

their respective chapters. The pathophysiology of each is unknown. Idiopathic chronic fatigue is used to describe the syndrome of unexplained chronic fatigue in the absence of enough additional clinical features to meet the diagnostic criteria for chronic fatigue syndrome.

APPROACH TO THE PATIENT: Fatigue

A detailed history focusing on the quality, pattern, time-course, associated symptoms, and alleviating factors of fatigue is critical in defining the syndrome, determining whether fatigue is the appropriate designation, determining whether the symptoms are acute or chronic, and determining whether fatigue is primarily mental, physical, or both in order to direct further evaluation and treatment. The review of systems should attempt to distinguish fatigue from excessive daytime sleepiness, dyspnea on exertion, exercise intolerance, and muscle weakness. The presence of fever, chills, night sweats, or weight loss should raise suspicion for an occult infection or malignancy. A careful review of prescription, over-the-counter, herbal, and recreational drug and alcohol use is mandatory. Circumstances surrounding the onset of symptoms and potential triggers should be investigated. The social history is important, with attention paid to job stress and work hours, the social support network, and domestic affairs including a screen for intimate partner violence. Sleep habits and sleep hygiene should be questioned. The impact of fatigue on daily functioning is important to understand the patient's experience and gauge recovery and the success of treatment.

The physical examination of patients with fatigue is guided by the history and differential diagnosis. A detailed mental status examination should be performed with particular attention to symptoms of depression and anxiety. A formal neurologic examination is required to determine whether objective muscle weakness is present. This is usually a straightforward exercise, although occasionally patients with fatigue have difficulty sustaining effort against resistance and sometimes report that generating full power requires substantial mental effort. On confrontational testing, they are able to generate full power for only a brief period before suddenly giving way to the examiner. This type of weakness is often referred to as *breakaway weakness* and may or may not be associated with pain. This is contrasted with weakness due to lesions in the motor tracts or lower motor unit, in which the patient's resistance can be overcome in a smooth and steady fashion and full power can never be generated. Occasionally, a patient may demonstrate fatigable weakness, in which power is full when first tested but becomes weak upon repeat evaluation without interval rest. Fatigable weakness, which usually indicates a problem of neuromuscular transmission, never has the sudden breakaway quality that one occasionally observes in patients with fatigue. If the presence or absence of muscle weakness cannot be determined with the physical examination, electromyography with nerve conduction studies can be a helpful ancillary test.

The general physical examination should screen for signs of cardiopulmonary disease, malignancy, lymphadenopathy, organomegaly, infection, liver failure, kidney disease, malnutrition, endocrine abnormalities, and connective tissue disease. Although the diagnostic yield of the general physical examination may be relatively low in the context of evaluation of unexplained chronic fatigue, elucidating the cause of 2% of cases in one prospective analysis, the yield of a detailed neuropsychiatric and mental status evaluation is likely to be much higher, revealing a potential explanation for fatigue in up to 75–80% of patients in some series. Furthermore, the rite of physical examination demonstrates a thorough and systematic approach to the patient's complaint and helps build trust and a therapeutic alliance.

Laboratory testing is likely to identify the cause of chronic fatigue in only about 5% of cases. Beyond a few standard screening tests, laboratory evaluation should be guided by the history and physical examination; extensive testing is more likely to lead to false-positive

results that require explanation and unnecessary investigation and should be avoided in lieu of frequent clinical follow-up. A reasonable approach to screening includes a complete blood count with differential (to screen for anemia, infection, and malignancy), electrolytes (including sodium, potassium, and calcium), glucose, renal function, liver function, and thyroid function. Testing for HIV and adrenal function can also be considered. Published guidelines defining chronic fatigue syndrome also recommend an erythrocyte sedimentation rate (ESR) as part of the evaluation for mimics, but unless the value is very high, such nonspecific testing in the absence of other features is unlikely to clarify the situation. Routine screening with an antinuclear antibody (ANA) test is also unlikely to be informative in isolation and is frequently positive at low titers in otherwise healthy adults. Additional unfocused studies, such as whole-body imaging scans, are usually not indicated; in addition to their inconvenience, potential risk, and cost, they often reveal unrelated incidental findings that can prolong the workup unnecessarily.

TREATMENT FATIGUE

The first priority of treatment is to address the underlying disorder or disorders that account for fatigue, because this can be curative in select contexts and palliative in others. Unfortunately, in many chronic illnesses, fatigue may be refractory to traditional disease-modifying therapies, and it is important in such cases to evaluate for other potential contributors, because the cause may be multifactorial. Antidepressant treatment ([Chap. 466](#)) may be helpful for treatment of chronic fatigue when symptoms of depression are present and may be most effective in the context of a multimodal approach. However, antidepressants can also cause fatigue and should be discontinued if they are not clearly effective. Cognitive-behavioral therapy has also been demonstrated to be helpful in the context of chronic fatigue syndrome as well as cancer-associated fatigue. Graded exercise therapy in which physical exercise, most typically walking, is gradually increased with attention to target heart rates to avoid overexertion, was shown to modestly improve walking times and self-reported fatigue measures in patients in the United Kingdom with chronic fatigue syndrome in the large 2011 randomized controlled PACE trial. Psychostimulants such as amphetamines, modafinil, and armodafinil can help increase alertness and concentration and reduce excessive daytime sleepiness in certain clinical contexts, which may in turn help with symptoms of fatigue in a minority of patients, but they have generally proven to be unhelpful in randomized trials for treating fatigue in posttraumatic brain injury, Parkinson's disease, and MS.

Development of more effective therapy for fatigue is hampered by limited knowledge of the biologic basis of this symptom. Tentative data suggests that proinflammatory cytokines, such as interleukin 1 β and tumor necrosis factor α , might mediate fatigue in some patients; thus, cytokine antagonists represent one possible future approach.

PROGNOSIS

Acute fatigue significant enough to require medical evaluation is more likely to lead to an identifiable medical, neurologic, or psychiatric cause than unexplained chronic fatigue. Evaluation of unexplained chronic fatigue most commonly leads to diagnosis of a psychiatric condition or remains unexplained. Identification of a previously undiagnosed serious or life-threatening culprit etiology is rare on longitudinal follow-up in patients with unexplained chronic fatigue. Complete resolution of unexplained chronic fatigue is uncommon, at least over the short term, but multidisciplinary treatment approaches can lead to symptomatic improvements that can substantially improve quality of life.