

Review

“Brain Fog” as a symptom of the “Long-COVID” syndrome, its impact on the mental health of those affected by COVID-19 and its treatment

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ABSTRACT: The impact of the COVID-19 pandemic on people’s lives is dramatic. The relationship between Brain Fog and Long-COVID, the consequences on the mental health of patients, and its treatment are the objectives of this systematic review. An electronic search was carried out and databases searched included PubMed, Emerald, EMBASE, and Science Direct. Regarding the review, data collection included English papers with full bibliographies, abstracts, and keywords, published in electronic form in the last 2 years (2020–2022). The findings indicate the importance of a holistic approach and treatment of Post-COVID Brain Fog. It is also necessary for healthcare workers to investigate the biological and psychosocial background of Brain Fog symptoms in detail to provide the appropriate health service. However, more scientific studies are needed on the effectiveness of treatment approaches for the benefit of public health and well-being.

Keywords: Brain Fog; Long-COVID; mental health; patients

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease brought about by serious acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection. The COVID-19 pandemic is the biggest public health crisis of recent years on a global scale. The unprecedented impact of the pandemic due to the necessary measures to prevent the spread of the virus and the subsequent economic crisis remains enormous and multifaceted, both for the quality of life and the mental health of citizens. The term “Long-COVID-19 syndrome” determines the signs and symptoms of COVID-19 that persist or develop after the acute phase lasting up to 4 weeks from infection with SARS-COV 2 and cannot be explained by an alternative diagnosis [1].

Like the acute phase, Post-COVID-19 syndrome, which lasts much longer than 12 weeks, is characterized by multisystem organ dysfunction, with fatigue, dyspnea, sleep disturbance, and myalgia among the most common long-term symptoms, which may be independent of the severity of the acute phase [2]. In terms of the psychological impact of Long COVID, findings suggest that up to a third of people experience anxiety, depression, or even Post-traumatic stress disorder (PTSD). Reduced quality of life is noticed in 51%–67% of cases, accompanied by mobility problems and pain which are considered to be the factors that mostly affect a person’s quality of life [3]. Kaseda and Levine argue that the emergence of Brain Fog after

contracting COVID-19 may be linked to PTSD, an effect that was clearly observed in both Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) in the past [4].

Cognitive dysfunction may also be a feature of long-term COVID-19, with 5%–22% of individuals infected with SARS-CoV-2 reporting cognitive impairment throughout the Post-COVID-19 phase [5]. “Brain Fog” is a term that is used to portray this cognitive dysfunction including symptoms such as concentration problems, word-finding difficulties, poor memory, or disorientation [6]. Albeit Brain Fog is not a recognized medical diagnosis, it can be a debilitating manifestation of previous issues, such as stress, diet, sleep deprivation, physical and mental illness, and their possible association [3,7]. Findings indicate that neurocognitive symptoms, such as Brain Fog, experienced by people with Long COVID constitute a recognizable symptom complex primarily characterized by fatigue, dizziness, myalgia, word-finding difficulties, and memory impairment, and have adverse psychological and psychomotor correlations [8].

2. Brain Fog

Brain Fog is considered a consequence of neuroinflammation [9] and is among the leading symptoms reported by patients suffering from the disease of COVID-19. According to Kaseda and Levine those who have become severely ill with COVID-19 tend to develop hypoxia (reduced amount of oxygen to body tissues) which leads to brain damage [4]. This health condition has been linked to psychiatric and cognitive impairments. The cognitive dysfunction that is observed includes Brain Fog which may indicate acute problems with memory, receptive language, mental focus, and executive function [10,11]. However, due to the dysfunction of the autonomic nervous system (Dysautonomia-ANS) severe symptoms of Brain Fog are possible, especially in those seriously ill individuals with COVID-19. Furthermore, long-term cognitive impairment can be identified in 20% to 40% of patients discharged from Intensive Care Units (ICU) [12,13].

On the other hand, a combination of potential sequelae due to “Post Intensive Care Unit” syndrome (PICS) is significantly associated with cognitive problems and physical changes such as Brain Fog, neuropathies, severe fatigue, and delirium which causes mental confusion. In many cases, patients continue to experience delusions or hallucinations even after recovery or during rehabilitation. The Brain Fog symptom is so severe after recovering from COVID-19 that sometimes patients feel like they just have a blank in their memory due to cognitive and physical deficits, but strong enough to suffer moral collapse [14].

3. Relationship between Long-COVID and Brain Fog

SARS-CoV2 that brings about COVID-19 can infect the central nervous system, gastrointestinal system, lungs, and cardiovascular system. Over time, the extensive infection increases the total viral load in the infected individual. SARS-CoV-2 can integrate its genome into mitochondria to reduce energy metabolism. However, the brain is particularly vulnerable to hypoxia, which is also proinflammatory, because cognitive neural processes are poorly adapted to hypoxic conditions [15].

Therefore, as the viral load increases, cognitive impairment and confusion increase, a condition known as Brain Fog. Ongoing neuronal dysfunction is an important factor in understanding the long-term pathogenesis of central nervous system infection with SARS-CoV-2. Combined with its induced pro-inflammatory response, SARS-CoV-2 infection leads to neuronal dysfunction, thus resulting in the manifestation of Brain Fog, as cognitive function requires a high and uninterrupted supply of oxygen [15]. Severe cognitive impairment, specifically Brain Fog, can persist for months not only in patients who were hospitalized with COVID-19 but even in people who did not need to be hospitalized [16].

COVID-19 can damage the human brain in several ways; encephalitis and cerebrovascular disease have already been reported in the international literature. However, other long-term effects of COVID-19 on the brain, such as a persistent decline in sustained attention or cognitive function, are becoming more subtle. Brain Fog is frequently used to portray the feeling of being mentally slow, confused, or disoriented, as it substantially has an influence on a person's ability to think comprehensively or focus. Many adult former patients with COVID-19 strongly complain of suffering from brain confusion after recovering from the disease, which not only interferes with their activities of daily living but also delays their full recovery [5,17]. Factors that significantly determine the presence of Brain Fog in Long-COVID include women, as they show Brain Fog at much higher rates compared to men, people who undergo respiratory problems at the beginning of the infection as well as those individuals that are admitted to the intensive care unit (ICU) [5]. Equally interesting remains the study by Matias-Guiu et al. which pointed out the development of cognitive symptoms (Brain Fog) in a patient immediately after her infection with COVID-19 and of cerebrospinal fluid biomarkers that strongly indicated Alzheimer's disease. This is why it is necessary to thoroughly examine patients, especially the elderly, with cognitive symptoms after COVID-19 to investigate neurodegenerative processes at an early stage [18].

4. The impact of Brain Fog on mental health

The psychological and debilitating symptoms that people suffer from Brain Fog not only have led to lost working hours and jobs but also to a reduction in productivity in comparison to the levels of work capacity before their illness, due to the cognitive dysfunction they experience. However, when returning to work, individuals have reported relapses caused by mental strain, job insecurity, and stress, requesting time off too often. The morbidity rate has been largely overlooked, as patients experience multisystemic symptoms for more than seven months, with serious consequences concerning their lives and livelihood. Memory and cognitive dysfunction are among the most lasting neurological symptoms for all age groups and with a significant impact on the work environment, family, and social life [19,20].

Persistent fatigue, shortness of breath, and psychological distress, such as PTSD, anxiety, a lot of guilt and terror, lack of concentration, and sleep abnormalities, were observed in almost 30% of the participants. Brain Fog's impact on the mental health of those affected by COVID-19 is depicted in their existential thoughts, too. Existential

crises or traumatic events can trigger existential crisis and apprehension because individuals begin to realize their own mortality [13, 21].

5. Social stigma

Social stigma, as a both psychological and social consequence, caused due to Long COVID, has become very common, due to its seriously influence on mental health and the quality of human life. Many psychologists express concern about the guilt or stigma experienced by people who have contracted COVID-19 [13]. A significant percentage of patients mainly face stigma and depression as well as psychological morbidity, Brain Fog, and cognitive impairment during their stay initially in the hospital from their family and then from their neighbors and social circle after their recovery [21, 22]. Exposure to stigma and discrimination related to COVID-19 suggests that patients often face social challenges while trying to continue their daily activities. That is why further expansion of the public health system is required to support former patients with COVID-19 as well as promote initiatives on the part of the state and private medical institutions to implement appropriate measures to eliminate stigma [23].

6. Methodology

The formulation of the research questions focuses on the mental health disorder of patients with COVID-19 due to Brain Fog and the ways to effectively deal with it. An electronic search was carried out and databases included PubMed, Emerald, EMBASE, and Science Direct. As far as the review, data collection included papers in the English language with full bibliography, abstracts, and keywords, published in electronic form in the last 2 years (2020–2022). In the context of establishing the inclusion and exclusion criteria of the studies, the PICO framework was used. A total of 10 scientific studies were selected; 3 randomized controlled trials, 1 observational cross-sectional study, 2 study surveys, 1 study analysis, 1 combination study, 1 quantitative study, and 1 retrospective case-control study. PRISMA 2009 review protocol was also used to present the flow of data during the different phases of the particular systematic review (Figure 1).

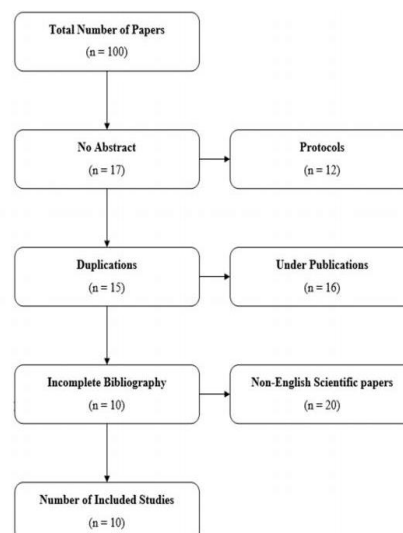


Figure 1. PRISMA 2009 review protocol.

7. Results

According to the following table of the systematic review articles (**Table 1**), Zilberman-Itskovitch et al. [24] in their randomized control trial investigated the efficacy of hyperbaric oxygen therapy (HBOT or HBO₂ therapy) in patients over 18 years of age with Post-COVID-19 ongoing symptoms for approximately 3 months after their infection. HBOT treatment improves dysexecutive functioning, somatization, depression, anxiety symptoms, mental fatigue as well as pain interference symptoms. Rathi et al. [25] carried out a randomized controlled trial in 200 patients, men and women aged ≥ 18 and ≤ 75 years, suffering from fatigue caused by the Post-COVID-19 syndrome aiming to assess the safety and effectiveness of the following supplements ImmunoSEB (systemic enzyme complex) and ProbioSEB CSC3 (probiotic complex). This study shows that taking ImmunoSEB + ProbioSEB CSC3 supplements for 14 days solves tiredness and fatigue due to Post COVID-19 syndrome making better patients' life quality and functional status. Hawkins et al. [26] conducted a randomized control trial to assess the probability of inhalation of "Longevity", a patented mixture of essential oils of thyme, clove bud, orange peel, and frankincense to raise energy levels in women who survived COVID-19 and carry on experiencing physical and mental fatigue for at least 5 months after recovering from acute infection due to COVID-19. The particular usage of essential oils demonstrates increased vigor, quality of life as well as energy levels in comparison to their previous behavioral and mental fatigue, and cognitive impairment due to Post-COVID Brain Fog.

Tabacof et al. [27] carried out an observational, cross-sectional study in pre-vaccinated hospitalized patients to examine repeated symptoms connected with Post-acute COVID-19 syndrome (PACS) and their impact on physical and cognitive function, and the Health-Related Quality of Life (HRQOL). Brain Fog, dyspnea, headache, fatigue, and lack of social participation were in high percentages. Ferrucci et al. [28] aimed to study cognitive abnormalities in 38 people ages 22 to 74, five months after their discharge from the hospital. The Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) diagnostic test, the Beck's Depression Inventory-II (BDI-II), and the Subjective Scale of Damage (SSD) questionnaire were used in the particular research. Patients diagnosed with Acute Respiratory Distress Syndrome (ARDS) during hospitalization had a bad performance regarding verbal memory tests. This outcome is in agreement with memory impairment on account of hospitalization for ARDS. The connection between ARDS and verbal memory can be clarified by the tendency of medial temporal lobe structures to get affected by hypoxic injury. Krishnan et al. [29] presented in the clinical vignette the case of a 35-year-old nurse who worked in a hospital ICU. Possible etiologies for Brain Fog are traced to untreated mood disorders, possible sleep disorders, and dietary changes, which led to referrals to appropriate specialists such as a psychologist, sleep specialist, and medical dietitian. This clinical vignette highlighted factors associated with Post-COVID-19 Brain Fog that can aid in the recovery process. D'Arcy et al. [30] conducted a study analysis of the existing knowledge on neuroinflammation and neurological sequelae referring to COVID-19, as central nervous system (CNS) involvement is frequent. Even if evidence of CNS damage in patients with COVID-19 was provided, it would not be possible to prove the direct viral infection of the brain. Thus, neurological manifestations should

be diagnosed and treated immediately to decrease the long-term sequelae. Hellmuth et al. [31] presented a combination study of 2 cases of outpatients who suffered from Acute COVID-19 and developed constant neurocognitive symptoms involving deficits in working memory and executive function. Surprisingly, cognitive deficits were not depicted by the MMSE or MoCA tests, meaning neuropsychological testing is justified. Also, ADHD symptoms in the first patient could create a selective susceptibility raising the danger of cognitive symptoms.

Humphreys et al. [32] carried out a quantitative study through semi-structured telephone interviews and two Zoom interviews examining 18 people with Long-COVID symptoms, aged 18–74. The results underlined the need for clarity and tailor-made physical activity advice to enhance patient motivation against the Long-Term dangers of COVID-19. The adoption of holistic care models that confront psychological and physical consequences by improving the personal development and well-being of vulnerable individuals should also be strengthened. Wang et al. [33] conducted a retrospective case-control study of almost 12,000 US adults and elderly patients aged ≥ 18 years diagnosed with COVID-19. According to the study, comorbidities (including pulmonary and cardiovascular diseases as well as metabolic disorders) appear to increase the risk for COVID-19 in patients with vascular dementia, while vascular brain pathology itself could also be involved in SARS-CoV-2 infection or subsequent brain damage.

Table 1. Table of the systematic review articles.

Scientists	Purpose	Methodology	Limitations	Results	Conclusions
Zilberman-Itskovich et al. (2022)	Investigation of treatment effectiveness with HBOT	A 3-month prospective randomized, sham, double-blind clinical trial	Small sample of participants—Small number of sessions (40)	HBOT treatment can induce neuroplasticity—A noticeable improvement in life	To determine in future research the exact number of sessions and obtain a larger sample
Rathi et al. (2021)	Efficacy and safety evaluation of ImmunoSEP and ProbioSEB CSC3 health supplements	Randomized, multicenter double-blind, placebo-controlled trial	Short duration of study (92 weeks)—No follow-up	Significantly reduces mental-physical fatigue—Helps in the recovery of patients with COVID-19	Future recurrence of fatigue
Hawkins et al. (2022)	Increased energy levels among women who survived COVID-19 5 months after recovery	Randomized double-blind, placebo-controlled clinical trial	The male population has not been included	High rates of cognitive impairment due to Post-COVID Brain Fog	To study whether such interventions help people with respiratory conditions
Tabacof et al., (2022)	Examining PACS symptoms in physical and cognitive functioning—Quality of life	A cross-sectional observational study	Need for elucidation of COVID-19—PACS, underlying mechanisms and therapies	Impact of PACS on health and social participation	Need for PACS and COVID-19 research
Ferrucci et al. (2021)	Study of occurrence of cognitive disorders	Study research	Unavailable calculation of basic cognitive functions—Lack of control sample—numerical superiority of men	ARDS is associated with poor long-term verbal memory performance—Delayed verbal recall	Participate more women—Design of cognitive rehabilitation interventions needed
Krishnan et al. (2022)	Emergence of factors associated with Brain Fog COVID-19	Clinical vignette	The patient’s heavy medical history affects recovery	Multidisciplinary approach to treating Post-COVID Brain Fog	Psychoeducation of patients is necessary—cooperation of psychologists with specialists
D’Arcy et al. (2021)	Relationship of neuroinflammation and neurological sequelae to COVID-19	Study analysis	CNS damage in patients with COVID-19 cannot be determined to be due to direct viral infection of the brain	Using a bio-psychosocial model helps Post-COVID-19 Brain Fog sufferers’ recovery and resilience	Cost-effective—Clinically effective interventions are needed

Table 1. (Continued).

Scientists	Purpose	Methodology	Limitations	Results	Conclusions
Hellmuth et al. (2021)	Study of neurocognitive symptoms for working memory and executive function deficits	Two case studies + observational cohort study	The cognitive deficits of the observational cohort study were not captured by the MMSE and MoCA	Neuropsychological tests showed that the deficits were not associated with sleep, mood, or fatigue problems	Research is needed on symptom prevalence in affected populations—Clinical involvement and underlying mechanisms
Humphreys et al. (2021)	Examination of reduced physical function, psychological and cognitive effects due to Long COVID, difficulty in finding and interpreting advice, and physical activity	Quantitative study	Views of digitally excluded populations are not included—Lack of demographics	Need for clear advice + physical activity	Enhancing the adoption of holistic care models
Wang et al. (2021)	Screening for pre-dementia and long-COVID risk	Retrospective case-control study	Not representative of the general population	Comorbidities and cerebrovascular pathology do not help the patient with long-COVID	Immediate need to protect patients with dementia

8. Discussion

In this particular review, HBOT alternative treatment has recently been proven to work effectively for the benefit of patients. It involves breathing 100% oxygen in a controlled pressurized chamber which is pretty much possible to induce neuroplasticity in parts of the brain associated with emotional and cognitive roles [24]. Moreover, the use of ImmunoSEB + ProbioSEB CSC3 supplements for a period of 2 weeks helps a lot in dealing with Brain Fog. However, it is very significant their beneficial results be verified by bigger well-designed randomized controlled trials (RCTs) [36,37]. Also, a different version of Brain Fog symptom management is presented, giving emphasis on aromatherapy, specifically, the use of a blend of orange peel, thyme, frankincense, and clove bud essential oils [26]. Aromatherapy, such as Phytotherapy, is recommended not only for the relief of neurological and respiratory symptoms but also for cardiovascular ones, as well [38]. However, it is necessary to continue scientific research in order to ensure a larger sample size and follow-up of trials/studies. Persistent symptoms due to PACS and their severe influence on physical health, quality of life, Brain Fog, and social participation, have also been examined, highlighting the important role of existing underlying diseases and of appropriate treatment options [27].

In addition, cases of patients who were diagnosed with ARDS and during their hospitalization showed verbal memory deficits more intense compared to their memory impairment after their hospitalization have also been well analyzed. The impact of reduced cognitive speed, fatigue as well as memory and concentration deficits can lead to a problematic social and professional life. ARDS, as a common clinical observation in several hospitalized COVID-19 patients, is connected with serious neurodegeneration; that's why inspection and follow-up are necessary to help patients gradually return safely to their lives [28]. Sleep disturbance, change in diet, and mood that are related to Post-COVID-19 Brain Fog can be reduced during the recovery process if there is an appropriate psychoeducation of the patients and proposed treatment from a psychologist based on the medical and psychiatric history [30].

In this review, there has also been a possible indication of CNS damage in patients with COVID-19 as well as acute cerebrovascular disease with an increased risk of stroke, gradually leading to brain confusion. The use of a bio-psychosocial model would particularly help the recovery and resilience of Post-COVID-19 patients as well

as enhance their functional improvement through exercise, proper nutrition, quality sleep, and social participation [30]. In addition, a neuropsychological evaluation of participants seemed to be necessary, as the cognitive deficits of patients were not captured by the MMSE and MoCA. This finding is very important when further research is necessary to determine the prevalence of symptoms in affected populations and the underlying mechanisms [31]. The initial difficulties participants faced due to their limited physical functioning, and the psychological and cognitive effects of Long-COVID were also analyzed. The adoption of holistic care models to improve personal development and ensure the well-being of vulnerable people is of vital importance [32].

Furthermore, it is underlined that pre-existing dementia, including vascular dementia and Alzheimer's, makes patients more susceptible to morbidity and mortality due to Long-COVID-19, beyond any existing co-morbidities, resulting in increased risk for cognitive decline and confusion. High incidence of dementia in the future as regards to previous patients with COVID-19 in comparison to not infected ones is anticipated [33]. The use of a bio-psychosocial model that integrates inflammatory influences with those associated with psychosocial and other stressors would particularly aid recovery and resilience in Post-COVID-19 sufferers and especially those experiencing Brain Fog. Nevertheless, prevention as well as recovery based on proper nutrition, exercise, sleep, and social participation remain very important [34]. It is necessary not only to investigate the biological and psychosocial background of Brain Fog symptoms in detail but also for the scientific community to take the initiative to suggest and promote therapeutic strategies suitable for mitigating the long-term cognitive consequences of COVID-19 [5].

On the other hand, health services and healthcare workers may consider adopting the technique of cognitive behavioral restructuring to help patients cope with their anxiety disorders to identify and focus on their strengths. For patients who have been unable to return to their work environment, psychotherapy may assist them get focusing more on accepting their new self, adapting to change, and adopting cognitive or behavioral strategies to deal with the new limitations in their lives [29]. Additionally, a rehabilitation program based on the concept of neuroplasticity or brain plasticity, which refers to the incredible ability of neural networks in the brain to change, adapt, and strengthen, could also help dysfunctional brain regions to recover from Long-COVID-19 [35].

9. Conclusions

The treatments described in this review focus on the holistic approach and treatment of Post-COVID Brain Fog. The treatment based on methods such as aromatherapy, combined with appropriate supplementation, exercise, social participation, nutrition, and medical care yields more beneficial results compared to a treatment that focuses solely on medication. HBOT alternative treatment, the use of ImmunoSEB + ProbioSEB CSC3 supplements, and psychoeducation of patients could help patients progressively become functional and productive in their everyday lives. More scientific studies regarding the effectiveness of the various treatment approaches and their particular characteristics (duration, intensity, age, gender) considered are

absolutely necessary to provide better public health services and ensure the quality of life of the patients.

10. Limitations

Since the first case of SARS-CoV-2 was recorded in late 2019, and the first official scientific reports of Brain Fog were in October 2020 [4] only three RCTs of Brain Fog were found to meet the necessary conditions. Other limitations refer to the small sample of participants in the studies that are included in this particular review as well as the few existing alternative treatments, e.g., aromatherapy, and psychoeducation [29,26].

Conflict of interest: The authors declare no conflict of interest.

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