# Approach to the adult patient with fatigue

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## INTRODUCTION

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.

This topic addresses the approach to the patient who presents with fatigue. Excessive daytime sleepiness and muscle weakness are addressed elsewhere. (See "Approach to the patient with excessive daytime sleepiness" and "Approach to the patient with muscle weakness".)

This topic also discusses the distinction between chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS); fibromyalgia; and other etiologies of chronic fatigue. CFS and fibromyalgia are discussed in detail separately. (See "Clinical features and diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome" and "Clinical manifestations and diagnosis of fibromyalgia in adults".)

## DEFINITION

The term “fatigue” can be used to describe difficulty or inability to initiate activity (subjective sense of weakness); reduced capacity to maintain activity (easy fatigability); or difficulty with concentration, memory, and emotional stability (mental fatigue) [1]. When some patients use the word “fatigue,” careful history taking reveals that they are referring to sleepiness or an uncontrollable need to sleep (see "Approach to the patient with excessive daytime sleepiness"). 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).

## EPIDEMIOLOGY

Twenty-one to 33 percent of patients seeking attention in primary care settings describe fatigue as an important problem (if not always the chief complaint) [2-6], resulting in approximately seven million office visits per year in the United States [7]. Fatigue is reported more commonly in females than males [4,5,8-11].

The prevalence of fatigue in population-based surveys in Britain and the United States is between 6.0 and 7.5 percent [12,13]. A cross-sectional survey of United States workers found the two-week period prevalence of fatigue to be 38 percent, with an estimated annual cost to employers exceeding USD $136 billion in lost productive work time [14].

## CAUSES

**Acute fatigue** — 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** — Subacute and chronic fatigue is likely to be associated with an underlying chronic medical or psychological condition, medication toxicity, or substance use (table 1). 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
- **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

- **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

The cause of chronic fatigue can be identified in approximately two-thirds of patients, but the frequency of specific diagnoses varies among studies [2,5,15-19]. In some cases, the complaint of chronic fatigue may simply be explained by overwork: in the United States, the length of the work week has been rising since the mid-1960s [20]

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 ( table 2) 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.

## EVALUATION OF CHRONIC FATIGUE

**Initial assessment of all patients** — The initial assessment of the patient presenting with subacute or chronic fatigue includes a comprehensive history and physical examination, basic laboratory studies, and updated cancer screening interventions to identify findings that could suggest a specific underlying cause ( table 1). Further evaluation is determined by the presence or absence of localized findings. (See 'Patients with localized findings' below and 'Patients without localized findings' below.)

Patients with acute fatigue associated with a recognizable medical or psychosocial condition require little or no evaluation.

**History** — Fatigue caused by an underlying medical or psychological condition usually presents as one of several reported symptoms. A specific etiology for fatigue is found less often when it is the principal or only complaint.

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. Questions such as "What do you mean by fatigue?" or "Please describe what you mean" may elicit responses that help distinguish fatigue from muscle weakness or somnolence. Patients should be asked if they have any ideas about what might be causing or contributing to their fatigue.

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

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

Examples of patient survey instruments that are used in clinical practice to assess fatigue include the Brief Fatigue Inventory ( table 3) and Fatigue Symptom Inventory [21].

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.

Associated symptoms may suggest specific etiologies ( table 1). For example, sleep apnea would be suspected in a patient who describe snoring and disrupted sleep, anemia in a patient who reports dizziness and weakness, and fibromyalgia in a patient who describes chronic diffuse muscle pain. The presence of fever may suggest underlying infection, and 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. (See "Somatic symptom disorder: Epidemiology and clinical presentation" and "Somatic symptom disorder: Assessment and diagnosis".)

All patients should be asked about symptoms suggestive of depression (eg, sad mood, anhedonia, alteration in sleep and/or eating habits) and anxiety disorder (eg, constant palpitations or sweating, occurrence of panic attacks and/or phobias) and screened for these conditions using validated instruments such as the Patient Health Questionnaire (PHQ)-2 or PHQ-9 ( table 4 and table 5 ) and the Generalized Anxiety Disorder-7 (GAD-7) ( table 6). (See "Screening for depression in adults", section on 'Screening options' and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis", section on 'Screening instrument'.)

The history should also screen for substance use (eg, alcohol, marijuana, opioids, cocaine/other stimulants) and domestic violence. (See "Screening for unhealthy use of alcohol and other drugs in primary care", section on 'Screening tests' and "Intimate partner violence: Diagnosis and screening".)

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. (See "Classification of sleep disorders".)

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 (eg, gabapentin) may be associated with fatigue.

A 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** — The physical examination is important to look for evidence of specific causes of fatigue ( table 1) and to establish rapport, assuring the patient that his or her complaint is a concern worth investigating. The physical examination should focus on:

- General appearance – Level of alertness, psychomotor agitation or retardation, grooming
- Evidence of thyroid disease – Bradycardia, tachycardia, goiter, skin changes, ophthalmopathy (see "Clinical manifestations of hypothyroidism" and "Diagnosis of hyperthyroidism", section on 'Clinical manifestations')
- Presence of lymphadenopathy or hepatosplenomegaly (see "Evaluation of peripheral lymphadenopathy in adults" and "Overview of the evaluation of hepatomegaly in adults" and "Evaluation of splenomegaly and other splenic disorders in adults")
- Cardiopulmonary examination – Signs of congestive heart failure or chronic obstructive pulmonary disease (see "Clinical manifestations and diagnosis of advanced heart failure" and "Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging")
- Neuromuscular examination – Muscle bulk, tone, and strength; deep tendon reflexes; sensory and cranial nerve evaluation; cognitive function (see "The detailed neurologic examination in adults" and "Approach to the patient with muscle weakness")

**Laboratory and radiologic studies** — We obtain the following initial laboratory studies in patients with subacute or chronic fatigue as the primary symptom:

- 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)

In addition, serologic testing for hepatitis C virus infection should be performed if it has not been done already; universal screening is recommended for all adults ≥18 years of age. Individuals with ongoing risk factors for hepatitis C infection (eg, those on maintenance hemodialysis, ongoing injection drug use, sexual exposure) may be retested. Serologic testing for HIV infection is

recommended if the patient has not been screened in the past or is at risk from sexual or drug use behaviors. (See "Screening and diagnosis of chronic hepatitis C virus infection", section on 'Diagnostic techniques' and "Screening and diagnostic testing for HIV infection", section on 'Tests'.)

Other diagnostic studies should be considered based on the findings on history and physical examination. For example, testing for tuberculosis (eg, purified protein derivative [PPD] or gamma-interferon release assay, chest radiograph, sputum collection) should be performed if appropriate based upon the patient's history and risk factors for exposure (see "Diagnosis of pulmonary tuberculosis in adults"). 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. (See "Clinical manifestations and diagnosis of polymyalgia rheumatica" and "Diagnosis of giant cell arteritis".)

Extensive laboratory or radiologic evaluation in the absence of a positive history or physical examination is of little diagnostic utility in the initial evaluation of chronic fatigue [10,22]. As an example, in a prospective study of 100 adults with the chief complaint of fatigue for at least one month, laboratory studies clarified the cause in only 5 percent of cases [22]. Nonspecific minor laboratory abnormalities were common and did not influence the clinical outcome. A low pretest probability for a specific disease leads to an increased risk of false-positive results and unnecessary follow-up diagnostic tests.

**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 ≥30 pack-year cigarette smoking history should undergo an annual low-dose computed tomography (CT) scan of the lungs; and females >40 years of age should be screened for breast cancer with mammography if not done within the past one to two years. (See "Overview of preventive care in adults", section on 'Cancer screening'.)

### 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 ( table 1). 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 (see "Clinical manifestations and evaluation of adults with suspected left-sided native valve endocarditis", section on 'Diagnosis'). A patient presenting with abnormal liver function tests should have viral hepatitis serologies and a hepatic ultrasound performed. (See "Approach to the patient with abnormal liver biochemical and function tests".)

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.

**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. In the absence of suggestive symptoms or physical findings ( table 1), we do **not** recommend routine testing for infection (eg, Epstein-Barr virus [EBV], cytomegalovirus [CMV], Lyme serologies), immunologic deficiency (eg, immunoglobulins), inflammatory disease (eg, antinuclear antibodies [ANA], rheumatoid factor), vitamin deficiencies, or celiac disease (eg, tissue transglutaminase antibody [TTGA] immunoglobulin A [IgA]). We also do **not** recommend radiologic imaging (eg, chest radiograph, abdominal CT scan) in the absence of clinical suspicion of a specific disease. Our approach is similar to that recommended by the US Centers for Disease Control and Prevention (CDC) and the International Chronic Fatigue Syndrome Study Group for the evaluation of chronic fatigue syndrome (CFS) [23].

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 ( table 2). Both of these conditions are diagnoses of exclusion.

CFS represents a minority of patients with chronic fatigue [23-25]. In a prospective cohort study of over 4000 patients in a health maintenance organization, the estimated crude point prevalence of ME/CFS ranged from 75 to 267 cases per 100,000 persons, whereas the point prevalence of idiopathic chronic fatigue ranged from 1775 to 6321 cases per 100,000 persons [15]. CFS symptoms should be present for at least six months and have moderate, substantial, or severe intensity at least one-half of the time. Other criteria include: post-exertional malaise, sleep problems, cognitive impairment, and orthostatic-related symptoms. (See "Clinical features and diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome".)

The definition of CFS is intentionally restrictive and designed mainly to identify a more homogeneous population for the purpose of research studies. Thus, some patients who do not meet diagnostic criteria for CFS may indeed have the same condition and prognosis as patients who meet them. Disability rates and health care utilization in patients with idiopathic chronic fatigue are similar to those with CFS [24].

## MANAGEMENT

**Establishing a supportive relationship** — The clinician should accept the symptom of chronic fatigue as real and potentially debilitating and act to establish therapeutic goals, which may include:

- Accomplishing activities of daily living
- Maintaining interpersonal relationships
- Returning to work (if applicable)

We schedule brief regular appointments to monitor clinical progress. These visits are preferred to having the patient being seen on an as-needed basis. We provide patient education brochures and other materials on chronic fatigue and offer referral to chronic fatigue support groups.

**Addressing underlying medical conditions** — Patients with an identified cause of chronic fatigue based upon the initial evaluation should be treated specifically for this condition. Their fatigue should be monitored with management of the underlying condition to see if it improves or resolves. If it does not, further evaluation may be warranted to determine if there is an alternative explanation. Repeating the initial evaluation is worthwhile in this setting to make sure that other potential diagnoses were not missed.

**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 ( table 7). 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.

- **Antidepressant therapy** – A trial of antidepressant drugs (eg, a selective serotonin reuptake inhibitor or a serotonin norepinephrine reuptake inhibitor) should be offered to patients with depressive symptoms (see "Unipolar major depression in adults: Choosing initial treatment"). These drugs have been used effectively in patients with chronic unexplained symptoms [26,27].

  Patients should be advised that an immediate effect from antidepressant therapy is not expected and that treatment may need to be dose-adjusted over several weeks before their response can be accurately assessed. Antidepressant therapy should be discontinued in patients who do not demonstrate improvement on a therapeutic dose over two months.

- **Cognitive behavioral therapy** – CBT may be useful in some patients with idiopathic chronic fatigue. It typically involves a series of one-hour sessions designed to alter beliefs and behaviors that may delay recovery. CBT components include explanation of the model for chronic fatigue, challenging beliefs and awareness of fatigue and reorienting these beliefs, achievement of physical activity goals and other personal goals, and helping the patient attain

control over symptoms. CBT in the management of chronic fatigue syndrome (CFS) is discussed separately.

- **Exercise therapy** – Exercise therapy may be useful in some patients with idiopathic chronic fatigue. It is based on a physiological model of deconditioning. Unlike CBT, exercise therapy does not address cognition. A randomized trial comparing exercise therapy and CBT in primary care patients with over three months of unexplained fatigue showed comparable efficacy [27]. Twenty-five percent of patients who met criteria for CFS and 60 percent of patients who did not meet these criteria responded to treatment with either CBT or exercise therapy. Exercise therapy in the management of CFS is discussed separately. (See "Treatment of myalgic encephalomyelitis/chronic fatigue syndrome".)

The management of CFS is described elsewhere. (See "Treatment of myalgic encephalomyelitis/chronic fatigue syndrome", section on 'Management overview'.)

## PROGNOSIS

The prognosis in idiopathic chronic fatigue and chronic fatigue syndrome (CFS) is not favorable for full recovery. However, rates of decreased symptoms and improved function are higher in patients with chronic fatigue who do not meet diagnostic criteria for CFS [28,29]. (See "Treatment of myalgic encephalomyelitis/chronic fatigue syndrome", section on 'Prognosis'.)

Fatigue has been associated with excess mortality after adjusting for multiple potential confounders. In a population-based cohort study of 18,101 participants over a mean follow-up period of 16.6 years, the quartile with the highest fatigue score based on the SF36-VT questionnaire had an increased risk of mortality compared with the quartile with the lowest score (hazard ratio [HR] 1.40, 95% CI 1.25-1.56) [30]. This association was observed for cardiovascular, but not cancer-related, deaths. Another observational study found that the risk of suicide was higher in patients with idiopathic chronic fatigue, but not CFS, compared with the general population [31].

## SUMMARY AND RECOMMENDATIONS

- 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. The term “fatigue” can be used to describe difficulty or inability to initiate activity (subjective sense of weakness); reduced capacity to maintain activity (easy fatigability); difficulty with concentration, memory, and emotional stability (mental fatigue); or 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. (See 'Introduction' above and 'Definition' above.)

- Subacute and chronic fatigue is likely to be associated with an underlying chronic medical or psychological condition, medication toxicity, or substance use. The cause of chronic fatigue can be identified in approximately two-thirds of patients. In the remaining cases, chronic fatigue is designated as idiopathic chronic fatigue or attributed to chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), in patients who meet diagnostic criteria ( table 2). Both of these conditions are diagnoses of exclusion. (See 'Causes' above.)

- The initial assessment of the patient presenting with subacute or chronic fatigue includes a comprehensive history and physical examination, basic laboratory studies, and updated cancer screening interventions to identify findings that could suggest a specific underlying cause ( table 1). Further diagnostic evaluation is determined by the presence or absence of localized findings. (See 'Initial assessment of all patients' above.)

- Patients with acute fatigue associated with a recognizable medical or psychosocial condition require little or no evaluation. For patients with subacute or chronic fatigue as the primary symptom, we obtain the following 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 present)

  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. (See 'Laboratory and radiologic studies' above and 'Updating of cancer screening interventions' above.)

- Patients with an identified cause of chronic fatigue based upon the initial evaluation should be treated specifically for the condition. 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 (**Grade 2C**). We do **not** suggest the empiric use of stimulants or other drug therapies (**Grade 2C**). If there is no improvement, we suggest a trial of cognitive behavioral therapy (CBT) and/or graded exercise therapy (**Grade 2C**). The management of CFS is discussed in detail elsewhere. (See 'Establishing a diagnosis' above and "Treatment of myalgic encephalomyelitis/chronic fatigue syndrome", section on 'Management overview'.)

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## GRAPHICS

### 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, polydipsia/polyuria, nausea | 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*** | | | |
| | Variable | Generally normal exam | None |
| **Substance use¶** | | | |
| | Variable | Generally normal exam | None |

ACTH: adrenocorticotropic hormone; HIV: human immunodeficiency virus; PPD: purified protein derivative; PHQ-2: Patient Health Questionnaire-2; GAD-7: Generalized Anxiety Disorder-7; SSS-8: Somatic Symptom Scale-8.
* Benzodiazepines, antidepressants, muscle relaxants, first-generation antihistamines, beta-blockers, opioids, GABA analogues.
¶ Alcohol, marijuana, opioids, cocaine/other stimulants.

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## 2015 IOM diagnostic criteria for ME/CFS

Diagnosis requires that the patient have the following three symptoms*:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than six months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.
2. Post-exertional malaise - Worsening of a patient's symptoms and function after exposure to physical or cognitive stressors that were normally tolerated before disease onset.
3. Unrefreshing sleep.

At least one of the two following manifestations is also required*:

1. Cognitive impairment - Problems with thinking or executive function exacerbated by exertion, effort, or stress or time pressure.
2. Orthostatic intolerance - Worsening of symptoms upon assuming and maintaining upright posture. Symptoms are improved, although not necessarily abolished, by lying back down or elevating the feet.

ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome.
* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

*From: Institute of Medicine of the National Academies. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an illness. Report Brief, February 2015. Reprinted with permission from the National Academies Press,* 

Graphic 99875 Version 10.0

## Components of a Brief Fatigue Inventory (BFI)

| **1. Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week?** | **Yes/No** |
|---|---|
| **2. Please answer the following questions by rating your fatigue (weariness, tiredness) on a scale from 0 to 10, with 0 representing "no fatigue" and 10 representing "the worst fatigue you can imagine."** | |
| A) Which number best represents your fatigue right **now?** | |
| B) Which number best describes your **usual** level of fatigue within the past 24 hours? | |
| C) Which number best describes your **worst** level of fatigue within the past 24 hours? | |
| **3. Please use a scale from 0 to 10 to answer the following questions that describe how, during the past 24 hours, your fatigue has interfered with aspects of your life. 0 represents "no interference" and 10 represents "complete interference."** | |
| A) General activity | |
| B) Mood | |
| C) Walking ability | |
| D) Normal work (including both work outside the home and daily chores) | |
| E) Relations with other people | |
| F) Enjoyment of life | |

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## Short Patient Health Questionnaire (PHQ-2)

| **Name:** | | **Date:** | | | |
|---|---|---|---|---|---|
| **Over the past 2 weeks, how often have you been bothered by any of the following problems?** | | **Not at all** | **Several days** | **More than half the days** | **Nearly every day** |
| Little interest or pleasure in doing things? | | 0 | 1 | 2 | 3 |
| Feeling down, depressed, or hopeless? | | 0 | 1 | 2 | 3 |
| **Total point score:** | _____ | _____ | + _____ | + _____ | + _____ |

**Score interpretation[1]:**

| **PHQ-2 score** | **Probability of major depressive disorder (%)** | **Probability of any depressive disorder (%)** |
|---|---|---|
| 1 | 15.4 | 36.9 |
| 2 | 21.1 | 48.3 |
| 3 | 38.4 | 75.0 |
| 4 | 45.5 | 81.2 |
| 5 | 56.4 | 84.6 |
| 6 | 78.6 | 92.9 |

*Reference:*

1. *Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003; 41:1284.*

*PHQ-2 reproduced with the permission of Pfizer Inc.*

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## PHQ-9 depression questionnaire

| **Name:** | **Date:** | | | |
|---|---|---|---|---|
| **Over the last 2 weeks, how often have you been bothered by any of the following problems?** | **Not at all** | **Several days** | **More than half the days** | **Nearly every day** |
| Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| Poor appetite or overeating | 0 | 1 | 2 | 3 |
| Feeling bad about yourself, or that you are a failure, or that you have let yourself or your family down | 0 | 1 | 2 | 3 |
| Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| Moving or speaking so slowly that other people could have noticed? Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual. | 0 | 1 | 2 | 3 |
| Thoughts that you would be better off dead, or of hurting yourself in some way | 0 | 1 | 2 | 3 |
| **Total ___ =** | **___** | **+ ___** | **+ ___** | **+ ___** |
| **PHQ-9 score ≥10: Likely major depression** | | | | |
| **Depression score ranges:** | | | | |
| 5 to 9: mild | | | | |
| 10 to 14: moderate | | | | |
| 15 to 19: moderately severe | | | | |
| ≥20: severe | | | | |
| **If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?** | Not difficult at all ___ | Somewhat difficult ___ | Very difficult ___ | Extremely difficult ___ |

PHQ: Patient Health Questionnaire.

*Developed by Drs. Robert L Spitzer, Janet BW Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer, Inc. No permission required to reproduce, translate, display or distribute.*

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## GAD-7 anxiety scale

| | Not at all | Several days | More than half the days | Nearly every day |
|---|---|---|---|---|
| **Over the last 2 weeks, how often have you been bothered by the following problems?** | | | | |
| 1. Feeling nervous, anxious, or on edge | 0 | 1 | 2 | 3 |
| 2. Not being able to stop or control worrying | 0 | 1 | 2 | 3 |
| 3. Worrying too much about different things | 0 | 1 | 2 | 3 |
| 4. Trouble relaxing | 0 | 1 | 2 | 3 |
| 5. Being so restless that it is hard to sit still | 0 | 1 | 2 | 3 |
| 6. Becoming easily annoyed or irritable | 0 | 1 | 2 | 3 |
| 7. Feeling afraid as if something awful might happen | 0 | 1 | 2 | 3 |
| **Total score***¶ _____ = | Add Columns | _____ + | _____ + | _____ |
| If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? | | | | |
| **Circle one** | Not difficult at all | Somewhat difficult | Very difficult | Extremely difficult |

* Score: 5 to 9 = mild anxiety; 10 to 14 = moderate anxiety; 15 to 21 = severe anxiety.
¶ This is a form that can be printed out and filled out by hand rather than a calculator that can be filled in online.

*Developed by Drs. Robert L Spitzer, Janet BW Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer, Inc. No permission required to reproduce, translate, display or distribute. Published in: Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006; 166:1092.*

Graphic 77755 Version 23.0

## DSM-5 diagnostic criteria for a major depressive episode

| |
|---|
| **A.** Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. |
| **NOTE:** Do not include symptoms that are clearly attributable to another medical condition. |
| 1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful). (NOTE: In children and adolescents, can be irritable mood.) |
| 2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). |
| 3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.) |
| 4) Insomnia or hypersomnia nearly every day. |
| 5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). |
| 6) Fatigue or loss of energy nearly every day. |
| 7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). |
| 8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others). |
| 9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. |
| **B.** The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. |
| **C.** The episode is not attributable to the direct physiological effects of a substance or to another medical condition. |
| **NOTE:** Criteria A through C represent a major depressive episode. |
| **NOTE:** Responses to a significant loss (eg, bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgement based on the individual's history and the cultural norms for the expression of distress in the context of loss. |
| **D.** The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders. |
| **E.** There has never been a manic or hypomanic episode. |
| **NOTE:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition. |
| *Specify*: |
| With anxious distress |
| With mixed features |
| With melancholic features |
| With atypical features |
| With psychotic features |
| With catatonia |
| With peripartum onset |
| With seasonal pattern |

Graphic 89994 Version 13.0

## Contributor Disclosures

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