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“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.

CASE ▶ Lauren C, age 35, comes to the clinic because of fatigue, which she says started at least 8 months ago and has gotten progressively worse. The patient, a clerical worker, says she manages to do an adequate job but goes home feeling utterly exhausted each night.

Ms. C says she sleeps well, getting more than 8 hours of sleep per night on weekends but fewer than 7 hours per night during the week. But no matter how long she sleeps, she never awakens feeling refreshed. Ms. C reports that she doesn’t smoke, has no more than 4 alcoholic drinks per month, and adheres to an “average” diet. She is too tired to exercise.

Ms. C 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 Ms. C 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 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 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 Centers for Disease Control and Prevention (CDC), published in 1994 (**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 2 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 4 of the CDC’s 8 concurrent symptoms (eg, headache, unrefreshing sleep, and postexertion malaise lasting >24 hours) are present, idiopathic fatigue, rather than CFS, is diagnosed.⁶



Patients with an organ-based medical illness tend to associate their fatigue with activities that they are unable to complete, while those with fatigue that is not organ-based typically say that they're tired all the time.

■ International Consensus Criteria (ICC).

In 2011, the ICC for ME were proposed in an effort to provide more specific diagnostic criteria (TABLE 2).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 A diagnosis of somatization disorder, in particular, depends largely on a subjective interpretation of whether or not 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}

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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.

TABLE 1

The CDC's diagnostic criteria for chronic fatigue syndrome^{5,6}

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: <ul style="list-style-type: none"> • postexertional malaise lasting >24 hrs • 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

CDC, Centers for Disease Control and Prevention.

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

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

An emerging body of evidence suggests that CFS and MDD have some common oxidative and nitrosative biochemical pathways. Activated by infection, psychological 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 flu-like 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

TABLE 2

International Consensus Criteria for myalgic encephalomyelitis⁷

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 4 following 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 disturbances
Immune, GI, and GU impairments: ≥ 1 symptom from 3 of the following 5 categories	
1.	Flu-like symptoms (may be recurrent or chronic and typically activate or worsen with exertion)
2.	Susceptibility to viral infections, with prolonged recovery periods
3.	GI tract
4.	GU
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

GI, gastrointestinal; GU, genitourinary.

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 during 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



Several infectious agents have been associated with ME/CFS, including the Epstein-Barr virus, herpes simplex virus 6, parvovirus, Q fever, and Lyme disease.



Routine testing for infectious diseases and conditions associated with fatigue, such as Epstein-Barr virus or Lyme disease, immune deficiency, and inflammatory disease, is unlikely to be helpful.

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 contribute to fatigue (TABLE 3).^{5,24,25} Include a medication history, as well, to help determine whether the fatigue is drug-related (TABLE 4).^{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 (<http://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 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 child-bearing 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
- human immunodeficiency virus 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 dis-

TABLE 3

Differential diagnosis of ME/CFS^{5,24,25}

Cardiopulmonary: CHF, COPD, peripheral vascular disease, atypical angina
Disturbed sleep: sleep apnea, sleep disorder, allergic or vasomotor rhinitis, anatomic respiratory obstruction
Endocrine: DM, hyper- or hypothyroidism, pituitary insufficiency, hypercalcemia, adrenal insufficiency, chronic renal disease, hepatic failure
Gastroenterologic: Celiac disease, malabsorption, GERD
Infectious: endocarditis, TB, mononucleosis, hepatitis, parasitic disease, HIV, cytomegalovirus
Inflammatory: rheumatologic disorders, systemic lupus erythematosus, fibromyalgia, Sjögren's syndrome, polymyalgia rheumatica, temporal arteritis, idiopathic inflammatory myopathy
Neurologic: MS, neuromuscular diseases, epilepsy, stroke, head injury with residual neurologic deficits, spinal cord disease
Psychological: depression, anxiety, somatization disorder, dysthymic disorder
Toxins: abuse of alcohol and/or other substances, heavy metal toxicity
Other: chronic illness such as cancer

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus; MS, multiple sclerosis; TB, tuberculosis.

ease (eg, antinuclear antibodies, rheumatoid factor), celiac disease, vitamin D deficiency, 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.

CASE ► Ms. C's medical history reveals that she also suffers from irritable bowel syndrome, which she manages with diet and over-the-counter 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 physician, 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



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Bupropion, which is somewhat stimulating, may be considered as an initial treatment for patients with depression and clinically significant fatigue.

TABLE 4
Is the fatigue drug-related?
Ask about these medications^{5,25}

Analgesics
Antibiotics
Antidepressants
Antihistamines
Antihypertensives
Chemotherapeutic agents
Fibrates
Muscle relaxants
Opioids
PPIs
Sedative-hypnotics
Statins

PPIs, proton-pump inhibitors.

3 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.

CASE ▶ Ms. C receives a referral for CBT and is scheduled for a return visit in 4 weeks.

At the advice of both her primary care physician and the behavioral therapist, Ms. C gradually makes several lifestyle changes. She begins going to bed earlier on weeknights to ensure that she sleeps for at least 7 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 3 hours per week. After 4 months she adds a weekly trip to a gym, where she practices resistance training for about 40 minutes.

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

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