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therapy. Vestibular suppressant medications should not be used, as they will increase the imbalance. Evaluation by a neurologist is important not only to confirm the diagnosis but also to consider any other associ ated neurologic abnormalities that may clarify the etiology. ■ ■CENTRAL VESTIBULAR DISORDERS Central lesions causing vertigo typically involve vestibular pathways in the brainstem and/or cerebellum. They may be due to discrete lesions, such as from ischemic or hemorrhagic stroke (Chaps. 437–439), demyelination (Chap. 455), or tumors (Chap. 95), or they may be due to neurodegenerative conditions that include the vestibulocerebellum (Chaps. 442–445). Subacute cerebellar degeneration may be due to immune, including paraneoplastic, processes (Chaps. 99 and 450). Table 24-1 outlines important features of the history and examination that help to identify central vestibular disorders. Acute central vertigo is a medical emergency, due to the possibility of life-threatening stroke or hemorrhage. All patients with suspected central vestibular disorders should undergo brain MRI, and the patient should be referred for full neurologic evaluation. ■ ■FUNCTIONAL DIZZINESS Psychological factors play an important role in chronic dizziness. First, dizziness may be a somatic manifestation of a psychiatric condition such as major depression, anxiety, or panic disorder (Chap. 463). Second, patients may develop anxiety and autonomic symptoms as a consequence or comorbidity of an independent vestibular disorder. One particular form of this has been termed variously phobic postural vertigo, psychophysiologic vertigo, or chronic subjective dizziness, but is now referred to as persistent postural-perceptual dizziness (PPPD). These patients have a chronic feeling (3 months or longer) of fluctuat ing dizziness and disequilibrium that is present at rest but worse while standing. There is an increased sensitivity to self-motion and visual motion (e.g., watching movies) and a particular intensification of symptoms when moving through complex visual environments such as supermarkets. Although there may be a past history of an acute vestib ular disorder (e.g., vestibular neuritis), the neuro-otologic examination and vestibular testing are normal or indicative of a compensated ves tibular deficit, indicating that the ongoing subjective dizziness cannot be explained by a primary vestibular pathology. Anxiety disorders are particularly common in patients with chronic dizziness; when present, TABLE 24-2 Treatment of Vertigo AGENTa DOSEb Antihistamines Meclizine 25–50 mg 3 times daily Dimenhydrinate 50 mg 1–2 times daily Promethazine 25 mg 2–3 times daily (also can be given rectally and IM) Benzodiazepines Diazepam 2.5 mg 1–3 times daily Clonazepam 0.25 mg 1–3 times daily Anticholinergic Scopolamine transdermalc Patch Physical therapy Repositioning maneuversd Vestibular rehabilitation Other Diuretics and/or low-sodium (1000 mg/d) diete Antimigrainous drugsf Selective serotonin reuptake inhibitorsg aAll listed drugs are approved by the U.S. Food and Drug Administration, but most are not approved for the treatment of vertigo. bUsual oral (unless otherwise stated) starting dose in adults; a higher maintenance dose can be reached by a gradual increase. cFor motion sickness only. dFor benign paroxysmal positional vertigo. eFor Ménière’s

disease. fFor vestibular migraine. gFor persistent postural-perceptual vertigo and anxiety.

they contribute substantially to the morbidity. Treatment approaches for PPPD include pharmacological therapy with selective serotonin reuptake inhibitors (SSRIs), cognitive-behavioral psychotherapy, and vestibular rehabilitation. Vestibular suppressant medications generally should be avoided.

■ ■TREATMENT Table 24-2 provides a list of commonly used medications for suppres sion of vertigo. As noted, these medications should be reserved for short-term control of active vertigo, such as during the first few days of acute vestibular neuritis, or for acute attacks of Ménière's disease. They are less helpful for chronic dizziness and, as previously stated, may hin der central compensation. An exception is that benzodiazepines may attenuate psychosomatic dizziness and the associated anxiety, although SSRIs are generally preferable in such patients. Fatigue CHAPTER 25 Vestibular rehabilitation therapy promotes central adaptation pro cesses that compensate for vestibular loss and also may help habituate motion sensitivity and other symptoms of perceptual dizziness. The general approach is to use a graded series of exercises that progressively challenge gaze stabilization and balance. For patients with bilateral vestibular hypofunction, an implanted vestibular prosthesis has shown promise as a future option. ■ ■FURTHER READING Altissimi G et al: Drugs inducing hearing loss, tinnitus, dizziness and vertigo: An updated guide. Eur Rev Med Pharmacol Sci 24:7946, 2020. Kim JS, Zee DS: Benign paroxysmal positional vertigo. N Engl J Med 370:1138, 2014. Smyth D et al: Vestibular migraine treatment: A comprehensive practical review. Brain 145:3741, 2022. Staab JP: Persistent postural-perceptual dizziness. Neurol Clin 41:647, 2023. Jeffrey M. Gelfand, Vanja C. Douglas

Fatigue Fatigue is one of the most common symptoms in clinical medicine. It is a prominent manifestation of a number of systemic, neurologic, and psychiatric syndromes, although a precise cause will not be identified in a substantial minority of patients. Fatigue refers to the subjective experience of physical and mental weariness, sluggishness, low energy, and exhaustion. In the context of clinical medicine, fatigue is most practically defined as difficulty initiating or maintaining voluntary mental or physical activity. Nearly everyone who has ever been ill with a self-limited infection has experienced this near-universal symptom, and fatigue is usually brought to medical attention only when it is either of unclear cause, fails to remit, or the severity is out of propor tion with what would be expected for the associated trigger. Fatigue should be distinguished from muscle weakness, a reduction of neuromuscular power (Chap. 26); most patients complaining of fatigue are not truly weak when direct muscle power is tested. Fatigue is also distinct from somnolence, which refers to sleepiness in the context of disturbed sleep-wake physiology (Chap. 33), and from dyspnea on exertion, although patients may use the word fatigue to describe any of these symptoms. The task facing clinicians when a patient presents with fatigue is to identify the underlying cause and develop a therapeu tic alliance, the goal of which is to spare patients expensive and fruitless diagnostic workups and steer them toward effective therapy.

■ ■EPIDEMIOLOGY AND GLOBAL CONSIDERATIONS Variability in the definitions of fatigue and the survey instruments used in different studies makes it difficult to arrive at precise figures about the global burden of fatigue. The point prevalence of fatigue was 6.7% and the lifetime prevalence was 25% in a large National Institute of Mental Health survey of the U.S. general population. In primary care clinics in Europe and the United States, between 10 and 25% of patients surveyed endorsed

symptoms of prolonged (present for >1 month) or chronic (present for >6 months) fatigue, but in only a minority was fatigue the primary reason for seeking medical attention. In a com munity survey of women in India, 12% reported chronic fatigue. By contrast, the prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (Chap. 461), as defined by the U.S. Centers for Disease Control and Prevention, is low.

PART 2 Cardinal Manifestations and Presentation of Diseases ■ ■DIFFERENTIAL DIAGNOSIS Psychiatric Disease Fatigue is a common somatic manifestation of many major psychiatric syndromes, including depression, anxiety, and somatoform disorders (Chap. 463). Psychiatric symptoms are reported in more than three-quarters of patients with unexplained chronic fatigue. Even in patients with systemic or neurologic disorders in which fatigue is independently recognized as a symptom, comorbid psychiatric disease may still be an important contributor. Neurologic Disease Patients with fatigue often say they feel weak, but upon careful examination, objective muscle weakness is rarely discernible. If found, muscle weakness must then be localized to the central nervous system, peripheral nervous system, neuromuscular junction, or muscle, and appropriate follow-up studies obtained (Chap. 26). Fatigability of muscle power is a cardinal manifestation of some neuromuscular disorders such as myasthenia gravis and is distinguished from fatigue by finding clinically evident diminution of the amount of force that a muscle generates upon repeated contrac tion (Chap. 459). Fatigue is one of the most common and bothersome symptoms reported in multiple sclerosis (MS) (Chap. 455), affecting nearly 90% of patients; fatigue in MS can persist between MS attacks and does not necessarily correlate with magnetic resonance imag ing (MRI) disease activity. Fatigue is also increasingly identified as a troublesome feature of many neurodegenerative diseases, including Parkinson’s disease (Chap. 446), amyotrophic lateral sclerosis (Chap. 448), and central nervous system dysautonomias (Chap. 451). Fatigue after stroke (Chap. 437) is a well-described but poorly understood entity with a widely varying prevalence. Episodic fatigue can be a pre monitory symptom of migraine (Chap. 441). Fatigue is also a frequent consequence of traumatic brain injury (Chap. 454), often occurring in association with depression and sleep disorders. Sleep Disorders Obstructive sleep apnea is an important cause of excessive daytime sleepiness in association with fatigue and should be investigated using overnight polysomnography, particularly in those with prominent snoring, obesity, or other predictors of obstructive sleep apnea (Chap. 308). Whether the cumulative sleep deprivation that is common in modern society contributes to clinically apparent fatigue is not known (Chap. 33). Endocrine Disorders Fatigue, sometimes in association with true muscle weakness, can be a heralding symptom of hypothyroid ism (Chap. 395), particularly in the context of hair loss, dry skin, cold intolerance, constipation, and weight gain. Fatigue associated with heat intolerance, sweating, and palpitations is typical of hyperthyroidism (Chap. 396). Adrenal insufficiency (Chap. 398) can also manifest with unexplained fatigue as a primary or prominent symptom, often with anorexia, weight loss, nausea, myalgias, and arthralgias; hyponatremia, hyperkalemia, and hyperpigmentation may be present at time of diag nosis. Mild hypercalcemia can cause fatigue, which may be relatively vague, whereas severe hypercalcemia can lead to lethargy, stupor, and coma (Chap. 422). Both hypoglycemia and hyperglycemia can cause lethargy, often in association with confusion; diabetes mellitus, in particular type 1 diabetes, is also associated with fatigue independent

of glucose levels (Chap. 415). Fatigue may also accompany Cushing’s disease, hypoaldosteronism, and hypogonadism. Low vitamin D status has also been associated with fatigue. Liver and Kidney Disease Both chronic liver failure and chronic kidney disease can cause fatigue. Over 80% of

hemodialysis patients complain of fatigue, which makes it one of the most common symp toms reported by patients in chronic kidney disease (Chap. 322). Obesity Obesity (Chap. 413) is associated with fatigue and sleepi ness independent of the presence of obstructive sleep apnea. Obese patients undergoing bariatric surgery experience improvement in daytime sleepiness sooner than would be expected if the improvement were solely the result of weight loss and resolution of sleep apnea. A number of other factors common in obese patients are likely contribu tors as well, including physical inactivity, diabetes, and depression. Physical Inactivity Physical inactivity is associated with fatigue, and increasing physical activity can improve fatigue in some patients. Malnutrition Although fatigue can be a presenting feature of malnutrition (Chap. 345), nutritional status may also be an impor tant comorbidity and contributor to fatigue in other chronic illnesses, including cancer-associated fatigue. Infection Both acute and chronic infections commonly lead to fatigue as part of the broader infectious syndrome. Evaluation for undi agnosed infection as the cause of unexplained fatigue, and particularly prolonged or chronic fatigue, should be guided by the history, physical examination, and infectious risk factors, with particular attention to risk for tuberculosis, HIV, chronic hepatitis, and endocarditis. Infectious mononucleosis may cause prolonged fatigue that persists for weeks to months following the acute illness, but infection with the Epstein-Barr virus is only very rarely the cause of unexplained chronic fatigue. Postin fectious fatigue may also occur following a variety of acute infections. For example, a substantial minority of patients who have recovered from SARS-CoV-1, SARS-CoV-2, Dengue, and Ebola virus experience persistent fatigue. Almost one-third of patients report fatigue 3 or more months following SARS-CoV-2 (COVID-19) diagnosis. Drugs Many medications, drugs, drug withdrawal, and chronic alcohol use can all lead to fatigue. Medications that are more likely to be causative include antidepressants, antipsychotics, anxiolytics, opi ates, antispasticity agents, antiseizure agents, and beta blockers. Cardiovascular and Pulmonary Disorders Fatigue is one of the most taxing symptoms reported by patients with congestive heart failure and chronic obstructive pulmonary disease and negatively affects quality of life. In a population-based cohort study in Norfolk, United Kingdom, fatigue was associated with an increased hazard of all-cause mortality in the general population, but particularly for deaths related to cardiovascular disease. Malignancy Fatigue, particularly in association with unexplained weight loss, can be a sign of occult malignancy, but cancer is rarely identified in patients with unexplained chronic fatigue in the absence of other telltale signs or symptoms. Cancer-related fatigue is experi enced by 40% of patients at the time of diagnosis and by >80% at some time in the disease course. Hematologic Disorders Chronic or progressive anemia may present with fatigue, sometimes in association with exertional tachy cardia and breathlessness. Anemia may also contribute to fatigue in chronic illness. Low serum ferritin in the absence of anemia may also cause fatigue that is reversible with iron replacement. Immune-Mediated Disorders Fatigue is a prominent complaint in many chronic inflammatory disorders, including systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis, inflam matory bowel disease, antineutrophil cytoplasmic antibody (ANCA)– associated vasculitis, sarcoidosis, and Sjögren’s syndrome, but is not usually an isolated symptom. Fatigue is also associated with primary immunodeficiency diseases.

Pregnancy Fatigue is very commonly reported by women during all stages of pregnancy and postpartum. Disorders of Unclear Cause Myalgic encephalomyelitis (ME)/ chronic fatigue syndrome (CFS) (Chap. 461) and fibromyalgia (Chap. 385) incorporate chronic fatigue as part of the syndromic definition when fatigue is present in association with other criteria, as discussed in the respective chapters. Chronic multisymptom illness, also known as Gulf-War syndrome, is another

symptom complex with prominent fatigue; it is most commonly, although not exclusively, observed in veterans of the 1991 Gulf War conflict (Chap. S8). Idio pathic 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 ME/CFS. APPROACH TO THE PATIENT Fatigue A detailed history focusing on the quality, pattern, time course, associated symptoms, and alleviating factors of fatigue is neces sary to define the syndrome and help direct further evaluation and treatment. It is important to determine if fatigue is the appropriate designation, whether symptoms are acute or chronic, and if the impairment is primarily mental, physical, or a combination of the two. The review of systems should attempt to distinguish fatigue from excessive sleepiness, dyspnea on exertion, exercise intoler ance, 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 required. Circum stances surrounding the onset of symptoms and potential triggers should be investigated. The social history is important, with atten tion paid to life stressors and adverse experiences, workhours, 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 exami nation is required to determine whether objective muscle weak ness 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, full power may be generated for only a brief period before the patient suddenly gives 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. Fati gable weakness, which usually indicates a problem of neuromuscu lar 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 physi cal 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, organo megaly, infection, liver failure, kidney disease, malnutrition, endo crine abnormalities, and connective tissue disease. In patients with associated widespread musculoskeletal pain, assessment of tender points may help to reveal fibromyalgia. Although the diagnostic

yield of the general physical examination may be relatively low in the context of evaluation of unexplained chronic fatigue, elucidat ing the cause of only 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, a complete physical examination demonstrates a serious and system atic 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 likely to lead to incidental findings that require explanation and unnecessary follow-up 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 for ME/CFS 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 anti nuclear 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 find ings that can prolong the workup unnecessarily. Fatigue CHAPTER 25 TREATMENT Fatigue The first priority is to address the underlying disorder or disor ders 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, but it is nevertheless important in such cases to evaluate for other potential contributors because the cause may be multifac torial. Antidepressants (Chap. 463) may be helpful for treatment of chronic fatigue when symptoms of depression are present and are generally most effective as part 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 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 stan dard medical care in patients in the United Kingdom with chronic fatigue. These benefits were maintained after a median follow-up of 2.5 years. Exercise as an intervention has also demonstrated some benefit for patients with fatigue related to cancer, MS, and diabetes, among other conditions. Psychostimulants such as amphetamines, modafinil, and armodafinil can help increase alertness and concen tration 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 unhelp ful 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, includ ing how fatigue is detected and registered in the nervous system.

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