



Approach to fatigue

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Fatigue definition

- “fatigue” can be used to describe difficulty or inability to **initiate** activity
(**subjective sense of weakness**); or
- reduced capacity to **maintain** activity (**easy fatigability**); or
- difficulty with **concentration**, memory, and emotional stability
(**mental fatigue**)

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- Fatigue is a common, nonspecific symptom with a broad range of etiologies including acute and chronic medical disorders, psychological conditions, medication toxicity, and substance use.
 - When some patients use the word “fatigue,” careful history taking reveals that they are referring to **sleepiness or an uncontrollable need to sleep.**
 - Patients may report one or a combination of these symptoms, and they may occur alone or in conjunction with localized complaints.

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- Patients may report one or a combination of these symptoms, and they may occur alone or in conjunction with localized complaints.
 - **Acute fatigue** is defined as lasting one month or less,
 - **subacute fatigue** as lasting between one and six months, and
 - **chronic fatigue** as lasting over six months. Patients can have a state of chronic fatigue without meeting criteria for chronic fatigue syndrome (CFS).

Causes

Acute fatigue:

- is most often attributable to an acute medical condition, which can often be diagnosed on the basis of its other clinical manifestations.

For example, a patient with influenza will describe fatigue in association with fever and respiratory symptoms.

- Acute fatigue may also be the result of a recent life stressor.

For example, a patient who starts drinking alcohol to address a stressful situation at home or work may also present with fatigue. Patients with acute fatigue associated with a recognizable medical or psychosocial condition require little or no evaluation.

Subacute and chronic fatigue

is likely to be associated with an underlying chronic medical or psychological condition.

Etiologies include:

- **Cardiopulmonary conditions** – Congestive heart failure, chronic obstructive pulmonary disease, sleep apnea
- **Endocrinologic/metabolic conditions** – Hypothyroidism, hyperthyroidism, chronic renal disease, chronic hepatic disease, adrenal insufficiency, electrolyte abnormalities

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- Hematologic/neoplastic conditions – Anemia, occult malignancy
 - Infectious diseases – Mononucleosis syndrome, viral hepatitis, human immunodeficiency virus (HIV) infection, subacute bacterial endocarditis, tuberculosis
 - Rheumatologic conditions – Fibromyalgia, polymyalgia rheumatica, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome

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- **Psychological conditions** – Depression, anxiety disorder, somatization disorder
 - **Neurologic conditions** – Multiple sclerosis
Medication toxicity – Benzodiazepines, antidepressants, muscle relaxants, first-generation antihistamines, beta-blockers, opioids
 - **Substance use** – Alcohol, marijuana, opioids, cocaine/other stimulants

Table 4. Differential Diagnosis of Chronic Fatigue

Endocrine	Neurologic	Rheumatologic (<i>continued</i>)
Addison disease	Dementia	Polymyalgia rheumatica
Adrenal insufficiency	Multiple sclerosis	Polymyositis
Cushing disease	Narcolepsy	Rheumatoid arthritis
Diabetes mellitus	Parkinson disease	Sjögren syndrome
Hyperthyroidism	Psychiatric	Systemic lupus erythematosus
Hypothyroidism	Bipolar disorder	Temporal arteritis
Hematologic/oncologic	Eating disorder	Other
Anemia	Major depressive disorder	Celiac disease
Malignancy	Schizophrenia	Heart failure
Infectious	Somatoform disorders	Heavy metal toxicity
Chronic hepatitis	Substance abuse	Pharmacologic adverse effect
Human immunodeficiency virus	Rheumatologic	Sleep apnea
Lyme disease	Dermatomyositis	Vitamin deficiency
Tuberculosis	Fibromyalgia	

- In a small minority of cases, the presenting complaint of chronic fatigue is explained by **chronic fatigue syndrome (CFS)**, a disorder of unknown cause but with strong evidence of neurologic dysfunction. Patients who do not meet criteria for CFS and have no other explanation for their fatigue are said to be suffering from **idiopathic chronic fatigue**. Both of these conditions are diagnoses of exclusion.

Table 1. Oxford Criteria for Chronic Fatigue Syndrome

Primary symptom is fatigue

Definite onset of symptoms

Fatigue is severe, disabling, and affects physical and mental functioning

Symptoms for at least six months and present more than 50 percent of the time

Other symptoms must be present, particularly myalgia, and mood and sleep disturbances

Certain patients should be excluded:

Those with an established medical condition known to produce chronic fatigue

Those with a current diagnosis of schizophrenia, manic-depressive illness, substance abuse, eating disorder, or proven organic brain disease

*NOTE: All criteria must be met to make the diagnosis.
Information from reference 6.*

Table 2. Centers for Disease Control and Prevention Diagnostic Criteria for Chronic Fatigue Syndrome

Severe fatigue for longer than six months, and at least four of the following symptoms:

Headache of new type, pattern, or severity

Multijoint pain without swelling or erythema

Muscle pain

Postexertional malaise for longer than 24 hours

Significant impairment in short-term memory or concentration

Sore throat

Tender lymph nodes

Unrefreshing sleep

Information from reference 7.



Case Scenario :

A 38-year-old female presents with a history of persistent **fatigue** for the **past 8 months**. The fatigue has a **clear onset** and has progressively worsened. It is **severe, disabling, and not relieved by rest**. The patient reports that her symptoms get **worse with minimal physical or mental activity, significantly affecting her daily functioning**.

She also complains of **frequent myalgia, recurrent headaches, poor concentration, and unrefreshing sleep** occurring on most days. The symptoms are present for **more than 50% of the time**.

On physical examination, no abnormalities are found. Other medical conditions that could cause fatigue (such as thyroid disease, anemia, or depression) have been excluded.

Evaluation of CF.



HISTORY



EXAMINATION



INVESTIGATIONS

History

1. Fatigue concomitant with an underlying medical or psychological condition usually presents as one of several reported symptoms.
2. A specific etiology for fatigue is found less often when it is the principal or only complaint.
3. In taking a history, the clinician should rely upon open-ended questions, encouraging the patient to describe the fatigue in his or her own words.
4. Questions such as "What do you mean by fatigue?" or "Please describe what you mean", Patients should be asked if they have any ideas about what might be causing or contributing to their fatigue.

5. The history should also determine the characteristics, severity, and pattern of fatigue:

- a) Onset – Abrupt or gradual, relationship to illness or life event
- b) Course – Stable, improving, or worsening
- c) Duration and daily pattern
- d) Factors that alleviate or exacerbate it
- e) Impact on daily life – Ability to work, socialize, participate in usual activities
- f) Accommodations that the patient/loved ones have had to make to deal with symptoms



6. Patients with underlying medical conditions often associate fatigue with activities they are unable to complete. By contrast, patients with fatigue that is related to psychological conditions, medication toxicity, or substance use may be tired all the time; their fatigue is not necessarily related to exertion, and it does not improve with rest.

7. **Specific etiologies may be suspected as:**

- ❑ sleep apnea would be suspected in a patient who describe snoring and disrupted sleep.
- ❑ anemia in a patient who reports dizziness and weakness.
- ❑ fibromyalgia in a patient who describes chronic diffuse muscle pain.

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- ❑ The presence of fever may suggest underlying infection.
 - ❑ unintended weight loss may indicate an occult neoplasm or recurrent disease in a patient with a history of malignancy.
 - ❑ If history suggests a chronic pattern of unexplained physical symptoms, somatization should also be considered.
 - ❑ All patients should be asked about symptoms suggestive of depression (e.g., sad mood, anhedonia, alteration in sleep and/or eating habits) and anxiety disorder (e.g., constant palpitations or sweating, occurrence of panic attacks and/or phobias).
 - ❑ The history should also screen for substance use (e.g., alcohol, marijuana, opioids, cocaine/other),/ Domestic violence.

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- ❑ The quantity and quality of the patient's sleep should be assessed and whether or not sleep reduces the level of fatigue. Such improvement may suggest a primary sleep disorder as an etiology.
 - ❑ A complete list of medications, including prescription, over-the-counter, and complementary/alternative drugs, should be obtained. Use of benzodiazepines, antidepressants, muscle relaxants, first-generation antihistamines, beta-blockers, opioids, and the GABA analogues (gabapentin)
 - ❑ family medical history should also be performed to determine if there is a genetic predisposition to any specific cancer(s) or other chronic medical conditions. A social history should be obtained with emphasis on any changes or stressors in the home or work environment.

Physical examination

- General appearance – Level of alertness, psychomotor agitation or retardation, grooming.
- Evidence of thyroid disease – Bradycardia, tachycardia, goiter, skin changes, ophthalmopathy.
- Presence of lymphadenopathy or hepatosplenomegaly.
- Cardiopulmonary examination – Signs of congestive heart failure or chronic obstructive pulmonary disease.
- Neuromuscular examination – Muscle bulk, tone, and strength; deep tendon reflexes; sensory and cranial nerve evaluation; cognitive function

Investigations (Laboratory and radiologic studies)

1) initial laboratory studies:

- ✓ Complete blood count with differential count
- ✓ Chemistries (including glucose, electrolytes, calcium, renal and hepatic function tests)
- ✓ Thyroid-stimulating hormone
- ✓ Creatine kinase (if muscle pain or weakness is present)
- ✓ Serologic testing for hepatitis C virus infection

2) **Other tests that may be done according to history and examination:**

- ✓ Serologic testing for HIV infection
- ✓ Testing for tuberculosis
- ✓ Erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hs-CRP) should be performed in older patients who also have symptoms consistent with polymyalgia rheumatica or giant cell (temporal) arteritis
- ✓ Updating of cancer screening interventions

- **Updating of cancer screening interventions**

Appropriate cancer screening interventions based upon the patient's age and sex should be updated as necessary to exclude common occult malignancies as a potential cause for fatigue. For example:

patients ≥ 50 year of age should be screened for **colon cancer** with colonoscopy or another acceptable modality if not done within the past 10 years;

patients 55 to 74 years of age with ≥ 20 pack-year cigarette smoking history should undergo an annual low-dose computed tomography (CT) scan for **the lung cancer**;

Females >40 years of age should be screened for **breast cancer** with mammography if not done within the past one to two years.

Establishing a diagnosis

- **Patients with localized findings** – Additional diagnostic studies should be obtained as warranted in patients with localized findings on history or physical examination or abnormal initial laboratory testing.
- **For example**, a patient presenting with fatigue associated with fever/chills, night sweats, and myalgias associated with a new heart murmur should have blood cultures and an echocardiogram performed for evaluation of subacute bacterial endocarditis.
- A patient presenting with abnormal liver function tests should have viral hepatitis serologies and a hepatic ultrasound performed.

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- In patients with a newly identified medical condition that may be responsible for fatigue, it is important to monitor their response to treatment. If there is no improvement in the level of fatigue with management of the medical condition, the patient should be monitored and evaluated as noted below.

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- **Patients without localized findings** — Patients without an identified cause following the initial evaluation should be reassessed in one to three months and have baseline laboratory studies repeated at that time if there continue to be no localizing symptoms or signs.
 - Additional diagnostic studies in patients without localized findings on history or physical examination or abnormal initial laboratory testing is unlikely to yield useful results.

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- Patients who remain **undiagnosed** with an identifiable condition after **six months** are designated as having **idiopathic chronic fatigue or CFS** if they meet diagnostic criteria. Both conditions are diagnoses of exclusion.

Table 3. Red Flag Symptoms in Persons with Suspected Chronic Fatigue Syndrome

<i>Red flags</i>	<i>Disease process indicated</i>
Chest pain	Cardiac disease
Focal neurologic deficits	Central nervous system malignancy or abscess, multiple sclerosis
Inflammatory signs or joint pain	Autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus)
Lymphadenopathy or weight loss	Malignancy
Shortness of breath	Pulmonary disease

Information from reference 8.

Causes of subacute and chronic fatigue

Condition	Symptoms	Physical findings	Supportive diagnostic studies
Cardiopulmonary			
Congestive heart failure	Dyspnea on exertion, orthopnea, leg swelling	S3 gallop, inspiratory rales, elevated jugular venous distension, peripheral edema	Chest radiograph, echocardiogram
Chronic obstructive pulmonary disease	Dyspnea, chronic cough, sputum production	Evidence of hyperinflation, wheezing, rales	Chest radiograph
Sleep apnea	Snoring, interrupted breathing during sleep	Obesity, hypertension	Sleep study

Endocrinologic/metabolic			
Hypothyroidism	Cold intolerance, weight gain, constipation, dry skin	Bradycardia, goiter, slow deep tendon reflex relaxation phase	Thyroid function tests
Hyperthyroidism	Heat intolerance, weight loss, diarrhea, moist skin	Tachycardia, goiter, ophthalmopathy	Thyroid function tests
Chronic renal disease	Nausea/vomiting, mental status changes, decreased urine	Hypertension, peripheral edema	Renal function tests/ serum electrolytes
Chronic hepatic disease	Abdominal distention, gastrointestinal bleeding	Jaundice, palmar erythema, gynecomastia, splenomegaly, evidence of ascites	Hepatic function tests
Adrenal insufficiency	Weight loss, salt craving, gastrointestinal complaints	Hypotension, hyperpigmentation, vitiligo	Morning cortisol/ACTH, ACTH stimulation test
Electrolyte abnormalities			
Hyponatremia	Nausea, malaise, cognitive dysfunction	Generally normal exam	Serum sodium level
Hypercalcemia	Anorexia, nausea polydipsia/polyuria,	Generally normal exam	Serum calcium/albumin levels

Hematologic/neoplastic			
Anemia	Dizziness, weakness, palpitations, dyspnea	Tachycardia, pallor	Complete blood count
Occult malignancy	Weight loss, localized symptoms may be present depending upon type	Variable	Variable depending upon type
Infectious diseases			
Mononucleosis syndrome	Fever, sore throat, tender lymph nodes	Fever, exudate pharyngitis, tender cervical adenopathy	Complete blood/differential count, monospot
Viral hepatitis	Fever, nausea/vomiting, abdominal discomfort	Fever, jaundice, tender hepatomegaly	Hepatic function tests, viral hepatitis serologies
HIV infection	Weight loss, variable localized complaints	Variable physical findings	HIV serology
Subacute bacterial endocarditis	Fever/chills, night sweats, myalgias	Fever, new (regurgitant) murmur, peripheral manifestations	Blood cultures, echocardiogram
Tuberculosis	Fever/chills, night sweats, fatigue, weight loss	Cough, chest pain, dyspnea, hemoptysis	PPD/gamma-interferon assay, chest radiograph

Rheumatologic			
Fibromyalgia	Chronic diffuse muscle pain	Multiple "tender points" on palpation	None
Polymyalgia rheumatica	Aching/morning stiffness of shoulders, neck, and hips	Decreased range of motion of shoulders, neck, and hips	Erythrocyte sedimentation rate
Psychological			
Depression	Sad mood, anhedonia, altered sleep, cognitive dysfunction	Generally normal exam	Screening test (eg, PHQ-2, PHQ-9)
Anxiety disorder	Generalized nervousness, panic attacks, phobias	Tachycardia, muscle tension	Screening test (eg, GAD-7)
Somatization disorder	Multiple chronic constitutional and localized complaints	Generally normal exam	Screening test (eg, SSS-8)
Medication toxicity*			

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	Variable	Generally normal exam	None
Substance use[†]			
	Variable	Generally normal exam	None

Q1- A 65-year-old man presents with fatigue, exertional dyspnea, and lower extremity swelling. Exam: BP 110/70, pulse 90, JVP elevated, bibasilar crackles, ankle edema.

What is the most likely underlying cause of his fatigue?

- A. Heart failure**
- B. Hypothyroidism**
- C. Chronic fatigue syndrome**
- D. Major depression**
- E. Sleep apnea**

Q2-A 52-year-old obese man reports daytime fatigue, poor concentration, and loud snoring at night. His wife witnessed apneic episodes. Exam shows BMI 35, BP 150/95.

What is the next step in diagnosis?

- A. Polysomnography (sleep study)**
- B. Echocardiography**
- C. Thyroid function tests**
- D. Serum cortisol levels**
- E. ECG**

Q3-A 60-year-old man with hypertension complains of fatigue, exercise intolerance, and erectile dysfunction since starting a new medication. Vitals are stable. His only medication is metoprolol. Which of the following is the most likely cause of his fatigue?

- A. Iron deficiency anemia**
- B. Depression**
- C. Beta-blocker side effect**
- D. Diabetes mellitus**
- E. Hypothyroidism**

Management

(1) Establishing a supportive relationship

- * The physician should accept the symptoms of CF as real debilitating disease.
- * We schedule brief regular appointments to monitor clinical progress.
- * We should try to return the patient to his routine daily activity as he can and his work if applicable and
- * maintain interpersonal relationship.

(2) Addressing underlying medical conditions

(3) Addressing residual or idiopathic fatigue

- In patients with residual or idiopathic fatigue, we suggest an empiric trial of **antidepressant therapy** for patients with depressive symptoms even if they do not meet diagnostic criteria for major depression.
- We do not suggest the empiric use of stimulants or other drug therapies.
- If there is no improvement, we suggest a trial of **cognitive behavioral therapy (CBT)** and/or **exercise therapy** as tolerated, depending on patient preference.

What is the first-line non-drug management for unexplained fatigue?

A. CBT and lifestyle advice

B. Antidepressants

C. Corticosteroids

D. Vitamin supplements

E. Energy drinks



THANK YOU!