

Fatigue

Chapter 25 | Part 2: Cardinal Manifestations and Presentation of Diseases | Part 2 – Cardinal Manifestations & Presentation | DETAILED EDITION

KEY CLINICAL POINTS

1. Fatigue is defined as the subjective experience of physical and mental weariness, sluggishness, low energy, and exhaustion.
2. Fatigue must be distinguished from muscle weakness (reduction of neuromuscular power), somnolence (sleepiness), and dyspnea (shortness of breath).
3. In unexplained chronic fatigue, laboratory testing identifies the cause in only about 5% of cases; extensive testing often leads to incidental findings.
4. A complete blood count, electrolytes, glucose, renal/liver/thyroid function, HIV, and adrenal function are standard screening tests.
5. Antidepressants may be helpful for chronic fatigue when depression is present but can also cause fatigue and should be discontinued if ineffective.
6. Cognitive-behavioral therapy (CBT) and graded exercise therapy (walking with target heart rates) modestly improve fatigue in ME/CFS, cancer, MS, and diabetes.
7. Psychostimulants (amphetamines, modafinil, armodafinil) can increase alertness but have generally proven unhelpful in randomized trials for posttraumatic brain injury, Parkinson's, cancer, and MS.
8. Vitamin D replacement may lead to improvement in fatigue in patients with low vitamin D status.
9. Obesity is associated with fatigue and sleepiness independent of obstructive sleep apnea.
10. Post-infectious fatigue may occur following SARS-CoV-2, SARS-CoV-1, Dengue, and Ebola virus, with up to one-third of patients reporting fatigue 3+ months post-diagnosis.

FIGURES IN THIS CHAPTER

1. Figure / Illustration

1. DEFINITION & OVERVIEW

Fatigue is one of the most common symptoms in clinical medicine and a prominent manifestation of systemic, neurologic, and psychiatric syndromes. A precise cause is not identified in a substantial minority of patients.

1.1 Definition

Harrison's defines fatigue as: *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.*

1.2 Distinctions

Fatigue must be distinguished from other symptoms to ensure accurate diagnosis and management.

2. EPIDEMIOLOGY

Variability in definitions and survey instruments makes precise figures difficult to arrive at.

2.1 Prevalence

Point prevalence of fatigue was 6.7% and lifetime prevalence was 25% in a large National Institute of Mental Health survey of the U.S. general population.

2.2 Global Burden

The global burden of fatigue is variable due to survey instrument differences.

3. ETIOLOGY & PATHOPHYSIOLOGY

Fatigue is a common somatic manifestation of many major psychiatric syndromes, including depression, anxiety, and somatoform disorders. Psychiatric symptoms are reported in more than three-quarters of patients with unexplained chronic fatigue.

3.1 Psychiatric Disease

Fatigue is a common somatic manifestation of many major psychiatric syndromes, including depression, anxiety, and somatoform disorders. 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.

3.2 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.

3.3 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. Whether the cumulative sleep deprivation that is common in modern society contributes to clinically apparent fatigue is not known.

3.4 Endocrine Disorders

Fatigue, sometimes in association with true muscle weakness, can be a heralding symptom of hypothyroidism, 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. Adrenal insufficiency 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 diagnosis. Mild hypercalcemia can cause fatigue, which may be relatively vague, whereas severe hypercalcemia can lead to lethargy, stupor, and coma. 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. Fatigue may also accompany Cushing's disease, hypoadosteronism, and hypogonadism. Low vitamin D status has also been associated with fatigue.

3.5 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 symptoms reported by patients in chronic kidney disease.

3.6 Obesity

Obesity is associated with fatigue and sleepiness 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 contributors as well, including physical inactivity, diabetes, and depression.

3.7 Malnutrition

Although fatigue can be a presenting feature of malnutrition, nutritional status may also be an important comorbidity and contributor to fatigue in other chronic illnesses, including cancer-associated fatigue.

3.8 Infection

Both acute and chronic infections commonly lead to fatigue as part of the broader infectious syndrome. Evaluation for undiagnosed 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. Postinfectious fatigue may also occur following a variety of acute infections. 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.

3.9 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, opiates, antispasticity agents, antiseizure agents, and beta blockers.

3.10 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.

3.11 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 experienced by 40% of patients at the time of diagnosis and by >80% at some time in the disease course.

3.12 Hematologic Disorders

Chronic or progressive anemia may present with fatigue, sometimes in association with exertional tachycardia 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.

3.13 Immune-Mediated Disorders

Fatigue is a prominent complaint in many chronic inflammatory disorders, including systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis, inflammatory 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.

3.14 Pregnancy

Fatigue is very commonly reported by women during all stages of pregnancy and postpartum.

3.15 Disorders of Unclear Cause

Myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) and fibromyalgia incorporate chronic fatigue as part of the syndromic definition when fatigue is present in association with other criteria. 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. 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 ME/CFS.

4. CLINICAL FEATURES

A detailed history focusing on the quality, pattern, time course, associated symptoms, and alleviating factors of fatigue is necessary 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 intolerance, and muscle weakness. The presence of fever, chills, night sweats, or weight loss should raise suspicion for an occult infection or malignancy.

4.1 Quality and Pattern

Detailed history focusing on quality, pattern, time course, associated symptoms, and alleviating factors.

4.2 Time Course

Acute or chronic. Chronic fatigue is present for >1 month or >6 months.

4.3 Impairment Type

Primarily mental, physical, or a combination of the two.

4.4 Red Flags

Fever, chills, night sweats, or weight loss should raise suspicion for an occult infection or malignancy.

5. DIFFERENTIAL DIAGNOSIS

The task facing clinicians when a patient presents with fatigue is to identify the underlying cause and develop a therapeutic alliance, the goal of which is to spare patients expensive and fruitless diagnostic workups and steer them toward effective therapy.

5.1 Psychiatric

Depression, anxiety, somatoform disorders.

5.2 Neurologic

Multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, central nervous system dysautonomias, stroke, migraine, traumatic brain injury, myasthenia gravis.

5.3 Sleep

Obstructive sleep apnea.

5.4 Endocrine

Hypothyroidism, hyperthyroidism, adrenal insufficiency, diabetes mellitus, Cushing's disease, hypoadosteronism, hypogonadism, vitamin D deficiency.

5.5 Liver/Kidney

Chronic liver failure, chronic kidney disease.

5.6 Obesity

Obesity, physical inactivity, diabetes, depression.

5.7 Infection

Tuberculosis, HIV, chronic hepatitis, endocarditis, infectious mononucleosis, SARS-CoV-1, SARS-CoV-2, Dengue, Ebola virus.

5.8 Drugs

Antidepressants, antipsychotics, anxiolytics, opiates, antispasticity agents, antiseizure agents, beta blockers, alcohol.

5.9 Cardiovascular/Pulmonary

Congestive heart failure, chronic obstructive pulmonary disease.

5.10 Malignancy

Occult malignancy.

5.11 Hematologic

Anemia, low serum ferritin.

5.12 Immune-Mediated

Systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis, inflammatory bowel disease, ANCA-associated vasculitis, sarcoidosis, Sjögren's syndrome, primary immunodeficiency diseases.

5.13 Pregnancy

All stages of pregnancy and postpartum.

5.14 Unclear Cause

ME/CFS, fibromyalgia, Gulf-War syndrome, idiopathic chronic fatigue.

6. INVESTIGATIONS & DIAGNOSIS

A detailed history and physical examination are necessary. 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.

6.1 Screening Tests

A reasonable approach to screening includes a complete blood count (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.

Table 1 Table 25-1: Standard Screening Tests for Fatigue

Test	Purpose	Notes
Complete Blood Count (CBC)	Screen for anemia, infection, malignancy	Standard
Electrolytes	Sodium, potassium, calcium	Standard
Glucose	Diabetes screening	Standard
Renal Function	Kidney disease	Standard
Liver Function	Liver disease	Standard
Thyroid Function	Hypothyroidism/Hyperthyroidism	Standard
HIV Test	Infection screening	Considered
Adrenal Function	Adrenal insufficiency	Considered
Erythrocyte Sedimentation Rate (ESR)	Inflammation (ME/CFS guidelines)	Only if very high

6.2 Tests to Avoid

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 findings that can prolong the workup unnecessarily.

6.3 Physical Examination

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, 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. 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. In patients with associated widespread musculoskeletal pain, assessment of tender points may help to reveal fibromyalgia.

7. MANAGEMENT & TREATMENT

The first priority 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, but it is nevertheless important in such cases to evaluate for other potential contributors because the cause may be multifactorial. Antidepressants 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 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. 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 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.

7.1 Underlying Disorder

Address underlying disorder or disorders. Curative in select contexts, palliative in others.

7.2 Antidepressants

Helpful for treatment of chronic fatigue when symptoms of depression are present. Generally most effective as part of a multimodal approach. Can also cause fatigue and should be discontinued if not clearly effective.

7.3 Cognitive-Behavioral Therapy (CBT)

Demonstrated to be helpful in ME/CFS as well as cancer-associated fatigue.

7.4 Graded Exercise Therapy

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7.5 Psychostimulants

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.

7.6 Vitamin D

In patients with low vitamin D status, vitamin D replacement may lead to improvement in fatigue.

8. PROGNOSIS & COMPLICATIONS

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. In many chronic illnesses, fatigue may be refractory to traditional disease-modifying therapies. In patients with low vitamin D status, vitamin D replacement may lead to improvement in fatigue.

8.1 Refractory Nature

Fatigue may be refractory to traditional disease-modifying therapies in many chronic illnesses.

8.2 Multifactorial Causes

The cause may be multifactorial; it is important to evaluate for other potential contributors.

8.3 Biologic Basis

Limited knowledge of the biologic basis of this symptom, including how fatigue is detected and registered in the nervous system.

9. SPECIAL CONSIDERATIONS

Pregnancy is a special consideration where fatigue is very commonly reported by women during all stages of pregnancy and postpartum.

9.1 Pregnancy

Fatigue is very commonly reported by women during all stages of pregnancy and postpartum.

10. KEY PEARLS & CLINICAL TRAPS

The presence of fever, chills, night sweats, or weight loss should raise suspicion for an occult infection or malignancy. 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 findings that can prolong the workup unnecessarily. A complete physical examination demonstrates a serious 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 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.

10.1 Red Flags

Fever, chills, night sweats, or weight loss should raise suspicion for an occult infection or malignancy.

10.2 Diagnostic Pitfalls

Routine screening with ANA test is unlikely to be informative in isolation. Whole-body imaging scans are usually not indicated; inconvenience, potential risk, cost, unrelated incidental findings.

10.3 Therapeutic Alliance

A complete physical examination demonstrates a serious and systematic approach to the patient's complaint and helps build trust and a therapeutic alliance.

10.4 Yield of Testing

Laboratory testing is likely to identify the cause of chronic fatigue in only about 5% of cases.

FIGURES & ILLUSTRATIONS — FROM HARRISON'S



Harrison's 22e · Figure 1

Diagnostic algorithm for the evaluation of fatigue: History and physical examination lead to screening labs (CBC, electrolytes, glucose, renal/liver/thyroid, HIV, adrenal, ESR if high). Avoid routine ANA and whole-body imaging. Treatment focuses on addressing underlying disorders, CBT, graded exercise therapy, and vitamin D replacement.