

Understanding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and the Emerging Osteopathic Approach: A Narrative Review

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating syndrome of unknown origin, characterized by profound postexertional malaise and fatigue, unrefreshing sleep, cognitive impairments, immune dysfunction, pain, autonomic dysfunction, and neuroendocrine symptoms. Although ME/CFS is well documented within the medical literature, it remains difficult to diagnosis and manage. Some of the current challenges include an absence of diagnostic markers, differing diagnostic criteria, and an overall lack of awareness within the medical community. As a result, patients are often frustrated by the difficulties in acquiring a diagnosis and from the overall lack of available treatments. In an effort to increase awareness, this review discusses disease pathophysiology, clinical presentation, and treatment options, while also highlighting the benefits of an osteopathic approach.

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex disease characterized by multiple symptoms that can include postexertional malaise and fatigue, unrefreshing sleep, cognitive impairments, immune dysfunction, pain, autonomic dysfunction, and neuroendocrine symptoms.¹⁻⁴ On average, 10% of patients receive a diagnosis within 5 years.⁵ This delay in diagnosis is primarily attributed to the absence of specific diagnostic tests and an overall lack of clinical awareness. Although documented clinical cases span more than 2 centuries, universally accepted diagnostic criteria do not exist. Instead, there are nearly 20 clinical definitions.¹⁻⁸ Multiple name changes add further confusion. The most notable names include neurasthenia, chronic fatigue immune disorder syndrome (CFIDS), chronic fatigue syndrome (CFS), myalgic encephalomyelitis (ME), and, more recently, systemic exertion intolerance disease (SEID).

With so much variation in defining the diagnostic criteria and naming the disease, confusion and doubt persist within the medical community. In a recent effort to unify definitions and focus on the primary features of the disease, the National Academy of Medicine, formerly the Institute of Medicine, suggested new diagnostic criteria and the change of name to SEID.¹ However, SEID's diagnostic criteria are less specific and do not exclude psychiatric disorders. In particular, the new diagnostic criteria do not

exclude individuals with major depressive disorder, which alters interpretations of epidemiology, etiology, and treatment research. Without more specific diagnostic criteria, limitations in research remain, and a better understanding within medical communities is hindered. Often causing patients to be bedridden, ME/CFS can be severely disabling and, as such, quicker diagnosis and appropriate treatment is needed. Further adding to the burden of the disease is the stigma associated with ME/CFS. Without a greater consensus among clinicians (physicians, physician assistants, and nurse practitioners) about the validity of this disease, patients will continue to feel alienated.

In an effort to reduce the confusion surrounding ME/CFS, this review provides a comprehensive summary of current ME/CFS understanding and highlights the benefits of the osteopathic approach for this condition. Using Pubmed and UpToDate, articles were selected on the basis of journal quality and content. Journal quality was determined using the journal impact factor, the publishing institute, and the number of times an article had been referenced. Content focused on current pathophysiology and treatments, osteopathic ME/CFS research, and methods for diagnosis.

Societal Impact

A population-based study⁹ on ME/CFS prevalence was conducted from 1995 to 1998 with a sample size of 18,675 people. The study revealed an approximated prevalence of 420 cases per 100,000 individuals. Rates were higher among minorities than whites and higher among low-income populations than high-income populations. In the United States, the National Academy of Medicine reports the number of people with the disease to be between 836,000 to 2.5 million.¹ However, the accuracy of these estimates is debated because prevalence rates are largely dependent on the diagnostic criteria used.

Similar to prevalence rates, the economic loss is challenging to accurately estimate. In one study,¹⁰ the annual economic cost was estimated to be between

\$17 to \$24 billion. In other studies,^{11,12} the estimated individual economic loss was between \$11,780 to \$20,000 annually. These amounts are similar to a previous UK study¹³ that found a mean cost to patients of £3,515 over a 3-month span. Variances in estimations may be attributed to study populations. Unemployment among patients with CFS is estimated to be approximately 50% to 54%.^{14,15} Costs related to loss of employment owing to chronic fatigue account for 61% of patients' total economic cost.¹⁶

ME/CFS Pathophysiology

Myalgic encephalomyelitis/chronic fatigue syndrome is a heterogeneous disorder with an unknown origin. Several proposed hypotheses include microbial triggers, immune dysregulation, mitochondrial dysfunction, oxidative stress, and endocrine abnormalities in genetically susceptible people.

Microbial Triggers

Reports¹⁷⁻¹⁹ describing disease outbreaks that have resembled ME/CFS in “closed populations” such as hospitals and convents can be traced back more than 60 years. Because these outbreaks occurred among persons in close proximity, it has been suggested that the ME/CFS is either infectious or results from an infectious agent. To support this hypothesis, prospective studies have found the development of ME/CFS in 11% of people after serious infections with the Epstein Barr virus (EBV), non-EBV-associated glandular fever, Ross River virus, *Giardia lamblia*, parvovirus B19, and Q fever infections.²⁰⁻²³ Despite differences in the acute phase of infection by EBV, Ross River virus, and Q fever, severity of the acute illness was shown to be predictive of the development of a postinfective fatigue disease.²⁰ The frequency of ME/CFS was 8 times higher in patients with confirmed *Giardia* infection when compared with the general population, and fatigue symptoms were still present up to 5 years after infection in some patients.²¹⁻²² Other infectious agents correlated to the development of ME/CFS

include Borna virus,^{24,25} enterovirus,²⁶ and human herpesviruses 6 and 7.²⁷⁻²⁹

The host microbiome has also been implicated as a source of dysregulation leading to ME/CFS. Individuals with ME/CFS present with alterations in their oral and intestinal microbiomes when compared with healthy controls.³⁰⁻³² These alterations, coupled with dysfunction of the intestinal mucosal barrier, can precipitate an inappropriate immune response. Translocations of enteric bacteria into systemic circulation during periods of high activity may contribute to the postexertional malaise.³³ Investigation into the role of microbial triggers continues; however, it is likely to be the primary cause of this disease. Given that each virus, bacteria, and parasite is uniquely different, the resulting infection is more likely due to an underlying dysfunction in the patient's immune system and not the microbe itself.

Immune Dysregulation

Studies have revealed reduced natural killer cell function in patients with ME/CFS, which supports the findings of immune dysregulation.³⁴⁻³⁷ A primary role of natural killer cells is to destroy virally infected cells. A defect in this response would increase susceptibility to viral infections. Additional supporting evidence is the observation of increased immune cell activation markers (CD38, HLA-DR) on CD8 cells using flow cytometry.³⁸ Activated CD8 cells, also called cytotoxic T cells, target damaged host cells and virally infected cells. Overactivation of CD8 cells has been linked to autoimmune diseases and supports the theory of immune dysregulation. An elevation in interleukin-1 β (IL-1 β), IL-12, IL-8, IL-10, and IL-13 after moderate-intensity exercise has also been observed,³⁹ with sustained increase in plasma tumor necrosis factor- α , in patients with ME/CFS compared with healthy controls.³⁹ Tumor necrosis factor- α and IL-1 β are known inducers of acute-phase reactants and not typically elevated after exercise. In addition, a more exaggerated response in complement and an apparent alteration in immune cell gene expression after physical

exertion, most notably toll-like receptor 4, has been uncovered.⁴⁰ Overall, these studies point to a likely involvement in immune dysregulation, resulting in secondary infections, altering the microbial trigger narrative.

Mitochondrial Dysfunction

Patients with ME/CFS have decreased intracellular pH and lower adenosine triphosphate (ATP) production after exercise, impaired oxidative phosphorylation, and mitochondrial damage.⁴¹⁻⁴⁴ A study⁴² showed that carnitine, an essential compound correlated to functional capacity of the mitochondria, was decreased in patients with ME/CFS. Using an "ATP Profile" test, the study further revealed the degree of mitochondrial dysfunction in neutrophils correlated with severity of the patients' illness.⁴² Postexertional fatigue, a common symptom, is also exhibited in patients with mitochondrial disease. In another study,⁴⁵ citrate synthase, a critical enzyme needed for the tricarboxylic cycle, was found at reduced levels in patients with ME/CFS when compared with healthy controls. Additionally, other mitochondrial transmembrane enzyme complexes, including succinate reductase and cytochrome-C oxidase, were reduced in patients with ME/CFS.⁴⁶ The mitochondrial hypothesis is attractive because it could explain symptoms unrelated to fatigue given that mitochondrial dysfunction in specific organs would affect organ function and could explain comorbidities associated with the disease.

Genetic Predisposition

The possibility of a genetic link or predisposition is another area of interest. Genealogy data from 3 generations in the Utah Population Database showed an increased relative risk among first-degree relatives (2.70), second-degree relatives (2.34), and third-degree relatives (1.93). In a twin study, the concordance rate was found to be higher in monozygotic twins (55%) than dizygotic twins (19%).⁴⁹ The expression of major histocompatibility complex class II antigens HLA-DQA1*01 and HLA-DR4 may also be a potential

risk factor for developing ME/CFS.⁵⁰ Additionally, single nucleotide polymorphism in the tumor necrosis factor- α and interferon- γ genes may provide a genetic link to explain the dysregulation of inflammatory cytokine production in patients with ME/CFS.⁵⁰ Single nucleotide polymorphisms were also identified in the glutamate ionotropic receptor kainate type subunit 3 gene, which codes for transmembrane subunits of neuroexcitatory receptors. In addition, a single nucleotide polymorphism in the neuronal PAS domain protein 2 gene, which is a circadian clock gene, was found in an ME/CFS patient cohort.⁵⁰

Oxidative Stress and Endocrine Abnormalities

Oxidative stress and hypothalamic-pituitary-adrenal axis abnormalities are 2 additional areas of investigation. In a study⁵¹ evaluating oxidative stress in patients with ME/CFS compared with a control group, results revealed a greater increase in oxidative stress markers after exertion compared with the control group. Biomarkers evaluated included thiobarbituric acid reactive substance and reduced ascorbic acid. Because the accumulation of reactive oxygen species is known to modify mitochondrial proteins and lipids, oxidative stress may be influencing mitochondrial function.

Hypoactivity with the hypothalamic-pituitary-adrenal (HPA) axis has also been observed. In particular, patients with ME/CFS have been found to have higher adrenocorticotrophic hormone (ACTH) autoantibodies, blunted dehydroepiandrosterone (DHEA) response to ACTH injections, and increased prolactin in response to buspirone.⁵² An increase in ACTH autoantibodies would disrupt the HPA axis, ultimately resulting in depressed cortisol production and psychologic disturbances. Decreased DHEA levels would not only influence androgen production, but also cognitive function and inflammation. The hormone DHEA is a neurotrophin that promotes nerve cell survival and is also an uncompetitive inhibitor of glucose-6-phosphate dehydrogenase, reducing free radical production. An

increase in prolactin would suppress gonadotropin-releasing hormone, further altering the HPA axis.

ME/CFS Diagnostic Criteria and Comorbidities

An estimated 10% of patients with ME/CFS obtain a diagnosis within 5 years, which leaves a vast majority of patients untreated.⁵ The delay in diagnosis can be attributed to a present lack of known biologic markers, varying diagnostic criteria, and inadequate education about ME/CFS among clinicians. The 2 most commonly used diagnostic criteria, both in clinical practice and research, are the 2015 Institute of Medicine criteria¹ and the more commonly used 2003 Canadian Consensus Criteria⁴ (**Figure 1**). For coding purposes, ME/CFS in the *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10) is G04.81.

Treating a patient requires taking a thorough patient history, satisfying the clinical case definition criteria, and ruling out other conditions. A complete laboratory workup should also be obtained to provide a more detailed picture of a patient's condition and to discover any comorbidities that may be present (**Figure 2**). Recognizing a comorbidity is important, as it may sometimes be the clue that leads to a ME/CFS diagnosis and alters the treatment approach. Routine laboratory tests that include thyroid function, liver function, complete blood cell count, and autoimmune testing are necessary for developing a treatment approach. Although no known ME/CFS biological markers are currently known, 2 available methods to reach diagnosis are the 2-day cardiopulmonary exercise test (CPET) and an osteopathic evaluation.

Postexertional malaise is the worsening of a patient's symptoms and function after physical or cognitive activity that was easily endured premorbidly. While fatigue in general can be considered a subjective complaint, accurate energy consumption can be measured using a CPET. The CPET is used to measure exercise capacity in an individual and

2015 The Institute of Medicine Diagnostic Criteria¹
Each Required:
Substantial reduction or impairment in the ability to engage in pre-illness levels of occupation, education, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset, is not the result of ongoing excessive exertion, and is not substantially alleviated by rest
Postexertional malaise
Unrefreshing sleep
Must Have at Least 1 of the Following:
Cognitive impairment
Orthostatic intolerance
2003 Canadian Consensus Criteria⁴
Required:
Fatigue, postexertional malaise and/or fatigue, sleep dysfunction, and pain
Must Have ≥2 Neurological/Cognitive Manifestations:
Confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disorientation and inability to focus vision
Must have ≥1 Symptoms From 2 of the Following Categories:
Autonomic: Orthostatic intolerance, postural orthostatic tachycardia syndrome (POTS), delayed postural hypotension, light-headedness, extreme pallor, nausea, irritable bowel syndrome, urinary frequency, bladder dysfunction, palpitations with or without cardiac arrhythmias, exertional dyspnea
Neuroendocrine: Loss of thermostatic stability, sweating episodes, recurrent feelings of feverishness and cold extremities, intolerance of extremes of heat and cold, weight change, anorexia, loss of adaptability, worsening of symptoms with stress
Immune manifestations: Tender lymph nodes, recurrent sore throat, recurrent flu-like illness, general malaise, new food sensitivities and/or chemical sensitivities
Illness Must Persist for at Least 6 Months

Figure 1.

Descriptions of the 2 most commonly used myalgic encephalomyelitis/chronic fatigue syndrome diagnostic criteria.

provides both objective and reproducible measures of functional capacities for cardiovascular and pulmonary disease. Aerobic/oxidative metabolism is the primary pathway for energy production in activities lasting longer than 90 seconds. In patients with ME/CFS, aerobic metabolism may be impaired, thereby causing activity performed for longer than 90 seconds to rely on anaerobic metabolism. Studies show that despite maximal effort on 2 consecutive days, patients show a decrease in functional capacity.⁵²⁻⁵⁴ While this test objectively measures the hallmark symptom of postexertional fatigue, it is not commonly used in clinical practice because of limited availability and patient tolerance.

Treatment Approaches

As part of an individualized treatment plan, clinicians should educate patients about the disease and encourage a healthy lifestyle. Clinicians should address energy pacing, symptom management, and management of comorbidities. The main focus should include the use of integrated modalities to enable patients to better adapt and manage their chronic disease. A more holistic approach through osteopathic medicine can be used to complement more traditional methods described in this section. Specialists should also be consulted to build a more collaborative treatment plan that is beneficial in managing comorbidities. For example, a cardiologist should diagnose and

Fibromyalgia
Temporomandibular joint syndrome
Irritable bowel syndrome
Multiple chemical sensitivities
Myofascial pain syndrome
Interstitial cystitis
Raynaud phenomenon
Hashimoto thyroiditis
Prolapsed mitral valve
Migraines
Allergies
Sicca syndrome

Figure 2.

List of comorbid conditions with myalgic encephalomyelitis/chronic fatigue syndrome.

manage postural orthostatic tachycardia syndrome, which is a common comorbidity of ME/CFS and a form of dysautonomia that affects blood flow through the body and often causes a person to become dizzy on standing.

Education

Patient education is imperative for the understanding and management of care. However, in our opinion, it is more important to educate clinicians how to diagnose and manage ME/CFS. Because most patients often report feelings of isolation and frustration resulting from negative experiences with clinicians who lack knowledge about ME/CFS, educating clinicians about the disease would improve patient care. Clinicians knowledgeable about ME/CFS would be able to recognize the disease, initiate treatment, and improve patient outcomes earlier than those without an understanding of ME/CFS.

Informed clinicians would result in early disease recognition, timely treatments, and better patient outcomes. Through increased understanding, clinicians can set realistic expectations and achieve improved treatment compliance.

Energy Management

A key diagnostic criterion is profound fatigue absent of ongoing exertion. With energy deficits being a major feature of the disease, educating patients in energy management techniques is helpful. Pacing is one energy management technique that can be taught. The goal of pacing is for a patient to live within his or her individual “energy envelope.” Patients learn to listen to their bodies and stop activities before their symptoms relapse. They learn to divide their daily activities into manageable portions alternating with rest periods throughout the day to avoid overexertion. Decreasing stress can also be effective in maintaining an energy envelope and influencing overall health. Techniques for stress reduction can include meditation, yoga, and tai chi. However, before engaging in alternative methods for stress reduction, an individual’s energy tolerance should be considered.

Sleep Disorders

Unrefreshing sleep is a diagnostic criterion of ME/CFS. If not treated, cognitive function, memory, and pain perception can all be affected. In developing a treatment plan, actions to improve sleep hygiene should be taken. Improving sleep quality has the potential to decrease symptom severity. As such, it is important to manage sleep disorders. If not successful, medications can then be prescribed ([Figure 3](#)).

Diet

For many patients with ME/CFS, maintaining a balanced diet can be challenging because of lack of money to buy food, lack of energy to purchase food, and lack of energy to prepare food. With these restraints present, diet management becomes an important component of treatment. Multivitamin supplementation should be encouraged to offset vitamin and mineral deficiencies and promote better energy metabolism.

Supplements of particular interest include zinc, essential fatty acids, coenzyme Q10 (CoQ10), and vitamin B₁₂.⁵² Zinc deficiency has been linked to reduced natural killer cell function, a known immune impairment

Sleep Medications
Dimenhydrinate, 25-50 mg
Melatonin, 1-3 mg
Tryptophan, 500 mg-3g
Zopiclone, 5-15 mg
Clonazepam, 0.5-1 mg
Doxepin, 2-200 mg
Amitriptyline, nortriptyline, 5-50 mg
Ropinirole or pramipexole, 0.125-0.25 mg
Pain Management
Acetaminophen, 500-1000 mg every 8h as needed
Aspirin, 300-600 mg every 6-8h as needed
Diclofenac, 75-100 mg daily
Naproxen, 500-1000 mg daily
Trazodone, 12.5-150 mg
Cyclobenzaprine, 5-10 mg
Mirtazapine, 7.5-15 mg
Zolpidem, 2.5-10 mg
Gabapentin, 100-1500 mg
Pregabalin, 50-450 mg
Quetiapine, 12.5-100 mg
Antidepressants
Sertraline, 50-200 mg/d
Duloxetine, 20-80 mg/d
Fluoxetine, 20-60 mg/d
Amitriptyline, 25-00 mg/d

Figure 3.

List of medications and dosages that are helpful in managing myalgic encephalomyelitis/chronic fatigue syndrome.

of patients with ME/CFS.^{55,56} Essential fatty acid supplementation has been shown to improve some patient symptoms, as has CoQ10 supplementation.^{57,58} Plasma CoQ10 concentrations are typically low in many patients with ME/CFS because CoQ10 is an important coenzyme in the electron transport chain of the mitochondria, supplementing 100 to 400 mg daily may help.⁵¹ Vitamin B₁₂ can be beneficial. Low levels of vitamin B₁₂ have been found in CSF samples from patients with ME/CFS.⁵⁹ In a 2015 study, frequent vitamin B₁₂ injections

combined with daily doses of oral folic acid was shown to improve energy levels among patients.⁶⁰

Intestinal Dysbiosis

Altered intestinal bacteria may influence the processing of emotions. A connection between intestinal bacteria and the central nervous system, via vagal sensory nerve fibers and the peripheral immune system, is becoming an area of increasing interest.^{61,62} In a 2009 study,⁶³ small amounts of microbes were found to be capable of influencing the paraventricular hypothalamus, the amygdala, and the bed nucleus of the stria terminalis. Because these regions are important for emotion and mood processing, altered intestinal flora may contribute to ME/CFS symptoms. After supplementation with *Lactobacillus casei* strain Shirota for 8 weeks, reduction in anxiety was found.⁶³

Acute presentation of D-lactic acidosis, a result of intestinal *Streptococcus* species overgrowth, has overlapping features with ME/CFS. In a study where intestinal *Streptococcus* was reduced using oral erythromycin, ME/CFS patient outcomes revealed improved quality of sleep and cognition; however, no mood or fatigue symptoms were improved.⁶⁴ While antibiotic therapy is not recommended for ME/CFS management, the alteration of gut bacteria, either by supplementation or removal, seems to have an effect on patient health.

Antidepressants

Since a curative treatment has not been found, the management of comorbidities in patients with ME/CFS is crucial. In addition to fatigue, patients often experience degrees of pain, depression, and anxiety.^{1,2,6-9} While there is stronger evidence for the efficacy of antidepressants in conditions such as fibromyalgia, antidepressants can also work to alleviate depression brought on by dealing with a chronic medical condition.⁶⁵ In a double-blind crossover study,⁶⁶ 60 mg/day of nortriptyline was shown to relieve depressive symptoms and fatigue (as measured by the Beck Depression Inventory and Chronic Fatigue Symptom Checklist). In addition, a case report⁶⁵ has also shown benefit following a

regimen of amitriptyline and doxepin (25-50 mg at night). Cognitive behavioral therapy can also be beneficial when used in conjunction with antidepressants.⁶⁴

Osteopathic Medicine

The unique benefits of the osteopathic approach, which recognizes the person as a unit of body, mind, and spirit, provide an individualized approach to care and may provide temporary relief for some patients. The combination of osteopathic manipulation, thorough treatment discussions, and clarity of information were each reported by patients to be a unique benefit provided from the osteopathic approach.⁶⁷

The use of osteopathic manipulation, whether provided by US-trained osteopathic physicians or foreign-trained osteopaths, has shown measurable improvements with muscle function, pain reduction, and emotional distress.⁶⁸⁻⁷⁶ In a pilot study by Perrin et al,⁶⁸ postexercise muscle function was found to improve after osteopathic manipulation. Considering that postexertional fatigue is a key symptom of ME/CFS, osteopathic manipulation could be a powerful treatment option. In particular, cervical and thoracic muscle energy techniques, while not directly cited in ME/CFS research, are techniques that can be used to reduce the muscle strain that is often present in these patients. Lymphatic techniques such as pedal pump, thoracic pump, and effleurage can also be used to decrease lymphatic congestion that may result from a sedentary history. Additionally, osteopathic manipulation has been shown to influence the components of pain throughout the course of chronic illnesses. Osteopathic manipulation can modify neuronal connections, increase lymphatic drainage, improve musculoskeletal dysfunctions, and, ultimately, alter a patient's perception of pain.⁷⁰

Although osteopathic ME/CFS research is limited, enough is known about OMM to support its application for patients with ME/CFS. Treatments have been shown to decrease muscle pain, cortical potentials, and muscle spasms.⁷¹ Osteopathic manipulation can increase anti-inflammatory cytokine IL-10 and decrease proinflamma-

tory cytokine IL-1 β .⁷² Repetitive treatments have shown to reduce chronic pain.^{72,73} Postural orthostatic tachycardia syndrome, a common comorbidity in which heart rate increases with the change of position, can also be managed better with OMM.⁷⁴ Osteopathic manipulation has been shown to alter changes in the sensorimotor cortical areas and alter autonomic nervous system activity.⁷⁵

Conclusion

Myalgic encephalomyelitis/chronic fatigue syndrome does not originate from a single cause; it results from a multitude of factors that likely include biological and environmental factors. Although ME/CFS research is advancing, a clear need for more progress remains. Currently, there are no known biomarkers. Many clinicians remain uneducated about the disease, and available treatments do not directly target a root cause. To fill these gaps, research needs to expand and uncover diagnostic biomarkers that can speed up recovery. An increase in awareness is also needed to inform both medical communities and the public. Increased awareness would alleviate emotional strain that patients can experience from persons in doubt of the disease's existence and open doors for new research. Including osteopathic medicine in a patient's treatment regimen could provide temporary relief. Yet despite the many obstacles faced, current research is providing a better understanding of ME/CFS, which we believe will lead to better care for patients.

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