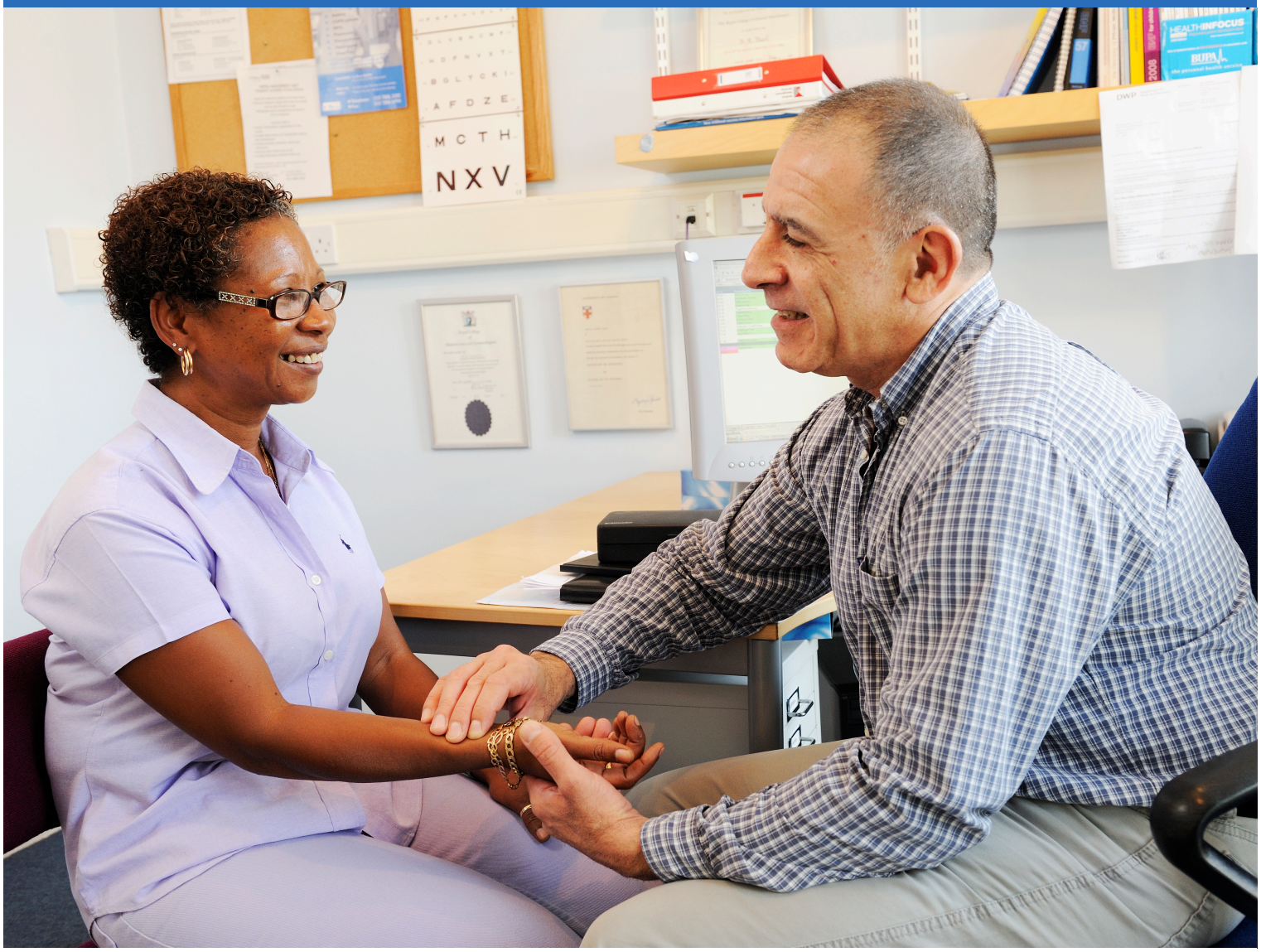
BMJ Best Practice

Assessment of fatigue

Straight to the point of care



Last updated: Jun 25, 2024

Table of Contents

Summary

Fatigue may be a symptom of almost any medical condition. For the purpose of this topic, the differentials discussed concentrate on people presenting with fatigue or where fatigue is the only symptom. Conditions in which fatigue may not necessarily be an initial complaint, but is still regarded as a markedly significant and debilitating symptom, are also included.

Definition

There are numerous definitions and classifications of fatigue, reflecting the multitude of interpretations, depending on being a patient, a physician, a biologist, or a physiologist. A common and practical definition defined fatigue as a sensation of exhaustion during or after usual activities, or a feeling of inadequate energy to begin these activities.[1]

Epidemiology

Fatigue is a common complaint in the general population, with a prevalence between 4.3% and 21.9%.[2] [3] [4] [5] [6] [7] In the US, primary care-based surveys have shown that between 11% and 33% of patients report significant fatigue, resulting in approximately 7 million surgery visits per year.

In the primary care setting, a medical or psychiatric diagnosis is found in the majority of patients presenting with fatigue (at least two-thirds).[8] [9] [10] [11] [12] A Dutch study identified a specific diagnosis in 63% of patients presenting to general practitioners with general weakness or tiredness for any length of time.[11] One study identified the most common diagnoses, in descending order, as viral illness, upper respiratory infection, iron-deficiency anaemia, acute bronchitis, adverse effects of a medical agent in the proper dose, and depression or other mental disorder.[13] The most frequent psychiatric illnesses included major depression, panic disorder, and somatisation disorder. A systematic review and meta-analysis of studies reporting on the differential diagnosis of tiredness in primary care found serious somatic disease was a rare cause. The prevalences of the following causes were found to be: anaemia (2.8%); malignancy (0.6%); serious somatic disease (4.3%); depression (18.5%).[14]

The prevalence of fatigue seems to be higher in women than men, due to iron deficit as a consequence of menstruation, and to psychosocial factors.[1] [6] [7][15] [16] [17]

Classification

Fatigue can be divided into categories based on origin, attribution, and duration of symptoms. The origin of fatigue may be:

- Central (brain-derived)
- Peripheral (usually a neuromuscular origin).

It may be attributed to:[8]

- Physical illness
- Psychological (e.g., psychiatric disorder), social (e.g., family problems), and physiological factors (e.g., old age)
- Occupational illness (e.g., workplace stress).

The duration of symptoms may refer to:

- Recent fatigue (symptoms lasting <1 month)
- Prolonged fatigue (symptoms lasting >1 month)
- Chronic fatigue (symptoms lasting >6 months).

When unexplained, clinically evaluated chronic fatigue can be separated into chronic fatigue syndrome (also known as myalgic encephalomyelitis [ME]) and idiopathic chronic fatigue.[18] [19] Chronic fatigue syndrome represents a small subset of those who report actual chronic fatigue. Even in patients with fatigue of 6 months or longer in duration, the prevalence is <40%. European studies have shown that patients with fatigue lasting longer than 6 months were given a diagnosis of chronic fatigue syndrome in up to one third of cases.[9] [13] [20] [21] [22] The US Institute of Medicine has clustered several key symptoms associated with chronic fatigue syndrome, and has proposed the term 'systemic exertion intolerance disease' (SEID) as an alternative to chronic fatigue syndrome.[23]

Aetiology

Sleep disorders

- Insomnia: this is the most common sleep disorder, with a prevalence of approximately 19% in the general population.[24] The DSM-5-TR defines insomnia disorder as dissatisfaction with sleep quantity and/or quality that causes significant distress or impairment, and which is associated with difficulty in initiating, maintaining, and/or returning to sleep (i.e., with early morning awakening) on at least 3 nights per week, for at least 3 months, and despite adequate opportunity to sleep.[25] Most patients with insomnia do not necessarily report disordered sleep but rather accompanying symptoms such as fatigue. Insomnia disorder may be associated with an underlying cause, such as:
    - Use of stimulants such as caffeine, nicotine, alcohol, quinine, and tobacco
    - Sleep-breathing disorders
    - Periodic limb disorder/restless legs syndrome
    - Panic attacks or recurrent nightmares during sleep
    - Post-traumatic stress disorder
    - Psychiatric disorders
    - Sleep phase disorders: shift work, jet lag
    - Concurrent medical conditions or their treatment, including any form of pain, and drug intoxication or withdrawal
    - Prescription drugs: beta-blockers, theophylline, stimulants, decongestants, thyroid hormone, corticosteroids, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, ticagrelor, and phenytoin.
- Obstructive sleep apnoea/hypopnoea syndrome (OSAHS): patients with OSAHS have a non-restorative sleep, which leads to physical and mental fatigue.[26]
- Obesity hypoventilation syndrome (OHS): patients with OHS have a BMI ≥class 1 (≥30 kg/m²) and features of OSAHS (including fatigue) or features of nocturnal hypoventilation such as waking headaches, peripheral oedema, hypoxaemia (arterial oxygen saturation less than 94% on air) and unexplained polycythaemia.[26]
- Restless legs syndrome (RLS): associated with symptoms of fatigue. Impairment of subjective sleep quality depends on the severity of RLS.[27] Among older people, the severity of RLS symptoms affects both quality of sleep and quality of life, including daily functioning, social functioning, general well-being, and emotional experience.[28]

Psychiatric and psychosocial disorders

- Depression: studies done in the community and in primary care settings have shown a strong association of unexplained chronic fatigue with general psychiatric disorders, mainly depression.[4] [9] [12] [29] However, this relationship is unclear, as fatigue may be a cause or a result of depression. In an attempt to clarify this, one study examined psychosocial variables and unexplained chronic fatigue through a community survey in the UK.[5] A greater prevalence of unexplained chronic fatigue in people with psychiatric morbidity was found. This prevalence seemed to increase with increasing severity of psychiatric disease.
- In addition to depression, anxiety and somatisation disorders, as well as psychosocial stressors may be associated with fatigue.

Haematological disorders

- Fatigue is a cardinal symptom of anaemia regardless of cause. It has been found that even in the absence of anaemia, checking ferritin levels in menstruating women is relevant to identify patients likely to respond to iron supplementation. Women without anaemia but with a ferritin level <112 picomol/L (<50 nanogram/mL) report a reduction of fatigue when given iron supplements.[16] [17] [30] [31]
- Chronic myeloid leukaemia, myelodysplastic syndrome, and lymphoma all present with fatigue in addition to other symptoms.
- Heavy metal toxicity can very rarely be the cause of fatigue. An occupational history is required. Risk factors for lead toxicity include battery production, glass artisans, and use of very old household paints or Ayurvedic medicines. Risk factors for mercury toxicity include consumption of fish and amalgam dental fillings. In one study, fatigue was one of the most common symptoms in patients with elevated levels of cobalt and chromium after metal-on-metal hip implant.

Cardiovascular disease

- The cardinal symptoms limiting exercise in patients with heart failure are fatigue and/or dyspnoea. Fatigue has been shown to be the major presenting symptom in 10% to 20% of new cases of heart failure.[32] [33]
- Studies have shown that in women diagnosed with acute myocardial infarction, 71% experienced unusual fatigue as a prodromal symptom, and 43% experienced fatigue as an acute symptom, whereas only 57% suffered chest pain.[34] [35]
- In general, women are more likely than men to have a delayed presentation and to present more frequently with unstable angina and non-ST-segment elevation and without chest pain.[36] [37]
- In addition to heart failure and acute myocardial ischaemia, atrial fibrillation may also present with fatigue along with other symptoms.

Endocrine disorders

- Hypothyroidism: in a large cross-sectional study, it was observed that the association between fatigue and hypothyroidism was only marginally significant. Furthermore, the fatigue symptom has a very low sensitivity (16%) for the diagnosis of hypothyroidism. Therefore, not reporting a specific symptom such as fatigue does not rule out thyroid disease.[38] Further randomised studies are required to assess the effect of thyroid replacement therapy on symptoms of fatigue in people with subclinical hypothyroidism (mildly elevated TSH with normal level of free thyroid hormones), which affects up to 10% of the adult population.[39]
- Diabetes mellitus: fatigue is viewed as a common presentation of diabetes mellitus type 1, as well as type 2. However, data regarding the frequency of fatigue in patients with diabetes are very sparse. In one of the few studies performed, fatigue in children with diabetes was assessed. Fatigue was noted in 52% of children under 15 years of age with type 1 diabetes and was the first symptom experienced in 7%.[40]
- Fatigue may be a significant symptom (although not always a presenting symptom) of other, more rare endocrine disorders, such as Addison's disease, vitamin D deficiency (osteomalacia), hypopituitarism, acromegaly, growth hormone deficiency, hyperthyroidism, Cushing's syndrome, and diabetes insipidus.[41] [42] [43]

Infectious disease

- Epstein-Barr virus (EBV): fatigue has typically been associated with EBV infectious mononucleosis. The diagnostic accuracy of symptoms was evaluated in a study of patients ≥16 years presenting with a sore throat. The presence of fatigue had a sensitivity of 93%, a specificity of 23%, and a 0.30 negative likelihood ratio, which led to the conclusion that, as a symptom of infectious mononucleosis, the absence of fatigue is helpful in ruling out the diagnosis.[44]
- HIV infection: fatigue is the most frequent and debilitating complaint affecting those with HIV.[45] HIV-positive patients >35 years of age reported significantly higher levels of fatigue than younger HIV-positive patients.[45] The causes of fatigue in HIV are multiple. Anaemia is the most common haematological abnormality. In addition, hypothyroidism, deficiency of cortisol, and depression are frequent causes of fatigue that should be excluded.
- Long COVID: describes the signs and symptoms that continue or develop after acute coronavirus 2 (SARS-CoV-2) infection. Fatigue is an important manifestation of long COVID.[46] [47]
- Lyme disease: a prospective study showed that fatigue was present in more than half of patients with confirmed early Lyme disease, and that the complaint of fatigue was more frequent than arthralgia, myalgia, or headache.[48] Lyme disease may also lead to post-treatment Lyme disease syndrome (fatigue, musculoskeletal pain, and neurocognitive difficulties) that may last for years despite antibiotic treatment.[49] Prolonged antibiotic therapy is not useful.[50]
- Cytomegalovirus, toxoplasmosis, Q fever, brucellosis, and tuberculosis may all present with fatigue. Although coxsackie B virus, *Chlamydia* , and *Mycoplasma* infections can also cause fatigue, it is not usually the chief complaint.
- Influenza virus, which affects the upper and lower respiratory tract. Fever, headache, myalgia, and fatigue are often associated with upper respiratory symptoms such as sore throat and lower respiratory symptoms of cough.[51]

Drugs and toxins

- Drugs, both recreational and medicinal, are common causes of fatigue. Therefore, when a patient presents with a history of fatigue a careful evaluation of medicine, both prescribed and over-the-counter, should be undertaken and recreational drug use explored.
- Pharmacological drugs most frequently associated with fatigue include antihistamines, antihypertensives, anti-arrhythmics, antidepressants, anti-emetics, antiepileptics, corticosteroids, diuretics, and neuroleptic agents. Ticagrelor, known to produce dyspnoea, has also been associated with reports of central sleep apnoea (causing fatigue).[52]
- Chronic alcohol misuse may also result in fatigue and should not be overlooked.
- Heavy metal toxicity can very rarely be the cause of fatigue. An occupational history is required. Risk factors for lead toxicity include battery production, glass artisans, use of very old household paints, or the use of Ayurvedic medicines. Risk factors for mercury toxicity include consumption of fish and amalgam dental fillings.[53] In one study, fatigue was one of the most common symptoms in patients with elevated levels of cobalt and chromium after a metal-on-metal hip implant.[54]

Pulmonary disease

- COPD is often associated with symptoms of fatigue.[55] In addition to dyspnoea, fatigue contributes to a reduced quality of life and decreased exercise tolerance.[56] [57] Therefore, fatigue is a symptom to investigate and manage in all patients with COPD.[55]

- Other pulmonary diseases that may be associated with fatigue include sarcoidosis, asthma, pulmonary hypertension, pleural disease, and pneumonitis.[58][59] [60] However, the presence of more specific symptoms usually points to diagnosis.

Gastrointestinal disorders

- Coeliac disease: typically, coeliac disease in childhood presents with steatorrhoea, weight loss, and failure to thrive. However, only one third of adults with the disease report such complaints. The most frequent presenting symptom in adults with coeliac disease is fatigue, emphasising the fact that presentation in this group is often atypical.[61] [62]
- Chronic liver disease: fatigue has been well recognised as a complaint of patients with chronic liver disease including viral and cholestatic liver disease. One study showed that intensity of fatigue was higher in patients suffering from primary biliary cirrhosis (PBC) compared with age- and sex-matched controls.[63] The fatigue impact score was significantly higher (worse) in the PBC patient group in contrast to the controls. No difference was seen between the fatigue scores in the PBC patients with Child-Pugh scores of 5 and those with Child-Pugh scores of >5.[63] In patients with chronic hepatitis C and hepatitis B virus infections, the Short Form-36 (SF-36) score, a questionnaire that allows assessment of patient quality of life, was substantially reduced in items concerning energy and fatigue, compared with the score of a control population.[64] [65]
- Inflammatory bowel disease (IBD): the pathogenesis of fatigue is only partially understood.[66] It may be caused by malnutrition, weight loss, and inflammation.
- Irritable bowel syndrome (IBS): fatigue is a frequent complaint in IBS and correlates with female sex and younger age.[67]

Renal disorders

- Fatigue and lack of energy are the most important problems reducing the quality of life for patients undergoing haemodialysis.[68] Patients with renal failure are prone to anaemia, malnutrition caused by uraemia, and loss of appetite. In addition, they are usually subject to dietary restrictions. These factors all contribute to developing fatigue.[69]

Neurological disorders

- Parkinson's disease: about 40% of patients with Parkinson's disease report fatigue among their main symptoms and it still remains even after adjusted for the presence of depression, dementia, and sleep disturbances.[70] [71] [72]
- Stroke: investigations demonstrated that two-thirds of patients reported fatigue after stroke and 40% considered fatigue one of the worst sequelae, lasting for some patients for at least 3 years. A pilot study suggests that fatigue correlates with the location of brain lesions, with a higher frequency in brainstem lesions.[73] A meta-analysis of 24 studies (n=2102) has shown that factors associated with post-stroke fatigue include female sex, depressive symptoms, longer time since stroke and greater disability.[74]
- Multiple sclerosis: fatigue has been found to be the most disabling symptom in patients suffering from multiple sclerosis. One study found a correlation between the presence and the severity of fatigue and the localisation of lesions in the brain. Fatigue severity was significantly higher in patients with parietal lobe, internal capsule, or peri-ventricular trigone lesions.[70] [75] [76] [77]

- Fatigue is also regarded as a common and often debilitating feature of lateral amyotrophic sclerosis, myasthenia gravis, dystonias, and myopathies.[70] However, these conditions usually present with more specific symptoms than fatigue.

Rheumatological disorders

- Half of patients with systemic lupus erythematosus report fatigue as their most disabling symptom.[78] Psychosocial variables seem to be strongly related to fatigue in these patients.[79]
- Other rheumatological aetiologies include fibromyalgia and rheumatoid arthritis (although rheumatoid arthritis does not usually present with fatigue).[80]

Cancer

- Fatigue is the most common unrelieved symptom of cancer.[81] [82] A specific diagnostic has been proposed, cancer-related fatigue, which is defined as diminished energy and mental capacity, as well as increased need to rest that is disproportionate to any recent change in activity level and is evident nearly every day during any 2-week period in the past month.[83] Causes of cancer-related fatigue are multiple and include cachexia, weight loss, anaemia, cytokine increase, and psychological factors, especially depression.[84]

Idiopathic causes

- Chronic fatigue syndrome (also known as myalgic encephalomyelitis [ME]) has been defined by the 1994 US Center for Disease Control criteria (the 'Fukuda' criteria) as clinically evaluated, unexplained, persistent or relapsing fatigue lasting at least 6 months, plus 4 or more specifically defined associated symptoms including subjective memory impairment, myalgia, arthralgia, headache, unrefreshing sleep, and post-exertional malaise (lasting >24 hours).[18] More recently, the US Institute of Medicine has proposed the term 'systemic exertion intolerance disease' (SEID) as an alternative to chronic fatigue syndrome.[23] SEID is classified as profound fatigue of new or definite onset that reduces or impairs ability to engage in pre-illness activities; lasts >6 months; is not a result of ongoing excessive exertion; is not alleviated by rest; is accompanied by both post-exertional malaise and unrefreshing sleep; and occurs with either cognitive impairment or orthostatic intolerance.[23] The UK National Institute of Health and Care Excellence state that there is no diagnostic test or universally accepted definition for ME/CFS.[85]
- The aetiology of chronic fatigue syndrome (myalgic encephalomyelitis) remains unknown. Neuroendocrine, neuroinflammation, genetic, immunologic, psychological, metabolomic, and infectious causes have been investigated as initial triggers.[86] [87] [88] No chronic active viral, prion, or other infection has been found in the vast majority of patients with ME/CFS.[89]
- Idiopathic chronic fatigue is defined as clinically evaluated unexplained chronic fatigue with no obvious medical cause that fails to meet the criteria for chronic fatigue syndrome.[18]

Urgent considerations

(See **Differentials** for more details)
The majority of conditions presenting with fatigue are not regarded as immediately life-threatening. However, a few may require urgent diagnosis or action to prevent death or serious sequelae.

Cardiovascular emergencies

Patients with signs and symptoms suggestive of acute myocardial ischaemia should be stabilised immediately and promptly evaluated for re-vascularisation therapy.

Haemodynamically unstable patients with atrial fibrillation require urgent direct-current cardioversion.

Endocrine disorders

Severe hyper- or hypoglycaemia, diabetic ketoacidosis, or non-ketotic hyperglycaemic states require urgent control of blood sugar and correction of volume and electrolyte abnormalities.

Addison's disease requires urgent substitution of deficient adrenal hormones.

Infectious disease

Untreated tuberculosis may result in respiratory failure and spread of disease.

HIV, if not diagnosed or treated appropriately with antiretroviral drugs, may result in overt AIDS and eventually death.

Neurological emergencies

Suspected stroke requires urgent evaluation for possible intervention (e.g., thrombolysis.)

Approach

The history is the most important part of the evaluation of fatigue, while the physical examination and laboratory studies provide supporting data.[90] [91] [92]

The evidence on the yield of clinical evaluation is poor, and the recommendations that follow are based on a few observational studies and experts' opinions.[90] [91] [92] [93] [94] [95]

A 7-step approach to the diagnosis of fatigue

1. Characterise the fatigue
2. Assess presence of complaints suggesting organic illness associated with fatigue
3. Evaluate medicines used and/or substances misused
4. Perform psychiatric screening
5. Ask questions on sleep quantity and/or quality
6. Perform a physical examination
7. Undertake investigations

History

Key components of a detailed history include:

- Characteristics of the fatigue based on:
    - Duration (recent, prolonged, or chronic)
    - Sudden or progressive onset (e.g., chronic fatigue syndrome [myalgic encephalomyelitis] is usually sudden-onset, with normal levels of physical fitness, activity, and energy existing prior to onset)
    - Recovery period (e.g., the course of chronic fatigue syndrome is associated with intermittent periods of recovery lasting hours or days)
    - Impact of rest (physiological versus non-physiological fatigue)
    - Impact of physical activity or mental activity (e.g., chronic fatigue syndrome is typically exacerbated by relatively minor physical or mental activity)
    - Level of physical activity (sedentary lifestyle is a cause of fatigue, and patients may benefit from exercise therapy) and concomitant presence of weakness (e.g., reduced muscle power at rest may point to a neuromuscular disorder)
    - Seasonality and any current influenza outbreak (which occur most commonly in the winter).
- Historical features and risk factors for specific diseases:
    - Age: people 60 years or older usually have an underlying cause for chronic fatigue, whereas in the 30 to 39 years age group the cause is more likely to be prolonged fatigue with no obvious causes[6] [96]
    - Residence in, or travel to, areas where certain infections are endemic (e.g., tuberculosis) or where community transmission has been reported (e.g., influenza)
    - Exposure to infections via work with cows or ingestion of unpasteurised dairy products (brucellosis); or via ingestion of uncooked meat or contact with a kitten (toxoplasmosis)
    - History of immunosuppression or use of immunosuppressive drugs (cytomegalovirus infection)

- Occupational, recreational, and residential exposure to tick-infested woods or fields near woods (Lyme disease)
- History of intravenous drug use and unprotected sexual intercourse (HIV/hepatitis B or C virus infection)
- Sleep deprivation and a sedentary lifestyle are important causes of fatigue but are often overlooked
- Cardiovascular risk factors (acute coronary syndrome)
- Steatorrhoea, weight loss (coeliac disease)
- Sore throat (Epstein-Barr virus [EBV] infection)
- Fever with cough, sore throat, runny nose (influenza infection)
- Menometrorrhagia (anaemia)[97]
- Polyuria, polydipsia (diabetes mellitus, hypopituitarism)
- Dyspnoea (cardiac failure, chronic lung disease)
- Visual field defect (multiple sclerosis)
- Cold intolerance, overweight (hypothyroidism)
- Heat intolerance, decreased weight despite increased appetite (hyperthyroidism)
- Arthralgia or rash (autoimmune disease)
- Weight loss, blood in stool (malignancy, anaemia)
- Recent viral infection (post-viral illness)
- Neurological symptoms such as paraesthesias, blurred vision, psychiatric changes, cognitive decline, tremor, ataxia (heavy metal toxicity)
- History of stroke (cerebrovascular disease).

- Evaluation of medicines, both prescribed and over-the-counter, should be undertaken and recreational drug use carefully explored. Drugs frequently associated with fatigue include:

  - Anti-arrhythmics
  - Antidepressants
  - Anti-emetics
  - Antiepileptics
  - Antihistamines
  - Antihypertensives
  - Corticosteroids
  - Diuretics
  - Neuroleptic agents.

  An occupational history should be taken if heavy metal toxicity is suspected. Risk factors for lead toxicity include battery production, glass artisans, use of very old household paints, or the use of Ayurvedic medicines. Risk factors for mercury toxicity include consumption of fish and amalgam dental fillings.[53] In one study, fatigue was one of the most common symptoms in patients with elevated levels of cobalt and chromium after metal-on-metal hip implant.[54]
- Screening for psychiatric disorders (depression, anxiety disorders, somatisation disorders, and substance misuse):

  - Because one quarter to one third of patients presenting with fatigue in a primary care setting are depressed, early diagnosis of depression is important in clinical practice.[93] [98]
  - The 2-question patient health questionnaire (PHQ-2) enquires about the frequency of depressed mood and anhedonia (if people are able to experience any joy or pleasure) over the past 2 weeks, scoring each question as 0 ('not at all') to 3 ('nearly every day').[99]

- PHQ-9 is adapted from PRIME MD (The Primary Care Evaluation of Mental Disorders) as a brief screening instrument aiding in recognition of depression in the primary care setting. PRIME MD requires 8 minutes to complete, whereas the PHQ-9 takes less than 3 minutes.[100] [101] [102]
- The CAGE Questionnaire is a simple screening tool to assess alcohol dependence: Have you ever felt the need to cut down on drinking? Have you ever felt annoyed by criticism of your drinking? Have you ever had guilty feelings about your drinking? Do you ever take a 'morning eye opener' (a drink first thing in the morning to steady your nerves or get rid of a hangover)?[103]
- The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire and is especially helpful in identifying less severe drinking problems.[104]

- Questions on sleep quantity and/or quality to investigate whether fatigue is due to or causing sleep disturbance:

  - A brief self-reported insomnia questionnaire has been evaluated: this short insomnia questionnaire (known as the Sleep Disturbance Questionnaire or SDQ) has a sensitivity of 95%, a specificity of 87%, and a positive likelihood ratio of 7 for screening insomnia. Sleep problems such as excessive sleepiness, sleep apnoea, and parasomnias are also investigated in this questionnaire.[105] The UK National Institute for Health and Care Excellence suggests that the STOP-Bang Questionnaire can be considered.[26]
  - [STOPBang.ca: STOP-Bang questionnaire] (http://www.stopbang.ca/osa/screening.php)
  - For the screening of obstructive sleep apnoea, the use of the Epworth Sleepiness Scale is advised.[26] [106] [107]

Measurement of fatigue

Fatigue is very subjective and difficult to measure. Because there is no reference standard to evaluate fatigue, clinicians generally prefer to use a single question using a visual analogue scale that rates the patient's fatigue on a 0-to-10 scale: '0' represents no fatigue and '10' the worst fatigue. More sophisticated instruments have been developed, especially for research purposes. A systematic review found that only 4 measures demonstrate the ability to detect change over time:[108]

- Brief fatigue inventory (BFI)[109]
- Fatigue severity scale (FSS)[110]
- Fatigue symptom inventory (FSI)[111]
- Multidimensional assessment of fatigue scale (MAF).[112]

Physical examination

Performing a physical examination is important not only to rule out specific causes of fatigue, such as cancer or hypothyroidism, but also to ensure that the patient feels his or her complaint is being taken seriously and viewed as a health problem worth investigating.[4] [22] [92]

After assessing the general appearance of the patient for possible signs of a psychiatric disorder (e.g., diminished level of alertness, psychomotor agitation or retardation, and poor grooming), evaluation for lymphadenopathy, a possible sign of chronic infection or malignancy, should be performed. The search for pallor, tachycardia, and a systolic ejection murmur should then be undertaken; presence of these signs suggests anaemia. Iron deficiency leads to impaired collagen synthesis, and therefore the choroids can be

seen through a thin sclera; this results in a bluish tinge to the sclera.[113] One study noted that the presence of blue sclera had a positive predictive value of 87% for iron deficiency, and 70% for mucosal pallor.[113]

Eventually, more specific signs suggesting a particular disease should be sought. These are usually guided by history. A formal cardiopulmonary examination should focus on excluding congestive heart failure (CHF) and chronic lung disease, both important causes of fatigue. Finally, a preliminary neurological examination is warranted, including assessment of muscle bulk, tone, and strength; abnormalities would suggest an underlying neurological disorder accounting for the patient's fatigue.

Specific clinical signs of organic diseases associated with fatigue include the following:

- Pallor, tachycardia, systolic ejection murmurs: anaemia
- Blue sclera: iron deficiency
- Jaundice, palmar erythema, Dupuytren's contracture: chronic liver disease
- Goitre or thyroid nodule, dry skin, delayed deep tendon reflexes, peri-orbital puffiness, ophthalmological changes: hypothyroidism
- Weight loss, hyper-reflexia, tachycardia, atrial fibrillation, fine tremor, goitre: hyperthyroidism
- Hypotension, pigmentation in skin creases, scars, and buccal mucosa: Addison's disease
- Increased central adiposity, dry skin, reduced muscle mass and strength, visual field defects, circulatory collapse (if acute presentation): hypopituitarism[114]
- Lip pursing, prolonged expiration, wheezing, cyanosis: COPD
- Pulmonary stasis, elevated jugular venous pressure, ankle oedema: heart failure
- Lymphadenopathy and/or hepatosplenomegaly: malignancy, chronic liver disease, HIV infection, EBV, cytomegalovirus, brucellosis
- Decreased breath sounds and presence of rales (secondary bacterial pneumonia): influenza infection
- Pruritus, excoriations, xanthelasma: primary biliary cirrhosis
- Red butterfly rash on the face, joint deformity: systemic lupus erythematosus (SLE)
- Tender points evaluation: fibromyalgia[115]
- Tremor, rigidity, bradykinesia: Parkinson's disease
- Loss of sensation to light touch and vibration: diabetes mellitus
- Babinski's reflex, ataxic nystagmus: multiple sclerosis
- Erythema migrans, arthralgia: Lyme disease.[116]

Investigations

It should be acknowledged that in the absence of a positive history or physical examination, laboratory tests are rarely helpful.[92] Although minor laboratory abnormalities are common, they do not often contribute to the diagnostic process.[92] However, even though laboratory evaluations rarely play a crucial role, they should be used to exclude underlying organic illness.

Initial tests to order

Include FBC with differential, erythrocyte sedimentation rate (ESR) (in patients ≥65 years, ESR helps to screen for systemic disease and neoplasia), chemistry screen (urea, electrolytes, and creatinine) as well as LFTs, fasting blood glucose, and measurement of serum creatine kinase, calcium, phosphate, and thyroid-stimulating hormone (TSH) levels. Serum levels for heavy metals (e.g., lead, mercury, cobalt, chrome) should be ordered if heavy metal toxicity is suspected.

An ECG, cardiac enzymes, natriuretic peptide biomarkers, and chest x-ray are indicated if an underlying cardiac or pulmonary disorder is suspected.[117] A nocturnal polysomnography or overnight pulse oximetry are helpful in characterising specific sleep disorders.

Further testing for specific underlying causes

Highly variable and depends on the clinical evaluation.

A ferritin level should be measured to screen for iron deficiency (particularly in menstruating females) and a urinalysis performed to detect the presence of protein, blood, and glucose.

The carbohydrate-deficient transferrin (CDT) test is a useful tool to identify possible chronic heavy alcohol consumption. It has a better performance than liver enzymes.[118] Urine and serum toxicology are indicated if a history of drug dependence is suspected. In patients with suspected cardiac failure, an elevated B-type natriuretic peptide (BNP) and echocardiogram abnormalities will support this diagnosis.

Addison's disease may be detected on serum cortisol level; however, if this is normal and the disease is clinically suspected, a short ACTH stimulation test should be performed.[119]

The endocrine assessment of a patient with suspected hypopituitarism usually involves measurement of basal anterior pituitary hormones and their respective target gland hormone levels (cortisol, TSH, free T4, free T3, FSH, LH, oestrogen, testosterone, prolactin, and GH). Serum electrolytes should be performed as part of the initial evaluation. Hyponatraemia is present in ACTH and TSH deficiencies.[120] Hypernatraemia suggests diabetes insipidus. A cosyntropin (synthetic ACTH) test may be required to assess the adrenal axis. Insulin tolerance test (ITT) may be required in some patients at risk of panhypopituitarism, to assess the ACTH-adrenal axis and GH secretory reserves comprehensively. Cosyntropin test is safer and more common than ITT. Patients with clinical symptoms or biochemical evidence for diabetes insipidus should have a urine specific gravity and osmolality, and consideration for possible water deprivation or desmopressin tests performed under expert guidance.

HIV testing and hepatitis serology should be considered based on a history of at-risk behaviour, or if lymphoma is suspected (e.g., constitutional or B symptoms present [fevers, night sweats, and/or weight loss]). The monospot test is suggested if EBV is suspected (e.g., history of fever, sore throat, rash, drowsiness, myalgia, loss of appetite), with EBV antibodies performed if there is a high clinical suspicion and the monospot test is negative. All patients residing in, or having recently travelled to, an endemic area should be tested for TB. Testing includes sputum microscopy and culture, chest x-ray and nucleic acid amplification tests. Specific testing for Lyme disease involves immunological studies, such as the immunofluorescence assay (IFA) and ELISA studies. Western blot is used to confirm the diagnosis if the IFA or ELISA is positive or equivocal. Patients who are at risk for brucellosis (e.g., those with a history of animal contact or ingestion of unpasteurised dairy products) should have a blood and bone marrow culture. Toxoplasmosis and cytomegalovirus serology are indicated when such diagnoses are suspected (e.g., history of ingestion of uncooked meat and contact with a kitten [toxoplasmosis], or history of immunosuppression or use of immunosuppressive drugs [cytomegalovirus infection]).

Patients with GI symptoms suggestive of coeliac disease (e.g., diarrhoea, steatorrhoea, abdominal pain, weight loss) require anti-tissue transglutaminase and endomysial antibodies, and confirmation of the diagnosis by small intestine biopsy. Testing for the presence of anti-mitochondrial antibodies via immunofluorescence or ELISA may help to establish a diagnosis of primary biliary cirrhosis.

CT or MRI of the head is indicated for patients with neurological examination findings suggestive of stroke or multiple sclerosis. Radioiodine scan may be indicated for patients with suspected hyperthyroidism (e.g., decreased weight, emotional lability, oligomenorrhoea, heat intolerance, goitre).

ANAs, dsDNA, and Smith antigen testing may be indicated if signs and symptoms suggest SLE. When considering a diagnosis of vitamin D deficiency, a serum vitamin D 25-hydroxy level should be requested.

Investigations for possible underlying malignancy will depend on clinical evaluation, and may include chest imaging, imaging of abdomen and pelvis, specimens sent for cytology, or biopsy. Abnormalities on FBC or blood film may indicate the need for bone marrow aspiration to exclude haematological malignancies. Tumour markers, such as LDH, may be an important indicator of disease activity in lymphomas.

Laboratory tests are not required to establish a diagnosis of long COVID. COVID-19 status can be determined by: positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR), which can ascertain current, or re-infection; serological test, which can help assess for previous infection.[121] Quality of life, functional status, exercise capacity, tests to determine cardiovascular or respiratory pathology (including laboratory), and neurobehavioural, psychiatric and sleep assessments may all have their place in the investigation of patients with suspected long COVID.[121] [122]

Differentials overview

Common
Insomnia disorder
Depression
Iron-deficiency anaemia
Iron deficiency without anaemia
Chronic heart failure
Diabetes mellitus
Hypothyroidism
Hyperthyroidism
EBV infection
Influenza infection
Long COVID
Medicine-induced fatigue
Alcohol dependence
Drug dependence
HIV infection
Acute myocardial ischaemia
Atrial fibrillation
COPD
Tuberculosis
Toxoplasmosis
Stroke

Uncommon

- Obstructive sleep apnoea/hypopnoea syndrome (OSAHS)
- Obesity hypoventilation syndrome (OHS)
- Restless legs syndrome
- Coeliac disease
- Addison's disease
- Hypopituitarism
- Myelodysplastic syndrome
- Chronic myeloid leukaemia
- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- Cytomegalovirus infection
- Lyme disease
- Brucellosis
- Chronic renal disease
- Multiple sclerosis
- Parkinson's disease
- Fibromyalgia
- Vitamin D deficiency (osteomalacia)
- Systemic lupus erythematosus
- Primary biliary cirrhosis
- Underlying malignancy (non-lymphoma)
- Chronic fatigue syndrome (myalgic encephalomyelitis)/systemic exertion intolerance disease

Uncommon

Chronic idiopathic fatigue

Heavy metal toxicity

Differentials

Common

◊ Insomnia disorder

History	Exam	1st Test	Other tests
difficulty in initiating sleep, waking frequently, poor concentration, depressed mood	decreased alertness, red and puffy eyes, absence of physical signs suggesting organic illness	»**none:** diagnosis based on history and clinical examination	

Depression

History	Exam	1st Test	Other tests
depressed mood, sadness, emotional distress, anxiety, irritability, anhedonia, feeling hopeless, loss of self-esteem, sleep problems, appetite troubles, weight loss or gain, loss of energy, poor concentration, suicidal ideation, symptoms of psychosis or mania	psychomotor slowing, agitation, blunted affect	»**2-item screening tool (PHQ-2):** positive if 1 answer is yes Use of depression screening instruments may help to exclude a depressive disorder when assessing a complaint of fatigue. The 2-question patient health questionnaire (PHQ-2) asks only how often the patient feels depressed and if he or she is able to experience any joy or pleasure.[99] Case-finding instruments for depression in primary care have on average a sensitivity of 84%, a specificity of 72%, and a likelihood ratio of 3.[123] Given a prior probability of 25%, the post-test probability that the patient has depression is 50%	

Common

Depression

History	Exam	1st Test	Other tests
		with a positive result instrument. Conversely, the negative likelihood ratio is 0.2, and therefore only 7% with a negative result instrument will have depression. »**PHQ-9 screening tool:** PHQ-9 score: 5 to 9: mild depression; 10 to 14: moderate depression; 15 to 19: moderately severe depression; ≥20: severe depression PHQ-9 is adapted from PRIME MD (The Primary Care Evaluation of Mental Disorders) as a brief screening instrument aiding in recognition of depression in the primary care setting. PRIME MD requires 8 minutes to complete, whereas the PHQ-9 takes <3 minutes.[100] [101] [102]	

◊ Iron-deficiency anaemia

History	Exam	1st Test	Other tests
asthenia, hair loss, dyspnoea, menorrhagia, dysphagia (Plummer-Vinson's syndrome)	pallor, tachycardia, systolic ejection murmur, blue sclera	»**FBC:** decreased Hb and Hct; decreased MCV, MCH, and MCHC Microcytic hypochromic anaemia. »**ferritin:** decreased	

Common

◊ Iron deficiency without anaemia

History	Exam	1st Test	Other tests
asthenia, hair loss, menorrhagia	examination may be unrevealing	»**FBC:** normal »**ferritin:** <67 picomol/L (<30 nanograms/mL) In menstruating females complaining of fatigue, iron treatment is recommended at a ferritin level <112 picomol/L (<50 nanograms/mL) (treatment goal: ferritin ≥112 picomol/L [≥50 nanograms/mL]).[16] [17] [30] In cases of hair loss the treatment goal may be as high as 157 picomol/L (70 nanograms/mL).[124] [125]	

Chronic heart failure

History	Exam	1st Test	Other tests
decreased exercise tolerance, dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, previous myocardial infarction	oedema, displaced cardiac apex, hepatojugular reflux, jugular venous distension, S3 gallop, pulmonary rales, hepatomegaly	»**brain natriuretic peptide (BNP)/ N-terminal prohormone BNP (NT-proBNP):** elevated »**chest x-ray:** cardiomegaly, pulmonary oedema, pleural effusion »**ECG:** anterior q waves or bundle branch block, atrial or ventricular arrhythmias, left axis deviation, ventricular hypertrophy	»**FBC:** normal or abnormal Anaemia can exacerbate chronic heart failure. WBC count may be elevated in presence of comorbid lung infection. »**echocardiogram:** may show systolic and/or diastolic dysfunction, valve lesions, signs of pericardial injury or cardiomyopathy

Common

Chronic heart failure

History	Exam	1st Test	Other tests
		Presence of anterior q waves suggests previous MI.	

Diabetes mellitus

History	Exam	1st Test	Other tests
polyuria, polydipsia, weakness, myalgia, weight loss, polyphagia, nausea, vomiting, altered state of consciousness, decreased vision	signs of volume depletion (dry mucous membranes, decreased skin turgor); confusion (in ketoacidosis or non-ketotic hyperglycaemia); neuropathy, retinopathy	»**fasting blood glucose level:** ≥6.9 mmol/L (≥125 mg/dL) Fasting blood glucose levels between 5.6 and 6.9 mmol/L (100 to 125 mg/dL) suggest impaired fasting glucose rather than overt diabetes mellitus. »**HbA1c:** ≥48 mmol/mol (≥6.5%) An initial screening test. [133]	»**oral glucose tolerance test:** 2-hour post-load blood sugar ≥11 mmol/L (≥199 mg/dL) Levels of 7.8 to 11 mmol/L (140 to 199 mg/dL) indicate impaired glucose tolerance. Useful in evaluating patients with a normal or impaired fasting blood glucose but high level of clinical suspicion.

◊ Hypothyroidism

History	Exam	1st Test	Other tests
weakness, cold intolerance, dry skin, hair and eyebrow loss, weight gain, constipation, peri-orbital swelling, depression, hoarseness, dyspnoea on exertion, menstrual disturbance (menorrhagia), cognitive dysfunction	bradycardia, hypothermia, hypotension (if severe); diastolic hypertension, slow movement and speech, delayed relaxation of tendon reflexes, peri-orbital oedema, enlargement of the tongue, goitre; myxedema coma (unusual)	»**TSH:** elevated Confirms the presence of primary hypothyroidism. In subclinical disease, levels are only mildly elevated.	»**T4 (serum free thyroxine):** low or normal Low free T4 with an elevated TSH is diagnostic of primary hypothyroidism. However, free T4 may be normal in subclinical hypothyroidism, despite a mildly elevated TSH.

Common

◊ Hyperthyroidism

History	Exam	1st Test	Other tests
decreased weight despite increased appetite, emotional lability, oligomenorrhoea, heat intolerance	weight loss, hyper-reflexia, tachycardia, irregularly irregular pulse (atrial fibrillation), fine tremor, goitre may be present	»**TSH:** low »**free T4 and/or free T3:** elevated	»**radioiodine scan:** shows increased uptake in areas of hyperfunction

◊ EBV infection

History	Exam	1st Test	Other tests
fever, sore throat, rash, drowsiness, myalgia, loss of appetite	generalised lymphadenopathy, hepatosplenomegaly, rash	»**FBC:** leukocytosis, atypical lymphocytes »**LFTs:** elevated AST and ALT »**monospot test:** positive Test for heterophile antibody (Paul-Bunnell IgM). False negative common early in course. Antibodies usually persist for 3 months.	»**Epstein-Barr antibodies:** positive Indicated if monospot test is negative, to differentiate EBV infection from other infectious causes of mononucleosis. Helps to differentiate acute disease from past infection. Viral capsid antigen: IgM positive early infection, IgG positive for life. Early antigen: IgG appears within weeks then disappears. EBV nuclear antigen (EBNA): positive for life.

◊ Influenza infection

History	Exam	1st Test	Other tests
winter season, fever with cough, sore throat, runny nose, current influenza outbreak	decreased breath sounds, presence of rales (uncommon, occurs in secondary bacterial pneumonia)	»**none:** diagnosis is clinical (febrile respiratory illness during a known seasonal influenza outbreak) There are no pathognomonic	»**rapid diagnostic tests:** positive for influenza A and/or influenza B, depending on particular test used »**viral culture:** detection of influenza virus or viral antigen

Common

◊ Influenza infection

History	Exam	1st Test	Other tests
		features of influenza and further testing is indicated only when the results are likely to affect diagnosis and treatment decisions and to provide community disease surveillance.[134]	»**direct immunofluorescent-antibody staining:** detection of influenza virus »**reverse transcription polymerase chain reaction:** detection of influenza virus »**enzyme immunoassay:** detection of influenza virus »**serology:** 4-fold or greater rise in antibody titre from acute to convalescent sample »**chest x-ray:** normal in uncomplicated cases; may show infiltrates consistent with pneumonia in complicated cases

◊ Long COVID

History	Exam	1st Test	Other tests
breathlessness, fatigue, post-exertional malaise and/or poor endurance, 'brain fog', cough, chest pain, headache, palpitations, arthralgia, myalgia, paraesthesia, abdominal pain, diarrhoea, insomnia and other sleep difficulties, lightheadedness, impaired daily function and mobility, pain, mood changes, anosmia or dysgeusia, menstrual cycle irregularities	new onset postural orthostatic tachycardia syndrome (POTS), tachycardia, fever, rash (e.g., urticaria, 'covid toes'), cognitive impairment, muscle weakness, generalised focal neurological signs	»**blood count, electrolytes, liver and renal function, CRP, vitamin D, vitamin B12:** usually normal in long covid; investigations to exclude other causes of fatigue »**SARS-CoV-2 antibodies:** positive Not essential to make the diagnosis.[121] »**fatigue severity scale:** score ≥4 indicates fatigue	»**chest x-ray:** may show pulmonary sequelae of acute infection including loss of lung volume, fibrosis, ground glass opacification and reticular opacities/ peripheral atelectasis The UK guidance recommends chest x-ray if respiratory symptoms persist for 12 weeks following acute COVID-19 infection.[122] Note that normal plain chest x-ray

Common

◊ Long COVID

History	Exam	1st Test	Other tests
		»**modified Medical Research Council Dyspnoea Scale (mMRC):** 0 = dyspnoea only with strenuous exercise; 1 = dyspnoea when hurrying or walking up a slight hill 2 = walks slower than people of the same age because of dyspnoea or has to stop for breath when walking at own pace; 3 = stops for breath after walking 91 m or after a few minutes; 4 = too dyspnoeic to leave house or breathless when dressing	does not rule out lung disease. »**Montreal Cognitive Assessment (MoCA):** abnormal below 26 »**high-sensitivity troponin:** elevated in infarction and myocarditis Specialised test requested if symptoms indicate it is appropriate.[121] »**D-dimer to rule out pulmonary emboli:** abnormal above 500 ng/mL Specialised test requested if symptoms indicate it is appropriate.[121]

◊ Medicine-induced fatigue

History	Exam	1st Test	Other tests
history of taking medicine associated with fatigue: most commonly antihistamines, antihypertensives, anti-arrhythmics, antidepressants, anti-emetics, antiepileptics, corticosteroids, diuretics, or neuroleptic agents	no specific findings	»**medicine withdrawal if safely achievable:** resolution of fatigue Withdrawal of medicine usually results in resolution of fatigue within 48 to 72 hours.	

Common

◊ Alcohol dependence

History	Exam	1st Test	Other tests
history of alcohol misuse	malnutrition, ascites, jaundice, peripheral neuropathy, palmar erythema, splenomegaly, telangiectasias, caput medusae	»**alcohol use disorders identification test (AUDIT):** score ≥8 suggests hazardous drinking; use in primary care The AUDIT is a 10-item questionnaire and is especially helpful in identifying less severe drinking problems.[104] »**CAGE questionnaire:** positive if answer to any 1 question is yes CAGE questionnaire: Have you ever felt the need to cut down on drinking? Have you ever felt annoyed by criticism of your drinking? Have you ever had guilty feelings about your drinking? Do you ever take a 'morning eye opener' (a drink first thing in the morning to steady your nerves or get rid of a hangover)?[103] Further investigation must be initiated if a positive answer is given to any of the above questions.	»**FBC:** macrocytosis, leukopenia, and/or thrombocytopenia Alcohol may cause bone marrow suppression. »**gamma-GT, ALT, AST:** elevation of ALT, AST, and gamma-GT with serum AST > ALT (ratio >2) »**carbohydrate-deficient transferrin (CDT):** positive if >2.5% Tool to identify possible chronic heavy alcohol consumption. Better performance than liver enzymes.[118]

Common

◊ Drug dependence

History	Exam	1st Test	Other tests
history of drug misuse, insomnia (particularly associated with nicotine, caffeine, marijuana, cocaine, and heroin misuse), aggressive behaviour, agitation, depressed mood; specific symptoms related to type of drug	clinical signs vary depending on the type of drug	»**urine toxicology:** positive for specific drug Indicates recent drug use. Negative screens do not exclude misuse. Hair samples useful when chronic misuse suspected. »**blood toxicology:** positive for specific drug Indicates recent drug use. Negative screens do not exclude misuse. Hair samples useful when chronic misuse suspected.	»**HIV serology:** positive or negative Risk of infection high among people who misuse intravenous drugs. »**hepatitis B and C studies:** positive or negative serology Risk of infection high among people who misuse intravenous drugs.

HIV infection

History	Exam	1st Test	Other tests
often asymptomatic; fever, myalgia, diarrhoea, unexplained weight loss, rashes; history of high-risk sexual activity (multiple partners, unprotected or male-male intercourse) or intravenous drug use	persistent generalised lymphadenopathy, other signs vary depending on the stage of disease	»**HIV antibodies:** positive; may be negative in early disease Incidence is increasing worldwide. Therefore, all patients with FUO should be tested. Acute and chronic HIV disease commonly associated with FUO.	»**HIV RNA:** positive Positive even in early disease.

Common

Acute myocardial ischaemia

History	Exam	1st Test	Other tests
history of cardiovascular risk factors: hypertension, obesity, diabetes mellitus, smoking, family history of heart disease; chest pain, nausea, vomiting, sweating, dizziness, shortness of breath	variable, may appear pale or grey, hypotension	»**ECG:** ischaemic changes: ST elevation, inverted T waves »**troponin:** elevated in infarction »**chest x-ray:** may be normal or have evidence of pulmonary oedema	»**coronary angiography:** vessel narrowing, occluding thrombus in acute infarction

Atrial fibrillation

History	Exam	1st Test	Other tests
exercise intolerance, palpitations, lightheadedness, syncope, dyspnoea	tachycardia, signs of heart failure: oedema, displaced cardiac apex, hepatojugular reflux, jugular venous distension, pulmonary rales	»**ECG:** absent P waves; presence of fibrillatory waves that vary in size, shape, and timing; irregularly irregular QRS complexes Rate may be very rapid: 350 to 450 bpm.	»**chest x-ray:** cardiomegaly, in particular left atrial enlargement; signs of heart failure; other precipitating pathology, such as pneumonia »**TSH:** normal or decreased Decreased if underlying hyperthyroidism.

COPD

History	Exam	1st Test	Other tests
dyspnoea, chronic cough, smoking history	barrel chest, findings on auscultation: hyper-resonance, decreased breath sounds, wheezing, rhonchi, decreased oxygen saturation on pulse oximetry	»**spirometry:** FEV1/FVC ratio <70% with no evidence of reversibility with bronchodilator COPD is classified based on the patient's FEV1 and its percentage of the predicted FEV1. »**chest x-ray:** hyperinflation May also show features of exacerbating	»**FBC:** elevated haematocrit, possible increased WBC count Elevated haematocrit may indicate long-term hypoxia. Elevated WBC count may suggest acute exacerbation or infection.

Common

COPD

History	Exam	1st Test	Other tests
		condition: for example, pneumonia.	

Tuberculosis

History	Exam	1st Test	Other tests
fever, chills, chronic cough, weight loss, night sweats; history of travel to endemic areas, HIV infection, or immunosuppression	pulmonary signs: tachypnoea, decreased breath sounds, crackles, dullness to percussion; extrapulmonary: findings dependent on site affected, generalised lymphadenopathy common	»**chest x-ray:** may demonstrate atelectasis from airway compression, pleural effusion, consolidation, pulmonary infiltrates, mediastinal or hilar lymphadenopathy, upper zone fibrosis Evidence of unrecognised pulmonary TB or evidence of old healed TB (e.g., upper lobe fibrosis) may be present; such abnormalities should prompt sputum collection for smear, culture, and nucleic acid amplification testing »**sputum acid-fast bacilli smear and culture:** presence of acid-fast bacilli (Ziehl-Neelsen stain) in specimen. Testing of 3 specimens (minimum 8 hours apart, including an early morning specimen) is recommended in many countries; consult local guidance.[135]	»**bronchoscopy and bronchoalveolar lavage:** positive for acid-fast bacilli Bronchoalveolar lavage may be indicated in patients in whom sputum induction is unsuccessful or in whom smear and NAAT are negative. Bronchoscopy is useful when other diagnoses are strongly considered or in patients in whom pulmonary TB is still suspected after other methods proved non-diagnostic. Transbronchial lung biopsies are useful in the diagnosis of miliary disease as granulomas may be visible. »**lateral flow urine lipoarabinomannan (LF-LAM) assay:** positive One Cochrane review found the lateral flow urine lipoarabinomannan (LF-LAM) assay to

Common

Tuberculosis

History	Exam	1st Test	Other tests
		Sputum specimen should be tested in patients with suspected extrapulmonary TB, as active pulmonary TB is seen in 15% to 20% of patients with extrapulmonary TB.[136] [137] [138] Culture of *Mycobacterium tuberculosis* typically takes several weeks (up to 8), decisions on treatment are usually made before culture results are known. »**acid-fast bacilli smear and culture of extrapulmonary biopsy specimen:** positive Microscopy should be performed on specimens collected from sites of suspected extrapulmonary TB.[135] [139] Culture result may take several weeks. »**nucleic acid amplification tests (NAAT):** positive for *M tuberculosis* NAAT should be performed on at least one respiratory specimen (or specimen collected from sites of suspected extrapulmonary TB)	have a sensitivity of 42% in diagnosing TB in HIV-positive individuals with TB symptoms, and 35% in HIV-positive individuals not assessed for TB symptoms.[142] WHO recommends that LF-LAM can be used to assist in the diagnosis of active TB in HIV-positive adults, adolescents, and children with signs and symptoms of TB, or in those with advanced HIV or who are seriously ill.[141] Culture would still be required for drug susceptibility testing (DST). »**contrast-enhanced chest computed tomography scan:** primary TB: mediastinal tuberculous lymphadenitis with central node attenuation and peripheral enhancement, delineated cavities; postprimary TB: centrilobular nodules and tree-in-bud pattern Bronchiectasis can be seen in chronic cases. Haemoptysis usually originates from bronchial arteries, but Rasmussen's

DIAGNOSIS

Common

Tuberculosis

History	Exam	1st Test	Other tests
		when a diagnosis of TB is being considered. NAAT may speed the diagnosis in smear-negative cases and may be helpful to differentiate non-tuberculous mycobacteria when sputum is AFB smear positive but NAAT negative.[140] Genotyping might be considered useful in outbreaks of TB to identify transmission of TB, especially when contact had not been appreciated in the course of epidemiologic investigations. Although NAATs were originally designed and approved for respiratory specimens, they may also be requested on specimens from other sites where involvement of TB is suspected (e.g., cerebrospinal fluid, lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid, or urine).[135] [141] In the US, use of NAATs for extrapulmonary specimens is not	aneurysms from a pulmonary artery adjacent to a cavity can be the source of bleeding. Residual bronchiectasis from old TB can cause haemoptysis.

Common

Tuberculosis

History	Exam	1st Test	Other tests
		approved by the US Food and Drug Administration, and use would be off-label. Several rapid NAATs are available for the diagnosis of TB and some are also able to detect genes encoding resistance to TB drugs.[141]	

◊ Toxoplasmosis

History	Exam	1st Test	Other tests
mild fever, chills, sweats; rarely: headaches, myalgia, sore throat, rash; most cases are asymptomatic	bilateral cervical adenopathy, pharyngitis, maculopapular rash, hepatosplenomegaly	»**serology:** positive IgG and IgM antibodies If only IgG are positive, tests for the avidity of IgG antibodies may discriminate between recently acquired infection and those obtained in the more distant past.[145]	

Stroke

History	Exam	1st Test	Other tests
weakness of the face, blurred vision, diplopia, decreased vision, sudden paresis/ paralysis of limbs, headache, vomiting	abnormal neurological examination, difficulty in speaking: slurred speech, confused speech; paresis/ paralysis of limbs	»**CT head:** ischaemic: hypo-attenuation (darkness) of the brain parenchyma; loss of grey matter-white matter differentiation, and sulcal effacement; haemorrhagic: enhancing lesion	

Uncommon

◊ Obstructive sleep apnoea/hypopnoea syndrome (OSAHS)

History	Exam	1st Test	Other tests
snoring, diurnal somnolence, agitation and sweating at night, headache, morning xerostomia (dry mouth) and sore throat, depressed mood, irritability, loss of libido; total score of ≥11 on Epworth sleepiness scale supports the diagnosis	elevated BP, obesity, nasal obstruction, macroglossia, tonsillar hypertrophy, obstruction by the palate, low soft palate, retrognathism, micrognathia	»**polysomnography:** apnoea/hypopnoea index ≥15 episodes/hour (in the absence of symptoms) or ≥5 events/hour associated with the typical symptoms of OSA Typical symptoms of OSA include sleepiness, fatigue, insomnia, or other symptoms leading to impaired sleep-related quality of life (e.g., unrefreshing sleep, daytime sleepiness, fatigue or insomnia, awakening with a gasping or choking sensation, loud snoring, or witnessed apnoeas).[126] Polysomnography is the definitive test.[127] General parameters measured include electroencephalogram, electro-oculographic recording, air flow assessment, electromyogram, capnography, oesophageal manometry, ECG, pulse oximetry, respiratory effort signals, synchronised polysomnography video, and body position.[128]	»**fibre-optic endoscopy:** may see nasal polyps or tumours, or hypertrophic lingual tonsils

Uncommon

◊ Obstructive sleep apnoea/hypopnoea syndrome (OSAHS)

History	Exam	1st Test	Other tests
		Polysomnography may be a full night study or a split study. »**portable multichannel sleep tests:** Respiratory Event Index (REI) of ≥15 episodes/hour or REI ≥5 with symptoms or comorbidities Used for patients with higher probability of OSA and without complex comorbidities (e.g., cardiopulmonary disease, chronic opioid therapy, or neuromuscular disease). Portable tests typically include a smaller selection of channels than the polysomnogram (nasal pressure, oximetry, thoracoabdominal effort sensors, heart rate), but usually do not measure sleep. Portable tests may underestimate the REI as obstructions are measured for recording time, not sleep time.	

◊ Obesity hypoventilation syndrome (OHS)

History	Exam	1st Test	Other tests
obesity (body mass index [BMI] ≥ 30 kg/m²), dyspnoea, nocturia, lower extremity oedema,	mild hypoxaemia awake (arterial oxygen saturation less than 94% on air), with significant hypoxaemia	»**serum bicarbonate:** >24 mmol/L (>24 mEq/L)	»**polysomnography:** demonstrates hypoventilation, particularly during REM sleep

Uncommon

◊ Obesity hypoventilation syndrome (OHS)

History	Exam	1st Test	Other tests
excessive daytime sleepiness, fatigue, loud disruptive snoring, witnessed apnoeas, waking headaches	when asleep, awake daytime hypercapnia, unexplained polycythaemia	May be used to screen for the presence of alveolar hypoventilation, but does not confirm the diagnosis. Guidelines recommend serum bicarbonate levels for patients with low to moderate probability of having OHS (<20%) to decide when to measure $PaCO_2$.[129] »**arterial blood gas:** $PaCO_2$ >45 mmHg Awake resting $PaCO_2$ >45 mmHg at sea level (awake daytime hypercapnia), in the presence of obesity (BMI ≥30 kg/m²) and sleep disordered breathing defines OHS (after excluding other causes of hypoventilation)[129] Measure first in patients strongly suspected of having OHS to confirm the diagnosis.[130]	Identifies associated obstructive sleep apnoea in patients with OHS.[131] In addition, it may identify patients with OHS prior to developing awake elevations in $PaCO_2$.[132] General parameters measured include electroencephalogram, electro-oculographic recording, air flow assessment, electromyogram, capnography, oesophageal manometry, ECG, pulse oximetry, respiratory effort signals, synchronised polysomnography video, and body position.[128] Polysomnography may be a full night study or a split study.

◊ Restless legs syndrome

History	Exam	1st Test	Other tests
limb discomfort at rest, involuntary limb movement, restlessness, disturbed sleep, depressed mood	no specific findings	»**none:** diagnosis is clinical	

Uncommon

◊ Coeliac disease

History	Exam	1st Test	Other tests
diarrhoea, steatorrhoea, abdominal pain, weight loss	pallor, easy bruising, aphthous stomatitis; abdominal distension	»**anti-tissue transglutaminase antibodies:** elevated titre False-negative results are found in IgA deficiency. Therefore, IgA immunoglobulin level should also be requested. »**IgG DGP or IgA/IgG DGP (deamidated gliadin peptide):** elevated titre Test of choice for individuals with IgA deficiency.	»**small intestine biopsy:** presence of intra-epithelial lymphocytes, villous atrophy, and crypt hyperplasia Required for diagnosis.

Addison's disease

History	Exam	1st Test	Other tests
weakness, anorexia, weight loss, nausea, vomiting, abdominal pain, fever, myalgia, arthralgia	signs of volume depletion (dry mucous membranes, decreased skin turgor), hypotension, tachycardia, hyper-pigmentation	»**morning serum cortisol:** decreased Blood should be drawn between 8.00 am and 9.00 am, when cortisol levels peak. »**serum electrolytes:** decreased sodium; elevated potassium, creatinine, and urea	»**short ACTH stimulation test:** cortisol <497 nanomol/L (<18 micrograms/dL) A normal response to ACTH (250 micrograms as an intravenous bolus) is a rise in serum cortisol concentration after 30 or 60 minutes to a peak of 497 to 552 nanomol/L (18 to 20 micrograms/dL) or more.[143]

Uncommon

◊ Hypopituitarism

History	Exam	1st Test	Other tests
symptoms vary depending on underlying cause: energy loss, muscle weakness, decreased sweating, anorexia, weight loss or weight gain, abdominal pain, reduction in amount of axillary and pubic hair in women, erectile dysfunction, oligomenorrhoea/ amenorrhoea, breast atrophy, loss of libido, infertility, cold intolerance, dry skin, polyuria, polydipsia, nocturia	may have increased central adiposity, dry skin, reduced muscle mass and strength, visual field defects, circulatory collapse if acute presentation	»**LH:** low »**FSH:** low »**oestrogen:** low Useful for evaluation of premenopausal women. »**TSH:** low »**free T4 and T3:** low »**basal serum cortisol:** low	»**testosterone:** low »**prolactin:** low or high Hypopituitarism may occur with large prolactinomas or interruption of the hypothalamic-pituitary axis. »**cortisol reserve:** low (with cosyntropin stimulation) »**FBC:** anaemia »**metabolic panel:** may show hyponatraemia, hyperkalaemia, hypoglycaemia »**insulin tolerance test:** reduced growth hormone and cortisol responses Definitive test but associated with substantial risks. »**urine specific gravity:** low in diabetes insipidus »**water deprivation test:** urine osmolality less than serum osmolality following water deprivation Only if suspected diabetes insipidus. Dehydration should be done with caution and by an expert. »**desmopressin test:** after desmopressin, urine osmolality increases in central diabetes insipidus

Uncommon

◊ Hypopituitarism

History	Exam	1st Test	Other tests
			Dehydration should be done with caution and by an expert.

◊ Myelodysplastic syndrome

History	Exam	1st Test	Other tests
dyspnoea, leg swelling, bleeding, history of bacterial or fungal infections	petechiae, purpura, leg oedema	»**FBC and differential:** pancytopenia, abnormal cells, anaemia	»**bone marrow biopsy:** hyperactive or hypoactive marrow and abnormal cells

Chronic myeloid leukaemia

History	Exam	1st Test	Other tests
fever, weight loss, night sweats, history of bruising	hepatosplenomegaly, petechiae, purpura	»**FBC and peripheral blood smear:** elevated or abnormal WBC count, low platelet count; myeloid maturing cells, elevated basophils and eosinophils	»**bone marrow biopsy:** granulocyte hyperplasia Abnormalities include promyelocytes, myelocytes, metamyelocytes, and band forms.

◊ Non-Hodgkin's lymphoma

History	Exam	1st Test	Other tests
persistently enlarged lymph nodes, possibly extranodal sites, constitutional or B symptoms (fevers, night sweats, and/or weight loss) and occasionally pruritus	generalised, local, or regional lymphadenopathy; hepatosplenomegaly	»**lymph node excision biopsy:** histology and immunohistochemistry, cytogenetics, flow cytometric and molecular genetic analysis confirm the type and grade of lymphoma	»**FBC:** evaluation for cytopenias Hypoproliferative anaemia can be secondary to inflammation or bone marrow replacement, and often presents with normochromic, normocytic indices. Alternatively, anaemia can result

Uncommon

◊ Non-Hodgkin's lymphoma

History	Exam	1st Test	Other tests
			from autoimmune haemolysis (Coombs test positive) associated with an underlying lymphoma. »**LDH:** elevated LDH is an important marker of disease activity and prognosis in lymphomas. »**bone marrow biopsy:** indicated for staging in newly diagnosed lymphoma »**CT scan of neck, chest, abdomen, and pelvis:** evaluation of the extent of lymphadenopathy and performance of accurate staging CT scan also provides important information about splenic and extranodal sites of involvement. »**whole-body positron emission tomography (PET scan) or integrated PET/CT:** regions affected by lymphoma will appear to be highly metabolically active on PET scan »**HIV serology:** may be positive HIV patients are at high risk for development of lymphoma. »**hepatitis B and C serology:** may be positive

Uncommon

◊ Non-Hodgkin's lymphoma

History	Exam	1st Test	Other tests
			As with HIV, hepatitis B and hepatitis C infections correlate with an increased risk for the development of malignant lymphoma.

Hodgkin's lymphoma

History	Exam	1st Test	Other tests
painless cervical and/or supraclavicular lymphadenopathy in a young adult is common; constitutional or B symptoms (fevers, night sweats, and/or weight loss), occasionally pruritus, possibly pain following alcohol ingestion at sites of lymphadenopathy	generalised, local, or regional lymphadenopathy; hepatosplenomegaly	»**lymph node excision biopsy:** Hodgkin's cell can be a characteristic Reed-Sternberg cell, or variants such as the lacunar cell in the nodular sclerosis subtype; in nodular lymphocyte-predominant Hodgkin's lymphoma, the characteristic cell is the lymphocytic and histiocytic cell (popcorn cell)	»**FBC:** evaluation for cytopenia »**bone marrow biopsy:** indicated for staging in newly diagnosed lymphoma »**CT scan of neck, chest, abdomen, and pelvis:** evaluation of the extent of lymphadenopathy and performance of accurate staging CT scan also provides important information about splenic and extranodal sites of involvement. »**whole-body positron emission tomography (PET scan) or integrated PET/CT:** regions affected by lymphoma will appear to be highly metabolically active on PET scan

Uncommon

◊ Cytomegalovirus infection

History	Exam	1st Test	Other tests
usually asymptomatic unless immunocompromised; fever, malaise, night sweats, arthralgia, weakness, weight loss; symptoms specific to infection site: for example, reduced vision, pneumonia, encephalitis, diarrhoea	dependent on site of infection; includes lymphadenopathy and hepatosplenomegaly, retinal changes	»**CMV IgM and IgG antibodies:** positive Acute infection suggested by presence of IgM.	»**CMV polymerase chain reaction:** positive »**CMV antigenaemia test:** positive Detects the presence of CMV proteins in the peripheral smear; most useful in immunocompromised patients. »**blood culture:** positive Results take 3 weeks. »**urine culture:** positive Results take 3 weeks. »**tissue biopsy:** positive for CMV viral particles May be required for localised infection.

◊ Lyme disease

History	Exam	1st Test	Other tests
fever, lethargy, headache, myalgia, neck stiffness, inflammation of large joints	erythema migrans: bull's-eye lesion(s)	»**immunofluorescence assay (IFA):** antibodies to *Borrelia burgdorferi* »**ELISA:** positive	»**Western blot:** positive Used to confirm the diagnosis if the IFA or ELISA is positive or equivocal. »**2nd ELISA:** positive May be used instead of a western blot to confirm the diagnosis if the IFA or first ELISA is positive or equivocal.[144]

Uncommon

◊ Brucellosis

History	Exam	1st Test	Other tests
history of animal contact or ingestion of unpasteurised dairy products; fever, sweats, malaise, arthralgia, depression, weight loss	fever, lymphadenopathy, hepatosplenomegaly	»**blood culture:** positive for *Brucella*	»**bone marrow culture:** positive for *Brucella*

◊ Chronic renal disease

History	Exam	1st Test	Other tests
weakness, pruritus, loss of appetite, nausea, vomiting, headache, dizziness, muscle pain, cramps, arthralgia, dyspnoea	generalised oedema, elevated BP, purpura, mental status changes	»**serum creatinine:** elevated	»**estimation of GFR:** reduced GFR Regarded as chronic renal disease stage 1 if GFR >90 mL/minute/1.73 m², stage 5 if <15 mL/minute/1.73 m² or patient on dialysis. Calculated based on Cockroft-Gault formula.[146] »**renal ultrasound:** small kidney size; presence of obstruction/ hydronephrosis; kidney stones

◊ Multiple sclerosis

History	Exam	1st Test	Other tests
unilateral visual disturbance, leg cramping, strange sensory phenomena, bladder and bowel dysfunction	increased muscle tone, increased deep tendon reflexes, abnormalities on eye examination	»**MRI brain and spinal cord:** hyper-intensities in the peri-ventricular white matter	

Uncommon

◊ Parkinson's disease

History	Exam	1st Test	Other tests
tremor, bradykinesia, dysphagia, blurred vision	tremor, bradykinesia, rigidity, postural instability, hypomimia (masked facial expression), speech impairment, sialorrhoea, hypometric saccades, impaired vestibulo-ocular reflex, micrographia, dystonia, myoclonus	»**none:** diagnosis is clinical Diagnosis can be made if bradykinesia is present plus at least 1 of the following: muscular rigidity; 4 to 6 Hz rest tremor; postural instability not caused by visual, vestibular, cerebellar, or proprioceptive dysfunction.[147]	

◊ Fibromyalgia

History	Exam	1st Test	Other tests
widespread musculoskeletal pain, abdominal pain, chest pain, pelvic pain, bladder symptoms suggestive of cystitis	>11 out of 18 tender points present on palpation of soft tissues	»**none:** diagnosis is strictly clinical	

◊ Vitamin D deficiency (osteomalacia)

History	Exam	1st Test	Other tests
often asymptomatic, diffuse bone pain, myalgia, muscle weakness	fractures, diffuse bony tenderness; skeletal deformities are rare in adults	»**serum vitamin D 25-hydroxy level:** <50 nanomol/L (20 nanograms/mL)	»**DEXA:** reduced bone density, thinning of the cortex Non-specific; DEXA reveals a decreased bone density in both osteoporosis and osteomalacia.

Uncommon

◊ Systemic lupus erythematosus

History	Exam	1st Test	Other tests
rash, fever, weight loss, hair loss, arthralgia, chest pain and dyspnoea, abdominal pain, nausea, vomiting, diarrhoea	oral ulcers, alopecia, butterfly rash, discoid rash, photosensitive rash, lymphadenopathy, hypertension, oedema, Raynaud's phenomenon	»**ANA, dsDNA, Smith antigen:** positive ANA is positive in almost all patients with SLE and confirms the diagnosis in the presence of relevant clinical findings. However, a positive ANA alone is not diagnostic, as it may be positive in other connective tissue diseases. Anti-dsDNA and anti-Smith antibodies are specific for SLE and often confirm the diagnosis, if present.[148] [149]	

Primary biliary cirrhosis

History	Exam	1st Test	Other tests
personal history or family history of autoimmune disease, history of hypercholesterolaemia, pruritus, sleep disturbance, family history of primary biliary cirrhosis, dry eyes and mouth, postural dizziness/blackouts	hepatomegaly; less commonly, signs associated with advanced liver disease and portal hypertension (e.g., skin hyperpigmentation, splenomegaly, jaundice, xanthelasmata)	»**LFTs:** elevated gamma-GT, bilirubin, and Alk phos »**anti-mitochondrial antibodies:** present Presence of these antibodies is established by means of immunofluorescence or ELISA.	

Uncommon

Underlying malignancy (non-lymphoma)

History	Exam	1st Test	Other tests
history of weight loss, possible family history of cancer, additional symptoms dependent on cancer type	variable; lymphadenopathy and/or hepatosplenomegaly may be present; more specific findings related to cancer type	»**variable (e.g., mammography, CT scan, pathology):** depends on cancer type	

◊ Chronic fatigue syndrome (myalgic encephalomyelitis)/ systemic exertion intolerance disease

History	Exam	1st Test	Other tests
severe disabling fatigue lasting >6 months; not due to ongoing exertion, not relieved with rest, reduced levels of activity, symptoms present for >50% of time; may involve memory/cognitive impairment, myalgia, arthralgia, headache, unrefreshing sleep, post-exertional malaise (lasting >24 hours), and/or orthostatic intolerance	tender lymphadenopathy, muscle pain, and other non-specific signs	»**none:** diagnosis is based on history, and clinical signs and symptoms All active, unresolved, or suspected diseases likely to cause fatigue, including psychotic disorders, melancholic or bipolar depression, dementia, anorexia or bulimia nervosa, alcohol or substance misuse, and severe obesity, are regarded as exclusion criteria.[18] Various laboratory tests may be ordered as a means of ruling out organic disease. Extensive laboratory testing is not indicated.	

Uncommon

◊ Chronic idiopathic fatigue

History	Exam	1st Test	Other tests
fatigue lasting more than 6 months, does not meet criteria for chronic fatigue syndrome	tender lymph nodes, muscle pain, and other non-specific signs	»**none:** diagnosis is clinical	

◊ Heavy metal toxicity

History	Exam	1st Test	Other tests
history of metal-on-metal hip implant (cobalt or chrome toxicity); dental amalgams, excess fish consumption (mercury toxicity); exposure to very old paints, glass artisans, battery production, use of Ayurvedic medicines (lead toxicity); paraesthesias, blurred vision, psychiatric changes, cognitive decline	tremor, ataxia	»**serum level (lead, mercury, cobalt, chrome):** elevated	

Guidelines

United Kingdom

Obstructive sleep apnoea/hypopnoea syndrome and obesity hypoventilation syndrome in over 16s (https://www.nice.org.uk/guidance/ng202)

Published by: National Institute for Health and Care Excellence
Last published: 2021

Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management (https://www.nice.org.uk/guidance/ng206)

Published by: National Institute for Health and Care Excellence
Last published: 2021

COVID-19 rapid guideline: managing the long-term effects of COVID-19 (https://www.nice.org.uk/guidance/ng188)

Published by: National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network and the Royal College of General Practitioners
Last published: 2024

North America

Myalgic encephalomyelitis/chronic fatigue syndrome (https://www.cdc.gov/me-cfs)

Published by: Centers for Disease Control and Prevention
Last published: 2023

Online resources

1. STOPBang.ca: STOP-Bang questionnaire *(external link) (http://www.stopbang.ca/osa/screening.php)*

REFERENCES

Key articles

- National Institute for Health and Care Excellence. Myalgic encephalomyelitis (or encephalopathy)/ chronic fatigue syndrome: diagnosis and management. Oct 2021 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng206)
- Centers for Disease Control and Prevention. Myalgic encephalomyelitis/chronic fatigue syndrome, etiology and pathophysiology. Jul 2018 [internet publication]. Full text (https://www.cdc.gov/me-cfs/healthcare-providers/presentation-clinical-course/etiology-pathophysiology.html)
- Cornuz J, Guessous I, Favrat B. Fatigue: a practical approach to diagnosis in primary care. CMAJ. 2006 Mar 14;174(6):765-7. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1402370) Abstract
- Hamilton W, Watson J, Round A. Investigating fatigue in primary care. BMJ. 2010 Aug 24;341:c4259. Abstract

References

1. Chen MK. The epidemiology of self-perceived fatigue among adults. Prev Med. 1986 Jan;15(1):74-81. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3714661?tool=bestpractice.bmj.com)
2. Hickie IB, Hooker AW, Hadzi-Pavlovic D, et al. Fatigue in selected primary care settings: sociodemographic and psychiatric correlates. Med J Aust. 1996 May 20;164(10):585-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8637460?tool=bestpractice.bmj.com)
3. Wessely S, Chalder T, Hirsch S, et al. The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. Am J Public Health. 1997 Sep;87(9):1449-55. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1380968) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9314795?tool=bestpractice.bmj.com)
4. Kroenke K, Wood DR, Mangelsdorff AD, et al. Chronic fatigue in primary care. Prevalence, patient characteristics, and outcome. JAMA. 1988 Aug 19;260(7):929-34. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3398197?tool=bestpractice.bmj.com)
5. Skapinakis P, Lewis G, Meltzer H. Clarifying the relationship between unexplained chronic fatigue and psychiatric morbidity: results from a community survey in Great Britain. Int Rev Psychiatry. 2003 Feb-May;15(1-2):57-64. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12745311?tool=bestpractice.bmj.com)
6. Steele L, Dobbins JG, Fukuda K, et al. The epidemiology of chronic fatigue in San Francisco. Am J Med. 1998 Sep 28;105(3A):83S-90S. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9790487?tool=bestpractice.bmj.com)
7. Galland-Decker C, Marques-Vidal P, Vollenweider P. Prevalence and factors associated with fatigue in the Lausanne middle-aged population: a population-based, cross-sectional survey. BMJ Open. 2019

Aug 24;9(8):e027070. Full text (https://www.doi.org/10.1136/bmjopen-2018-027070) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31446404?tool=bestpractice.bmj.com)

8. Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. Lancet. 2006 Jan 28;367(9507):346-55. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16443043?tool=bestpractice.bmj.com)

9. Wessely S, Chalder T, Hirsch S, et al. Psychological symptoms, somatic symptoms, and psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in the primary care setting. Am J Psychiatry. 1996 Aug;153(8):1050-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8678174?tool=bestpractice.bmj.com)

10. Cathebras PJ, Robbins JM, Kirmayer LJ, et al. Fatigue in primary care: prevalence, psychiatric comorbidity, illness behavior, and outcome. J Gen Intern Med. 1992 May-Jun;7(3):276-86. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1613608?tool=bestpractice.bmj.com)

11. Okkes IM, Oskam SK, Lamberts H. The probability of specific diagnoses for patients presenting with common symptoms to Dutch family physicians. J Fam Pract. 2002 Jan;51(1):31-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11927060?tool=bestpractice.bmj.com)

12. Walker EA, Katon WJ, Jemelka RP. Psychiatric disorders and medical care utilization among people in the general population who report fatigue. J Gen Intern Med. 1993 Aug;8(8):436-40. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8410409?tool=bestpractice.bmj.com)

13. Bates DW, Schmitt W, Buchwald D, et al. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. Arch Intern Med. 1993 Dec 27;153(24):2759-65. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8257251?tool=bestpractice.bmj.com)

14. Stadje R, Dornieden K, Baum E, et al. The differential diagnosis of tiredness: a systematic review. BMC Fam Pract. 2016 Oct 20;17(1):147. Full text (https://www.doi.org/10.1186/s12875-016-0545-5) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27765009?tool=bestpractice.bmj.com)

15. Bensing JM, Hulsman RL, Schreurs KM. Gender differences in fatigue: biopsychosocial factors relating to fatigue in men and women. Med Care. 1999 Oct;37(10):1078-83. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10524374?tool=bestpractice.bmj.com)

16. Verdon F, Burnand B, Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. BMJ. 2003 May 24;326(7399):1124. Full text (http://www.bmj.com/cgi/content/full/326/7399/1124) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12763985?tool=bestpractice.bmj.com)

17. Vaucher P, Druais PL, Waldvogel S, et al. Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: a randomized controlled trial. CMAJ. 2012 Aug 7;184(11):1247-54. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22777991?tool=bestpractice.bmj.com)

18. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994 Dec 15;121(12):953-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7978722?tool=bestpractice.bmj.com)

19. Reid S, Chalder T, Cleare A, et al. Chronic fatigue syndrome. BMJ. 2000 Jan 29;320(7230):292-6. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1117488) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10650029?tool=bestpractice.bmj.com)

20. Buchwald D, Umali P, Umali J, et al. Chronic fatigue and the chronic fatigue syndrome: prevalence in a Pacific Northwest health care system. Ann Intern Med. 1995 Jul 15;123(2):81-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7778839?tool=bestpractice.bmj.com)

21. Darbishire L, Ridsdale L, Seed PT. Distinguishing patients with chronic fatigue from those with chronic fatigue syndrome: a diagnostic study in UK primary care. Br J Gen Pract. 2003 Jun;53(491):441-5. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1314617) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12939888?tool=bestpractice.bmj.com)

22. Ridsdale L, Evans A, Jerrett W, et al. Patients with fatigue in general practice: a prospective study. BMJ. 1993 Jul 10;307(6896):103-6. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1693499) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8343705?tool=bestpractice.bmj.com)

23. Institute of Medicine. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. Washington, DC: The National Academies Press; 2015.

24. Ohayon MM. Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. J Psychiatr Res. 1997 May-Jun;31(3):333-46. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9306291?tool=bestpractice.bmj.com)

25. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed., text revision (DSM-5-TR). Washington, DC: American Psychiatric Publishing; 2022.

26. National Institute for Health and Care Excellence. Obstructive sleep apnoea/hypopnoea syndrome and obesity hypoventilation syndrome in over 16s. Aug 2021 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng202)

27. Hornyak M, Kopasz M, Berger M, et al. Impact of sleep-related complaints on depressive symptoms in patients with restless legs syndrome. J Clin Psychiatry. 2005 Sep;66(9):1139-45. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16187772?tool=bestpractice.bmj.com)

28. Cuellar NG, Strumpf NE, Ratcliffe SJ. Symptoms of restless legs syndrome in older adults: outcomes on sleep quality, sleepiness, fatigue, depression, and quality of life. J Am Geriatr Soc. 2007 Sep;55(9):1387-92. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17915343?tool=bestpractice.bmj.com)

29. Lawrie SM, Pelosi AJ. Chronic fatigue syndrome in the community. Prevalence and associations. Br J Psychiatry. 1995 Jun;166(6):793-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7663830?tool=bestpractice.bmj.com)

30. Krayenbuehl PA, Battegay E, Breymann C, et al. Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration. Blood. 2011 Sep 22;118(12):3222-7. Full text (http://bloodjournal.hematologylibrary.org/content/118/12/3222.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21705493?tool=bestpractice.bmj.com)

31. Favrat B, Balck K, Breymann C, et al. Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women--PREFER a randomized, placebo-controlled study. PLoS One. 2014 Apr 21;9(4):e94217. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3994001) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24751822?tool=bestpractice.bmj.com)

32. Drexler H, Coats AJ. Explaining fatigue in congestive heart failure. Annu Rev Med. 1996;47:241-56. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8712779?tool=bestpractice.bmj.com)

33. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016 Jul 14;37(27):2129-200. Full text (http://eurheartj.oxfordjournals.org/content/early/2016/06/08/eurheartj.ehw128.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27206819?tool=bestpractice.bmj.com)

34. McSweeney JC, Cody M, O'Sullivan P, et al. Women's early warning symptoms of acute myocardial infarction. Circulation. 2003 Nov 25;108(21):2619-23. Full text (http://circ.ahajournals.org/cgi/content/full/108/21/2619) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14597589?tool=bestpractice.bmj.com)

35. Blakeman JR, Stapleton SJ. An integrative review of fatigue experienced by women before and during myocardial infarction. J Clin Nurs. 2018 Mar;27(5-6):906-16. Full text (https://www.doi.org/10.1111/jocn.14122) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29076243?tool=bestpractice.bmj.com)

36. Khan NA, Daskalopoulou SS, Karp I, et al. Sex differences in acute coronary syndrome symptom presentation in young patients. JAMA Intern Med. 2013 Nov 11;173(20):1863-71. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24043208?tool=bestpractice.bmj.com)

37. Crea F, Battipaglia I, Andreotti F, et al. Sex differences in mechanisms, presentation and management of ischaemic heart disease. Atherosclerosis. 2015 Jul;241(1):157-68. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25988360?tool=bestpractice.bmj.com)

38. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000 Feb 28;160(4):526-34. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10695693?tool=bestpractice.bmj.com)

39. Biondi B, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. JAMA. 2019 Jul 9;322(2):153-60. Full text (https://www.doi.org/10.1001/jama.2019.9052) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31287527?tool=bestpractice.bmj.com)

40. Levy-Marchal C, Patterson CC, Green A, et al. Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. European and Diabetes. Diabetologia. 2001 Oct;44(suppl 3):B75-80. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11724421?tool=bestpractice.bmj.com)

41. Lovas K, Loge JH, Husebye ES. Subjective health status in Norwegian patients with Addison's disease. Clin Endocrinol (Oxf). 2002 May;56(5):581-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12030907?tool=bestpractice.bmj.com)

42. Biermasz NR, van Thiel SW, Pereira AM, et al. Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. J Clin Endocrinol Metab. 2004 Nov;89(11):5369-76. Full text (http://jcem.endojournals.org/cgi/content/full/89/11/5369) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15531483?tool=bestpractice.bmj.com)

43. Wallymahmed ME, Foy P, MacFarlane IA. The quality of life of adults with growth hormone deficiency: comparison with diabetic patients and control subjects. Clin Endocrinol (Oxf). 1999 Sep;51(3):333-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10469013?tool=bestpractice.bmj.com)

44. Aronson MD, Komaroff AL, Pass TM, et al. Heterophil antibody in adults with sore throat: frequency and clinical presentation. Ann Intern Med. 1982 Apr;96(4):505-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6895981?tool=bestpractice.bmj.com)

45. Barroso J. A review of fatigue in people with HIV infection. J Assoc Nurses AIDS Care. 1999 Sep-Oct;10(5):42-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10491802?tool=bestpractice.bmj.com)

46. Crook H, Raza S, Nowell J, et al. Long covid-mechanisms, risk factors, and management. BMJ. 2021 Jul 26;374:n1648. Full text (https://www.doi.org/10.1136/bmj.n1648) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34312178?tool=bestpractice.bmj.com)

47. Chen C, Haupert SR, Zimmermann L, et al. Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review. J Infect Dis. 2022 Nov 1;226(9):1593-607. Full text (https://academic.oup.com/jid/article/226/9/1593/6569364) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35429399?tool=bestpractice.bmj.com)

48. Nadelman RB, Nowakowski J, Forseter G, et al. The clinical spectrum of early Lyme borreliosis in patients with culture-confirmed erythema migrans. Am J Med. 1996 May;100(5):502-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8644761?tool=bestpractice.bmj.com)

49. Cairns V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. Int J Epidemiol. 2005 Dec;34(6):1340-5. Full text (http://ije.oxfordjournals.org/cgi/content/full/34/6/1340) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16040645?tool=bestpractice.bmj.com)

50. Berende A, ter Hofstede HJ, Vos FJ, et al. Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease. N Engl J Med. 2016 Mar 31;374(13):1209-20. Full text (https://www.doi.org/10.1056/NEJMoa1505425) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27028911?tool=bestpractice.bmj.com)

51. Monto AS, Gravenstein S, Elliott M, et al. Clinical signs and symptoms predicting influenza infection. Arch Intern Med. 2000 Nov 27;160(21):3243-7. Full text (http://archinte.jamanetwork.com/article.aspx?articleid=485554) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11088084?tool=bestpractice.bmj.com)

52. Revol B, Jullian-Desayes I, Tamisier R, et al. Ticagrelor and Central Sleep Apnea. J Am Coll Cardiol. 2018 May 22;71(20):2378-9. Full text (https://www.doi.org/10.1016/j.jacc.2018.03.447) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29773166?tool=bestpractice.bmj.com)

53. Clarkson TW, Magos L, Myers GJ. The toxicology of mercury - current exposures and clinical manifestations. N Engl J Med. 2003 Oct 30;349(18):1731-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14585942?tool=bestpractice.bmj.com)

54. Leikin JB, Karydes HC, Whiteley PM, et al. Outpatient toxicology clinic experience of patients with hip implants. Clin Toxicol (Phila). 2013 May;51(4):230-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23421810?tool=bestpractice.bmj.com)

55. Breslin E, van der Schans C, Breukink S, et al. Perception of fatigue and quality of life in patients with COPD. Chest. 1998 Oct;114(4):958-64. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9792561?tool=bestpractice.bmj.com)

56. Guyatt GH, Berman LB, Townsend M, et al. A measure of quality of life for clinical trials in chronic lung disease. Thorax. 1987 Oct;42(10):773-8. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC460950) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3321537?tool=bestpractice.bmj.com)

57. Wijkstra PJ, Van Altena R, Kraan J, et al. Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. Eur Respir J. 1994 Feb;7(2):269-73. Full text (http://erj.ersjournals.com/content/erj/7/2/269.full.pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8162979?tool=bestpractice.bmj.com)

58. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022 Oct 11;43(38):3618-731. Full text (https://academic.oup.com/eurheartj/article/43/38/3618/6673929)

59. Alsina-Restoy X, Torres-Castro R, Caballería E, et al. Pulmonary rehabilitation in sarcoidosis: a systematic review and meta-analysis. Respir Med. 2023 Nov-Dec;219:107432. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37858728?tool=bestpractice.bmj.com)

60. Atkins C, Wilson AM. Managing fatigue in sarcoidosis - a systematic review of the evidence. Chron Respir Dis. 2017 May;14(2):161-73. Full text (https://journals.sagepub.com/doi/10.1177/1479972316661926) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27507833?tool=bestpractice.bmj.com)

61. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med. 2002 Jan 17;346(3):180-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11796853?tool=bestpractice.bmj.com)

62. Jelsness-Jørgensen LP, Bernklev T, Lundin KEA. Fatigue as an Extra-Intestinal Manifestation of Celiac Disease: A Systematic Review. Nutrients. 2018 Nov 3;10(11):. Full text (https://www.doi.org/10.3390/nu10111652) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30400298?tool=bestpractice.bmj.com)

63. Goldblatt J, Taylor PJ, Lipman T, et al. The true impact of fatigue in primary biliary cirrhosis: a population study. Gastroenterology. 2002 May;122(5):1235-41. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11984509?tool=bestpractice.bmj.com)

REFERENCES

64. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology. 1998 Jan;27(1):209-12. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9425939?tool=bestpractice.bmj.com)

65. Witt-Sullivan H, Heathcote J, Cauch K, et al. The demography of primary biliary cirrhosis in Ontario, Canada. Hepatology. 1990 Jul;12(1):98-105. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2197212?tool=bestpractice.bmj.com)

66. Grimstad T, Norheim KB. Fatigue in inflammatory bowel disease. [in nor]. Tidsskr Nor Laegeforen. 2016 Nov;136(20):1721-4. Full text (https://www.doi.org/10.4045/tidsskr.16.0134) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27830906?tool=bestpractice.bmj.com)

67. Han CJ, Yang GS. Fatigue in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis of Pooled Frequency and Severity of Fatigue. Asian Nurs Res (Korean Soc Nurs Sci). 2016 Mar;10(1):1-10. Full text (https://www.doi.org/10.1016/j.anr.2016.01.003) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27021828?tool=bestpractice.bmj.com)

68. Laupacis A, Muirhead N, Keown P, et al. A disease-specific questionnaire for assessing quality of life in patients on hemodialysis. Nephron. 1992;60(3):302-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1565182?tool=bestpractice.bmj.com)

69. McCann K, Boore JR. Fatigue in persons with renal failure who require maintenance haemodialysis. J Adv Nurs. 2000 Nov;32(5):1132-42. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11114998?tool=bestpractice.bmj.com)

70. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol. 1996 Dec;9(6):456-60. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9007405?tool=bestpractice.bmj.com)

71. Karlsen K, Larsen JP, Tandberg E, et al. Fatigue in patients with Parkinsons disease. Mov Disord. 1999 Mar;14(2):237-41. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10091615?tool=bestpractice.bmj.com)

72. Beiske AG, Svensson E. Fatigue in Parkinson's disease: a short update. Acta Neurol Scand Suppl. 2010;(190):78-81. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20586741?tool=bestpractice.bmj.com)

73. Staub F, Bogousslavsky J. Fatigue after stroke: a major but neglected issue. Cerebrovasc Dis. 2001 Aug;12(2):75-81. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11490100?tool=bestpractice.bmj.com)

74. Cumming TB, Yeo AB, Marquez J, et al. Investigating post-stroke fatigue: An individual participant data meta-analysis. J Psychosom Res. 2018 Oct;113:107-12. Full text (https://www.doi.org/10.1016/j.jpsychores.2018.08.006) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30190042?tool=bestpractice.bmj.com)

75. van der Werf SP, Jongen PJ, Lycklama a Nijeholt GJ, et al. Fatigue in multiple sclerosis: interrelations between fatigue complaints, cerebral MRI abnormalities and neurological disability. J Neurol

Sci. 1998 Oct 8;160(2):164-70. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9849800?tool=bestpractice.bmj.com)

76. Vercoulen JH, Hommes OR, Swanink CM, et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol. 1996 Jul;53(7):642-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8929171?tool=bestpractice.bmj.com)

77. Colombo B, Martinelli Boneschi F, Rossi P, et al. MRI and motor evoked potential findings in nondisabled multiple sclerosis patients with and without symptoms of fatigue. J Neurol. 2000 Jul;247(7):506-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10993490?tool=bestpractice.bmj.com)

78. Krupp LB, LaRocca NG, Muir J, et al. A study of fatigue in systemic lupus erythematosus. J Rheumatol. 1990 Nov;17(11):1450-2. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2273484?tool=bestpractice.bmj.com)

79. Omdal R, Waterloo K, Koldingsnes W, et al. Fatigue in patients with systemic lupus erythematosus: the psychosocial aspects. J Rheumatol. 2003 Feb;30(2):283-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12563681?tool=bestpractice.bmj.com)

80. Riemsma RP, Rasker JJ, Taal E, et al. Fatigue in rheumatoid arthritis: the role of self-efficacy and problematic social support. Br J Rheumatol. 1998 Oct;37(10):1042-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9825741?tool=bestpractice.bmj.com)

81. Stone P, Richardson A, Ream E, et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum. Ann Oncol. 2000 Aug;11(8):971-5. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11038033?tool=bestpractice.bmj.com)

82. Levy M. Cancer fatigue: a review for psychiatrists. Gen Hosp Psychiatry. 2008 May-Jun;30(3):233-44. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18433655?tool=bestpractice.bmj.com)

83. Cella D, Lai JS, Chang CH, et al. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002 Jan 15;94(2):528-38. Full text (http://onlinelibrary.wiley.com/doi/10.1002/cncr.10245/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11900238?tool=bestpractice.bmj.com)

84. Harter M, Reuter K, Aschenbrenner A, et al. Psychiatric disorders and associated factors in cancer: results of an interview study with patients in inpatient, rehabilitation and outpatient treatment. Eur J Cancer. 2001 Jul;37(11):1385-93. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11435069?tool=bestpractice.bmj.com)

85. National Institute for Health and Care Excellence. Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management. Oct 2021 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng206)

86. Muller AE, Tveito K, Bakken IJ, et al. Potential causal factors of CFS/ME: a concise and systematic scoping review of factors researched. J Transl Med. 2020 Dec 14;18(1):484. Full

text (https://www.doi.org/10.1186/s12967-020-02665-6) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33317576?tool=bestpractice.bmj.com)

87. Huth TK, Eaton-Fitch N, Staines D, et al. A systematic review of metabolomic dysregulation in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis/Systemic Exertion Intolerance Disease (CFS/ME/SEID). J Transl Med. 2020 May 13;18(1):198. Full text (https://www.doi.org/10.1186/s12967-020-02356-2) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32404171?tool=bestpractice.bmj.com)

88. Centers for Disease Control and Prevention. Myalgic encephalomyelitis/chronic fatigue syndrome, etiology and pathophysiology. Jul 2018 [internet publication]. Full text (https://www.cdc.gov/me-cfs/healthcare-providers/presentation-clinical-course/etiology-pathophysiology.html)

89. Miller RR, Uyaguari-Diaz M, McCabe MN, et al. Metagenomic Investigation of Plasma in Individuals with ME/CFS Highlights the Importance of Technical Controls to Elucidate Contamination and Batch Effects. PLoS One. 2016;11(11):e0165691. Full text (https://www.doi.org/10.1371/journal.pone.0165691) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27806082?tool=bestpractice.bmj.com)

90. Bombardier CH, Buchwald D. Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Disability and health-care use. Med Care. 1996 Sep;34(9):924-30. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8792781?tool=bestpractice.bmj.com)

91. Cornuz J, Guessous I, Favrat B. Fatigue: a practical approach to diagnosis in primary care. CMAJ. 2006 Mar 14;174(6):765-7. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1402370) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16534080?tool=bestpractice.bmj.com)

92. Lane TJ, Matthews DA, Manu P. The low yield of physical examinations and laboratory investigations of patients with chronic fatigue. Am J Med Sci. 1990 May;299(5):313-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2337122?tool=bestpractice.bmj.com)

93. Ridsdale L, Evans A, Jerrett W, et al. Patients who consult with tiredness: frequency of consultation, perceived causes of tiredness and its association with psychological distress. Br J Gen Pract. 1994 Sep;44(386):413-6. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1238992) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8790655?tool=bestpractice.bmj.com)

94. Hamilton W, Watson J, Round A. Investigating fatigue in primary care. BMJ. 2010 Aug 24;341:c4259. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20736254?tool=bestpractice.bmj.com)

95. Wright J, O'Connor KM. Fatigue. Med Clin North Am. 2014 May;98(3):597-608. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24758963?tool=bestpractice.bmj.com)

96. Yu DS, Lee DT, Man NW. Fatigue among older people: a review of the research literature. Int J Nurs Stud. 2010 Feb;47(2):216-28. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19524240?tool=bestpractice.bmj.com)

97. Guidelines and Protocols Advisory Committee, British Columbia Medical Services Commission. Iron deficiency: diagnosis and management. April 2019 [internet publication]. Full text (https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/iron-deficiency)

98. Ebell MH, Belden JL. Clinical inquiries. What is a reasonable initial approach to the patient with fatigue? J Fam Pract. 2001 Jan;50(1):16-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11195474?tool=bestpractice.bmj.com)

99. Kroenke K, Spitzer RL, Williams JB. The patient health questionnaire-2: validity of a two-item depression screener. Med Care. 2003 Nov;41(11):1284-92. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14583691?tool=bestpractice.bmj.com)

100. Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 study. JAMA. 1994 Dec 14;272(22):1749-56. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7966923?tool=bestpractice.bmj.com)

101. Jackson JL, Houston JS, Hanling SR, et al. Clinical predictors of mental disorders among medical outpatients. Arch Intern Med. 2001 Mar 26;161(6):875-9. Full text (http://archinte.ama-assn.org/cgi/content/full/161/6/875) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11268232?tool=bestpractice.bmj.com)

102. Spitzer RL, Kroenke K, Williams JB; Patient Health Questionnaire Primary Care Study Group. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA. 1999 Nov 10;282(18):1737-44. Full text (http://jama.jamanetwork.com/article.aspx?articleid=192080) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10568646?tool=bestpractice.bmj.com)

103. Ewing JA. Detecting alcoholism: the CAGE questionnaire. JAMA. 1984 Oct 12;252(14):1905-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6471323?tool=bestpractice.bmj.com)

104. Babor TF, Higgins-Biddle JC, Saunders JB, et al. The alcohol use disorders identification test: guidelines for use in primary care. 2nd ed. World Health Organization. Department of Mental Health and Substance Dependence. Geneva, Switzerland: WHO; 2001. Full text (http://apps.who.int/iris/bitstream/10665/67205/1/WHO_MSD_MSB_01.6a.pdf)

105. Violani C, Devoto A, Lucidi F, et al. Validity of a short insomnia questionnaire: the SDQ. Brain Res Bull. 2004 Jun 30;63(5):415-21. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15245769?tool=bestpractice.bmj.com)

106. Nguyen AT, Baltzan MA, Small D, et al. Clinical reproducibility of the Epworth Sleepiness Scale. J Clin Sleep Med. 2006 Apr 15;2(2):170-4. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17557491?tool=bestpractice.bmj.com)

107. Rosenthal LD, Dolan DC. The Epworth sleepiness scale in the identification of obstructive sleep apnea. J Nerv Ment Dis. 2008 May;196(5):429-31. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18477888?tool=bestpractice.bmj.com)

108. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manage. 2009 Jan;37(1):107-28. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19111779?tool=bestpractice.bmj.com)

109. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer. 1999 Mar 1;85(5):1186-96. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10091805?tool=bestpractice.bmj.com)

110. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989 Oct;46(10):1121-3. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2803071?tool=bestpractice.bmj.com)

111. Hann DM, Jacobsen PB, Azzarello LM, et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. Qual Life Res. 1998 May;7(4):301-10. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9610214?tool=bestpractice.bmj.com)

112. Belza B, Miyawaki CE, Liu M, et al. A Systematic Review of Studies Using the Multidimensional Assessment of Fatigue Scale. J Nurs Meas. 2018 Apr 1;26(1):36-75. Full text (https://www.doi.org/10.1891/1061-3749.26.1.36) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29724278?tool=bestpractice.bmj.com)

113. Kalra L, Hamlyn AN, Jones BJ. Blue sclerae: a common sign of iron deficiency? Lancet. 1986 Nov 29;2(8518):1267-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2878143?tool=bestpractice.bmj.com)

114. Prabhakar VK, Shalet SM. Aetiology, diagnosis, and management of hypopituitarism in adult life. Postgrad Med J. 2006 Apr;82(966):259-66. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2585697) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16597813?tool=bestpractice.bmj.com)

115. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum. 1990 Feb;33(2):160-72. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2306288?tool=bestpractice.bmj.com)

116. Centers for Disease Control and Prevention. Signs and symptoms of untreated Lyme disease. Jan 2021 [internet publication] Full text (https://www.cdc.gov/lyme/signs_symptoms/index.html)

117. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e895-e1032. Full text (https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000001063?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35363499?tool=bestpractice.bmj.com)

118. Anton RF, Moak DH. Carbohydrate-deficient transferrin and gamma-glutamyltransferase as markers of heavy alcohol consumption: gender differences. Alcohol Clin Exp Res. 1994 Jun;18(3):747-54. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7943686?tool=bestpractice.bmj.com)

119. Hanna FWF, Issa BG, Kevil B, et al. Investigating cortisol excess or deficiency: a practical approach. BMJ. 2019 Nov 26;367:l6039. Full text (https://www.doi.org/10.1136/bmj.l6039) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31771937?tool=bestpractice.bmj.com)

120. Oelkers W. Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. N Engl J Med. 1989 Aug 24;321(8):492-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2548097?tool=bestpractice.bmj.com)

121. Centers for Disease Control and Prevention. Evaluating and caring for patients with post-COVID conditions: interim guidance. Jun 2021 [internet publication]. Full text (https://emergency.cdc.gov/coca/calls/2021/callinfo_061721.asp)

122. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. Jan 2024 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng188)

123. Mulrow CD, Williams JW Jr, Gerety MB, et al. Case-finding instruments for depression in primary care settings. Ann Intern Med. 1995 Jun 15;122(12):913-21. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7755226?tool=bestpractice.bmj.com)

124. Rushton DH, Norris MJ, Dover R, et al. Causes of hair loss and the developments in hair rejuvenation. Int J Cosmet Sci. 2002 Feb;24(1):17-23. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18498491?tool=bestpractice.bmj.com)

125. Trost LB, Bergfeld WF, Calogeras E. The diagnosis and treatment of iron deficiency and its potential relationship to hair loss. J Am Acad Dermatol. 2006 May;54(5):824-44. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16635664?tool=bestpractice.bmj.com)

126. American Academy of Sleep Medicine. International classification of sleep disorders - third edition, text revision (ICSD-3-TR). Westchester, IL: American Academy of Sleep Medicine; 2023.

127. Gibson GJ. Obstructive sleep apnoea syndrome: underestimated and undertreated. Br Med Bull. 2005 Mar 29;72:49-65. Full text (https://academic.oup.com/bmb/article/72/1/49/272854) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15798032?tool=bestpractice.bmj.com)

128. American Academy of Sleep Medicine. The AASM manual for scoring of sleep and associated events. Feb 2023 [internet publication]. Full text (https://aasm.org/clinical-resources/scoring-manual)

129. Erratum: Evaluation and management of obesity hypoventilation syndrome. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2019 Nov 15;200(10):1326. Full text (https://www.doi.org/10.1164/rccm.v200erratum7)

130. Mokhlesi B, Masa JF, Brozek JL, et al. Evaluation and management of obesity hypoventilation syndrome. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2019 Aug 1;200(3):e6-24. Full text (https://www.atsjournals.org/doi/10.1164/rccm.201905-1071ST) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31368798?tool=bestpractice.bmj.com)

131. Mokhlesi B, Tulaimat A, Faibussowitsch I, et al. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath. 2007 Jun;11(2):117-24. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17187265?tool=bestpractice.bmj.com)

132. Sivam S, Yee B, Wong K, et al. Obesity hypoventilation syndrome: early detection of nocturnal-only hypercapnia in an obese population. J Clin Sleep Med. 2018 Sep 15;14(9):1477-84. Full text (https://jcsm.aasm.org/doi/10.5664/jcsm.7318) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30176974?tool=bestpractice.bmj.com)

133. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes-2024. Diabetes Care. 2024 Jan 1;47(suppl 1):S20-42. Full text (https://diabetesjournals.org/care/article/47/Supplement_1/S20/153954/2-Diagnosis-and-Classification-of-Diabetes) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/38078589?tool=bestpractice.bmj.com)

134. Centers for Disease Control and Prevention. Influenza signs and symptoms and the role of laboratory diagnostics. October 2016 [internet publication]. Full text (http://www.cdc.gov/flu/professionals/diagnosis/labrolesprocedures.htm)

135. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017 Jan 15;64(2):111-5. Full text (https://www.doi.org/10.1093/cid/ciw778) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28052967?tool=bestpractice.bmj.com)

136. Geldmacher H, Taube C, Kroeger C, et al. Assessment of lymph node tuberculosis in northern Germany: a clinical review. Chest. 2002 Apr;121(4):1177-82. Full text (https://www.doi.org/10.1378/chest.121.4.1177) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11948050?tool=bestpractice.bmj.com)

137. Weir MR, Thornton GF. Extrapulmonary tuberculosis. Experience of a community hospital and review of the literature. Am J Med. 1985 Oct;79(4):467-78. Full text (https://www.doi.org/10.1016/0002-9343(85)90034-8) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/4050833?tool=bestpractice.bmj.com)

138. Baydur A. The spectrum of extrapulmonary tuberculosis. West J Med. 1977 Apr;126(4):253-62. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1237539) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/855317?tool=bestpractice.bmj.com)

139. Nataraj G, Kurup S, Pandit A, et al. Correlation of fine needle aspiration cytology, smear and culture in tuberculous lymphadenitis: a prospective study. J Postgrad Med. 2002 Apr-Jun;48(2):113-6. Full text (https://www.jpgmonline.com/article.asp?issn=0022-3859;year=2002;volume=48;issue=2;spage=113;epage=6;aulast=Nataraj) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12215692?tool=bestpractice.bmj.com)

140. Centers for Disease Control and Prevention. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. Jan 2009 [internet publication]. Full text (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm)

141. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis: rapid diagnostics for tuberculosis detection. Mar 2024 [internet publication]. Full text (https://www.who.int/publications/i/item/9789240089488)

142. Bjerrum S, Schiller I, Dendukuri N, et al. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV. Cochrane Database Syst Rev. 2019 Oct 21;10(10):CD011420. Full text (https://www.doi.org/10.1002/14651858.CD011420.pub3) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31633805?tool=bestpractice.bmj.com)

143. Dickstein G, Shechner C, Nicholson WE, et al. Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. J Clin Endocrinol Metab. 1991 Apr;72(4):773-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2005201?tool=bestpractice.bmj.com)

144. Mead P, Petersen J, Hinckley A. Updated CDC Recommendation for Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep. 2019 Aug 16;68(32):703. Full text (https://www.doi.org/10.15585/mmwr.mm6832a4) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31415492?tool=bestpractice.bmj.com)

145. Hedman K, Lappalainen M, Seppala I, et al. Recent primary toxoplasma infection indicated by a low avidity of specific IgG. J Infect Dis. 1989 Apr;159(4):736-40. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2926163?tool=bestpractice.bmj.com)

146. Perazella MA, Reilly RF. Chronic kidney disease: a new classification and staging system. Hospital Physician. 2003 Mar;39:18-45.

147. Hughes AJ, Daniel SE, Kilford L, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992 Mar;55(3):181-4. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1014720) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1564476?tool=bestpractice.bmj.com)

148. Smeenk R, Brinkman K, van den Brink H, et al. Antibodies to DNA in patients with systemic lupus erythematosus: their role in the diagnosis, the follow-up and the pathogenesis of the disease. Clin Rheumatol. 1990 Mar;9(1 suppl 1):100-10. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2203588?tool=bestpractice.bmj.com)

149. Eaton RB, Schnneider G, Schur PH. Enzyme immunoassay for antibodies to native DNA. Specificity and quality of antibodies. Arthritis Rheum. 1983 Jan;26(1):52-62. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6337594?tool=bestpractice.bmj.com)

Disclaimer

BMJ Best Practice is intended for licensed medical professionals. BMJ Publishing Group Ltd (BMJ) does not advocate or endorse the use of any drug or therapy contained within this publication nor does it diagnose patients. As a medical professional you retain full responsibility for the care and treatment of your patients and you should use your own clinical judgement and expertise when using this product.

This content is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition, since such standards and practices in medicine change as new data become available, you should consult a variety of sources. We strongly recommend that you independently verify specified diagnosis, treatments and follow-up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the drug to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region.

Information included in BMJ Best Practice is provided on an “as is” basis without any representations, conditions or warranties that it is accurate and up to date. BMJ and its licensors and licensees assume no responsibility for any aspect of treatment administered to any patients with the aid of this information. To the fullest extent permitted by law, BMJ and its licensors and licensees shall not incur any liability, including without limitation, liability for damages, arising from the content. All conditions, warranties and other terms which might otherwise be implied by the law including, without limitation, the warranties of satisfactory quality, fitness for a particular purpose, use of reasonable care and skill and non-infringement of proprietary rights are excluded.

Where BMJ Best Practice has been translated into a language other than English, BMJ does not warrant the accuracy and reliability of the translations or the content provided by third parties (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages). BMJ is not responsible for any errors and omissions arising from translation and adaptation or otherwise.Where BMJ Best Practice lists drug names, it does so by recommended International Nonproprietary Names (rINNs) only. It is possible that certain drug formularies might refer to the same drugs using different names.

Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

Our full website and application terms and conditions can be found here: Website Terms and Conditions.

Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

Bernard Favrat, MD

Associate Professor
University of Lausanne, Department of Ambulatory Care and Community Medicine, Lausanne, Switzerland
DISCLOSURES: BF has received study grants and lecture/consultant fees from Vifor Pharma and Pierre Fabre Médicament. BF is an author of a number of references cited in this topic.

Jacques Cornuz, MD, MPH

Associate Director
University Hospital of Lausanne, Department of Ambulatory Care and Community Medicine, Lausanne, Switzerland
DISCLOSURES: JC is an author of a reference cited in this topic.

// Acknowledgements:

Dr Bernard Favrat and Dr Jacques Cornuz would like to gratefully acknowledge Dr Idris Guessous and Dr Baptiste Pedrazzini, previous contributors to this topic.
DISCLOSURES: IG is an author of a reference cited in this topic. BP declares that he has no competing interests.

// Peer Reviewers:

Chris Martin, MD

General Practitioner
Dr Moulds and Partners, Laindon Health Centre, Laindon, Essex, UK
DISCLOSURES: CM has received an NHS salary greater than 6 figures USD. CM declares that he has no competing interests.

Benjamin Natelson, MD

Professor of Neurosciences
UMDNJ, New Jersey Medical School, Newark, NJ
DISCLOSURES: BN declares that he has no competing interests.