REVIEW ARTICLE

COVID-19 FATIGUE: DIAGNOSIS AND TREATMENT FOR THE OSTEOPATHIC PHYSICIAN

Violeta B. Foss, OMS-III; Nicole Maddie, MS, OMS-III; Elisabeth L. Frankini, MPH, OMS-III; Scott Landman, OMS-III; Jennifer Maccagnano, DO, FACOEP, FACEP; Sheldon C. Yao, DO, FAAO

New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY

KEYWORDS

COVID-19

Chronic fatigue syndrome

Myalgic encephalomyelitis

Post-acute COVID-19 syndrome

ABSTRACT

The novel coronavirus disease 2019 (COVID-19) has given rise to a global pandemic, as well as a multitude of long-term sequelae that continue to perplex physicians around the world, including in the United States. Among the most common and impactful long-haul symptoms experienced by survivors is COVID-19 fatigue. This review will use long COVID-19, post-acute COVID-19 syndrome (PCS), and Post-Acute Sequelae of COVID-19 (PASC) as synonymous terms to refer to the chronic symptomatology; chronic fatigue associated with PASC will be referred to as COVID-19 fatigue. While the knowledge and research on the exact pathophysiological mechanisms involved in the disease is still limited, parallels have been drawn between fatigue as a component of long COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Current studies suggest applying principles of pathophysiology, diagnosis, and treatment similar to those for ME/CFS in order to aid in managing chronic fatigue in COVID-19 survivors, particularly in the primary care setting. The osteopathic family physician can use the proposed pharmacologic agents, along with osteopathic manipulative treatment (OMT), as therapeutic modalities that can be tailored to each patient's unique case. Nevertheless, research on proven successful treatments is still scarce. For that reason, it is essential that COVID-19 fatigue is recognized early, especially since its longitudinal impacts may be debilitating for many. This review of the available literature on COVID-19 fatigue aims to help provide quality care and lessen the disease burden experienced by patients.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), quickly became a worldwide pandemic following its discovery in 2019.[1,2] As of April 2022, the worldwide number of confirmed cases reached 500 million and over 6 million reported deaths.[3] Patients diagnosed with COVID-19 can experience symptoms ranging from cough, fever, sore throat, nausea and vomiting to septic shock, severe pneumonia, and acute respiratory distress syndrome (ARDS).[4,5]

Long COVID-19, post-acute COVID-19 syndrome (PCS), or Post-Acute Sequelae of COVID-19 (PASC) are synonymous terms defining the persistence of symptoms or other sequelae following acute COVID-19.[6-9] For this review, we will use long COVID-19, PCS, and PASC interchangeably to describe symptom continuation for more than 12 weeks after acute infection. Chronic multisystem symptoms include fatigue, dyspnea, anosmia, dysgeusia, arthralgia, amnesia, and difficulty concentrating.[6,7,10] Various studies suggest that chronic fatigue affects 28%–47% of all survivors (Figure 1).[6,7,10]

Fatigue can be defined as acute or chronic and is associated with multiple disease states.[11,12] Interestingly, fatigue prevalence in long COVID-19 patients does not depend on the severity of the acute illness and is one of the most commonly reported symptoms.[6,7,10] Since this PASC symptomatology is very similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), patients may fit ME/CFS diagnostic criteria.[12,13] Although there may be instances where ME and CFS occur independently, our focus will be on the ME/CFS complex illness. This review will refer to the diagnosis of fatigue associated with PASC as COVID-19 fatigue.

In the pediatric population, PASC fatigue can be a direct sequela of multisystem inflammatory syndrome in children (MIS-C), which has been associated with SARS-CoV-2 infection. Presenting symptoms of MIS-C are persistent fever, systemic inflammation, and related multi-organ involvement, such asabdominal pain, conjunctival injection, rash, and arthralgias.[14]

CORRESPONDENCE:
Sheldon C. Yao, DO, FAAO | syao@nyit.edu

ISSN: 1877-573X doi:10.33181/13090

Although fatigue can be a symptom of MIS-C secondary to COVID-19, this article focuses on COVID-19 fatigue in adults.

Since long COVID-19 involves various symptoms, the treatment methods must be individualized.[15] As for COVID-19 fatigue, there is currently no proven treatment. With this in mind, this review aims to consolidate the current research on diagnostic criteria, pathophysiology, and potential therapeutic approaches, including pharmacologic options and osteopathic manipulative treatment (OMT).

DIAGNOSIS

Post-infectious, or in this case, COVID-19 fatigue seems to bear a striking resemblance to ME/CFS due to the constellation of symptoms found in both conditions.[16] Because of the similarities in presentation and suggested etiology, the diagnosis of chronic fatigue as a component of PCS is approached using the current knowledge about ME/CFS, once the initial criterion of a laboratory proven COVID-19 infection has been met. Chronic fatigue has an extensive differential diagnosis with various etiologies, summarized in Table 1.[12,17] It is crucial to rule out common conditions, such as primary sleep disorders, diabetes mellitus, hypothyroidism, and vitamin deficiencies, before attributing fatigue to long COVID-19.

The National Academy of Medicine (NAM) introduced new diagnostic clinical criteria for ME/CFS in 2015. According to the report, a thorough history, physical examination, and targeted laboratory workup are necessary for diagnosis.[18] The NAM requires patients to have post-exertional malaise (PEM), unrefreshing sleep, and substantial impairment in function due to fatigue that does not improve with rest. PEM is an immediate or delayed exacerbation of symptoms and functional decline following a minor physical or mental exertion with intensity and duration disproportionate to the magnitude of the trigger.[17,19] Patients are also required to have either cognitive impairment or orthostatic intolerance with symptoms present at least 50% of the time for more than 6 months with moderate, substantial, or severe intensity.[17] Additionally, multiple types of pain, such as headaches, arthralgia or myalgia, gastrointestinal and genitourinary problems, and influenza-like symptoms (sore throat and tender axillary/cervical lymph nodes), sensitivity to external stimuli, respiratory and thermoregulatory issues may support a diagnosis of ME/CFS.[17,18]

Clinicians should elicit a history consistent with ME/CFS and rule out other medical conditions. Questions regarding the severity and duration of symptoms as chronic, frequent, and moderate or severe are required to distinguish ME/CFS from other illnesses.[18] In addition, physicians should inquire regarding fatigue, functional or cognitive impairment, post-exertional malaise, lack of restful sleep or sleep disturbances, and orthostatic intolerance.[18] Patients may describe symptoms without a clear understanding of the illness; for example, cognitive impairment may be described as "brain fog," "difficulty concentrating," or "absentmindedness." Key questions should include implications on instrumental activities of daily living (iADLs), such as household management and career, and activities of daily living (ADLs), like personal hygiene and ambulation.[18]

Physical examination may elicit nonspecific abnormal findings or may be unremarkable. Nonspecific signs and symptoms include low-grade fever, inability to maintain cognitive focus, abdominal tenderness, multiple tender joints without redness, warmth or swelling and allodynia/hyperalgesia.[17] The physical examination may also suggest comorbid conditions associated with ME/CFS. Those can include fibromyalgia, myofascial pain syndrome, temporomandibular joint syndrome, irritable bowel syndrome, interstitial cystitis, irritable bladder syndrome, Raynaud's phenomenon, prolapsed mitral valve, migraine, allergies, multiple chemical sensitivities, Sicca syndrome, obstructive or central sleep apnea, and reactive depression or anxiety.[18]

No single laboratory test can be used to diagnose ME/CFS; instead, testing is used to rule out other medical causes of fatigue that would reject the diagnosis of ME/CFS.[12] Laboratory testing can include complete blood count with differential, comprehensive metabolic panel, antinuclear antibody, C-reactive protein, erythrocyte sedimentation rate, ferritin, rheumatoid factor, thyroid-stimulating hormone, free thyroxine, vitamin B12, vitamin D 25-dihydroxy, four-point salivary cortisol, and urinalysis.[17] Like ME/CFS, COVID-19 fatigue is a diagnosis of exclusion.

PATHOPHYSIOLOGY

Although a lot is yet to be discovered about the specific pathophysiology of PCS, the long-lasting symptom of fatigue has been compared to ME/CFS due to its chronicity and often debilitating impact on ADLs. The proposed mechanisms underlying COVID-19 fatigue include dysregulated immune response, excess oxidative stress, changes in DNA methylation patterns, impediment of cerebrospinal fluid (CSF) outflow, and indirect neuropsychiatric insults.

It is suggested that the high inflammation caused by acute COVID-19 engages the immune system in a robust response involving various cytokines. The result is persistent dysregulation of signaling mediators even after the initial illness subsides, leading to an ongoing cycle of continuous immune overactivity.[20] Another inflammatory pathway to chronic fatigue involves oxidative stress the body cannot overcome. Physiologic changes during viral illness lead to increased reactive oxygen species, such as superoxide, as a defense mechanism. However, prolonged COVID-19 can imbalance free radicals and antioxidants, including vitamin E and coenzyme Q10 (CoQ10). This may cause further cell injury by damaging DNA and protein.[21] As a key source of reactive oxygen species, mitochondria are particularly vulnerable. Therefore, the central nervous system (CNS), where mitochondria dependence is crucial to meet energy demand, has increased susceptibility to oxidative stress. As a result, patterns of damage and chronic fatigue may be perpetuated. DNA methylation is an epigenetic process that usually silences gene expression on the molecular level. Alteration in methylation patterns has been linked to various conditions, including autoimmunity, cancer, and neurodegenerative disease.[22] Although the number of studies is limited, hypomethylation has been found in cases of ME/CFS. It is suggested that COVID-19 fatigue may follow a similar pattern of decreased epigenetic silencing, ultimately resulting in increased synthesis of inflammatory proteins.

An additional proposed mechanism involves the glymphatic system, which plays a crucial role in the fluid clearance of the CNS. Its impairment is suggested to underlie multiple neurologic conditions, including Alzheimer's disease.[23] COVID-19 has a tropism for lymph endothelial cells, leading to fewer olfactory sensory neurons. It is hypothesized that the decrease in nerve cells impedes the low-resistance pathway of CSF outflow through the cribriform plate.[24] The disrupted drainage of fluid may result in stasis and lingering inflammatory mediators, precipitating continuous CNS immune response and subsequently post-acute fatigue. This theory is further supported by multiple studies suggesting a positive correlation between ME/CFS and elevated intracranial pressure.[25]

COVID-19 fatigue may be considered a byproduct of the biopsychosocial impact of disease in addition to being a symptom of PASC. The lack of association between symptom burden and chronic fatigue has led researchers to consider that neuropsychiatric insults of non-viral etiology may be the primary culprit for this long-haul manifestation.[26] Regardless of acute viral illness severity, a correlation between psychiatric history and COVID-19 fatigue appears to be present. In a 2020 study exploring persistent fatigue, patients with a past diagnosis of anxiety or depression represented a significant proportion of those complaining of the long-haul symptom.[27]

The multiple pathophysiological phenomena likely involved in COVID-19 fatigue can help guide the approach to management and treatment.

TREATMENT

Current research on COVID-19 fatigue therapeutics is limited. However, literature on ME/CFS suggests several options that appear to have shown effectiveness in some patients. Functional improvement of chronic fatigue has been observed for nicotinamide adenine dinucleotide hydride (NADH), probiotics, high cocoa polyphenol rich chocolate, and a combination of NADH and CoQ10.[28] Herbal supplements and pharmacologic agents, such as aripiprazole, have also shown benefits. Nevertheless, potential side effects need to be considered when prescribing treatment. One instance is minocycline, associated with nausea and dizziness necessitating discontinuation in multiple patients.[29] There is limited evidence that dietary modifications may relieve ME/CFS.[28] Researched treatments are summarized in Table 2.[17,28,30-37] An additional tool that may help fill the gap, where traditional therapeutics fall short, is OMT.

Osteopathic Treatment Considerations:

OMT may also help address the symptomatology of COVID-19 fatigue. Considering biomechanics, neural pathways, circulation, metabolism/energy expenditure, and psychosocial factors, OMT can be utilized to target the different ways disease impacts the body. Proposed modalities focus on fatigue and indirect approaches promoting the body's natural healing response. For instance, based on osteopathic principles, the Perrin technique, which involves manually stimulating fluid motion to optimize drainage, is one method of normalizing neuro-lymphatic flow[24] Table 3 describes further how the five models of osteopathic medicine may provide a more holistic approach to targeting both somatic dysfunctions and fatigue symptoms in COVID-19 survivors.[24,29,38-42]

CONCLUSION

COVID-19 fatigue affects as many as 47% of patients following acute infection, making it a significant health care burden and a commonly encountered complaint for family practitioners.[6,43] The family medicine physician may be the first provider to interact with a patient suffering from long COVID-19 or MIS-C fatigue secondary to a SARS-CoV-2 infection. PCS fatigue is a diagnosis of exclusion; therefore, a thorough history is critical to making the diagnosis, and ruling out other serious diseases with similar symptoms. Considering how signaling molecules, epigenetic changes, oxidative damage, and neurological changes may work together to perpetuate inflammatory response and prolong COVID-19 fatigue, a number of treatment methods can be used in primary care to alleviate the burden of disease. Learning more about PCS pathophysiology can widen physicians' perspectives. Family medicine physicians can optimize patient care and improve public health outcomes by applying that knowledge to treat persistent fatigue pharmacologically or by using OMT.

TABLE 1:

Differential Diagnosis for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome[12,17]

CARDIOVASCULAR	ENDOCRINE	GASTROINTESTINAL	HEMATOLOGIC
Arrhythmia	Addison disease	Celiac disease	Anemia
Cardiomyopathy	Adrenal insufficiency	Food intolerance/allergy	Iron overload
Coronary artery disease	Cushing disease	Inflammatory bowel disease	Primary malignancy
Pulmonary hypertension	Diabetes mellitus	Small intestinal bacterial overgrowth	Secondary malignancy
Valvular heart disease	Hypercalcemia		
	Hyperthyroidism		
	Hypothyroidism		
INFECTIOUS	**NEUROLOGIC**	**PSYCHIATRIC**	**RHEUMATOLOGIC**
Coccidioidomycosis	Cerebrospinal fluid leak	Anxiety	Dermatomyositis
Epstein-Barr virus	Chiari malformation	Bipolar disorder	Fibromyalgia
Giardiasis	Craniocervical instability	Eating disorder	Polymyalgia rhemumatica
Hepatitis B/C	Dementia	Major depressive disorder	Polymyositis
Human immunodeficiency virus	Multiple sclerosis	Schizophrenia	Rheumatoid arthritis
Lyme disease	Myasthenia gravis	Somatoform disorder	Sjögren syndrome
Parvovirus B19	Narcolepsy	Substance use	Systemic lupus erythematosus
Q fever	Parkinson disease		Temporal arteritis
Syphilis	Seizure disorder		
Tuberculosis	Spinal stenosis		
West Nile Virus	Traumatic brain injury		
SLEEP	**TOXIC SUBSTANCE EXPOSURE**	**OTHER**	
Narcolepsy	Gulf War illness	Asthma	
Periodic limb movement disorder	Heavy metals (lead, mercury)	Athletic overtraining syndrome	
Sleep apnea	Medication adverse effect	Chronic obstructive pulmonary disease	
	Mold/mycotoxins	Overwork	
		Severe obesity (BMI >40 kg/m2)	
		Vitamin deficiency	

TABLE 2:

COVID-19 Fatigue Researched Treatments Summary

TREATMENT	NO. SUBJECTS	PERTINENT RESULT OF STUDY	ADDITIONAL NOTES
Q-14 (Hua Shi Bai Du herbal supplement)	204	Improved symptoms including fatigue, fever, cough, and chest discomfort after COVID-19 infection.[30]	Effective additive to traditional treatment.
Traditional Chinese medicine Bufei huoxue (BFHX) capsule	129	Improvement in a 6-minute walk distance relative to a baseline group; Significantly lower Fatigue Assessment Inventory (FAI).	Rate of adverse effects (liver injury and diarrhea) was higher in the BFHX group than in the placebo group.[31]
High-dose zinc and ascorbic Acid	214	Does not significantly improve the severity of COVID fatigue.[32]	N/A
Cognitive-behavioral therapy (CBT)	114	In clinical trials at The ReCOVer Study for severe COVID fatigue.[33]	The trial aims to assess if CBT may significantly decrease the severity of post-COVID fatigue.
Cardiopulmonary rehabilitation	40	In clinical trials at the COVID-Rehab study	The COVID-Rehab study aims to assess the effectiveness of optimizing functional capacity through improving cardiorespiratory fitness in patients suffering from post-COVID-19 sequelae, including fatigue; caution needs to be exercised and rehabilitation program individually tailored, as exercise that is too intense may lead to post-exertional malaise and worsen fatigue symptoms.[37]
*Pacing** (activity management)	N/A	Building stamina, alleviating the amount of exertion that would lead to PEM. Sometimes establishing a new functional baseline.	Patients counseled to reserve, balance, and understand their energy, especially after an episode of PEM.
Minocycline*	100	Shown to be a neural anti-inflammatory in animal models.[34]	One mechanism to ME/CFS is increased neural inflammation.[17]
Aripiprazole*	101	Shown to have some utility in decreasing ME/CFS symptoms.[35]	Dopamine agonist, also known to reduce inflammation.
Low-dose naltrexone (LDN)*	18	Improvement in impaired thought, concentration and cognitive overload, immune disturbances symptoms (sore throat, enlarged or tender lymph nodes, and susceptibility to colds/ influenza)	Acts at TRPM3 and opioid receptors in NK cells.[36]
CoQ10 and NADH supplementation*	73	Significant improvement in fatigue impact scale total score versus placebo, as well as improved biochemical parameters.[28]	N/A

*researched for ME/CFS

TABLE 3:

Osteopathic Manipulative Medicine Integration. Osteopathic manipulative techniques organized by each one of the five models of osteopathic medicine

OSTEOPATHIC MEDICINE MODEL	TREATMENT	PROPOSED MECHANISM	RELATED PATHOPHYSIOLOGY
Biomechanical	Indirect and direct (if tolerated) OMT techniques directed to key somatic dysfunctions of the spine, thoracic cage, pelvis and extremities	Removes somatic restrictions to reduce structural impediments and therefore, optimize biomechanics, and improve function[29]; early intervention during the acute phase of illness may prevent buildup of restrictions leading to dysfunction and minimize occurrence of long-haul COVID-19 symptoms, including fatigue	Inflammatory state resulting in persistent functional restrictions (somatic dysfunctions) and ultimately dysfunctional movement of the body; altered regional motion and tissue compliance can interfere with the function of vascular, lymphatic and neurologic components[42]
Neurologic	Suboccipital release, OA decompression, rib raising, sacral/pelvic techniques	Normalizes sympathetic and parasympathetic nervous system activity by decreasing soft tissue and muscle tone in order to modulate paravertebral ganglia and vagal tone[38]	Increased stress on the body due to a prolonged state of inflammation and immune dysregulation; continuous overactivation of the sympathetic nervous system leading to facilitation and viscerosomatic reflexes
Respiratory-Circulatory	Perrin technique/Thoracic pump/Pedal pump	Optimizes lymphatic drainage and promotes the body's natural healing response by normalizing neuro-lymphatic flow[24]	Continuous chronic inflammation due to stagnant lymph, inducing persistent neuro-inflammation
	Venous sinus drainage	Removes impediments from venous channels in the cranium and improves clearance of the CNS[39]	Glymphatic system impairment and disrupted CNS drainage
	Myofascial release of the thoracic inlet and thoracic diaphragm (doming)	Decreases inlet and diaphragm hypertonicity and improves lymphatic return[40]	Increased state of inflammation of the body due to dysregulated signaling mediators; increased number of mediators fostering prolonged inflammation
Metabolic-Energetic	Articulatory techniques, Indirect techniques targeting musculoskeletal (MSK) somatic dysfunctions	Removes MSK restrictions throughout the body to improve movement and function allowing conservation of energy, as well as improving the body's efficiency and ability to adapt in response to stressors[42]	Increased energy demand of the body and CNS as a result of prolonged inflammatory and disease state
Behavioral	Compression of the 4th ventricle (CV4)	Likely reduces anxiety and induces general relaxation[41]	Biopsychosocial impact of disease leading to long-haul COVID-19 fatigue

REFERENCES

1. Organization WH. *Coronavirus disease* 2019 (COVID-19) Situation Report - 51. 2020. https://apps.who.int/iris/bitstream/handle/10665/331475/nCoVsitrep11Mar2020-eng.pdf?sequence=1&isAllowed=y
2. Jin Y, Yang H, Ji W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. *Viruses*. 2020;12(4). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7232198/
3. Organization WH. *COVID-19 Weekly Epidemiological Update*. April 27 2022. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---27-april-2022
4. Galanopoulos M, Gkeros F, Doukatas A, et al. COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. *World J Gastroenterol*. 2020;26(31):4579-4588. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7445869/
5. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. 2020;76:71-76. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7105032/
6. Groff D, Sun A, Ssentongo AE, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: A systematic review. *JAMA Netw Open*. 2021;4(10):e2128568. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8515212/
7. Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. *J R Soc Med*. 2021;114(9):428-442. https://journals.sagepub.com/doi/full/10.1177/01410768211032850
8. Pretorius E, Vlok M, Venter C, et al. Persistent clotting protein pathology in long COVID/post-acute sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. *Cardiovasc Diabetol*. 2021;20(1):172. https://cardiab.biomedcentral.com/articles/10.1186/s12933-021-01359-7
9. Moreno-Perez O, Merino E, Leon-Ramirez JM, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect*. 2021;82(3):378-383. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7802523/
10. Han Q, Zheng B, Daines L, Sheikh A. Long-term sequelae of COVID-19: A systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. *Pathogens*. 2022;11(2). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8875269/
11. Finsterer J, Mahjoub SZ. Fatigue in healthy and diseased individuals. *Am J Hosp Palliat Care*. 2014;31(5):562-575.
12. Yancey JR, Thomas SM. Chronic fatigue syndrome: diagnosis and treatment. *Am Fam Physician*. 2012;86(8):741-746. https://www.aafp.org/afp/2012/1015/p741.html
13. Paul BD, Lemle MD, Komaroff AL, Snyder SH. Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. *Proc Natl Acad Sci U S A*. 2021;118(34). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8403932/
14. Yilmaz Ciftdogan D, Ekemen Keles Y, Karbuz A, et al. Multisystem inflammatory syndrome in children associated with COVID-19 in 101 cases from Turkey (Turk-MISC study). *J Paediatr Child Health*. 2022. https://onlinelibrary.wiley.com/doi/10.1111/jpc.15913
15. Proal AD, VanElzakker MB. Long COVID or post-acute sequelae of COVID-19 (PASC): An overview of biological factors that may contribute to persistent symptoms. *Front Microbiol*. 2021;12:698169. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8260991/
16. Komaroff AL, Bateman L. Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? *Front Med (Lausanne)*. 2020;7:606824. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7848220/
17. Bateman L, Bested AC, Bonilla HF, et al. encephalomyelitis/chronic fatigue syndrome: essentials of diagnosis and management. *Mayo Clin Proc*. 2021;96(11):2861-2878. https://www.mayoclinicproceedings.org/article/S0025-6196(21)00513-9/fulltext
18. myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. *Mil Med*. 2015;180(7):721-723.
19. Gaber T. Assessment and management of post-COVID fatigue. *Progress in Neurology and Psychiatry*. 2021;25(1):36-39. https://wchh.onlinelibrary.wiley.com/doi/full/10.1002/pnp.698
20. Komaroff AL, Lipkin WI. Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. *Trends Mol Med*. 2021;27(9):895-906. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8180841/
21. Wood E, Hall KH, Tate W. Role of mitochondria, oxidative stress and the response to antioxidants in myalgic encephalomyelitis/chronic fatigue syndrome: A possible approach to SARS-CoV-2 'long-haulers'? *Chronic Dis Transl Med*. 2021;7(1):14-26. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7680046/
22. Trivedi MS, Oltra E, Sarria L, et al. Identification of myalgic encephalomyelitis/chronic fatigue synd-associated DNA methylation patterns. *PLoS One*. 2018;13(7):e0201066. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0201066
23. Reeves BC, Karimy JK, Kundishora AJ, et al. Glymphatic system impairment in Alzheimer's disease and idiopathic normal pressure hydrocephalus. *Trends Mol Med*. 2020;26(3):285-295. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7489754/
24. Wostyn P. COVID-19 and chronic fatigue syndrome: Is the worst yet to come? *Med Hypotheses*. 2021;146:110469. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7836544/
25. Hulens M, Rasschaert R, Vansant G, Stalmans I, Bruyninckx F, Dankaerts W. The link between idiopathic intracranial hypertension, fibromyalgia, and chronic fatigue syndrome: exploration of a shared pathophysiology. *J Pain Res*. 2018;11:3129-3140. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6292399/
26. Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 symptom burden: What is long COVID and how should we manage it? *Lung*. 2021;199(2):113-119. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7875681/
27. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*. 2020;15(11):e0240784. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0240784
28. Campagnolo N, Johnston S, Collatz A, Staines D, Marshall-Gradisnik S. Dietary and nutrition interventions for the therapeutic treatment of chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. *J Hum Nutr Diet*. 2017;30(3):247-259. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5434800/
29. Li R, Jose A, Poon J, Zou C, Istafanos M, Yao SC. Efficacy of osteopathic manipulative treatment in patients with Parkinson's disease: a narrative review. *J Osteopath Med*. 2021;121(12):891-898. https://www.degruyter.com/document/doi/10.1515/jom-2021-0081/html

30. Liu J, Yang W, Liu Y, et al. Combination of Hua Shi Bai Du granule (Q-14) and standard care in the treatment of patients with coronavirus disease 2019 (COVID-19): A single-center, open-label, randomized controlled trial. *Phytomedicine*. 2021;91:153671. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8285932/

31. Chen Y, Liu C, Wang T, et al. Efficacy and safety of Bufei Huoxue capsules in the management of convalescent patients with COVID-19 infection: A multicentre, double-blind, and randomised controlled trial. *J Ethnopharmacol*. 2022;284:114830. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8575540/

32. Thomas S, Patel D, Bittel B, et al. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: The COVID A to Z randomized clinical trial.. *JAMA Netw Open*. 2021;4(2):e210369. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7881357/

33. Kuut TA, Muller F, Aldenkamp A, et al. 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. *Trials*. 2021;22(1):867. https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05569-y

34. Miwa K. Oral minocycline therapy improves symptoms of myalgic encephalomyelitis, especially in the initial disease stage. *Intern Med*. 2021;60(16):2577-2584. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8429282/

35. Crosby LD, Kalanidhi S, Bonilla A, Subramanian A, Ballon JS, Bonilla H. Off-label use of aripiprazole shows promise as a treatment for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a retrospective study of 101 patients treated with a low dose of aripiprazole. *J Transl Med*. 2021;19(1):50. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7860172/

36. Cabanas H, Muraki K, Eaton-Fitch N, Staines DR, Marshall-Gradisnik S. Potential therapeutic benefit of low dose naltrexone in myalgic encephalomyelitis/chronic fatigue syndrome: Role of transient receptor potential melastatin 3 ion channels in pathophysiology and treatment. *Front Immunol*. 2021;12:687806. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8313851/

37. Besnier F, Berube B, Malo J, et al. Cardiopulmonary rehabilitation in long-COVID-19 patients with persistent breathlessness and fatigue: The COVID-rehab study.. *Int J Environ Res Public Health*. 2022;19(7). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8998214/

38. Sheldon Yao DO, Nardine Mikhail OMS, III, George Koutsouras OMS, III, Allison Coombs OMS, III, Michael J. Terzella DO. Osteopathic considerations in the infections of the respiratory tract. *Osteopath Fam*. 2016;9(1). https://ofpjournal.com/index.php/ofp/article/view/484/405

39. Guernsey DT, 3rd, Leder A, Yao S. Resolution of concussion symptoms after osteopathic manipulative treatment: A case repor. *J Am Osteopath Assoc*. 2016;116(3):e13-17. https://www.degruyter.com/document/doi/10.7556/jaoa.2016.036/html

40. Yao S, Hassani J, Gagne M, George G, Gilliar W. Osteopathic manipulative treatment as a useful adjunctive tool for pneumonia. *J Vis Exp*. 2014(87). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4173698/

41. Abraham C, Sloan SNB, Coker C, et al.Osteopathic manipulative treatment as an intervention to reduce stress, anxiety, and depression in first responders: A pilot study. *Mo Med*. 2021;118(5):435-441. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8504517/

42. Seffinger MA, Hruby R, Willard FH, et al. *Foundations of Osteopathic Medicine: Philosophy, Science, CLinical Applications, and Research*. Fourth ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2018. https://meded.lwwhealthlibrary.com/book.aspx?bookid=2582

43. Organization WH. *COVID-19 Weekly Epidemiological Update*. March 22 2022. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---22-march-2022