

ME/CFS as well as cancer-associated fatigue. Both cognitive-behavioral therapy and graded exercise therapy, in which physical exercise, most typically walking, is gradually increased with attention to target heart rates to avoid overexertion, were shown to modestly improve walking times and self-reported fatigue measures when compared to standard medical care in patients in the United Kingdom with chronic fatigue. These benefits were maintained after a median follow-up of 2.5 years. 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, cancer, and MS. In patients with low vitamin D status, vitamin D replacement may lead to improvement in fatigue.

Development of more effective therapy for fatigue is hampered by limited knowledge of the biologic basis of this symptom, including how fatigue is detected and registered in the nervous system. Proinflammatory cytokines, such as interleukin 1 α and 1 β and tumor necrosis factor α , might mediate fatigue in some patients. While preliminary studies of biologic therapies that inhibit cytokines have suggested a benefit against fatigue in some patients with inflammatory conditions, this approach has largely not led to improvement in clinical trials that focused on fatigue as the primary endpoint. Nonetheless, specific targeting with cytokine antagonists could represent a possible future approach for some patients.

■ PROGNOSIS

Acute fatigue significant enough to require medical evaluation is more likely to lead to an identifiable medical, neurologic, or psychiatric cause than is 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, even with longitudinal follow-up of patients with unexplained