

“Doctor, I’m So Tired!”

Refining Your Work-up for Chronic Fatigue

Recent advances in our understanding of the pathophysiology of chronic fatigue and related disorders can help guide your response to this common complaint.

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CASE Lauren C, age 35, presents with fatigue, which she says started at least eight months ago and has progressively worsened. The patient, a clerical worker, says she manages to do an adequate job but goes home feeling utterly exhausted each night.

Lauren says she sleeps well, getting more than eight hours of sleep per night on weekends but less than seven hours per night during the week. But no matter how long she sleeps, she never awakens feeling refreshed. Lauren reports that she doesn’t smoke, has no more than four alcoholic drinks per month, and adheres to an “average” diet. She is too tired to exercise.

Lauren is single, with no children. Although she says she has a strong network of family and friends, she increasingly finds she has no energy for socializing. If Lauren were your patient, what would you do?

Fatigue is a common presenting symptom in primary care, accounting for about 5% of adult visits.¹ Defined as a generalized lack of energy, fatigue that persists despite adequate rest or is severe enough to disrupt an individual’s ability to participate in key social and/or occupational activities warrants a thorough investigation.

Because fatigue is a nonspecific symptom that may be linked to a number of medical and psychiatric illnesses or to medications used to treat them, determining the cause can be difficult. In about half of all cases, no specific etiology is found.² This review, which includes the elements of a work-up and management strategies for patients presenting with ongoing fatigue, will help you arrive at the appropriate diagnosis and provide optimal treatment.

CHRONIC FATIGUE: DEFINING THE TERMS

A definition of chronic fatigue syndrome (CFS) was initially published in 1988.³ In subsequent years, the term *myalgic*

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encephalomyelitis (ME) became popular. Although the terms are sometimes used interchangeably, ME often refers to patients whose condition is thought to have an infectious cause and for whom postexertional malaise is a hallmark symptom.⁴

CDC criteria. While several sets of diagnostic criteria for CFS have been developed, the most widely used is that of the CDC, published in 1994 (see Table 1).^{5,6} A diagnosis of CFS is made on the basis of exclusion, subjective clinical interpretation, and patient self-report.

When the first two criteria—fatigue not due to ongoing exertion or other medical conditions that has lasted ≥ 6 months and is severe enough to interfere with daily activities—but fewer than four of the CDC’s eight concurrent symptoms (eg, headache, unrefreshing sleep, and postexertion malaise lasting > 24 h) are present, idiopathic fatigue, rather than CFS, is diagnosed.⁶

International Consensus Criteria (ICC). In 2011, the ICC for ME were proposed in an effort to provide more specific diagnostic criteria (see Table 2, page 28).⁷ The ICC emphasize fatigability, or what the authors identify as “post-exertional neuroimmune exhaustion.”

The ICC have not yet been broadly researched. But an Australian study of patients with chronic fatigue found that those who met the ICC definition were sicker and more homogeneous, with significantly lower scores for physical and social functioning and bodily pain, compared with those who fulfilled the CDC criteria alone.⁸

CHRONIC FATIGUE & NEUROPSYCHIATRIC CONDITIONS: COMMON THREADS

Recent research has made it clear that depression, somatization, and CFS share some biological underpinnings. These include biomarkers for inflammation, cell-mediated immune activation—which may be related to the symptoms of fatigue—autonomic dysfunction, and hyperalgesia.⁹ Evidence suggests that up to two-thirds of patients with CFS also meet the criteria for a psychiatric disorder.¹⁰ The most common psychiatric conditions are major depressive disorder (MDD), affecting an estimated 22% to 32% of those with CFS; anxiety disorder, affecting about 20%; and somatization disorder, affecting about 10%—at least double the incidence of the general population.¹⁰

Others point out, however, that up to half of those with CFS do *not* have a psychiatric disorder.¹¹

TABLE 1
CDC Diagnostic Criteria
for Chronic Fatigue Syndrome

All of the following:

1. The individual has severe chronic fatigue for ≥ 6 consecutive months that is not due to ongoing exertion or other medical conditions associated with fatigue*
2. The fatigue significantly interferes with daily activities and/or work
3. The individual concurrently has ≥ 4 of the following 8 symptoms:
 - Postexertional malaise lasting > 24 h
 - Unrefreshing sleep
 - Significant impairment of short-term memory or concentration
 - Muscle pain
 - Multi-joint pain without swelling or redness
 - Headaches of a new type, pattern, or severity
 - Tender cervical or axillary lymph nodes
 - Sore throat that is frequent or recurring

* Other medical conditions associated with fatigue must be ruled out by a clinician after diagnostic tests have been conducted.

Sources: Fukuda et al. *Ann Intern Med.* 1994⁵; CDC.⁶

A diagnosis of somatization disorder, in particular, depends largely on a subjective interpretation of whether the presenting symptoms have a physical cause.¹⁰

CFS and MDD comorbidity. The most widely studied association between CFS and psychiatric disorders involves MDD. Observational studies have found patients with CFS have a lifetime prevalence of MDD of 65%,^{12,13} which is higher than that of patients with other chronic diseases. Overlapping symptoms include fatigue, sleep disturbance, poor concentration, and memory problems. However, those with CFS have fewer symptoms related to anhedonia, poor self-esteem, guilt, and suicidal ideation compared with individuals with MDD.^{12,13}

There are several possible explanations for CFS and MDD comorbidity, which are not necessarily mutually exclusive.¹⁰ One theory is that CFS is an atypical form of depression; another holds that the disability associated with CFS leads to depression, as is the case with many other chronic illnesses; and a third points to overlapping pathophysiology.¹⁰

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TABLE 2
International Consensus Criteria
for Myalgic Encephalomyelitis

Postexertional neuroimmune exhaustion:
Compulsory

1. Marked, rapid physical and/or cognitive fatigability in response to exertion
2. Postexertional symptom exacerbation
3. Postexertional exhaustion
4. Recovery period is prolonged
5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level

Neurologic impairments: ≥ 1 symptom from 3 of the following 4 categories

1. Neurocognitive
 - a. Difficulty processing information
 - b. Short-term memory loss
2. Pain
 - a. Headaches
 - b. Significant pain
3. Sleep disturbance
 - a. Disturbed sleep patterns
 - b. Unrefreshed sleep
4. Neurosensory, perceptual, and motor disturbance

Immune, gastrointestinal, and genitourinary impairments: ≥ 1 symptom from 3 of the following 5 categories

1. Flulike symptoms (may be recurrent or chronic and typically activate or worsen with exertion)
2. Susceptibility to viral infections, with prolonged recovery periods
3. Gastrointestinal tract
4. Genitourinary
5. Sensitivities to food, medications, odors, or chemicals

Energy production/transportation impairments: ≥ 1 symptom

1. Cardiovascular
2. Respiratory
3. Loss of thermostatic stability
4. Intolerance of extremes of temperature

Source: Carruthers et al. *J Intern Med.* 2011.⁷

An emerging body of evidence suggests that CFS and MDD have some common oxidative and nitrosative biochemical pathways. Activated by in-

fection, psychologic stress, and immune disorders, they are believed to have damaging free radical and nitric oxide effects at the cellular level.¹⁴ The cellular effects can result in fatigue, muscle pain, and flulike malaise.

Cortisol response differs

CFS and MDD might be distinguishable by another pathway—the hypothalamic-pituitary-adrenal (HPA) axis. MDD is classically associated with activation and *raised* cortisol levels, while CFS is consistently associated with impaired HPA axis functioning and *reduced* cortisol levels.¹⁰ The majority of patients with CFS report symptoms of cognitive decline, with the acquisition of new verbal learning and information-processing speed particularly likely to be impaired.¹⁵

A meta-analysis of 50 studies of patients with CFS showed deficits in attention, memory, and reaction time, but not in fine motor speed, vocabulary, or reasoning.¹⁶ Autonomic dysfunction has also been observed, including disordered sympathetic activity. The most frequently observed abnormalities on autonomic testing are postural hypotension, tachycardia syndrome, neurally mediated hypotension, and heart rate variability during tilt table testing.¹⁶

THE LINK BETWEEN INFECTION AND CFS

Several infectious agents have been associated with ME/CFS, including the Epstein-Barr virus (EBV), herpes simplex virus 6, parvovirus, Q fever, and Lyme disease.^{8,17,18} Most agents that have been linked to ME/CFS are associated with persistent infection and thus incitement of the immune system.

Numerous observational studies^{17,18} have documented postinfectious fatigue syndromes after acute viral and bacterial infections and symptoms suggestive of infection, such as fever, myalgias, and respiratory and gastrointestinal distress. In one prospective Australian study,¹⁹ investigators identified 253 cases of acute EBV, Ross River virus, and Q fever. Of those 253 patients, 12% went on to develop CFS, with a higher likelihood among those with more severe acute symptoms. No correlation with preexisting psychiatric disorders was found.

Muscle mitochondria studies have demonstrated what appear to be acquired abnormalities in those with CFS.^{20,21} Signs of increased oxidative stress have been found in both blood and muscle samples from patients with CFS, and longitudinal studies suggest that oxidative stress is greatest dur-

TABLE 3

Differential Diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Cardiopulmonary: Congestive heart failure, COPD, peripheral vascular disease, atypical angina
Disturbed sleep: Sleep apnea, sleep disorder, allergic or vasomotor rhinitis, anatomic respiratory obstruction
Endocrine: Diabetes, hyper- or hypothyroidism, pituitary insufficiency, hypercalcemia, adrenal insufficiency, chronic renal disease, hepatic failure
Gastroenterologic: Celiac disease, malabsorption, GERD
Infectious: Endocarditis, tuberculosis, mononucleosis, hepatitis, parasitic disease, HIV, cytomegalovirus
Inflammatory: Rheumatologic disorders, systemic lupus erythematosus, fibromyalgia, Sjögren syndrome, polymyalgia rheumatica, temporal arteritis, idiopathic inflammatory myopathy
Neurologic: Multiple sclerosis, neuromuscular diseases, epilepsy, stroke, head injury with residual neurologic deficits, spinal cord disease
Psychologic: Depression, anxiety, somatization disorder, dysthymic disorder
Toxins: Abuse of alcohol and/or other substances, heavy metal toxicity
Other: Chronic illness such as cancer

Sources: Fukuda et al. *Ann Intern Med.* 1994⁵; Vincent et al. *Mayo Clin Proc.* 2012²⁴; Goroll et al. 2014.²⁵

ing periods of clinical exacerbation.²² Increased lactate levels suggest increased anaerobic metabolism in the central nervous system consistent with mitochondrial dysfunction. Several studies have demonstrated that exercise can precipitate oxidative stress in patients with CFS, in contrast with healthy controls and controls with other chronic illnesses, suggesting a physiologic basis for their postexertional symptoms.¹⁷

Autoinflammatory syndrome induced by adjuvants, a rare syndrome associated with vaccine administration, has been linked to postvaccination adverse events, exposure to silicone implants, Gulf War syndrome (related to multiple vaccinations), and macrophagic myofasciitis. All involve exposure to immune adjuvants and have similar clinical manifestations. The corresponding exposures appear to trigger an autoimmune response in susceptible individuals. The hepatitis B vaccine is most often associated with CFS, with symptoms occurring within 90 days of administration.²³

THE CLINICAL WORK-UP: PUTTING KNOWLEDGE INTO PRACTICE

Familiarity with potential causes of and connections with ME/CFS will help you ensure that patients who say they're always tired receive a thorough work-up. Start with a medical history, inquiring directly about medical and psychiatric disorders that may contrib-

ute to fatigue (see Table 3).^{5,24,25} Include a medication history as well, to help determine whether the fatigue is drug-related (see Table 4, page 30).^{5,25}

What to ask. Determine the onset, course, duration, daily pattern, and impact of fatigue on the patient's daily life. Inquire, too, about related symptoms of daytime sleepiness, dyspnea on exertion, generalized weakness, and depressed mood. The prominence of any of these rather than fatigue, per se, point to a diagnosis of a chronic illness other than ME/CFS.

Keep in mind, too, that patients with an organ-based medical illness tend to associate their fatigue with activities that they are unable to complete, such as shopping or light housework. In contrast, those with fatigue that is not organ-based typically say that they're tired all the time. Their fatigue is not necessarily related to exertion, nor does it improve with rest.²⁶

To address this distinction, take a sleep history, assessing both the quality and quantity of the patient's sleep to determine how it affects symptoms.²⁷ Consider using a questionnaire designed to help distinguish between *sleepiness*—and a primary sleep disorder—and fatigue,²⁸ such as the Fatigue Severity Scale of Sleep Disorders (www.healthywomen.org/sites/default/files/FatigueSeverityScale.pdf).

What to rule out. In addition to a medical history, the physical examination should be oriented toward ruling out secondary causes of fatigue. In addition to a system-by-system approach to the differential

TABLE 4

Drug-related Fatigue? Ask About These Medications

Analgesics	Fibrates
Antibiotics	Muscle relaxants
Antidepressants	Opioids
Antihistamines	Proton-pump inhibitors
Antihypertensives	Sedative-hypnotics
Chemotherapeutic agents	Statins

Sources: Fukuda et al. *Ann Intern Med.* 1994⁵; Goroll et al. 2014.²⁵

diagnosis, carefully observe the patient's general appearance, with attention to his or her level of alertness, grooming, and psychomotor agitation or retardation as possible signs of a psychiatric disorder. To rule out neurologic causes, evaluate muscle bulk, tone, and strength; deep tendon reflexes; and sensory and cranial nerves, as well.²⁹

Lab tests to consider. In most cases of ME/CFS, basic studies—complete blood count with differential, erythrocyte sedimentation rate, blood chemistry, and thyroid-stimulating hormone (TSH) levels—are sufficient. When no medical or psychiatric cause has been found, additional tests may be ordered on a case-by-case basis, although laboratory analysis affects the management of fatigue in less than 5% of such patients.³⁰ Tests to consider include:

- Creatine kinase (for patients who report pain or muscle weakness)
- Pregnancy test (for women of childbearing age)
- Ferritin testing (for young women who might benefit from iron supplementation for levels < 50 ng/mL even if anemia is not present)³¹
- Hepatitis C screening (recommended by the US Preventive Services Task Force for those born between 1945 and 1965)³²
- HIV screening and the purified protein derivative test for tuberculosis (based on patient history).

Forego routine testing for other infections

Routine testing for infectious diseases and conditions associated with fatigue, such as EBV or Lyme disease, immune deficiency (eg, immunoglobulins), inflammatory disease (eg, antinuclear antibodies, rheumatoid factor), celiac disease, vitamin D defi-

ciency, vitamin B₁₂ deficiency, or heavy metal toxicity, is unlikely to be helpful.²⁹ Additional testing simply to reassure a worried patient usually does not accomplish that objective.³³

Additional studies, referrals to consider. If you suspect that a patient has a sleep disorder, a referral to a sleep clinic to rule out idiopathic sleep disorders, obstructive sleep apnea, or movement disorders that interfere with sleep may be in order. Spirometry and echocardiography may be helpful for some patients. If you suspect peripheral muscle fatigue, a referral for neuromuscular testing is indicated.

Lauren's medical history reveals that she also has irritable bowel syndrome, which she manages with diet and OTC medication, as needed for constipation or diarrhea. She denies having any other chronic conditions. Her only other symptoms, she reports, are mild upper back pain after spending long hours at the computer and arthralgias in her left knee and both hands. She admits to being "somewhat depressed" in the last few months but denies the presence of anhedonia.

The patient's physical examination is normal, and her depression screen does not meet the criteria for MDD. Her metabolic chemistry panel, complete blood count, TSH, and sedimentation rate are all normal, as well.

SYMPTOM MANAGEMENT AND COPING STRATEGIES

When no specific cause of chronic fatigue is found, the focus shifts from diagnosis to symptom management and coping strategies. This requires engagement with the patient. It is important to acknowledge the existence of his or her symptoms and to reassure the patient that further investigation may be warranted later, should new symptoms emerge. Advise the patient, too, that periods of remission and relapse are likely.

Strategies designed to motivate patient self-management, as well as the formulation of patient-centered treatment plans, have been shown to reduce symptom scores.³⁴ Participation in a support group, as well as frequent follow-up visits with a primary care provider, a behavioral therapist, or both, may help to provide needed psychological support.

Evidence of the effectiveness of specific therapies for ME/CFS is limited; however, the best-studied approaches are cognitive behavioral therapy (CBT) and graded exercise therapy.³⁵ Exercise should be low intensity, such as walking or cycling for 30 minutes

three times a week, with a gradual increase in duration and frequency over a period of weeks to months. Patients with cancer-related fatigue may benefit from yoga, group therapy, and stress management.³⁶

Associated mood and pain symptoms should be treated, as well. Bupropion, which is somewhat stimulating, may be considered as an initial treatment for patients with depression and clinically significant fatigue.

Other potentially beneficial approaches include a healthy diet, avoidance of more than nominal amounts of alcohol, relative avoidance of caffeine (no more than one cup of a caffeinated beverage in the morning), and stress reduction techniques.

Attention to good sleep hygiene may be especially beneficial, including a regular bedtime routine and sleep schedule, and elimination of bedroom light and noise. Pharmacologic treatments for insomnia should be used with caution, if at all.

Lauren receives a referral for CBT and is scheduled for a return visit in four weeks. At the advice of both her primary care provider and the behavioral therapist, she gradually makes several lifestyle changes. She begins going to bed earlier on weeknights to ensure that she sleeps for at least seven hours. She improves her diet, with increasing emphasis on vegetables, fruits, and whole grains. She also starts a walking program, increasing gradually to a total of three hours per week. After four months, she adds a weekly trip to a gym, where she practices resistance training for about 40 minutes.

Lauren also increases her social activities on weekends and recently accepted an invitation to join a book club. Six months from her initial visit, she notes that although she is still more easily fatigued than most people, she has made significant improvement.

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