than that observed in the general population, where prevalence reaches only 4 % [21].

For specific populations, such as children, data remain very scarce and highly heterogeneous; the prevalence reported for the child population ranges from 2 % to 63 % [24,25]. In the older adult population, prevalence reports indicate 63 % for the frequency of sleep disorders among individuals over 73 years of age during the post-COVID-19 period, with the most common presentations being fragmented sleep, insomnia and increased sleep (27 %, 24 % and 12 %, respectively) [26].

The follow-up periods to evaluate the persistence of sleep disorders are also markedly heterogeneous; however, some reports indicate that these symptoms may persist for up to one year, with a prevalence of 22 % [27]. Furthermore, a recent meta-analysis involving a total of 257,348 individuals reported a prevalence ranging from 22 % to 30 % during systematic follow-up periods of six months to one year, representing one of the most comprehensive reports in terms of the magnitude and reliability of the analysis [28]. However, there is also a meta-analysis that placed sleep disorders and brain fog at a similar magnitude of prevalence in the post-COVID-19 period (32 % vs. 31 %) [29].

While the risk factors for the acute complications of COVID-19 are becoming increasingly clear—e.g., concerning

sex, men are more likely to develop acute complications—few studies have provided gender-disaggregated data on the sequelae of the infection, which would be useful for identifying the risk factors for post-COVID-19 syndrome, particularly with the intention of implementing early preventive measures and personalized therapeutic strategies [30]. Some reports describe that some factors such as being female, a history of other mental health issues and a higher number of comorbidities may increase the risk of sleep disorders in the post-COVID-19 period [10]. Likewise, a positive correlation has been described between age, being single, the presence of physical and emotional limitations, living in urban areas and the severity of post-COVID-19 insomnia [31] (Table 1).

Table 1. Summary of findings on the prevalence of sleep disorders in post-COVID-19 syndrome

Author	Country	Year	Study type	No. of patients	Prevalence
Wu et al. [59]	China	2023	Meta-analysis Short communication	The analyzed population ranges from 402 to 1,733	The incidence of obstructive sleep apnea (OSA) ranges from 21 % to 28.6 %.
Avittan et al. [25]	Latvia	2023	Narrative review	Not applicable	Prevalence of sleep disorders among children: 46 %.
Kotova et al. [23]	Russia	2023	Review article	Not applicable	Before the COVID-19 pandemic, the worldwide prevalence of insomnia ranged from 10.8 % to 15.1 %; after the pandemic, it has increased to 42 %, occurring in one in three people recovering from COVID-19.
Taruffi et al. [22]	Italy	2023	Retrospective observational	103 nonhospitalized patients	Prevalence of sleep disorders: 24.3 %.
Taskiran-Sag et al. [20]	Turkey	2022	Cohort	50 nonhospitalized patients with moderate COVID-19 infection	Prevalence of sleep disorders: 36 %.
Efstathiou et al. [10]	Greece	2022	Narrative review	Not applicable	Prevalence ranging from 4.9 % to 41.8 % among the various cited authors.
Premraj et al. [29]	Australia	2022	Systematic review Meta-analysis	10,530 patients	Average prevalence of sleep disorders: 31 % (19 % to 42 %).
Rass et al. [27]	Austria	2022	Cohort	81 patients with a history of COVID-19	Prevalence of sleep disorders: 22 %.
Alkodaymi et al. [28]	Saudi Arabia	2022	Systematic review Meta-analysis	257,348 participants	Prevalence of sleep disorders after 3 to 6 months: 24 %; after 6 to 9 months: 36 %, and after more than 12 months: 30 %.
Yong [16]	Malaysia	2021	Narrative review	Not applicable	Prevalence ranging from 17 % to 50 % among the various cited authors.
Zimmermann et al. [24]	Switzerland	2021	Narrative review	Not applicable	Prevalence ranging from 2 % to 63 % among children and adolescents.
Sykes et al. [18]	United Kingdom	2021	Cohort	387 patients discharged after COVID-19	Prevalence of sleep disorders: 35 %.
Huang et al. [19]	China	2021	Cohort	1,733 out of 2,469 discharged after COVID-19	Prevalence of sleep disorders: 23 %.
Jennings et al. [17]	Switzerland	2021	Systematic review	The analyzed population ranges from 32 to 1,733	Prevalence of sleep disorders ranging from 33 % to 36 %.
Lombardo et al. [21]	Italy	2021	Cohort	303 patients hospitalized and discharged after COVID-19	Prevalence of sleep disorders: 47 %
Aly et al. [26]	Egypt	2021	Retrospective cross-sectional	115 female older adults	Prevalence of sleep disorders: 63.47 %
El Sayed et al. [31]	Egypt	2021	Observational cross-sectional	500 patients with a history of COVID-19	Mild insomnia: 59 % Moderate insomnia: 27 % Severe insomnia: 5 %

Note: *Based on the reviewed literature.

Pathophysiology of sleep disorders in post-COVID-19 syndrome

SARS-CoV-2 is able to enter the body through the nasal cavity and trigger the antiviral response mediated by type I interferon and other presentation antigens such as the Spike protein (S protein), as well as CD4+ and CD8+ lymphocytes [32]. Moreover, it is capable of accessing the CNS, as demonstrated in animal models, through retrograde transport of viral antigens via the axons of the olfactory nerve, the vagus nerve and other cranial nerves [10,33-37]. Concomitantly, researchers have proposed a hematogenous entry mechanism along with transsynaptic pathways associated with the angiotensin-converting enzyme 2 (ACE2) receptor, which is present in various body cells [34].

At the molecular level, the viral S protein has the ability to cross the blood-brain barrier in animals, SARS-CoV-2 binds this protein to the ACE2 receptor, which is abundantly expressed in neural tissue, both in neurons and in glial cells and brain nuclei, involving the balance of the renin-angiotensin system [10,33,34]. Binding is facilitated by transmembrane serine protease 2 (TMPRSS2) that primes the S protein, and for this affinity, it uses CD147 as an entry route into cells, causing an intense immune response with the release of infected macrophages, as well as significant amounts of Th-1 cytokines (IL1ß, IL-6, interferon-γ, tumor necrosis factor α, CXCL10 and CCL2) and Th-2 cytokines (IL-4, IL-10 and IL-1 receptor agonist) [33]. IL-6 is the most important cytokine in the altered inflammatory response induced by the virus and has also been found to be elevated in depressive disorders [10,32,34,36,37].

The cytokine storm, as a part of the systemic inflammatory state in acute COVID-19 infection, leads to changes in cerebral perfusion, increasing the permeability of the blood-brain barrier and generating changes in astrocytes involved in synaptogenesis and neurotransmitter balance. It also alters the regulation of neurogenesis, causing neurons, oligodendrocytes and glial cells to lose their physiological function and neuronal plasticity [10,35]. The delayed return of neuroglia to their physiological state contributes to the late sequelae of COVID-19 as the changes include morphological and functional remodeling of astrocyte and microglia, which would explain the persistence of long-term neuropsychiatric disorders in COVID-19 [10]. A vicious circle of inflammation and mitochondrial dysfunction would occur, amplifying inflammatory processes and resulting in immuno-metabolic constraints on neuronal energy metabolism [32], with hypometabolism of glucose in the CNS [38,39]. The virus has not been identified in the cerebrospinal fluid (CSF), which points more towards the hypothesis of systemic inflammatory damage [35].

The systemic inflammatory immune index (SII = platelets × neutrophils/lymphocytes) reveals the host's inflammatory response and has been associated with anxiety and depression. Individuals with fewer markers have reduced neuropsychiatric symptoms [10,40]. On the other hand, neuropathological studies have confirmed the excessive recruitment of inflammatory cells, especially T cells and macrophages, in the perivascular spaces of patients with neuro-COVID [33].

The immune response to SARS-CoV-2 seems to differ according to sex. Males have higher infection rates and negative outcomes, including death, probably related to adaptive and innate immune responses influenced by genes, hormones and microbiota. They also have higher levels of cytokines IL-8, IL-18, CD15, CD16 and neutralizing IgG antibodies against SARS-CoV-2 S protein compared to females and healthy individuals. On the other hand, females have higher CD4 and CD8 T-cell activation but a poorer T-cell response [37].

In the nervous system, ACE2 receptors are expressed in the olfactory bulb, amygdala, hippocampus, middle temporal gyrus, posterior cingulate cortex and brainstem. Therefore, SARS-CoV-2 infection has been associated with symptoms such as hyposmia, mood disorders, cognitive impairment, sleep disorders and dysautonomia [34,40,41]. This virus is neurotropic; thus, it would affect, among others, the sleep pathways. This has been demonstrated by polysomnographic studies showing a higher prevalence of REM sleep without atonia in COVID-19 patients compared to the general population [42].

Sleep disorders as neurological sequelae seem to be more related to the overproduction of cytokines, neuroinflammation and direct invasion of the CNS. In contrast, vascular damage, endothelial dysfunction and hypercoagulable states are mechanisms for stroke or encephalopathies and encephalitis due to the SARS-CoV-2 virus [37,40,43]. All neuronal cells are capable of producing cytokines; e.g., type 1 astrocytes produce IL-1α, IL-1ß, IL2, IL13, IL15, IL17, interferons and tumor necrosis factor in response to the coronavirus, while microglia induce the production of IL-6, interferons and tumor necrosis factor [32,33]. IL-6 may influence memory processes such as long-term potentiation and depression by increasing activity in regions of the anterior cingulate cortex, reducing connectivity with the amygdala and medial prefrontal cortex, and promoting alterations in sleep-related processes [32].

Involvement of the vagus nerve could be a key factor in peripheral nervous system symptoms and autoantibodies against α/ß-adrenoreceptors and muscarinic receptors by promoting autonomic dysfunctions through an autoimmune process, as observed in Guillain-Barré syndrome (GBS) associated with SARS-CoV-2 infection [34]. A recently described atlas of COVID autoantigens at the molecular level could serve as a reference for research on COVID-induced autoimmunity and the potential autoimmune causes in post-COVID-19 syndrome [44].

In post-COVID-19 syndrome, it has also been hypothesized that SARS-CoV-2 causes a redox imbalance similar to that observed in post-viral chronic fatigue syndrome, due to decreased expression of genes encoded in the nucleus related to mitochondrial complex I. This disrupts mitochondrial function through still unknown mechanisms. The virus does not affect mitochondrial transcription, but does affect the biogenesis pathways of specific mitochondrial products [45,46]. It is also assumed that there may be microvascular dysfunction resulting in the production of antibodies against ß2 and acetylcholine receptors with systemic hypoperfusion [36,44,47].

Recent reports suggest that the virus causes demyelination, also due to cytokine storm and excessive activation of glial cells, both during acute and post-COVID-19 infection [33,43]. In view of these immune and inflammatory reactions, treatment with omega-3 polyunsaturated fatty acids is an option. Such treatment involves anti-inflammatory mechanisms that activate transcription factors such as peroxisome proliferator-activated receptor gamma (PPARγ), inhibition of leukocyte chemotaxis, deactivation of nuclear factor kappa B (NF-κB) and reduction of adhesion molecule expression and destabilizing membrane lipids [45].

Another explanation for sleep disorders, fatigue and muscle weakness in patients with persistent COVID-19 is based on the fact that SARS-CoV-2 infection causes long-term alterations in tryptophan absorption in the intestine due to ACE2 imbalance in the gastrointestinal system, promoting an increase in kynurenines, whose metabolites are neurotoxic [48]. Likewise, these symptoms of post-COVID-19 syndrome have been correlated with alterations in the intestinal microbiome, where decreased diversity and abundance—known as dysbiosis—favors a persistent inflammatory state that predisposes individuals to alterations in the gut-brain axis [37,39].

It cannot be determined whether sleep disorders, as well as the effects on circadian rhythms and mental health of adults, are only effects of SARS-CoV-2 or are also due to lockout, social and economic changes during the pandemic [37,42]. These psychological stressors—including fear of potentially life-threatening infection or a new variant and stigmatization—activate the hypothalamic-pituitary-adrenal (HPA) axis with glucocorticoid secretion, which is the normal hormonal response to physical or mental stress stimulus and may represent neurobiological mechanisms that inhibit neurogenesis and reduce proliferation and survival of nerve cells in the dentate gyrus of the hippocampus [10,37,45].

Some narrative reviews conclude that the mechanisms of direct invasion of the virus into the CNS, neuroinflammation with overproduction of cytokines, would be the mechanisms linked to post-COVID-19 syndrome disorders, such as depression, anxiety and sleep disorders [40,50] (Table 2).

Table 2. Summary of findings on pathophysiology of sleep disorders in post-COVID-19 syndrome

Author	Country	Year	Study Type	Findings
Efstathiou et al. [10]	Greece	2022	Review article	The virus enters through the hematogenous route and retrograde transport via the axons of the olfactory and vagus nerves, the latter causing cerebral dysregulation with subsequent hypoxia. A cytokine storm is triggered, disrupting the blood-brain barrier and activating apoptotic and demyelination cascades. Virus entry is facilitated by the ACE2 receptor on the surface of neurons. Serotonergic pathways cause a neurotransmitter imbalance, including acetylcholine, dopamine and histamine, leading to neuropsychiatric deficits in post-COVID-19 syndrome.
Desai et al. [35]	United States of América	2022	Review article	The virus has not been identified in the CSF; therefore, neurocognitive complications following SARS-CoV-2 infection are likely caused by systemic inflammatory damage.
Dressing et al. [38]	Germany	2022	Prospective cohort	Positron emission tomography revealed cerebral hypometabolism, which correlated with low scores on neuropsychological tests.
Shimohata [39]	Japan	2022	Review article	Following viral infection, microglial activation and abnormal mitochondrial function, along with the systemic inflammatory response, disrupt the blood-brain barrier causing CNS inflammation with changes similar to those seen in neurodegenerative diseases, including tau protein aggregation.

Author	Country	Year	Study Type	Findings
Ahmad et al. [40]	United States of America	2022	Review article	Subacute post-COVID-19 encephalopathy, known as "brain fog," is associated with elevated antinuclear antibodies, suggesting an autoimmune etiology in post-acute states. Neuroinflammation causes cerebral hypometabolism with negative effects that may be long-lasting on cognitive networks. In sleep disorders, social isolation exacerbates chronic disease.
Khazaal et al. [34]	Lebanon, France, China	2022	Review article	They report that the neurotropism of the virus and the subsequent effect of the cytokine cascade with neuroinflammation, together with the action of the renin-angiotensin-aldosterone system—which generate vasoconstriction, oxidative stress in the cerebral cortex and hippocampus with encephalic hypometabolism and release of neurotransmitters such as dopamine and acetylcholine—would be some pathophysiological mechanisms of the post-COVID-19 syndrome.
Yang et al. [45]	Taiwan China	2022	Review article	Unresolved systemic inflammation and oxidative stress, maladaptation of the renin-angiotensin-aldosterone system and the coagulation system, dysregulated immunity, dysfunction of neurotransmitters and the HPA axis, and psychosocial stress imposed by social changes in response to this pandemic are mechanisms that explain the post-COVID-19 syndrome.
Pozzi [46]	Japan	2022	Descriptive	SARS-CoV-2 infection alters the metabolism of small mitochondrial RNAs without affecting the mitochondrion as a whole, causing mitochondrial dysfunction.
Merikanto et al. [42]	Finland	2022	Descriptive	SARS-CoV-2 is neurotropic; therefore, it would affect, among others, sleep pathways with a higher prevalence of REM sleep without atonia in patients with COVID-19 than in the general population.
Wang et al. [44]	United States of America, China	2022	Analytical	It explains possible autoimmune causes of post-COVID-19 syndrome through a COVID-19 autoantigen atlas at the molecular level, serving as a reference for research on induced autoimmunity.
Castanares-Zapatero et al. [50]	Belgium	2022	Systematic review	Autonomic system dysfunction would explain immune dysregulation, autoimmunity, endothelial dysfunction, hidden viral persistence and coagulation activation as pathophysiological mechanisms of post-COVID-19 syndrome.
Kubota et al. [43]	Japan	2022	Narrative review	Direct neuronal damage leads to demyelination, neurodegeneration and reduced metabolic activity due to dysregulation of mitochondrial activity. Moreover, the prolonged inflammatory response triggered by the cytokine storm results in vascular inflammation and astrogliosis, accompanied by ischemia and cerebral microinfarcts.
Kappelmann et al. [32]	Germany, United States of America and United Kingdom	2021	Short communication	Alterations in T cells, dendritic cells, cytokine activity, and other interferon- and protein-induced disruptions affect brain tissue, leading to neuropsychiatric symptoms in post-COVID-19 syndrome.
Jesuthasan et al. [33]	United Kingdom and Germany	2021	Review article	After virus entry, cytokine storm has been shown to disrupt the blood-brain barrier. Furthermore, mitochondrial dysfunction allows the production of reactive oxygen species at such a level that mitochondria induce cytokine production and inflammation, which increases with interferons and predisposes to the neurological and neuropsychiatric symptoms of post-COVID-19 syndrome.
Research Accessibility Team (RAT) [36]	Egypt	2021	Review article	The long-lasting effects of COVID-19 are due to vascular abnormalities, such as hypercoagulability and cytokine-mediated injury, leading to vascular endothelial damage, microvascular thrombosis and ischemia.

Author	Country	Year	Study Type	Findings
Tizenberg et al. [37]	Belgium	2021	Review article	The virus exhibits neurotropism and activates inflammatory cytokine cascades that disrupt the blood-brain barrier, thus facilitating the entry of infected monocytes. Microglia mediate immune responses, and cytokines influence neuroplasticity, behavior and cognitive function. There may be a "dual reciprocal vulnerability and sequential activation," meaning that proinflammatory conditions create a persistent vulnerability for the usual mild stressors (immune, psychological or traumatic) to act as triggers and perpetuators.
Eroğlu et al. [48]	Turkey	2021	Review article	SARS-CoV-2 infection causes long-term disruption of tryptophan absorption in the intestine due to ACE2 imbalance in the gastrointestinal system, which favors to elevated kynurenines, whose metabolites are neurotoxic.
Hilpert et al. [49]	United Kingdom, Germany	2021	Review article	Dysbiosis promotes a persistent inflammatory state that predisposes to alterations of the gut-brain axis, as a possible explanation of post-COVID-19 syndrome.

Note: *Based on the reviewed literature.

Clinical presentation of sleep disorders in post-COVID-19 syndrome

Post-COVID-19 syndrome, like acute COVID-19, involves damage affecting multiple organs and systems—including the respiratory, cardiovascular, neurological, endocrine, urinary and immune systems—but unlike the acute phase, multi-organ symptoms can persist for 4-12 weeks [34,51,52].

Sleep disorders are one of the most common symptoms of post-COVID-19 syndrome and are attributed to a multifactorial origin, exacerbated by social isolation and decreased physical activity [21].

The risk factors associated with this condition are related to age, low educational level, diabetes mellitus, obesity, hypertension, severity of COVID-19, and high levels of C-reactive protein, D-dimer and ferritin [43,53]. Likewise, being female has been identified as a risk factor for sleep disorders, regardless of the severity of acute COVID-19 [31,43,54]. A cohort study was conducted in Italy with 303 post-COVID-19 patients over 18 years of age followed for one year, of whom 47 % had sleep disorders, a higher prevalence than in the general population, as well as a higher risk in women and an increased incidence with age [21].

The clinical spectrum described for sleep disorders in post-COVID-19 syndrome ranges from difficulty sleeping, including insomnia, sleep apnea, changes in the sleep-wake cycle, feeling of nonrestorative sleep, delayed sleep phase syndrome, sleep continuity disorders and even excessive daytime sleepiness, symptoms that may take months to resolve [20,21,23,43,55-57].

A 2021 study by the University of Texas used the Pittsburgh Sleep Quality Index questionnaire to assess sleep quality in post-COVID-19 patients, finding increased sleep apnea, insomnia and daytime sleepiness. It also determined that poor sleep quality predicted increased severity in anxiety; furthermore, it increased daytime dysfunction [58]. Other studies also report alterations in sleep quality and sleep latency [26,31] and, in addition, describe that acute sleep disorders are more associated with subacute cognitive symptoms than other central symptoms [20]. On the other hand, sleep apnea shows a prevalence between 21 % and 28.6 % [1,59] and restless legs syndrome described in women during post-COVID-19 is not more common than in the general population [60].

Insomnia is one of the most commonly identified sleep disorders and seems to be strongly associated with depressive disorders, anxiety, cognitive and olfactory dysfunction [61,62]. However, the effect of depressive conditions on insomnia and vice versa remains unclear [63]. Hypertension, being female, hypothyroidism, hypoxia and preexisting psychiatric symptoms are reported as risk factors for post-COVID-19 insomnia [61,64].

Patients with post-COVID-19 syndrome may present with fatigue, signs of depression and cognitive dysfunction more commonly than sepsis survivors, regardless of the severity of acute infection. Furthermore, signs of cognitive dysfunction are associated with hospitalization [31,54,65] (Table 3).

Table 3. Summary of findings on clinical manifestations and types of sleep disorders in post-COVID-19 syndrome

Author	Country	Year	Study Type	Findings
Kotova et al. [23]	Russia	2023	Review article	They reported insomnia, sleep continuity disorders, changes in the sleep-wake cycle, nonrestorative sleep and impaired sleep quality in patients with post-COVID-19 syndrome.
Takao et al. [61]	Japan	2023	Review article	Insomnia associated with anxiety, depression, and cognitive and olfactory dysfunction is common in post-COVID-19 syndrome. Likewise, hypertension, hypothyroidism, hypoxia and preexisting psychiatric symptoms are risk factors for sleep disorders.
Bocek et al. [64]	Czech Republic	2023	Review article	They identified mental illness and being female as risk factors for insomnia.
Paranhos et al. [62]	Brazil	2023	Analytical cross-sectional	They reported a high correlation between olfactory dysfunction and poor sleep quality.
Kubota et al. [43]	Japan	2022	Narrative review	They reported that delayed sleep phase syndrome was the most common clinical presentation, with being female, older age, low educational level, diabetes, obesity, hypertension, COVID-19 severity, and elevated C-reactive protein, ferritin and D-dimer as the most common risk factors.
Nowakowski et al. [58]	Unidos States of America	2022	Retrospective	After two months, post-COVID-19, fatigue and poor sleep quality associated with depression, anxiety and post-traumatic stress. Diagnoses of sleep apnea, excessive daytime sleepiness, and insomnia were identified, as well as an association between poor sleep quality and daytime dysfunction in post-COVID-19 syndrome.
Young [63]	Germany	2022	Case study	Insomnia was common, and hypersomnia was associated with post-COVID-19 autoantibodies.
Weinstock et al. [60]	United States of America	2022	Prospective cohort	Increased prevalence of restless legs syndrome.
Khazaal et al. [34]	Lebanon France	2022	Review article	In post-COVID-19 syndrome, pulmonary and cardiovascular symptoms may appear, along with psychological disorders such as anxiety, depression, insomnia and post-traumatic stress disorder.
Taskiran-Sag et al. [20]	Turkey	2022	Prospective cohort	Neurological complications in patients with subacute COVID-19 included headache, prolonged anosmia, prolonged taste disorders, fatigue, vertigo and sleep disorders. Among the sleep disorders, both hypersomnia and insomnia were reported.
Aly et al. [26]	Egypt	2021	Retrospective cross-sectional	Older adults have a higher tendency to develop post-COVID-19 complications due to the presence of stress, depression, fragmented sleep, insomnia, fatigue, cognitive disorders and an increased risk of falls.
El Sayed et al. [31]	Egypt	2021	Observational cross-sectional	Quality of life was affected in post-COVID-19 patients due to subclinical and moderate insomnia, poor sleep quality characterized by altered duration and efficiency, and increased use of medication.
Fernández-Lázaro et al. [52]	Spain	2021	Narrative review	Post-COVID-19 psychological symptoms include low mood, sadness, anxiety, difficulty sleeping, fear and stress resulting from brain infection, cerebrovascular diseases, medical interventions, social isolation and the impact of a new illness.
Lombardo et al. [21]	Italy	2021	Cohort study	The most common post-COVID-19 symptoms were fatigue, pain and sleep disorders—with a greater tendency in males—and were caused by multiple factors, including social isolation, decreased physical activity, and viral infection.
Schou et al. [54]	Denmark	2021	Systematic review	Twenty-four studies reported sleep disorders at 4-6 months of follow-up, which tended to decrease over time after recovery, regardless of COVID-19 severity; insomnia usually improved after three months.

Author	Country	Year	Study Type	Findings
Mazza et al. [56]	Italy	2021	Prospective cohort	Three months after COVID-19, depressive symptoms persisted, while post-traumatic stress disorder, anxiety and insomnia gradually decreased.
Nath [82]	United States of America	2021	Case review article	Long-term COVID-19 disorders include dysautonomia, exercise intolerance, general malaise, sleep disorders, cognitive impairment and mood disorders.
Terlizzi et al. [57]	United States of America	2021	Cross-sectional	In subacute and prolonged cases of COVID-19, neurological symptoms include gait disorders and symptoms related to sleep-wake disorders include insomnia.
Buttery et al. [65]	United Kingdom	2021	Quantitative and qualitative mixed method study	There was no variation between hospitalized and nonhospitalized patients with prolonged COVID-19; the most common symptoms were respiratory problems, fatigue, weakness, sleep disorders, problems with mental abilities, and mood changes affecting quality of life in these patients.

Note: *Based on the reviewed literature.

Treatment of sleep disorders in post-COVID-19

Initially, SARS-CoV-2 infection was thought to be an acute disease that would resolve within a few days. However, increasing reports now indicate that the infection can follow a prolonged course with systemic symptoms, including fatigue or muscle weakness (63 %), pain or discomfort (27 %) and dyspnea (26 %) [19].

A significant proportion of patients experience neurological sequelae associated with post-COVID-19, including sleep disorders [17]. It is known that sleep is related to quality of life, and any adverse event related to a disruption leads to significant impairment in the patient's daily functions, which has been corroborated in series of patients who have recovered from the acute COVID-19 infection [66].

Hence, efforts are currently underway to identify the most appropriate strategy for managing these sequelae, given the highly nonspecific presentation of post-COVID-19 symptoms, and as described, it is not exclusive to an age group and is not related to the severity of the initial disease: even patients with mild forms of infection have presented symptoms various weeks after the acute phase has resolved [3].

The treatments currently being considered as alternatives could be based on the experience acquired in managing other conditions with prolonged sequelae characteristic of viral postinfectious syndromes, such as those caused by SARS-CoV-1, Middle East respiratory syndrome (MERS), Epstein-Barr virus and even dengue virus. These postinfectious syndromes are characterized by the virus the presence of chronic fatigue as the primary symptom, along with psychiatric disability, including two well-defined conditions: myalgic encephalomyelitis and postural orthostatic tachycardia syndrome [16]. Based on this, the proposed therapies can be divided into pharmacological and nonpharmacological, but always taking into consideration the premise that at present there is no known and effective therapy proven with clinical trials to reverse the symptoms related to sleep disorders in post-COVID-19 syndrome.

Various treatments—e.g., antivirals, immunomodulators, analgesics, melatonin, and even nutritional and vitamin supplements—have been proposed as part of general pharmacological therapy. However, many of these treatments remain in the experimental phase [67-69].

The neuroinflammatory processes observed in patients with COVID-19 infection, as well as in animal models and in postmortem specimens, have been implicated in the pathogenesis of virus-induced sequelae [35]. Microglia is an important component of the immune response of neuronal tissue as it causes mast cell activation with a consequent increase in the inflammatory state and a greater predisposition to postinfectious processes. Therefore, it is postulated that drugs inhibiting the release of mast cells may be useful in halting the inflammatory response and slowing the progression to these processes [70]. It is also proposed that some natural flavonoids, such as luteolin and quercetin, may contribute to reduce inflammatory phenomena by controlling mast cell activation and could be used in liposomal forms such, as in the treatment of autism spectrum disorders [71].

Antidepressants are the most commonly used and prescribed medications. Drugs such as moclobemide and methylphenidate have demonstrated usefulness in improving chronic fatigue. Furthermore, drugs such as gabapentin and pregabalin may be useful in reducing the neurological sequelae of post-COVID-19 syndrome, particularly neuropathic pain [72,73].

Nonpharmacological therapy has been used as an alternative in chronic fatigue syndrome, for which rehabilitation, sleep hygiene, physiotherapy, phytotherapy and traditional Chinese medicine have been highly beneficial [11,43,74].

Regarding physical rehabilitation, it is suggested that it may be beneficial, provided it is personalized to the patient's pace and progressively tailored until functional performance improves [75]. Emphasis is placed on prior individualized evaluation before initiating physical therapy rehabilitation because it could be counterproductive if the patient has severe cardiac or pulmonary damage as an additional sequela [75,76]. The proposed exercises are aerobic, last between 5 to 10 minutes, and are associated with breathing exercises [77].

A potential benefit for reducing neurological symptoms of post-COVID-19 is a plant-based diet, which, due to its possible anti-inflammatory effect, has led to a significant improvement in sleep quality. In contrast, the Western diet with pro-inflammatory characteristics would not be able to achieve the same effect [78]. A diet rich in tryptophan has been reported to alleviate depressive symptoms and anxiety. Likewise, diets lacking this compound are associated with increased symptoms of post-COVID-19 syndrome [48]. It has been suggested that the presence of polyphenols in the diet—particularly from apples, cherries and onions—has great antidepressant potential [78]. Omega-3 fatty acids are also associated with anti-inflammatory and immunomodulatory processes, and in general, their consumption shows a positive effect on quality of life by improving attitude toward adverse events in patients [79].

Cognitive behavioral therapy was employed during the acute phase of the pandemic, when many people—especially healthcare personnel—suffered from the ravages of insomnia and depression, resulting in improved quality of life. However, in sleep disorders associated with post-COVID-19 syndrome, there are only a few case series reporting that cognitive behavioral therapy has achieved only modest symptom improvement, particularly for insomnia [80] (Table 4).

Table 4. Summary of therapeutic proposals for sleep disorders in post-COVID-19 syndrome

Author	Country	Year	Study Type	Findings
Kotova et al. [23]	Russia	2023	Review article	Treatment of sleep disorders depends on the treatment of mental illness and includes correction of vitamin and micronutrient deficiencies, prevention and correction of mental disorders; cognitive behavioral therapy for insomnia, symptomatic treatment of acute insomnia, and the use of antidepressants and other psychotropic drugs for chronic insomnia.
Shaik et al. [68]	United States of America	2023	Review article	The basic principles of sleep hygiene should be reinforced as part of treatment, along with the use of melatonin, behavioral therapy and alternative therapies such as yoga, physical therapy and meditation techniques.
Souissi et al. [69]	Tunisia	2023	Narrative review	The use of melatonin is proposed as a potential agent with beneficial effects on sleep disorders caused by post-COVID-19, based on its proven use in other sleep disorders such as sleep deprivation and jet lag syndrome, as well as its antioxidant and anti-inflammatory effects. However, further studies are needed to support its use.
Guezguez et al. [74]	Tunisia	2023	Narrative review	It prioritizes nonpharmacological therapy based on an individualized program combined with behavioral therapy associated with relaxation therapy and sleep hygiene. It also considers the careful use of hypnotics due to their side effects such as daytime sleepiness, rebound insomnia, impaired alertness and performance and, ultimately, withdrawal syndrome after discontinuation of therapy.
Kubota et al. [43]	Japan	2022	Narrative review	The use of substances known as "adaptogens" has been proposed, a type of medicinal herb that, according to some controlled studies, improved physical symptoms, shortened fatigue time and chronic pain, as well as reduced IL-6 levels compared to placebo in patients with post-COVID-19 syndrome.
Yong [16]	Malaysia	2021	Narrative review	Nonpharmacological measures have been proposed, such as rehabilitation with light, personalized aerobic exercises, as well as respiratory exercises and close psychological support.

Author	Country	Year	Study Type	Findings
Theoharides et al. [71]	United States of America	2021	Narrative review	It proposes the use of luteolin, a flavonoid that acts as an anti-inflammatory by inhibiting mast cell activity, thereby improving the neuroinflammatory process.
Moghimi et al. [73]	United States of America	2021	Narrative review	It proposes the use of a pharmacological therapy similar to the therapeutic approach used for myalgic encephalomyelitis and chronic fatigue syndrome, which are sequelae of various infectious agents and for which there is prior clinical experience. The proposed drugs include antidepressants, monoamine oxidase inhibitors such as moclobemide, methylphenidate, acetyl-L-carnitine, alpha-lipoic acid and N-acetylcysteine. Additionally, the use of opioids, such as morphine and naloxone, may be effective. Nonpharmacological therapies, such as behavioral therapy and exercise, have limited usefulness.
Storz [78]	Germany	2021	Narrative review	It proposes a nonpharmacological therapy based on a diet rich in vegetables and certain micronutrients such as tryptophan and magnesium, which are associated with improvements in sleep quality, duration, onset latency, as well as early awakening.
Richter et al. [11]	Germany	2021	Narrative review	It emphasizes the use of nonpharmacological therapy, nutrition and traditional Chinese medicine. However, it highlights the need for further studies on cognitive-behavioral therapy, particularly in the management of post-COVID-19 insomnia.
Demeco et al. [75]	Italy	2020	Narrative review	The proposal recommends starting early rehabilitation to improve long-term recovery. Virtual assistance through telerehabilitation may be beneficial in situations involving social restrictions, as may telemonitoring for patient-reported symptoms.
Wang et al. [77]	United States of America	2020	Narrative review	It focuses patient rehabilitation in the post-acute phase of COVID-19 with the implementation of individualized and progressive physical exercise, as well as occupational therapy, particularly in patients with prolonged hospitalization.
Chang et al. [79]	United Kingdom	2020	Narrative review	It proposes the beneficial effects of polyunsaturated fatty acids, particularly eicosapentaenoic acid, in reducing the inflammatory response to COVID-19, as inflammation is the factor most closely associated with sequelae, especially those of neurological origin. The author emphasizes the importance of a balanced diet rich in these nutrients.
Ballesio et al. [80]	Italy	2020	Narrative review	The author presents a proposal based on sleep management aimed at frontline health personnel. The approach proposes, among other guidelines, sleep care, time management to promote restorative sleep, conducive environments and avoiding the use of stimulants and hypnotics.

Note: *Based on the reviewed literature.

Postinfectious diseases have been primarily described in association with viruses, among which dengue, cytomegalovirus and Epstein-Barr virus stand out [63]. In this group of agents, coronaviruses that affect humans have also been associated with postinfectious processes. In this regard, there is some experience in managing them, particularly in severe acute respiratory syndrome (SARS) and MERS, where there is a clear approach regarding the course of symptoms. These symptoms are characterized by the presence of fatigue and psychiatric disorders, which can persist for up to four years following the acute infection, with some series describing persistence for a period close to 15 years [81].

The neurological sequelae of COVID-19 are more frequent than those caused by the influenza virus, particularly in patients admitted to the intensive care unit (ICU). On the other hand, the prevalence of chronic fatigue is much higher than that observed in dengue, Epstein-Barr virus and mononucleosis [16,53].

In cases where sleep disorders as manifestations of post-COVID-19 syndrome, the exact duration of persistence of this condition remains unknown as many observational studies are still ongoing [42].

The clinical spectrum that has been described so far with respect to sequelae in post-COVID-19 corresponds to a very diverse systemic symptomatology ranging from autonomic disorders to specific organ damage. The most critical aspects are prolonged neurological and neuropsychiatric disorders, among which sleep disorders are those that have caused significant morbidity, as well as functional problems related to quality of life, which are as equally or more severe than chronic fatigue, dyspnea and brain fog and are also described in many series [10,82].

While it is true that there is much to be elucidated regarding the prevalence, risk factors and clinical presentation of sleep disorders in post-COVID-19 syndrome, it is becoming clear that the female sex is the most affected, particularly when associated with mental or neuropsychiatric disorders [31]. Furthermore, the largest studies on the prevalence of sleep disorders in post-COVID-19 syndrome indicate that it does not exceed 50 % in all series, even in the largest and longest follow-up series, and that it appears to be decreasing over time, but all indications are that it is much higher than in the general population [10,17,21,28,54].

It is evident that SARS-CoV-2 is a virus with a tendency to cause systemic disorders due to its ability to invade noble organs, including the central nervous system. Moreover, the systemic inflammatory response is closely related to the sequelae, as we have attempted to understand in the pathophysiological origin of these disorders [10,40]. One aspect that remains poorly understood is the genetic predisposition to the neurological manifestations of post-COVID-19. In fact, there are descriptions of ACE2 genetic variants associated with the severity of acute presentation across different ethnicities; however, the genetic role in greater neurological involvement remains unknown, unlike variants described (e.g., for the herpes simplex virus) where innate mutations in the toll-like receptor 3 (TLR3) pathway have been discovered. It leads to a dysregulated response to the virus, and there remains the suspicion that a similar situation could occur with COVID-19 [33].

The management of post-COVID-19 symptoms, especially sleep disorders, is still an emerging field of research. Nevertheless, all indications suggest that, as these disorders fade over time, palliative care and behavioral therapy will be the predominant therapeutic methods. However, much is yet be elucidated about pharmacological and dietary therapy [16]. Regarding the latter, there is currently a very strong trend toward the adoption of a vegan diet, based on the lower risk of complications in individuals who consume diets free of animal protein and low in carbohydrates. Additionally, diets rich in antioxidants, such as omega-3 fatty acids, have emerged as interesting alternatives to combat the COVID-19 post-inflammatory sequelae [78].

CONCLUSIONS

We are facing a new and silent pandemic resulting from the still poorly understood sequelae of COVID-19. Neuropsychiatric disorders are causing a deterioration in individual functioning, with sleep disorders being among the most common issues such cases, with a prevalence ranging from 9.7 % to 50 %.

The origin of sleep disorders in post-COVID-19 could be explained by a series of factors, among which the viral tropism for the CNS, the inflammatory response, inadequate neuronal tissue regeneration and a psychosocial component not yet well studied—such as depression and social isolation—predominate.

Insomnia is one of the most common sleep disorders associated with post-COVID-19 syndrome and predominantly affects females, young adults and individuals with additional neuropsychiatric disorders.

The management of such disorders is still under investigation. Pharmacological therapy with antidepressants has demonstrated some usefulness. The same applies to nonpharmacological measures, such as short personalized physical therapy and alternative therapies, including Chinese medicine and vegan dietary therapy focused on the consumption of antioxidant foods, which may help control symptoms. To summarize, given the high prevalence and diversity of sleep disorders, it is important to conduct more in-depth studies that characterize them more specifically for their therapeutic approach, both pharmacological and nonpharmacological, considering their impact on quality of life.

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