Fatigue

Diagnosis/Condition:	Malaise and fatigue Chronic Fatigue Syndrome Other malaise and fatigue
Discipline:	ND
ICD-10 Codes:	R53.82; R53.2; G93.3; R93.3; R53.81; R53.83
Origination Date:	2007
Review/Revised Date:	10/2024
Next Review Date:	10/2026

Patient complaints of fatigue are very common in clinical practice. Statistics of those reporting significant fatigue in a primary care setting is 11-33%, generating over 7 million office visits a year as a primary complaint.[1] Studies on workforce fatigue and its contribution to lost productivity time (LPT) indicate that 66% of workers complaining of fatigue report health-related LPT, while 26% of those not complaining of fatigue report health related LPT.[2] Complaints of fatigue have been documented in all age groups and prevalence is generally higher in women.[3] Fatigue itself is a factor in presenteeism and fatigue accompanies many other causes of presenteeism, such as migraine, back pain and depression. Fatigue is a significant complication of many clinical conditions and treatment regimens and at the end of life. There are usually other co-morbidities and confounding factors to consider in evaluation, diagnosis, and treatment/management.

Myalgic Encephalomyelitis /Chronic fatigue syndrome (EM/CFS) is a common cause of fatigue and is included in this summary. CFS is primarily a disorder of young to middle-aged adults, but cases in children have been recognized. It may also occur in older adults, although coexisting medical conditions usually preclude its consideration in this population. Most series report that CFS is about twice as common in women as in men. The causes of ME/CFS are not fully understood, although evidence suggests that there are many factors involved, including infection as with EBV, Coxiella burnetti, Ross River virus, herpes viruses, mycoplasma, enterovirus, and retroviruses. Genetics, environmental factors, chronic inflammation, low functioning NK cells, T-cell changes, and physical or emotional trauma of any kind have also been evaluated as causes.[5] Research has postulated that mitochondria in CFS/ME patients may have altered function due to a combination of genetic susceptibility and exposure to mitochondrial toxins.[1] It may manifest after an acute infection syndrome with fever, malaise, aching muscles and joints, or respiratory/gastrointestinal symptoms. It can also follow sudden trauma such as MVA or surgery. Gradual onset can occur over many years.

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Symptoms can fluctuate and vary, and the patient may not appear ill at times. They generally experience substantial physical and mental impairment at some point in their illness. There can be remissions, but symptoms often recur. Many never regain full function, and early treatment is needed. The range of symptoms can range from mild to severe, with some being wheelchair-, house- or bed-bound. Symptoms may include recurrent sore throat, low grade fever, lymph node swelling, headache, muscle and joint pain, shortness of breath, irregular heart rate, weakness, intestinal discomfort, depression, profound fatigue, post-exertional malaise, chills and night sweats, allergies and sensitivities to foods, odors, chemicals, light or noise, and loss of concentration. It can be similar to the symptoms of fibromyalgia and conditions like long - COVID, and by definition lasts longer than 6 months. The 2015 revised Centers for Disease Control (CDC) definition of ME/CFS states that patients "must have clinically evaluated, unexplained, persistent or relapsing fatigue of new or definite onset; is not the result of ongoing exertion; is not alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities, plus four or more specifically defined associated symptoms." ME/CFS is considered a diagnosis of exclusion. There are specific criteria to follow, and they can be found here on the CDC website: http://www.cdc.gov/me-cfs/index.html

Subjective Findings and History

The symptom of fatigue can be poorly described by the patient. A thorough evaluation is needed to clarify complaints of "fatigue," "tiredness," or "exhaustion" and to distinguish lack of energy from loss of motivation, sleepiness, or depression which may point to a different cause and/or diagnosis. Fatigue described as loss of interest and enjoyment (anhedonia) for example, may be an indicator of depression. Prominent sleepiness suggests a sleep disorder. A thorough history and intake should cover:

- Systematic inquiry for personal or family history of diseases and medications often associated with fatigue.
- Symptoms of depression, anxiety and/or sleep disorder.
- Negative impact on activities of daily living (ADLs).
- Patients' own understanding of their illness and how they cope with it.
- Social stressors.
- Length and duration of fatigue (less than one month - recent, over one month-prolonged, over six months-chronic). Chronic fatigue does not always translate to CFS.[2]
- Concomitant symptoms (e.g., weight loss, night sweats) as an indicator for undiagnosed chronic illness.
- Screening for psychiatric disorders and/or domestic violence.

Pathophysiology

There are many causes of fatigue and sometimes the causative factor cannot be identified.[3,4] Some are associated with physical disease states such as rheumatoid conditions (including fibromyalgia and Lyme disease)[5], autoimmune disorders, such as lupus and multiple sclerosis,

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mild inflammatory states, endocrine problems like hypothyroid, diabetes and Addison's disease, infections (influenza, tuberculosis (TB), AIDS, Hepatitis A, B, or C, mononucleosis), and cardiovascular or renal disease. Patients with cancer are often chronically fatigued, especially when undergoing treatment. Psychosocial or mental health issues like depression, insomnia or disturbed sleep, grief, and anxiety are common causes of fatigue. Malnutrition from anorexia or eating disorders can also produce fatigue. End-of-life stages also are frequently associated with fatigue. Fatigue is a common undesirable side effect of many prescriptions and over the counter (OTC) medications, as well a recreational drug (including alcohol). Anxiety and depression can cause fatigue or be the result of chronic fatigue.

Objective Findings

- *Examination*—Both a physical and mental state examination must be performed to assess medical and psychiatric diagnoses associated with fatigue.
- *Routine investigations*—If there are no specific indications for special investigations, a standard set of screening tests is adequate.
- *Special investigations*—Immunological and virological tests are generally unhelpful as routine investigations. Sleep studies can be useful in excluding a primary sleep disorder, such obstructive sleep apnea and narcolepsy.
- *Psychological assessment*—It is important to inquire fully about patients' understanding of their illness (questions may include "What do you think is wrong with you?" and "What do you think the cause is?"). Patients may be worried that the fatigue is a symptom of a severe, as yet undiagnosed, disease or that activity will cause a long-term worsening of their condition, and this may alter their health state.
- *Fatigue scales*-- A large number of fatigue scales exist and there is no consensus on which fatigue measuring scales that are most appropriate for use in assessment of fatigue in different diseases.[6] A Quality of Life (QOL) scale combined with a patient-reported outcome measure (PROM) can be a useful tool for diagnosis and measuring treatment outcomes.[7]

Assessment

An assessment that distinguishes predisposing, precipitating, and perpetuating factors is valuable in providing an explanation to patients and for targeting intervention. Fatigue may not always be sufficiently described as a simple continuum from no fatigue to severe fatigue, and a multidimensional approach has been suggested, including physical, cognitive, emotional, and functional axes.[8]

Exam

Complete physical exam (cardiovascular, head and neck, abdominal, pulmonary, neurological, mental/emotional status).

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Labs

There is no diagnostic test for ME/CFS, diagnosis is purely clinical, based on the history and the exclusion of other fatiguing illnesses by physical examination and medical testing.[9]
Common screening laboratory tests for fatigue:

- Complete Blood Count (CBC)
- Ferritin
- Erythrocyte sedimentation rate (ESR) and/or C reactive protein (CRP)
- Chemistry screen (comprehensive metabolic panel) including liver and kidney function, glucose, and electrolytes
- HIV, monospot, tuberculosis (PPD) based on history and risk factors
- Thyroid function panel (including Free T4)
- Urine Dipstick analysis, including glucose and beta hCG in women
- Electrocardiogram (EKG)
- Fasting 2- hour Glucose Tolerance (2HGT) if dysglycemia is suspected

Special Tests

- Salivary cortisol testing for adrenal function[10,11]
- Stool analysis (dysbiosis)[12]
- Heavy metals assessment[13]
- Lactulose/mannitol absorption test
- Food allergy testing
- Hepatitis panel
- Viral and bacterial assays (Lyme's, EBV, CMV, etc.)
- Appropriate diagnostic imaging if there are suspicious findings

Plan

A treatment plan will be predicated on history and physical findings, and once a diagnosis is made of a causative factor, then treatment is based on that condition. When all labs and PE are normal, a diagnosis of ME/CFS, fibromyalgia, or long-virus syndrome like long-COVID must be considered. Caution should be used when assuming that mental health diagnoses are causative of fatigue.

There is no known specific medical therapy for the "cure" of ME/CFS, fibromyalgia, or other long-virus conditions that present with significant fatigue.[14] The clinician-patient relationship is of the utmost importance. Two-thirds of patients with ME/CFS reported that they were "dissatisfied with the quality of their medical care and felt their clinicians lacked communication skills and education regarding their diagnosis"[15]. When IH use was compared between fatigued and non-fatigued persons, "those with CFS-like illness or chronic fatigue were most likely to use body-based and mind-body therapies".[16]

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Explanation of the stepwise approach to assessment and clear establishment of mutual therapeutic goals is critical. Regularly scheduled brief appointments or communication should be planned to monitor patient progress and maintenance of goals.

Mind-Body Therapies:

- Meditation[17]
- Qi Gong[18,19]
- Music therapy may be an alternative treatment for ICF[20]
- A 2024 study concluded that Cognitive Behavior Therapy (CBT) for ME/CFS can lead to significant reductions of fatigue, functional impairment, and physical limitations[21]
- Body awareness interventions can play an important role[22]
- Regular sauna therapy (either radiant heat or far-infrared units) appears to be safe and effective in chronic fatigue[23]

Diet:

- Avoid canned foods and keep refined sugar to a minimum as it suppresses the immune system.
- Identify food allergies/sensitivities and limit intake of these foods.
- A good diet that includes fruits, vegetables and grains and emphasizes whole, natural, unprocessed selections. Fresh foods are preferable and frozen are acceptable.
- Limit caffeine intake and increase water. Although caffeine can provide energy and stimulation, regular intake may lead to fatigue.

Herbal Medicine (Traditional East Asian Medicine):

- A 2014 RCT study concluded "TCM appears to be effective to alleviate the fatigue symptom for people with CFS. However, due to the high risk of bias of the included studies, larger, well-designed studies are needed to confirm the potential benefit in the future."[24]

Herbal Medicine (Western):

- Processed Licorice (Glycyrrhiza glabra)[25]
- Ashwagandha[26]
- Adaptogenic herbs are often used in the treatment of fatigue to balance the stress response in the body. This approach is often taken in the initial treatment approach, while the cause of fatigue is being determined, as well as when there is evidence of adrenal dysfunction. While there are several herbs with adaptogenic qualities such as Eleutherococcus senticosus, Paullinia sorbilis (guarana, Asian ginseng (L. Panax ginseng), Siberian ginseng (Eleutherococcus senticosus), and rhodiola (L. rhodiola rosea).[27,28,29,30]

Homeopathy:

- There is weak but equivocal evidence that the effects of homeopathic medicine are superior to placebo.[31]

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Supplements and Nutrients:

- Ginseng herbal formulas improved fatigue severity compared to controls, especially among patients with CF.[32]
- A series of patients with chronic fatigue syndrome were treated solely with a high-eicosapentaenoic acid-containing essential fatty acid supplement. All showed improvement in their symptomatology within eight to 12 weeks.[33]
- Omega three fatty acid blood levels and supplementation with an omega three fatty acid supplement also displayed positive outcomes in relation to chronic fatigue syndrome symptom alleviation.[34]
- Magnesium supplementation.[35,36]
- l-carnitine, S-adenosylmethionine, and Magnesium are nonpharmacological supplements with the most potential for further research.[37]
- In another study Acetylcarnitine and propionylcarnitine showed beneficial effect on fatigue and attention concentration.[38]
- Treat gut dysbiosis. Elevated levels of gut dysbiosis markers positively correlated with severity of sickness behavior in patients with severe mental illness and chronic fatigue.[39]
- The effects of nutrients and phytonutrients have been shown to help with mental fatigue.[40,41]
- Supplements such as Coenzyme Q10,[42] vitamins B12 and B6,[43,44] Thiamine,[45] NADH,[46,47] DHEA,[48] and beta-carotene that potentiates the immune system and acts as an antioxidant.
- Vitamin C which enhances the destruction of viruses and bacteria.[49]
- Zinc, which is necessary for proper functioning of the thymus and for cellular immunity, and glandular extracts, which enhance immune function.
- Probiotics have demonstrated a significant effect on modulating the anxiety and inflammatory processes in CFS patients.[50]
- Oxaloacetate showed a significant reduction in physical and metal fatigue for ME/CFS patients after 6 weeks of treatment.[51]

Movement and Exercise:

- Results indicate that some individuals with CFS may be able to use low-level, intermittent exercise without exacerbating their symptoms. Thirty minutes of light-intensity, intermittent exercise on patients with chronic fatigue syndrome.[52]
- There is encouraging evidence that some patients may benefit from exercise therapy and no evidence that exercise therapy may worsen outcomes on average.[53]
- Exercise therapy probably has a positive effect on fatigue in adults with CFS compared to usual care or passive therapies.[54]
- Diaphragmatic breathing, good posture, relaxation, and bodywork (e.g., massage, spinal manipulation) are all important stress relievers.
- Activity pacing frameworks for exercise monitoring.[55]

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Soft Tissue Therapies:

- Massage: 2024 study suggest that massage therapy has a significant therapeutic effect on CFS, avoiding adverse reactions and improving fatigue symptoms.[56]
- The intelligent-turtle massage is an effective therapy for relieving the physical symptoms of CFS, and it may show certain effects on the immune functions.[57]

Acupuncture (excluding pharmocoacupture):

- Body acupuncture for 4 weeks in addition to usual care may help improve fatigue in CFS and ICF patients.[58]
- A 2019 study indicated that acupuncture was more effective than sham acupuncture and other interventions (Chinese herbal medicine, mainly).[59]
- A 2022 RCT study indicated the "effects of acupuncture and moxibustion in the treatment of CFS was significantly higher than that of other treatments."[60]

Biopsychosocial approach:

Persistent fatigue requires active management, preferably before it has become chronic. When a specific disease cause of fatigue can be identified, this should be the focus of treatment. If no other specific disease diagnosis can be made, or if medical treatment of disease fails to relieve the fatigue, a broader biopsychosocial management strategy is required. This is important as well due to the lack of laboratory abnormalities, so patients and clinicians may struggle with the validity of the disease and may experience feelings of guilt. Providing validation, support, and reassurance to the patient is key.

- Managing activity and avoidance—Gradual increases in activity can be advised unless there is a clear contraindication. It is critical, however, to distinguish between carefully graded increases carried out in collaboration with the patient and "forced" exercise. It is also important to explain that erratic variation between overactivity on "good" days and subsequent collapse does not help long-term recovery and that "stabilizing" activity is a prerequisite to graded increases.
- Depression and anxiety—If there is evidence of depression a trial of an antidepressant drug is warranted (e.g., tricyclic antidepressant (TCAs), Selective serotonin reuptake inhibitors (SSRIs), or Serotonin-norepinephrine reuptake inhibitors (SNRIs)).
- Up to 50% of patients in one trial attributed their chronic fatigue to mainly psychological causes.[2] Randomized trials and systematic reviews have shown psychological therapies, such as cognitive behavior therapy (CBT) to be equally effective for mild to moderate depression (note: results are dependent on therapy type and clinician experience).[61]
- Managing occupational and social stresses—Patients may be overstressed by working. Those who have left work may be inactive and demoralized and may not wish to return to the same job. These situations require a problem-solving approach to consider how to manage work demands, achieve a return to work, or to plan an alternate career.

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Pharmaceuticals (Prescription) for both fatigue and chronic fatigue syndrome include:

- Antidepressants (as described above), calcium-channel modulators, anti-virals, and anti-retrovirals, muscle relaxants, immune modulators, glucocorticoids, antibacterials, and analgesics.[62,63,64]

Surgical intervention:

- A small study found improvement in severe ME/CFS symptoms following surgery for cervical spinal stenosis.[65]

Referral Criteria

- Undiagnosed or suspected moderate- severe psychiatric disorder (including suicidal ideation).
- Suspected poor prognosis, or severe debilitating disease.
- Worsening symptoms.

Resources for Clinicians (links to authoritative evidence-based information)

Brief Fatigue Inventory. This tool is designed for end of life, but physicians may find this tool useful for evaluating fatigue. https://www.ons.org/assessment-tools/brief-fatigue-inventory-english

Fatigue Scales[66]

- Fatigue Severity scale.
- Fatigue scale.
- Modified Fatigue Impact Scale (MFIS).

Resources for Patients

Center for Disease Control and Prevention (CDC), US Department of Health and Human Services, 888-232-3228 (general CDC voice mail which leads to CFS information)
www.cdc.gov/cfs

Mayo Clinic.com. Fatigue: When to rest, when to worry.
http://www.mayoclinic.com/health/fatigue/HQ00673

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