



## Review

# Update of the Potential Treatments for Psychiatric and Neuropsychiatric Symptoms in the Context of the Post-COVID-19 Condition: Still a Lot of Suffering and Many More Things to Learn

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**Abstract:** Background: The World Health Organization (WHO) has defined a post-COVID-19 condition. Some of these symptoms can be categorized as psychiatric long COVID-19 if they appeared in the aftermath of COVID-19, including depression, anxiety, post-traumatic stress disorder, somatic symptoms disorders such as hyperventilation syndrome, fatigue, cognitive and sleep disorders. Psychiatric and neuropsychiatric post-COVID-19 present mental health specialists with difficult challenges because of its complexity and the multiple ways in which it integrates into a singular somatic context. Methods: We conducted a systematic research paradigm from SARS-CoV-2 using LitCOVID and Web of Science to search management strategies and potential treatments for psychiatric post-COVID-19 symptoms. Results: Management strategies must be based on a multidisciplinary approach to promote the global evaluation of psychiatric and physical symptoms, systematic detection and prevention. Selective serotonin reuptake inhibitors appear to be the best choice to treat post-COVID-19 depression and anxiety disorders, and tofisopam could be helpful for anxiety. Cognitive behavioral therapy techniques adjusted to post-COVID-19 fatigue, functional remediation, extracorporeal apheresis, transcutaneous auricular vagus nerve stimulation, monoclonal antibodies, flavonoids, oxytocin or L-carnitine all represent hypothetical therapeutic avenues that remain to be evaluated in clinical trials. Conclusions: Psychiatric and neuropsychiatric post-COVID-19 symptoms occur frequently and are debilitating. Attention should be paid to this condition and studies undertaken to specify the effective treatments.

**Keywords:** COVID-19; psychiatric; neuropsychiatric; multidisciplinary; post-COVID-19 syndrome; treatments; psychotherapy

## 1. Introduction

The clinical entity long COVID-19 made its initial appearance in the spring of 2020. At this time, many patients reported it on social media. The first standardized medical definition was suggested for symptoms in infected patients who did not recover for several weeks or months following the onset of COVID-19 [1]. Several medical and scientific definitions were then proposed. For instance, one from the American National Institutes of Health included a temporal limit, considering long COVID-19 to occur in patients who have symptoms four weeks after the onset of symptoms of COVID-19, as confirmed by positive test results for SARS-CoV-2, or who have symptoms suggestive of COVID-19 without a test [2]. More than four weeks after the onset of symptoms, around one-third of outpatients present persistent symptoms, mainly fatigue, dyspnea, and loss of taste or smell [3]. Numerous symptom clusters have been identified in COVID-19 [3], including the following: general (mainly fatigue); respiratory (cough, breathlessness, chest pain); cardiovascular

(e.g., myocarditis, pericarditis, postural orthostatic tachycardia syndrome) [4]; ear, nose, and throat (anosmia, ageusia); pain (headache, myalgia, arthralgia); and neuropsychiatric symptoms (e.g., “brain fog”, cognitive disorders, dizziness, sleep disorders, depression, anxiety, posttraumatic stress disorder [PTSD]). On 6 October 2020, the World Health Organization (WHO) defined the post-COVID-19 condition as a syndrome that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis [5].

Data suggest a high risk of psychiatric and neuropsychiatric issues at the acute phase of COVID-19 in comparison with other health events as well as psychiatric sequelae afterward, suggesting a role for specific mechanisms [6]. The post-COVID-19 condition, in particular psychiatric and neuropsychiatric post-COVID-19 symptoms, follows mild to severe forms of the acute phase of COVID-19, but its pathophysiology remains unclear [6]. Several hypotheses have been proposed such as virus persistence, persistent inflammatory factors, or immunological deficits [7].

### *1.1. What Are the Frequent Psychiatric and Neuropsychiatric Symptoms of Post-COVID-19 Syndrome?*

Studies that focus on post-COVID-19 syndrome show a frequent and high rate of depression varying from 30 to 40% [8]. Typical symptoms of depression that confirm post-COVID-19 syndrome include depressed mood, psychomotor slowdown, suicidal ideas or suicide attempts, anhedonia, abulia, and sleep and appetite disorders. Depressive symptoms can correspond with a depressive type of adjustment disorder or major depressive episodes. Although fatigue is present in more than 10% of patients with long COVID-19 [3], it is important to differentiate it from the fatigue that characterizes depressive syndrome. Fatigue in the depressive syndrome can regress with physical activity, whereas fatigue that is observed in long COVID-19 independently of a depressive comorbidity worsens with physical activity. This characteristic is similar to what occurs in chronic fatigue syndrome and appears to be unstable. Symptoms of anxiety are also frequent and mostly correspond to the anxious type of adjustment disorder criteria, but obsessive-compulsive disorders have also been described [7–11]. In addition, sleep disorders have been described, reaching a prevalence of 40% in one study [10].

In addition to these symptoms, many patients with post-COVID-19 syndrome show hyperventilation syndrome. This dysfunctional breathing pattern generates dyspnea, the prevalence of which is still unknown. Often associated with, or secondary to, anxiety or depressive disorders [12], this functional disorder can be explained by the fact that dyspnea becomes an anxiety-inducing stimulus and that stress maintains the process. Hyperventilation syndrome induces many other symptoms, some of which are related to hypocapnia. These symptoms related to hypocapnia can also be anxiety-inducing (e.g., yawning, sighing, mouth breathing, irritative cough, typical chest pain, palpitations or peripheral vasospasm with coldness, neurovegetative disorders, visual disturbances, tinnitus, tremor, myalgia or cramps, migrainelike headaches, paresthesia). Diagnosis must be made by a primary care physician and confirmed by a pulmonologist after obtaining blood gas measurements, a clinical Nijmegen score, and an induced hyperventilation test [12]. According to the good practice of functional disorders, this diagnosis must be announced and explained.

COVID-19 potentially constitutes a traumatic event because of its lethality and unpredictability, which was especially true during the first wave. Peritraumatic dissociation occurred in 44.9% of patients during hospitalization for COVID-19, and the rate of PTSD more than four weeks after the acute phase varied in studies from 10.6% to 30% [8–11]. Although the neurological etiology of cognitive disorders has to be considered, it is not the only explanation. Cognitive symptoms are common in most psychiatric disorders, and some of the cognitive disorders observed in post-COVID-19 syndrome are classic outside this context. In major depression, either unipolar or bipolar, many neurobiologi-

cal mechanisms such as disruption of monoaminergic transmission, dysregulation of the hypothalamic-pituitary-adrenal axis and the stress response, neuroinflammation, deficiency of neurogenesis, and neuroplasticity are involved. These perturbations result in impaired short-term memory, giving rise to an encoding disorder in long-term memory, in particular at the level of episodic and semantic memory that involves the emotional valence of memories. Such perturbations also result in disorders in executive functions with impaired procedural memory [13,14]. In PTSD, hyperactivation and augmentation in the volume of the amygdala and nucleus accumbens, on the one hand, and hypoactivation and a decrease in the volume of the prefrontal cortex and hippocampus, on the other, are involved in many cognitive impairments that are also debilitating for patients. Short-term memory associated with the trauma is fragmented with coexisting hypermnnesia and amnesia of the traumatic event [15]. Memory unrelated to the trauma is also impaired. Autobiographical memory is altered concerning positive valence memories, and spatial verbal memory is altered through the disruption of recovery mechanisms and disturbances in attention and concentration. Many disorders of executive functions are observed regarding cognitive flexibility, with perseverance, working memory, and attentional disturbances via vegetative overactivation making disengagement from aversive stimuli impossible [15]. The characterization of cognitive symptoms by a neurologist and, when necessary, a neuropsychological assessment are useful. It aids in understanding the impaired cognitive functions in order to adapt management strategies. Neuroimaging, electroencephalograms, and lumbar techniques can also help explore cognitive disorders when neurological disorders are suspected. In the context of post-COVID-19 syndrome, some typical cognitive symptoms associated with psychiatric issues can be wrongly attributed to direct and indirect neurobiological effects of SARS-CoV-2, although they are manifestations of a psychiatric disorder that needs to be treated. Some functional neurological disorders can also appear in this context and should be diagnosed after neurological investigation to exclude an organic cause.

Polyphagia was also clinically observed in post-COVID-19 syndrome in some patients. The possible mechanism might be related to the CNS meningoencephalitis following SARS-CoV-2 infection and the subsequent degeneration of neuronal and glial cells due to smoldering inflammatory response to SARS-CoV-2 virions, leading to neuronal degeneration [16].

### *1.2. What Are the Mechanisms Involved in Psychiatric and Neuropsychiatric Post-COVID-19?*

Stress is likely involved in psychiatric issues associated with having COVID-19 in both the short- and the long-term [17,18]. Many studies of the general population have also shown the presence of psychiatric issues during the COVID-19 pandemic, suggesting that stress plays a part [18]. Worldwide, people had to adapt to sanitary rules, social isolation, job loss, economic issues, and multiple and traumatic bereavements, in addition to the fear of being contaminated and the risk of potential complications of COVID-19. Contamination by SARS-CoV-2 at the acute phase could have been a highly stressful—even traumatic—event because of the fear of dying or of experiencing physical sequelae. It may have induced psychiatric issues such as depression, anxiety, and PTSD. Experiencing a physical illness, especially respiratory disease, is known to be a risk factor for these psychiatric complications, and a stress mechanism such as psychiatric history, previous traumatic events, and medical prognosis [19] should be considered among other known risk factors. In patients with post-COVID-19 syndrome, the fear of reinfection, the uncertainty concerning disease evolution, and the inability to return to work create a heavy stress burden.

The other etiological possibilities of post-COVID-19 syndrome remain unclear. It could result from the viral persistence of SARS-CoV-2, an autoimmune disease, and/or persistent inflammatory factors [10,20]. Psychiatric and neuropsychiatric post-COVID-19, as is the case for the physical symptoms of long COVID-19, could be associated with these specific SARS-CoV-2 mechanisms. Persistent neuroinflammatory mechanisms, for example, have been suspected in the pathophysiology of psychiatric post-COVID-19 syndrome.

These mechanisms are involved in depression because of the depletion of brain serotonin, dysregulation of the hypothalamus-pituitary-adrenal axis, and alteration of the continuous production of adult-generated neurons in the dentate gyrus of the hippocampus [20]. During the acute phase of severe forms of COVID-19, cytokine storm has been described, and persistent neuroinflammatory mechanisms could explain the post-COVID-19 condition and facilitate psychiatric issues by involving dysfunction of mitochondria and microglia [21]. A study at two to three months after COVID-19 onset showed abnormalities in cerebral magnetic resonance imaging, suggesting both an acute hypercoagulable state and chronic neuroinflammation associated with cerebrovascular diseases [10]. Inflammatory mechanisms could also be involved in psychiatric and neuropsychiatric sequelae [11], but the scant data suggest this hypothesis does not allow confirmation. The severity of depression and anxiety was not consistently associated with blood markers of inflammation [10,11], but more specific investigations on inflammatory and immunological mechanisms are needed.

At the acute phase, the SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) as a viral receptor to enter the cell by attaching its spike protein to the ACE2 receptor (ACE2-R), thereby reducing its availability. However, reduced availability of ACE2R has an effect on the hypothalamic-pituitary-adrenal stress axis by leading to a decrease in the mechanism downstream of the corticotropin-releasing hormone in the hypothalamus. That results in decreased production of glucocorticoids [21]. Because glucocorticoids limit excessive inflammation and prevent overactivation of the stress response, decreased production creates a perpetual stress response. This feedback loop is further maintained by stressful environmental conditions and comorbid psychiatric conditions that are produced in COVID-19 disease. In addition, the ACE2-R peripherally stimulates the sympathetic pathway, thus activating the adrenals and the production of glucocorticoids. Although the role of ACE2-R has been described in psychiatric issues at the acute phase of COVID-19, its role in psychiatric sequelae remains hypothetical.

Concerning risk factors of psychiatric and neuropsychiatric sequelae after acute COVID-19, although intensive care unit (ICU) survivors are at high risk of developing psychiatric and neuropsychiatric complications such as post-intensive care syndrome (19% to 22%) [22], previous data do not show an increased risk of psychiatric and neuropsychiatric issues for COVID-19 survivors who were admitted to the ICU compared to non-ICU COVID-19 survivors. Psychiatric and neuropsychiatric issues occur after mild to severe forms of the acute phase of COVID-19 [6,9,10]. The psychiatric and neuropsychiatric risk is more frequent in women than in men [6,9]. Finally, the etiology of psychiatric and neuropsychiatric post-COVID-19 symptoms is probably multifactorial and includes an environmental stress load effect, a personal history of previous traumatic events, personal and family psychiatric antecedents, immunological and neuroinflammatory factors, and viral persistence, as well as genetic factors that have previously been known to be involved in psychiatric disorders.

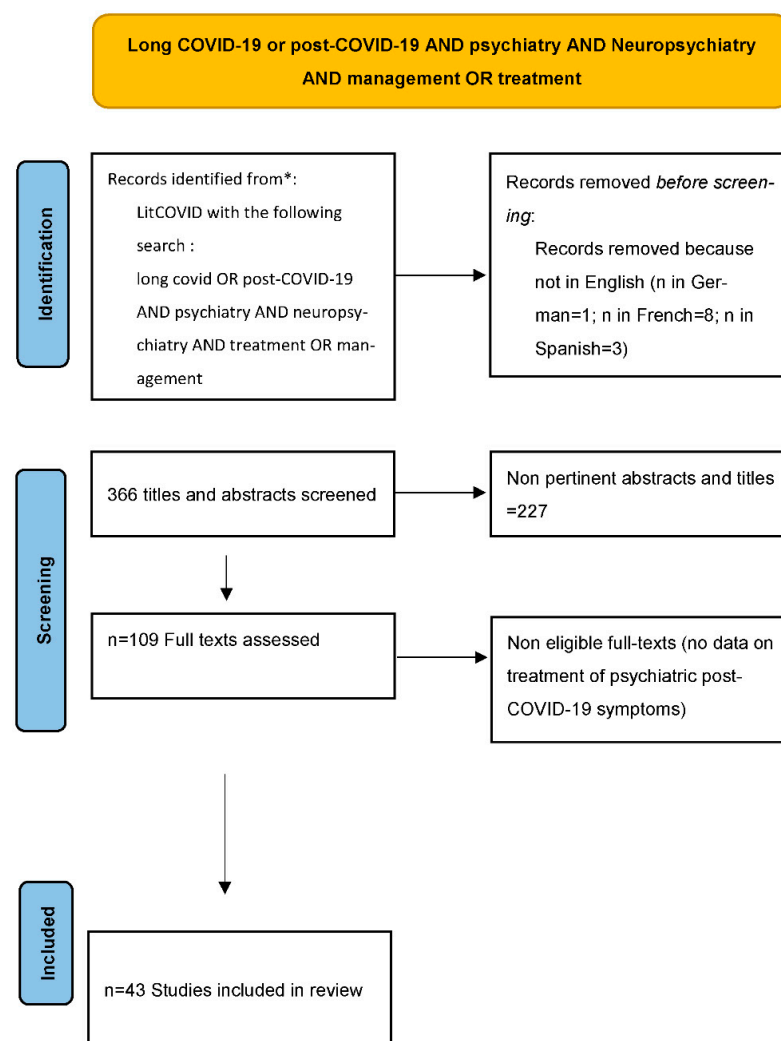
We deduce, from this brief synthesis that contextualizes our article, that many publications have focused on the clinical presentation and the mechanisms involved. The objective of this systematic review is to provide an overview of the knowledge, management strategies, and potential treatments of psychiatric and neuropsychiatric post-COVID-19 symptoms that could open up novel therapeutic perspectives.

## 2. Materials and Methods

We conducted a systematic research paradigm from SARS-CoV-2 onset to 1 January 2022 using LitCOVID (<https://www.ncbi.nlm.nih.gov/research/coronavirus/>, accessed on 5 February 2022) and Web of Science (<https://www.webofscience.com/wos/woscc/basic-search>, accessed on 5 February 2022). The LitCOVID search engine [23] was developed with the support of the US National Institutes of Health's intramural research program. It is an open-resource literature hub comprising a collection of research associated with SARS-CoV-2 and Web of Science. We included all clinical studies focusing on the post-COVID-19 condition according to the WHO's definition (psychiatric symptoms present

three months from the onset of COVID-19) and which described psychiatric symptoms. We excluded all the studies that did not include management and treatment of psychiatric and neuropsychiatric post-COVID-19 symptoms. The aim of this systematic research was to search research articles published in English about the management and treatment of psychiatric and neuropsychiatric symptoms associated with post-COVID-19 syndrome. The following search was performed LitCOVID: e\_condition: with the following search: long COVID OR post-COVID-19 AND psychiatry AND neuropsychiatry AND treatment OR management as well a second research on Web of Science, with the following search: (ALL = (long COVID-19 OR post-COVID-19 syndrome OR long haulers)) AND ALL = (treatment OR management).

Of the 348 publications, titles, and abstracts found, 12 were not in English and removed. The remaining 336 titles and abstracts were systematically checked, and those with no relevance were excluded ( $n = 227$  excluded). Finally, for the remaining articles, full text was assessed ( $n = 66$  excluded). The following exclusion criteria were performed for post-COVID-19 syndrome and treatment or management: irrelevance of the article; articles not assessing patients with psychiatric or neuropsychiatric post-COVID-19 symptoms; articles do not detail treatment or management of the psychiatric post-COVID-19 symptoms in the interpretation of the results. The remaining 43 articles are presented in the review of literature in the discussion section for management and treatment of psychiatric or neuropsychiatric post-COVID-19 symptoms (for whole process, see Figure 1 and Table 1).



**Figure 1.** Flowchart of the literature search from Page et al., 2020 [24]. \* Publications before 5 February 2022.



**Table 1.** Synopsis of articles reviewed.

Title	Author	Type of Article	Findings
Post-acute COVID-19 syndrome.	Nalbandian et al., 2021. [8]	Review	Principle of multidisciplinary management.
Excessive eating and weight gain: A rare post-acute COVID-19 syndrome.	Kaggwa et al., 2021. [16]	Review	Suggest avoiding medications that improve appetite (cannabis); propose behavioral therapy.
The Stanford Hall consensus statement for post-COVID-19 rehabilitation.	Barker-Davies et al., 2020. [25]	Review	Multidisciplinary care consensus.
Addressing the post-acute sequelae of SARS-CoV-2 infection: a multidisciplinary model of care.	Parker et al., 2021. [26]	Review	Need for multidisciplinary care.
Somatic symptom disorders and long COVID: A critical but overlooked topic.	Horn et al., 2021. [27]	Letter to editor	Usefulness of the <i>SSD scale</i> (SSD-12), designed to assess based on the DSM-5 criteria and importance of consultation-liaison psychiatrists.
Mind long COVID: Psychiatric sequelae of SARS-CoV-2 infection.	Llach and Vieta 2021. [28]	Letter to editor	Innovative therapeutics such as cognitive functional remediation for cognitive disorders, psychostimulants or erythropoietin.
Neuropsychiatric Complications of COVID-19.	Nakamura, 2021. [29]	Review	Management of post-acute COVID-19 neuropsychiatric symptoms.
Post-COVID Care Center to Address Rehabilitation Needs in COVID-19 Survivors: A Model of Care.	Ahmad et al., 2021. [30]		The need for early targeted rehabilitation Post-COVID-19 care centers.
Chronic fatigue syndrome and cognitive deficit are associated with acute-phase neuropsychiatric manifestations of COVID-19: A 9-month follow-up study.	Mirfazeli et al., 2022. [31]	Prospective observational study	Being female, having a higher number of symptoms, and experiencing constitutional neuropsychiatric symptoms in the acute phase were associated with having chronic fatigue syndrome at follow-up. Constitutional neuropsychiatric symptoms in the acute phase were associated with a lower MoCA score at follow-up
The Depression Anxiety Stress Scale 21: Development and Validation of the Depression Anxiety Stress Scale 8-Item in Psychiatric Patients and the General Public for Easier Mental Health Measurement in a Post-COVID-19 World.	Ali et al., 2021. [32]	Review	Prevention by the screening with the depression anxiety stress scale 21.
The Conundrum of 'Long-COVID-19': A Narrative Review.	Garg et al., 2021. [33]	Narrative review	Close follow-up for monitoring early, intermediate, and late complications but also a preparation and a self-management and supported self-management.
AI-Based Prediction and Prevention of Psychological and Behavioral Changes in Ex-COVID-19 Patients.	Ćosić et al., 2021. [34]	Review	Predictive tools based on AI to optimize prevention.
A Psychiatrist's Own Experience of Long COVID: Looking Beyond the Psychosomatic Perspective.	Sancak, B., & Kılıç, C. (2021). [35]	Letter to editor	Importance to recognize suffering and not just consider physical post-acute COVID-19 syndrome as somatization.
Post-COVID syndrome: Need to include risk of addiction in research and multi-disciplinary clinical work.	Håkansson, 2021. [36]	Review	Increased risk to initiate or increase addictive behaviors in context and consider this risk should be prevented.

Table 1. Cont.

Title	Author	Type of Article	Findings
Substance Use in Mild-COVID-19 Patients: A Retrospective Study.	Ismael, (2021). [37]	Review	Focused preventive interventions increasing the perceived risks of cannabis and non-medical benzodiazepine and analgesic use.
Long COVID and Post-infective Fatigue Syndrome: A Review.	Sandler et al., 2021. [38]	Review	Necessity to precisely assess fatigue and its main factors.
Do Anxiety and Depression Predict Persistent Physical Symptoms After a Severe COVID-19 Episode? A Prospective Study.	Bottemanne, H., et al., 2021. [39]	Observational and prospective study	Depression significantly interacted with the presence of pain at one month in predicting the persistence of pain at three months, with a similar trend for dyspnea.
Association Between Psychological Distress, Cognitive Complaints, and Neuropsychological Status After a Severe COVID-19 Episode: A Cross-Sectional Study.	Gouraud et al., 2021. [40]	Cross-sectional study	Anxiety and depression symptoms should be systematically screened after a severe COVID-19 episode in patients presenting with cognitive complaints.
Biomarkers of Post-COVID Depression.	Lorkiewicz et al., 2021. [41]	Review	Biomarkers found to prevent and early manage depression such as IL-6, sIL-6R, IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$ , IL-10, IL-2, sIL-2R, CRP, (MCP-1, SAA1, BDNF, TRP.
Circadian rhythm disorder and anxiety as mental health complications in post-COVID-19	Boiko et al., 2022. [42]	Review	Psychotherapeutic methods taking into account the biological rhythms.
Symptoms compatible with long-COVID in healthcare workers with and without SARS-CoV-2 infection—results of a prospective multicenter cohort.	Strahm et al., 2022. [43]	Review	Physical activity might be protective against neurocognitive impairment/fatigue symptoms.
Presentation and management of anxiety in individuals with acute symptomatic or asymptomatic COVID-19 infection and in the post-COVID-19 recovery phase.	Uzunova et al., 2021. [44]	Review	Overview of pharmacological and innovative treatments.
Rapid response to selective serotonin reuptake inhibitors in post-COVID depression.	Mazza et al., 2022. [45]	Clinical trial	N = 60, 92% had a reduction of HDRS >50% with antidepressant after one month.
Lessons from psychiatry for treating post-acute COVID-19 fatigue.	Wainwright L. (2021). [46]	Letter to editor.	Lisdexamfetamine efficacy and CBT for fatigue.
Role of Tofisopam in Post-COVID Neuro-psychiatric Sequelae: A Case Series.	Pattnaik et al., 2021. [47]	Review	Indicated for psychiatric post-COVID-19 symptoms because its anxiolytic effect on anxiety and depression, without sedative and muscle relaxant side effects, its antiamnesic properties, and its effects for both positive and negative symptoms of psychosis.
Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with post-acute sequelae of SARS-CoV-2 infection (PASC).	Fine et al., 2022. [48]	Review	Guidance statement defined Cognitive symptom assessment recommendation statements discussion and therapeutic interventions. The five recommendations are as follow (1) refer to a specialist with expertise in formal cognitive assessment and remediation; (2) Treat, in collaboration with appropriate specialists; (3) Complete, in collaboration with patient primary care provider, medication polypharmacy reduction; (4) Reinforce sleep hygiene techniques including nonpharmacologic approaches; (5) patients should be advised to begin an individualized and structured, titrated return to activity program.

Table 1. Cont.

Title	Author	Type of Article	Findings
Modulating neuroinflammation in COVID-19 patients with obsessive-compulsive disorder.	Nezgovorova et al., 2021. [49]	Review	Suggest that anticytokine treatments can help mitigate post-COVID-19 and new onset of the OC symptoms.
What can neuroimmunology teach us about the symptoms of long-COVID?.	Mondelli et al., 2021. [50]	Review	Potential therapeutic efficacy of immune targeted therapies (such as anticytokines and cytokine receptor blockers).
Psychiatric symptoms and cognitive impairment in “Long COVID”: the relevance of immunopsychiatry.	Penninx et al., 2021. [51]	Review	Potential immunopsychiatric therapeutic strategies in psychiatric post-COVID-19 symptoms treatment.
Chronic post-COVID-19 syndrome and chronic fatigue syndrome: Is there a role for extracorporeal apheresis?	Bornstein et al., 2021. [52]	Review ME/CFS in post-COVID-19 patients and therapeutic options	Potential therapeutic use of extracorporeal apheresis.
Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome.	Paul et al., 2021. [53]	Review	Potential redox-based therapeutics.
Cognitive decline following acute viral infections: literature review and projections for post-COVID-19.	Damiano et al., 2021. [54]	Review	Potential benefit for post-COVID-19 syndrome of natural molecules in post-COVID-19 syndrome to treat neuropsychiatric symptoms. Current randomized controlled trials (RCTs) are investigating the effect of antiviral therapy for the treatment of AD
Could SARS-CoV-2 Spike Protein Be Responsible for Long-COVID Syndrome ?	Theoharides, 2022. [55]	Review	Involvement of SARS-CoV-2 in post-COVID-19 and putative treatments of luteolin, quercetin, olive pomace.
Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue.	Theoharides, et al., 2021. [56]	Review	Quercetin in combination with luteolin to prevent and reduce cognitive impairment and neuroinflammation.
Can l-carnitine reduce post-COVID-19 fatigue?	Vaziri-Harami & Delkash, 2022. [57]	Review	l-carnitine efficacious on psychiatric symptoms treatment and prevention and fatigue.
Use of Transcutaneous Auricular Vagus Nerve Stimulation as an Adjuvant Therapy for the Depressive Symptoms of COVID-19: A Literature Review.	Guo et al., 2021. [58]	Review	Propose to use transcutaneous auricular vagus to treat depression knowing effects on cytokine. Involve cholinergic anti-inflammatory pathway and modulates brain circuits via the hypothalamic-pituitary-adrenal axis
A randomised controlled trial testing the efficacy of Fit after COVID, a cognitive behavioural therapy targeting severe post-infectious fatigue following COVID-19 (ReCOVer): study protocol.	Kuut et al., 2021. [59]	RCT	Study in progress to assess efficiency of adapted CBT for post-COVID-19 fatigue.
Could Cognitive Behavioural Therapy Be an Effective Treatment for Long COVID and Post-COVID-19 Fatigue Syndrome? Lessons from the Qure Study for Q-Fever Fatigue Syndrome.	Vink & vink-niese, 2020. [60]	Review	Potential efficiency of CBT as with Q-Fever Fatigue Syndrome.
A research agenda for post-COVID-19 fatigue. <i>Journal of psychosomatic research</i> , 154, 110726.	Verveen et al., 2022. [61]	Review	Treatment of post-COVID-19 fatigue could be CBT or exercise but studies are needed. Prevention strategies must be found.
Long COVID, a comprehensive systematic scoping review.	Akbarialiabad et al., 2021. [62]	Review	Few data on treatment for psychiatric post-COVID-19 symptoms but more on fatigue and general state.



Table 1. Cont.

Title	Author	Type of Article	Findings
Evaluation of Novel Concentrated Interdisciplinary Group Rehabilitation for Patients With Chronic Illnesses: Protocol for a Nonrandomized Clinical Intervention Study.	Kvale et al., 2021. [63]	Intervention study a non-randomized clinical intervention study	Study in progress of main therapeutic axes are first to prepare the patient for change prior to treatment; second, a focus on health promoting microchoices instead of symptoms; and third, to expect the patient to integrate the changes in everyday living with limited hands-on follow-up.
Efficacy of psychological intervention in patients with post-COVID-19 anxiety.	Priyamvada et al., 2021. [64]	Interventional study	Intervention consisting of breathing exercises, autogenic training activity scheduling, and social support and emotion regulation permitted a significant improvement of the MHI ( $n = 30$ ).
Intensive Care Unit-Specific Virtual Reality (ICU-VR) for Critically Ill COVID-19 Patients: A Multicenter, Randomized Controlled Trial.	Vlake et al., 2021. [65]	Multicenter RCT	No effects of ICU-specific virtual reality on psychological distress nor on quality of life but a better satisfaction.

### 3. Results

#### 3.1. A Multidisciplinary Approach

Psychiatric and neuropsychiatric issues related to COVID-19 fit into a physical disease context. For this reason, the first principle of a management strategy concerns the need for psychiatric interventions in a multidisciplinary framework that includes the main specialists involved in the acute phase of COVID-19 such as the post-COVID-19 condition. The individual assessment depends on clinical presentation (e.g., primary care; infectious diseases; pneumology; physiotherapy; neurology; psychiatry; ear, nose, and throat; physiotherapy), and we found this principle of management developed in several included studies [8,25–30]. More specifically, some authors argue that a multidisciplinary health care approach of somatic symptoms disorders (SSD) such as the frequent post-COVID-19 hyperventilation syndrome (HVS) in the context of COVID-19 is an important measure to reduce the psychological impact of the post-COVID-19 condition. The literature highlights the importance of consultation-liaison psychiatrists (CLPs) in the evaluation of hospitalized patients with COVID-19 such as outpatients followed for post-COVID-19 syndrome [27].

#### 3.2. Prevention and Diagnosis Strategies of Psychiatric and Neuropsychiatric Post-COVID-19 Symptoms

##### 3.2.1. A Systematic Screening of Psychiatric Symptoms at the Acute Phase of COVID-19

- In a prospective study with nine months follow-up, the authors assessed the predictive factors of post-COVID-19 syndrome [31]. They found that easy fatigability was the most common symptom (51.04%), followed by anxiety (38.54%), dyspnea (38.54%), and new-onset headache (38.54%) [31]. There was no association between COVID-19 severity in the acute phase and the number of long-COVID-19 symptoms and cognitive function (MoCA) scores at follow-up [31]. They also found that being female, having a higher number of symptoms, and experiencing constitutional neuropsychiatric symptoms in the acute phase were associated with having chronic fatigue syndrome at follow-up. Moreover, constitutional neuropsychiatric symptoms in the acute phase were associated with a lower MoCA score at follow-up [31]. These important results could be used to propose prevention strategies and early treatments to the patients presenting risk factors of developing post-COVID-19 syndrome mainly characterized by chronic fatigue syndrome and cognitive deficits.
- Early detection of psychiatric symptoms at the acute phase of COVID-19 by screening with the depression anxiety stress scale 21 [32] or screening peritraumatic dissociation to detect people at risk of PTSD [9] as well as early management could reduce the

risk of symptoms of long psychiatric COVID-19. Some authors suggest follow-up for monitoring early, intermediate, and late complications and also preparation, self-management and supported self-management but no specific recommendation to prevent psychiatric post-COVID-19 symptoms [33].

- Ćosić et coll. maintained that mental health COVID-19 recovery programs at post-COVID-19 clinics based on AI prediction and prevention strategies may significantly improve the global mental health of ex-COVID-19 patients and that they should be developed [34].
- After post-COVID-19 syndrome is diagnosed, customized therapeutic strategies are necessary. Sancak and Kılıç insisted in a letter to the editor that of recognizing suffering and not just considering physical post-acute COVID-19 syndrome is important because somatization could lead to wrong therapeutic choices and worsen the psychic state of the patient [35]. The primary care physician plays a crucial role in the management of patients with long COVID-19. Patients often lack knowledge derived from the medical and scientific community; thus, the first therapeutic step for patients with long COVID-19 is to recognize their suffering and avoid minimization of symptoms, even though more time is needed in the scientific and medical community to clarify its pathophysiology. The primary care physician should systematically look for psychiatric symptoms in the long COVID-19 context and refer the patient for an evaluation by a psychiatrist if there is suspicion of psychiatric disorders, especially in the case of neuropsychological impairment [8].
- A rigorous evaluation and exclusion of medical differential diagnosis is paramount. Suicidal risk must be well evaluated because patients with post-COVID-19 syndrome can experience a period of crisis, making them vulnerable to suicide [66].
- Some authors consider that patients suffering from post-COVID-19 syndrome have an increased risk to initiate or increase addictive behaviors in context and consider this risk should be prevented [36]. These authors invoke the risk of prescribing opioids considering the painful symptoms but also the vulnerability to alcohol and other substances as well as behavioral addictions such as problem gambling or other addictive online behaviors in this context. They suggest systematic assessment of addiction, easy access to specialized staff in addictive behaviors, and studies focusing on the addictive risk. A prospective study concluded that especially patients with mild COVID-19 should be monitored for substance use in the post-COVID-19 period. Preventive interventions for nonmedical analgesic use should be implemented and that focused preventive interventions would be useful, especially for those who reported previous substance use, could be useful [37].
- If the patient develops post-COVID-19 polyphagia, medications which can improve appetite such as psychoactive substances such as cannabis must be looked for and avoided [16].
- Concerning post-COVID-19 fatigue, some authors defined it as a dominant chronic and disabling symptom to that interrupts all or a majority of normal activities. Post-COVID-19 fatigue is persistent for six months or more if an adult (months months in children/adolescents), and emerged during confirmed acute COVID-19 (i.e., with a positive severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] test) without any symptom-free interval since onset. On the basis on the literature review, these authors suggested systematic brief screening questionnaires such as the Chalder fatigue scale or the SPHERE be administered to characterize the fatigue state. Related physical symptoms, mental health, and other relevant symptom domains as pain and sleep quality could be evaluated using an instrument such as the SF-36 [38].

### 3.2.2. Predictive Factors of Developing Psychiatric Post-COVID-19 Symptoms

- Some authors concluded that depression significantly interacted with the presence of pain at one month and was predictive of the persistence of pain at three months, with a similar trend for dyspnea [39]. The early detection and management of de-

pression could reduce the risk of persistent pain such as persistent dyspnea. The same team concluded in another study that anxiety and depression symptoms should be systematically screened after a severe COVID-19 episode in patients presenting with cognitive complaints because cognitive impairment is associated with anxiety and depression [40]. A review confirmed standard screening tools should be used to identify patients with anxiety, depression, sleep disturbances, PTSD, dysautonomia, and fatigue [8].

- Some authors proposed looking for biomarkers associated with post-COVID-19 depression. Among the most important that were frequently described in a systematic review were increased levels of interleukin 6 (IL-6), soluble interleukin 6 receptor (sIL-6R), interleukin 1  $\beta$  (IL-1 $\beta$ ), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interferon gamma (IFN- $\gamma$ ), interleukin 10 (IL-10), interleukin 2 (IL-2), soluble interleukin 2 receptor (sIL-2R), C-reactive protein (CRP), Monocyte Chemoattractant Protein-1 (MCP-1), serum amyloid A (SAA1), and metabolites of the kynurenine pathway. Decreased brain-derived neurotrophic factor (BDNF) and tryptophan (TRP) were also noted. The biomarkers identified by these authors indicate the etiopathogenesis of post-COVID-19 depression analogous to the leading inflammatory hypothesis of major depression disorder [41].
- Some authors showed that delayed sleep phase disorder occurs most frequently during the post-COVID-19 period [42]. However, circadian rhythm disorders can enhance affective disorders such as depressive or manic episodes.

### 3.2.3. Prevention Strategies

- Authors suggest targeting circadian dysfunction. They suggest to develop psychotherapeutic methods taking into account the biological rhythms and changes in working time and schedule in the first six months after the disease [42].
- Some authors conclude in a large prospective study on healthcare workers that physical activity might protect against neurocognitive impairment/fatigue symptoms after COVID-19, suggesting that physical activity could be a good preventive strategy to introduce and encourage [43].

## 3.3. Biological Treatments of Post-COVID-19 Psychiatric and Neuropsychiatric Symptoms

### 3.3.1. Usual Psychotropic Treatments

- Some authors suggested on the basis of putative mechanisms underlying post-COVID-19 anxiety, that selective serotonin reuptake inhibitor (SSRI) must be prescribed early because of their efficacy in treating anxiety disorders and COVID-19 infection through several mechanisms [44].
- They suggested avoiding other drugs in COVID-19 context, such as tricyclic antidepressants because of their anticholinergic effects, benzodiazepines because of their respiratory effects, and gabapentinoids, because of cardiac risk [44].
- Other authors investigated the efficacy of SSRI in treating post-COVID-19 depression and concluded that 92% patients of their sample showed a clinical response to antidepressants after four weeks based on a 50% HDRS reduction in the Hamilton depression rating scale (HDRS), defined as [45].
- Llach and Vieta suggested some alternative psychotropic treatments be used as psychostimulant drugs to treat post-COVID-19 syndrome [27]. Later, lisdexamfetamine efficacy was assessed in a small sample of post-COVID-19 patients with good results [46].
- Some authors tested tofisopam, a 2,3-benzodiazepine (2,3-BDZs) with a common chemical backbone to “classical” 1,4-benzodiazepines that does not interact with the classical benzodiazepine binding site of the GABA receptor, in a case series of three cases of post-COVID-19 patients. The cases showed potential therapeutic properties of tofisopam because of its anxiolytic effects in anxiety and depression, without sedative and muscle relaxant side effects, its anti-amnesic properties, and its effects for both positive and negative symptoms of psychosis [47].

- Knowing the frequent cognitive impairment sometimes presented in post-COVID-19 syndrome patients, some treatments must be considered with caution. The American Geriatrics Society created the Beers criteria (updated 2019), a list of potentially inappropriate medications for use in older adults, 65 years and older. The American Academy of Physical Medicine and Rehabilitation (AAPM&R) Multi-Disciplinary PASC Collaborative (PASC Collaborative) warned against these medications in its guidance statement [48]. Decreasing the anticholinergic burden in patients with mild cognitive symptoms has been recommended for older patients. It is important to note that the use of pharmacologic agents and supplements varies across post-COVID-19 syndrome clinics. Prescribing medications or supplements should be considered on a case-by-case basis, recognizing the limited scientific evidence. Additionally, there should be consideration of the out-of-pocket cost of supplements, the risk of medication interactions, lack of federal regulation and oversight of supplements, and possible side effects [48].

### 3.3.2. Immunopsychiatric Treatments

- Some authors suggest that anticytokine treatments can help mitigate post-COVID-19 and new onset of the OC symptoms [49]. Other authors suggest that immune targeted therapies such as anticytokines and cytokine receptor blockers will not only prevent severe illness but also benefit the brain and mental health [50].
- Monoclonal antibodies blocking IL-6 or IL-17 are expected to have therapeutic effects against COVID-19 associated anxiety, but their efficacy on psychiatric post-COVID-19 symptoms have not been studied [44]. Other authors also proposed the use of anti-inflammatory medications such as minocycline and tumor necrosis factor (TNF)-alpha inhibitors to treat post-COVID-19 depression, but no clinical study exists for these potential treatments at the time of writing this article [51]. Other authors suggest that anticytokine treatments can help mitigate post-COVID-19 and new onset OC symptoms [50]. Some authors considered common mechanisms underlying Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and post-COVID-19 fatigue. They explain that they observed elevations of neurotransmitter receptor antibodies similar to what they have seen in other forms of infection-triggered ME/CFS and think that extracorporeal apheresis or immune adsorption may offer a simple and effective treatment option [52].
- Other authors suggest using an anticholinergic agent such as adamantane for its neuroprotective property to reduce cytokine storm and deposition [53].

### 3.3.3. Treatments Targeting Redox Imbalance

- Some authors encouraged the study of the connections between redox imbalance, inflammation, and energy metabolism in long COVID-19 and in ME/CFS and suggested some therapeutics such as NO which inhibits the replication of SARS-CoV-2 in vitro and improves oxygenation in people with COVID-19 when administered by inhalation. Ubiquinol and a combination of NADH and CoQ10 and glutathione, *N*-acetyl cysteine, cysteamine, sulforaphane, nicotinamide, melatonin, selenium, vitamin C, vitamin D, vitamin E, melatonin plus pentoxifylline, disulfiram, ebisen, and corticosteroids are potential therapeutics. The authors reminded that in two cases of acute COVID-19, glutathione administered therapeutically counteracted dyspnea associated with COVID-19 pneumonia and reduced pulmonary inflammation [54].

### 3.3.4. Anti-Infectious Treatments

In a narrative review, some authors suggested that antimalarial drugs could prevent neuropsychiatric COVID-19 complications due to anti-inflammatory properties. An anticholinergic agent was proposed to reduce cytokine storm and A $\beta$  deposition, but no clinical study existed for these potential treatments at the time of writing this article [54].

### 3.3.5. Endogenous Hormones and Natural Molecules

- Some authors suggested oxytocin as an adjunctive treatment in COVID-19 infection because of its proimmune properties and management of stress and anxiety, and also melatonin for its antianxiety, anti-inflammatory, anti-oxidative, neuroprotective, and cardioprotective effects. Concerning the mechanisms of action, oxytocin would counteract the cytokine storm resulting from SARS-CoV-2 infection [44].
- Llach and Vieta proposed some alternative psychotropic treatments such as erythropoietin, but no clinical trial have assessed their efficacy on psychiatric post-COVID-19 symptoms [28].
- One review summarized the potential benefit of natural molecules for treating neuropsychiatric symptoms in post-COVID-19 syndrome patients to [54]. One is the flavonoid quercetin found in *Ginkgo biloba*. Quercetin has the potential to inhibit SARS-CoV-2 by blocking TNF $\alpha$ -induced reactive oxygen species from human aortic endothelial cells. The *Ginkgo biloba* extract EGb 761 has shown efficacy in generalized anxiety disorder and dementia, actions that may be useful for the neuropsychiatric aspects of long-COVID. Other studies have shown that green tea catechins could be useful in COVID-19, especially against entry of SARS-CoV-2. The broccoli extract sulforaphane inhibited expression of IL-6 and IL-8 induced by the SARS-CoV-2 spike protein in bronchial epithelial cells. Such flavonoids are found in green plants and seeds and possess potent antioxidant, anti-inflammatory, and cytoprotective properties, but their consumption as part of the diet does not provide sufficient systemic levels [55].
- Another review suggested luteolin could treat brain fog and prevent neuroinflammation, be neuroprotective, and reduce cognitive dysfunction [55].
- Quercetin has been discussed in a few recent studies, including an open-label clinical study showing good tolerability and benefit. A double-blind, placebo-controlled, randomized study using a liposomal preparation of luteolin (PureLut) in long-COVID-19 patients is underway [55].
- The same author explained combining quercetin with luteolin may provide additional benefits, especially when formulated in olive pomace oil (FibroProtek) that increases oral absorption, that is otherwise quite limited (<10%) and brings additional antiviral and anti-inflammatory benefits. Such liposomal preparations are available and have been successfully used in pilot clinical trials in which they reduced neuropsychiatric symptoms and associated serum IL-6 levels. These molecules could be proposed to patients who suffer from neuropsychiatric symptoms [56].
- L-carnitine is a micronutrient that is in nearly every cell of the body and is useful in energy metabolism and the production of cellular energy, can prevent muscle wasting or reduce muscle breakdown, modulates the composition and decomposition of proteins, and has antiapoptotic, antioxidant, and anti-inflammatory properties [57]. L-carnitine has been imagined as a potential treatment of post-COVID-19 fatigue [57].

### 3.4. Psychotherapeutic Treatment and Other Nonpharmacological Interventions for Psychiatric and Neuropsychiatric Post-COVID-19 Symptoms

- Some authors proposed adapting an existing cognitive behavioral therapy (CBT) manual for CFS to post-COVID-19 syndrome and called it “Fit after COVID” [58]. This psychotherapy consists of up to nine modules organized over a period of 17 weeks including an introductory module, an evaluation module to set treatment goals, and seven modules that address fatigue-perpetuating factors. Among these, are a disrupted sleep-wake pattern, low or unevenly distributed level of activity, and dysfunctional beliefs about fatigue. The authors plan four optional modules targeting perceived low social support, problems with processing the acute phase of COVID-19, fears and worries regarding COVID-19, and poor coping with pain. A randomized control trial is comparing the “Fit after COVID” program with traditional care regarding fatigue



12 months after the CBT program. Some authors, however, argue that CBT cannot be effective for post-COVID-19 fatigue [59].

- Because psychiatric post-COVID-19 symptoms are integrated with physical issues, a psychotherapeutic approach should consider both realms. Classical psychotherapeutic strategies can be limited for this reason. Taking into account the similarities of chronic fatigue syndrome (CFS), and the fatigue that exists in post-COVID-19 syndrome, some authors proposed cognitive behavioral therapy (CBT) known to be efficient for CFS [48,59,60].
- Other authors argued that post infective fatigue syndrome appears unlikely to be unique to COVID-19, the scale of the affected population is unprecedented, and further studies are needed [61,62].
- Llach and Vieta questioned the role of cognitive and functional remediation for cognitive disorders in post-COVID-19 syndrome [27]. However, no study results existed on this cognitive treatment in post-COVID-19 syndrome at the time of writing this article [28].
- A rehabilitation team built a protocol for different kinds of chronic illnesses including patients with post-acute COVID-19 syndrome in a non-randomized clinical intervention study that is ongoing at the time of writing this article [63]. The main therapeutic axes of this protocol are: first, to prepare the patient for change prior to treatment; secondly, a focus on health promoting microchoices instead of symptoms; and third, to expect the patient to integrate the changes in everyday living with limited hands-on follow-up [63].
- Some authors suggested giving patients with post-COVID-19 syndrome breathing exercises, known to reduced anxiety; autogenic training, which can change negative views and stress; affirming statements, which help self-esteem, self-enhancement; and activity scheduling to promote physical, social, recreational, and occupational activities and build social support and regulate emotions. These strategies help counter the lack of knowledge on post-COVID-19 syndrome and the stigmatization of people suffering from it [64]. They also have revealed a significant improvement in mental health-related issues after psychological intervention, as assessed by the mental health inventory (MHI) in a sample of 30 patients.
- For polyphagia, behavioral therapies can be useful [16].

### 3.5. Alternative Therapeutic Devices

- Knowing the important relationship between proinflammatory cytokines and depressive symptoms, some authors suggested using transcutaneous auricular vagus nerve stimulation (taVNS) [57]. This is derived from auricular acupuncture, widely used in China [57]. These authors suggest an efficacy of taVNS on post-COVID-19 depression that involves a cholinergic anti-inflammatory pathway and modulates brain circuits via the hypothalamic-pituitary-adrenal axis [58].
- A multicenter, randomized controlled trial explored the effects of intensive care unit (ICU)-specific virtual reality (VR) on mental health and on patients' perceived quality of, satisfaction with, and rating of ICU aftercare among COVID-19 ICU survivors. Patients in the ICU-VR group received the ICU-VR intervention once during the visit three months after hospital discharge and did not conclude differences concerning the psychological distress or quality of life but observed a better satisfaction [65].

### 3.6. Existing Specific Recommendations for Neuropsychiatric Post-COVID-19 Symptoms

- The American Academy of Physical Medicine and Rehabilitation (AAPM&R) Multi-Disciplinary PASC Collaborative (PASC Collaborative) was created and published a guidance statement with a specific focus on the cognitive-related symptoms of PASC that can occur in people who have been diagnosed with acute COVID-19 infection or presumed to have had the infection and initially experienced mild to severe symptoms [42]. This guidance statement defined Cognitive symptom assessment

recommendation statements discussion and therapeutic interventions. The five recommendations are as follows: (1) For patients who screen positive for cognitive symptoms, refer to a specialist with expertise in formal cognitive assessment and remediation; (2) Treat, in collaboration with appropriate specialists, underlying medical conditions, such as pain, insomnia/sleep disorders, and mood disorders that may be contributing to cognitive symptoms; (3) Complete, in collaboration with patient primary care provider, medication polypharmacy reduction, weaning or deprescribing medications if medically feasible with emphasis on medications that may impact cognition; (4) Reinforce sleep hygiene techniques including nonpharmacologic approaches as first line of sleep remediation; (5) Similar to patients experiencing “physical” fatigue, patients should be advised to begin an individualized and structured, titrated return to activity program; (5a) For patients who achieve a return to their normal, daily activities, regular exercise (at least 2–3 times/week of aerobic exercise) may be effective in improving cognition and also contribute to improved sleep patterns; (5b) Frequent assessment of the impact of return to normal, daily activities is recommended to ensure that symptoms do not flare and exercise is tolerated [48].

#### 4. Discussion

With this review, the importance of the multidisciplinary approach to properly treat post-COVID-19 syndrome in general and psychiatric and neuropsychiatric post-COVID-19 symptoms specifically is highlighted [26,36,43]. Some included articles also showed the addiction risk management challenge [36,37]. Unfortunately, the participation of psychiatrists and addiction specialists is lacking in long COVID-19 consultation at the time of writing this article, and this absence can potentially promote the feeling of stigmatization of patients who present psychiatric post-COVID-19 symptoms. A multidisciplinary approach must be the rule during all this very long clinical follow-up for post-COVID-19 patients to guarantee coherent, integrative and holistic care.

Prevention strategies must take gender into account, knowing that females are more at risk for developing post-COVID-19 fatigue [31]. This gender effect takes into account that there are four women for every man in the CFS and other gender effects that are known in psychiatric disorders such as anxiety, depression, or PTSD. The number of symptoms at the acute phase is also an important risk factor for developing post-COVID-19, syndrome perhaps because this parameter could reflect the importance of the systemic response [31–34]. Moreover, a systematic screening of psychiatric and neuropsychiatric symptoms at the acute phase of COVID-19 and targeting circadian dysfunction and encouraging physical activity in people at risk could be efficient ways to reduce psychiatric and neuropsychiatric post-COVID-19 symptoms [32–34,39–42]. All these very promising strategies should be studied further.

This review highlighted several potential therapeutic strategies for psychiatric post-COVID-19 symptoms that emerged because of the putative mechanisms. Most of them are far from routine clinical practice such as immunopsychiatric strategies [51] or natural molecules such as luteolin or quercetin which appear promising and safe [55,56]. Use of transcutaneous auricular vagus nerve treatments could also help treat depressive symptoms with a good tolerance [58]. However, without any clinical trial, these therapeutics remain hypothetical and should be explored in clinical trials.

The use of psychotropic drugs in the post-COVID-19 context should be explored more, knowing that the putative mechanisms underlying post-COVID-19 syndrome involve disturbances of the CNS and can have neuroinflammatory effects [8,10]. However, few studies investigated the efficiency of the usually recommended pharmacological treatments in psychiatric disorders. We found just one study focusing on the treatment by antidepressants for post-COVID-19 depression [45]. Studies comparing the efficiency of antidepressants between a post-COVID-19 group and a control group should be useful. Tofisopam should be assessed for post-COVID-19 symptoms because of its interesting

pharmacological profile [47]. Psychostimulants such as lisdexamfetamine [47] should be considered with caution because of the addictive risk.

Studies focusing on psychotherapeutic approaches were very few and concerned only CBT for fatigue [59,60]. We found no studies exploring other types of psychotherapy such as eyes movement desensitization reprocessing (EMDR) which has good efficacy for PTSD, knowing that PTSD is very common in post-COVID-19 syndrome.

Finally, thinking about psychiatric post-COVID-19 symptoms inevitably raises the question of the limit of what is considered psychiatric as opposed to somatic. However, this limit looks lapsed with COVID-19 based on a systemic disease model. Moreover, before the COVID-19 pandemic, biological psychiatry and neurosciences helped understand the potential interplay between psychiatric disorders, inflammation, and immunity [51].

First, endotoxin, interferon-alpha or typhoid vaccine interventions can induce illness involving depressive symptoms via the immune system. Second, persons with autoimmune conditions, are at increased risk for developing depression. Third, metaanalyses of biomarker studies indicate that levels of inflammatory markers, including cytokines—such as tumor necrosis factor, interleukin-1 beta, and interleukin-6—and acute phase proteins—such as C-reactive protein (CRP)—are significantly elevated in depressed patients compared to healthy controls. Moreover, large-scale genomewide DNA and RNA studies indicate that depressed persons have more genetic variants and enriched gene expression pathways involved in immune signaling. Finally, anti-inflammatory medication approaches have demonstrated efficacy in reducing depression symptoms.

Of note, findings suggesting a pathophysiological link to the immune system have also been reported for other dimensions relevant to COVID-19 such as cognitive impairment and fatigue. Longitudinally, high levels of inflammatory markers have been linked to long-term cognitive decline involving deterioration of memory and executive function. A proteome wide association study of older adult brain donors indicated increased inflammation in brains of cognitively impaired persons as compared to those of cognitive stable persons [51].

For all these reasons, the immunopsychiatry hypothesis should continue to be explored and potential therapeutic targets based on this hypothesis should be studied to enhance prognosis of psychiatric post-COVID-19 symptoms. Suggestions of therapeutics based on immunopsychiatry shown in this review such as monoclonal antibodies blocking IL-6, or IL-17 [44], anticytokine treatments [50], and extracorporeal apheresis [52] are just hypothetical and theoretical and must be confirmed in clinical trials.

Treatments based on redox imbalance such as ubiquinol, the combination of NADH and CoQ10 and glutathione, *N*-acetyl cysteine, cysteamine, sulforaphane, ubiquinol, nicotinamide, melatonin, selenium, vitamin C, vitamin D, vitamin E, melatonin plus pentoxifylline, disulfiram, ebselen, and corticosteroids offer good perspectives [53].

One other main limitation of this review is that no articles that were found discussed somatic symptom disorders such as hyperventilation syndrome, although it constitutes a major challenge for post-COVID-19 patients [12]. The physiopathology is based on stress or a traumatic component at the origin, and there is a perpetuation through anxiety and physical signs of hypocapnia [67]. Indeed, the acute phase of COVID-19 can be associated with significant distress and sometimes with the fear of dying, which can also shed light on the therapeutic approach to these functional respiratory symptoms. For post-COVID-19 syndrome, a combination of breathing exercises and psychotherapy such as CBT or EMDR should be studied in clinical trials.

Familial, social, and professional consequences of sustainable cognitive impairment and psychiatric disorders are disastrous for the patients who are young professionals, and social support must be accessed [63]. There is a high risk of stigmatization and marginalization for these patients who became unable to carry out their daily tasks and work. Consequences for daily life must be treated, in particular regarding cognitive disorders, which occur frequently and constitute a major concern among patients. Social and professional assistance must also be provided. Insurance organizations cannot ignore psychiatric long COVID-19 and should recognize the link between psychiatric sequelae

and COVID-19 in the context of viral exposure and occupational disease. Concerning this upsetting ordeal of post-COVID-19, interventions based on resilience, acceptance, and commitment therapy (ACT) should be assessed for patients suffering from psychiatric post-COVID-19 symptoms especially those with adjustment disorders.

This review has several limitations. One of the main limitations is that a majority of the preventive or therapeutic strategies that we presented were theoretical and must be assessed in clinical studies.

This review has the benefit of making all the potential preventive and therapeutic strategies for psychiatric and neuropsychiatric post-COVID-19 symptoms better known. This review could help clinicians, scientists, and the general population realize that: (1) COVID-19 brings long-term psychiatric and neuropsychiatric symptoms; (2) These symptoms remain difficult to treat; (3) These symptoms are accompanied by suffering; (4) Efforts are needed to improve their management.

## 5. Conclusions

Psychiatric and neuropsychiatric post-COVID-19 symptoms occur frequently and are debilitating. Their management is complex and difficult. Attention should be paid to this condition and studies undertaken to specify the underlying mechanisms, predictive factors for its evolution, prognosis, and effective treatments. Main strategic axes must consist of a multidisciplinary approach, a prevention axis based on the systematic detection of psychiatric symptoms and early management, a pharmacological axis consisting of antidepressant treatments, psychotherapy, and innovative immunopsychiatric therapies, treatments based on the redox balance, and natural molecules such as flavonoids. Studies are still needed to assess the effectiveness of most of these therapeutic strategies.

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