

## Tiredness/fatigue in adults - Management

### Scenario: Assessment of tiredness/fatigue in adults

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#### How should I assess an adult with tiredness?

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- **Take a full history.** In particular:
  - **Ask the person to say what they mean by tiredness or fatigue (or a synonym).**
  - Sleepiness may indicate sleep apnoea or another sleep disorder — see the CKS topics on [Sleep apnoea](#) and [Insomnia](#).
  - Weakness suggests a neuromuscular cause.
  - **Ask about: onset, duration, severity, and precipitating factors; the effect of sleep, rest, and exercise; and the impact on activities.**
  - Onset is typically *sudden* with infection, myocardial ischaemia, toxins or drugs, and post-traumatic stress.
  - Onset is usually *gradual* in uraemia, heart failure, liver failure, diabetes, hypercalcaemia, hypothyroidism, electrolyte abnormalities, anaemia, and depression.
  - Fatigue that is worst in the morning and which never goes away suggests depression.
  - Fatigue that occurs only after exercise (and not at rest) suggests a neuromuscular cause.
  - **Elicit the person's concerns** so that reassurance and explanation can be given, if possible *and appropriate*.
  - **Elicit the person's perceptions of the cause of their tiredness**, which may be important for successful management.
  - **Take a sleep history:** ask about sleep quality, quantity, patterns, and hygiene, snoring, witnessed sleep apnoea, nocturia, and restless legs (for further information, see the CKS topics on [Insomnia](#), [Restless legs syndrome](#), and [Sleep apnoea](#)).
  - **Take a lifestyle and psychosocial history:** ask about stress and stressful life events, work, rest, recreation, exercise, quality of personal relationships, illicit drug use, diet, and alcohol consumption, and whether the person is a carer for others (such as children, or elderly or disabled relatives).
  - **Ask about and screen for the presence of a depressive illness or an anxiety disorder.** Screen for depression using the following two questions (an answer of 'yes' to either question should trigger a more detailed assessment — see the CKS topic on [Depression](#)):

- 'During the last month have you often been bothered by feeling down, depressed, or hopeless?'
- 'During the last month have you often been bothered by having little interest or pleasure in doing things?'
- **Review medication**, including over-the-counter drugs.
- Tiredness may be caused by many drugs, including sedative-hypnotics, antidepressants, muscle relaxants, opioids, antihypertensives, and antihistamines.
- **Ask about:**
- Weight loss or gain (for malignancy, Addison's disease, diabetes mellitus, and thyroid dysfunction).
- Fever or night sweats (for malignancy, and infections such as hepatitis and tuberculosis).
- Muscle or joint pain, headache, sore throat, difficulty with memory or thinking, and chronic pain (symptoms of chronic fatigue syndrome and other conditions).
- Travel, insect or tick bites, and skin rash (for tropical infections and Lyme disease).
- Allergies, such as perennial rhino-sinusitis.
- **Determine if the person may be at risk of HIV, hepatitis, or tuberculosis.**
- **Do a complete physical examination, unless the cause is evident from the history, when a focused examination is appropriate.**
- If necessary, delay this until a second, longer consultation.
- **Consider whether [investigations](#) are needed.**

#### **Basis for recommendation**

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These recommendations are based on [evidence](#) from observational studies on the causes of tiredness, evidence on perceptions of the causes of tiredness, and on expert opinion from narrative reviews.

#### **Nature of fatigue**

- The recommendation to ask the person to say what they mean by tiredness or fatigue, and its justification, are derived from expert opinion in narrative reviews [[Morrison and Keating, 2001](#); [Rosenthal et al, 2008](#)].
- Other recommendations on establishing the nature of tiredness are based on a National Institute for Health and Clinical Excellence guideline on the diagnosis and management of chronic fatigue syndrome

(CFS)/myalgic encephalomyelitis or encephalopathy (ME) [[National Collaborating Centre for Primary Care, 2007](#)] and expert opinion from narrative reviews [[Ruffin and Cohen, 1994](#); [Rodriguez, 2000](#); [Morrison and Keating, 2001](#); [Simon, 2008](#)].

### **Eliciting concerns and perceptions**

- The recommendation to elicit the person's concerns and perceptions of the cause of their tiredness is based on expert opinion [[Ridsdale, 1989](#); [Godwin et al, 1999](#); [Rodriguez, 2000](#); [Moncrieff and Fletcher, 2007](#)], as well as the following:
  - There is evidence from a UK study (n = 151) that at least half of people with chronic tiredness attribute their symptoms to a physical cause [[Darbishire et al, 2003](#)].
  - There is evidence from a study of 220 people presenting to one of four general practices in the UK that GPs tend to perceive the cause of tiredness as psychological, whereas people with tiredness are more likely to perceive the cause as physical [[Ridsdale et al, 1993](#); [Ridsdale et al, 1994](#)].
  - One of the management strategies proposed in the literature is for the primary healthcare professional to try to broaden the person's perception of fatigue, so that psychosocial causes and solutions are validated and considered along with biomedical causes [[Ruffin and Cohen, 1994](#)].

### **Sleep history**

- This recommendation is based on expert opinion from narrative reviews [[Rodriguez, 2000](#); [Morrison and Keating, 2001](#); [Rosenthal et al, 2008](#)].

### **Lifestyle and psychosocial history; screening for depression and anxiety**

- These recommendations are based on expert opinion from narrative reviews [[Godwin et al, 1999](#); [Rodriguez, 2000](#); [Ebell and Belden, 2001](#); [Morrison and Keating, 2001](#); [Rosenthal et al, 2008](#); [Simon, 2008](#)] and on limited [evidence](#) from mainly observational studies that, in people presenting to primary care with a complaint of tiredness or fatigue, the underlying cause is commonly psychological or psychosocial (in 18–62% of people), or there is an associated psychological disorder or psychosocial problem.
- The screening questions are derived from the National Institute for Health and Clinical Excellence guideline, *Depression (amended): management of depression in primary and secondary care* [[NICE, 2007a](#)].

## Medication

- This recommendation is based on expert opinion from narrative reviews [[Godwin et al, 1999](#); [Rodriguez, 2000](#); [Morrison and Keating, 2001](#); [Rosenthal et al, 2008](#); [Simon, 2008](#)].

## Other symptoms/history

- This recommended list is derived from narrative reviews [[Rodriguez, 2000](#); [Morrison and Keating, 2001](#)] and from a North of England guideline on the medical assessment of people with suspected CFS/ME, which states that perennial rhino-sinusitis commonly causes fatigue [[Spickett, 2009](#)].

## At risk of HIV, hepatitis, or tuberculosis

- This recommendation is based on expert opinion from a narrative review and a New Zealand guideline [[Ruffin and Cohen, 1994](#); [BPAC NZ, 2006](#)].

## Examination

- CKS found no evidence on the diagnostic yield of a physical examination (or its constituents) for people with tiredness presenting to primary care. However, a physical examination is good medical practice and generally regarded (in narrative reviews) as appropriate [[Ruffin and Cohen, 1994](#); [Epstein, 1995](#); [Ebell and Belden, 2001](#); [Morrison and Keating, 2001](#); [Sharpe and Wilks, 2002](#); [Cornuz et al, 2006](#); [Rosenthal et al, 2008](#)].
  - Several authors suggest that a physical examination reassures the person (in particular, that their problem is being taken seriously) and cements the therapeutic relationship [[Ruffin and Cohen, 1994](#); [Cornuz et al, 2006](#); [Moncrieff and Fletcher, 2007](#)].
  - In a specialist US chronic fatigue clinic, physical examinations were judged to have provided diagnostic information in only 2% of people [[Lane et al, 1990](#)]. However, a specialist clinic would exclude people for whom a diagnosis had already been made in primary care, and CKS expert reviewers report higher yields in secondary care.
  - Some authors recommend a complete examination, particularly if the history does not suggest a cause [[Ruffin and Cohen, 1994](#); [Epstein, 1995](#); [Rodriguez, 2000](#); [Murtagh, 2003](#); [Simon, 2008](#)], while others recommend a more focused examination, guided by the history [[Godwin et al, 1999](#); [Moncrieff and Fletcher, 2007](#)].
  - The recommendation to delay a complete physical examination until a second, longer consultation, if necessary, is derived from narrative reviews [[Ruffin and Cohen, 1994](#); [Rodriguez, 2000](#)].

## What red flags should I identify in an adult with tiredness?

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▪ **Identify and appropriately manage the following red flags or alarm features:**

- Significant weight loss.
- Lymphadenopathy with signs of malignancy (for instance, a lymph node that is non-tender, firm, hard, larger than 2 cm across, progressively enlarging, supraclavicular, or axillary).
- Any other symptoms and signs of malignancy. For example:
- Haemoptysis — see the CKS topic on [Lung cancer - suspected](#).
- Dysphagia — see the CKS topics on [Head/neck cancer - suspected](#) and [GI \(upper\) cancer - suspected](#).
- Rectal bleeding — see the CKS topic on [GI \(lower\) cancer - suspected](#).
- Breast lump — see the CKS topic on [Breast cancer - suspected](#).
- Postmenopausal bleeding — see the CKS topic on [Gynaecological cancer - suspected](#).
- Localizing/focal neurological signs.
- Symptoms and signs of inflammatory arthritis, vasculitis (such as giant cell arteritis and polymyalgia rheumatica), or connective tissue disease — see the CKS topics on [Giant cell arteritis](#), [Polymyalgia rheumatica](#), and [Rheumatoid arthritis](#).
- Symptoms and signs of cardiorespiratory disease — see the CKS topics on [Angina](#), [Asthma](#), [Chronic obstructive pulmonary disease](#), and [Heart failure - chronic](#).
- Sleep apnoea — see the CKS topic on [Sleep apnoea](#).

### **Basis for recommendation**

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These recommendations are based on National Institute for Health and Clinical Excellence guidelines on referral for suspected cancer, and on the diagnosis and management of chronic fatigue syndrome (CFS)/myalgic encephalomyelitis or encephalopathy (ME) [[NICE, 2005](#); [NICE, 2007b](#)], on New Zealand guidelines on laboratory investigations of tiredness [[BPAC NZ, 2006](#)], and on a North of England guideline on the medical assessment of people with suspected CFS/ME [[Spickett, 2009](#)].

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## When should I suspect chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy?

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- **In adults, suspect chronic fatigue syndrome (CFS)/myalgic encephalomyelitis or encephalopathy (ME) if *both* of the following criteria are met:**
  - The person has fatigue that has *all* of the following features:
    - Persistent (for 4 months or longer) or recurrent.
    - New or had a specific onset (that is, it is not lifelong).
    - Unexplained by other conditions (including body mass index greater than 40 kg/m<sup>2</sup>).
    - Has resulted in a substantial reduction in activity level.
    - Characterized by post-exertional malaise and/or fatigue (typically delayed, for example by at least 24 hours, with slow recovery over several days).
  - The person has *one or more* of the following symptoms:
    - Difficulty with sleeping (such as insomnia, hypersomnia, unrefreshing sleep, or a disturbed sleep-wake cycle).
    - Muscle or joint pain that is multi-site and without evidence of inflammation.
    - Headaches.
    - Painful lymph nodes without pathological enlargement.
    - Sore throat.
    - Cognitive dysfunction (such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding, planning/organizing thoughts, and information processing).
    - Physical or mental exertion makes symptoms worse.
    - General malaise or flu-like symptoms.
    - Dizziness or nausea.
    - Palpitations in the absence of identified cardiac pathology.
- **The diagnosis of CFS/ME should be reconsidered if *none* of the following features are present:**
  - Post-exertional fatigue or malaise.

- Cognitive difficulties.
- Sleep disturbance.
- Chronic pain.

### **Basis for recommendation**

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These recommendations are based on a National Institute for Health and Clinical Excellence guideline on the diagnosis and management of chronic fatigue syndrome (CFS)/myalgic encephalomyelitis or encephalopathy (ME) [[National Collaborating Centre for Primary Care, 2007](#)], and in relation to body mass index greater than 40 kg/m<sup>2</sup>, a North of England guideline on the medical assessment of people with suspected CFS/ME [[Spickett, 2009](#)].

### **What first-line investigations should I offer to an adult with tiredness?**

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- **Offer investigations as indicated by the history and physical examination** — see [Assessment](#) and [Red flags](#).
- **If a physical cause is not evident clinically:**
  - **Consider delaying routine investigations until tiredness has lasted for 1 month.**
  - **Offer the following routine first-line investigations:**
    - Full blood count.
    - Erythrocyte sedimentation rate or C-reactive protein.
    - Thyroid stimulating hormone.
    - Random blood glucose.
    - IgA tissue transglutaminase for coeliac disease (provided the person consumes gluten-containing foods).
  - **Also consider offering the following additional investigations:**
    - Liver function tests — particularly if the person is obese, or is 60 years of age or older.
    - Creatinine and electrolytes — particularly if the person is 60 years of age or older.
    - Bone biochemistry — particularly if the person is 60 years of age or older.
    - Serum ferritin — in women of child-bearing age, as there is limited evidence that iron supplementation is effective even in the absence of anaemia.

- Testing for vitamin D deficiency, by bone biochemistry and serum 25–hydroxycholecalciferol concentration — if the person is at risk because of failure to spend time outdoors or regular use of sunscreens, inadequate diet, or reduced gut absorption.
- Testing for glandular fever (infectious mononucleosis), such as by the monospot test — if the person is younger than 40 years of age.
- HIV test — if the person is at risk.
- Hepatitis serology — if the person is at risk.
- Testing for tuberculosis (chest radiography and sputum samples) pending referral — if the person is at risk (see the CKS topic on [Tuberculosis](#)).
- **If tiredness/fatigue lasts for 3 months or longer, offer [second-line investigations](#).**

#### **Basis for recommendation**

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These recommendations are based on [evidence](#) on the most common causes of tiredness in primary care, on [evidence](#) on investigations for tiredness, and on expert opinion.

#### **Offer investigations as indicated by history and physical examination**

- This is a pragmatic recommendation, also based on expert opinion from international guidelines [[Godwin et al, 1999](#); [BPAC NZ, 2006](#)] and narrative reviews [[Ridsdale, 1989](#); [Rodriguez, 2000](#)].

#### **Delaying investigations until tiredness has lasted for 1 month**

- This recommendation is based on limited [evidence](#) from a randomized trial that postponing blood tests does not appear to miss serious diagnoses (provided there are no red flags or other symptoms and signs indicating the need for immediate investigation), with few people returning for postponed investigations [[Koch et al, 2009](#)]. It is also supported by a New Zealand guideline [[Godwin et al, 1999](#)].

#### **Choice of investigations for unexplained tiredness**

- **In the absence of large, prospective, randomized trials using reference standards for diagnoses and which are based in primary care, there is insufficient evidence to recommend withholding any investigations when the cause of tiredness is not identified clinically.**
- There is limited [evidence](#), from one randomized trial [[Koch et al, 2009](#)] and three observational studies [[Sugarman and Berg, 1984](#); [Ridsdale et al, 1993](#); [Gialamas et al, 2003](#)], that blood tests have low



diagnostic yield in people presenting to primary care with tiredness or fatigue, detecting a physical cause in just 8–11% of people.

- Harms have not been fully evaluated. Possible harms of under-investigation and false-negatives include missing serious or treatable causes, and damage to the therapeutic relationship. Possible harms of over-investigation and false-positives include unnecessary anxiety and cost [[Koch et al, 2009](#)], and damage to subsequent efforts to address psychological or psychosocial causes of tiredness.
- **Recommendations on the choice of initial, routine investigations** are based on:
  - [Evidence](#) from a randomized trial that a limited set of blood tests (including haemoglobin, erythrocyte sedimentation rate [ESR], glucose, and thyroid stimulating hormone) is almost as useful diagnostically as a more extensive set of tests [[Koch et al, 2009](#)].
  - National Institute for Health and Clinical Excellence guidelines, which recommend tests for anaemia, thyroid function, and coeliac disease in people with persistent fatigue, even when there are no other indications [[National Collaborating Centre for Primary Care, 2007](#); [NICE, 2009](#)].
  - [Evidence](#) that, although physical causes are less frequently identified compared with psychosocial causes, anaemia and diabetes mellitus are the more common physical causes of tiredness in people presenting to primary care with tiredness as a complaint. However, these illnesses individually account for only 0.6–6% of the total number of people presenting with tiredness.
  - Studies have identified malignancy in less than 1% of all people presenting to primary care with tiredness or fatigue [[Valdini, 1985](#)], but the rate may be higher in older people, who are poorly represented in aetiological studies.
  - Consensus of expert opinion in the published literature that a full blood count is an appropriate first-line investigation [[Rodriguez, 2000](#); [Ebell and Belden, 2001](#); [Sharpe and Wilks, 2002](#); [Murtagh, 2003](#); [BPAC NZ, 2006](#); [Moncrieff and Fletcher, 2007](#); [Rosenthal et al, 2008](#); [Simon, 2008](#)], with most also recommending ESR. C-reactive protein is recommended as an alternative to ESR on the basis of feedback from CKS expert reviewers. There was no consensus with regard to other investigations.
- **Recommendations on the choice of additional investigations to consider**
  - **Creatinine and electrolytes, liver function tests, bone biochemistry**
  - These investigations are recommended for older people on the basis of New Zealand and Canadian guidelines on the investigation of people with fatigue [[Godwin et al, 1999](#); [BPAC NZ, 2006](#)]. The New Zealand guideline recommends additional investigations in people older than 50 years of age, whereas the

threshold in the Canadian guideline is 65 years of age; 60 years of age is a compromise between these two opinions.

- Creatinine and electrolytes, and liver function tests were recommended by several CKS external reviewers for all people with tiredness/fatigue.
- There is evidence from one cohort study that fatigue is associated with non-alcoholic fatty liver disease (NAFLD) [[Newton et al, 2008](#)]. Fatigue in people with NAFLD was unrelated to severity of liver disease or to insulin resistance. People who were cases and controls were matched for body mass index, to prevent obesity confounding the relationship.
- **Ferritin in women of child-bearing age**
- This recommendation is based on [evidence](#) from one randomized, placebo-controlled trial that 4 weeks of iron supplementation reduced fatigue in women 18–55 years of age without anaemia who presented to primary care with fatigue [[Verdon et al, 2003](#)]. Only women with ferritin concentrations of 50 micrograms/L or less improved with treatment.
- **Testing for vitamin D deficiency**
- Although CKS found no published evidence on testing for vitamin D deficiency in people presenting with tiredness, this was recommended by several CKS expert reviewers. Risk factors for vitamin D deficiency are derived from an evidence-based narrative review [[DTB, 2006](#)].
- **Testing for glandular fever in people younger than 40 years of age**
- This recommendation is based on [evidence](#) that glandular fever is a relatively common cause of tiredness, and is detected even in people in whom it is not suspected [[Morrison, 1980](#); [Koch et al, 2009](#)]. However, it is the cause of tiredness in only 0.6–6% of people (of all ages) presenting to primary care with tiredness.
- Glandular fever is rare in people 40 years of age or older [[Petersen et al, 2006](#)], and one prospective study which detected glandular fever in 1.4% of people used 40 years of age as a cut-off [[Ridsdale et al, 1993](#)].
- **HIV test, hepatitis serology, and tuberculosis testing**
- This recommendation is based on expert opinion from a New Zealand guideline [[BPAC NZ, 2006](#)] and on the CKS topic on [Tuberculosis](#).

#### What second-line investigations should I offer, and when?

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- **If tiredness has persisted for 3 months or longer:**

- **Ensure that all of the following investigations have been done** to rule out other diseases and conditions besides chronic fatigue syndrome (CFS)/myalgic encephalitis or encephalopathy (ME):
- Urinalysis for protein, blood, and glucose.
- Full blood count.
- Urea and electrolytes.
- Liver function tests.
- Thyroid stimulating hormone.
- Erythrocyte sedimentation rate or plasma viscosity.
- C-reactive protein.
- Random blood glucose.
- Serum creatinine.
- Serum calcium.
- Creatine kinase.
- IgA tissue transglutaminase for coeliac disease (provided the person consumes gluten-containing foods).
- **Offer tests for the following infections *only* if the history is indicative:**
- Chronic bacterial infections, such as borreliosis (Lyme disease).
- Chronic viral infections, such as HIV or hepatitis B or C.
- Latent infections, such as toxoplasmosis, Epstein–Barr virus, or cytomegalovirus.

#### **Basis for recommendation**

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- These recommendations are based on a National Institute for Health and Clinical Excellence (NICE) guideline on the diagnosis and management of chronic fatigue syndrome (CFS)/myalgic encephalomyelitis or encephalopathy (ME) [[National Collaborating Centre for Primary Care, 2007](#)].
- The duration of tiredness for which second-line investigations are recommended (3 months) is pragmatic, based on the NICE recommendation that a diagnosis of CFS/ME should be made in adults when symptoms have persisted for 4 months [[National Collaborating Centre for Primary Care, 2007](#)].

- The choice of screening test for coeliac disease is based on the NICE guideline on the recognition and assessment of coeliac disease [[NICE, 2009](#)].

## Tiredness/fatigue in adults - Management

### Scenario: Tiredness/fatigue in adults

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#### Overview of management

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- **Establish a supportive therapeutic relationship**, taking the person's complaint seriously and adopting a holistic approach.
- **Try to identify an underlying cause**, bearing in mind that tiredness may be caused by one or a combination of physical, psychosocial, and physiological factors, or may be unexplained.
- Look for any [red flags](#).
- Consider easily missed conditions, such as Addison's disease, carbon monoxide poisoning, coeliac disease, domestic abuse, haemochromatosis, hypopituitarism, medication, pregnancy, renal failure, and sleep apnoea (see the CKS topics on [Carbon monoxide poisoning](#), and [Sleep apnoea](#)).
- Consider any existing chronic illnesses, psychiatric history, and current or recent infections.
- Take a history and do a physical examination (see [Assessment](#)).
- Arrange appropriate [investigations](#).
- Consider the possibility of chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy ([CFS/ME](#)).
- **Consider whether [referral](#) is indicated.**
- **Treat the underlying cause, if this is known.**
- **Consider [treatment strategies](#) for people with persistent, unexplained fatigue.**
- **In women of child-bearing age with a serum ferritin level of 50 micrograms/L or less without anaemia:**
  - Identify the cause and consider offering iron supplementation (80 micrograms/day elemental iron) for at least 4 weeks (off-label indication).

## **Basis for recommendation**

### **Therapeutic relationship**

- This recommendation is based on expert opinion from narrative reviews and a Canadian guideline [[Ruffin and Cohen, 1994](#); [Godwin et al, 1999](#); [Dick and Sundin, 2003](#); [Moncrieff and Fletcher, 2007](#)].

### **Identify the cause**

- The recommendation to identify a cause is based on consensus of expert opinion from narrative reviews [[Morrison, 1980](#); [Sugarman and Berg, 1984](#); [Kirk et al, 1990](#); [Ruffin and Cohen, 1994](#); [Sharpe and Wilks, 2002](#)].
- The recommendation to bear in mind that tiredness may be caused by physical, psychosocial, and physiological factors is based on [evidence](#) from two observational studies in which tiredness was judged to be both physical and psychosocial in 2–41% of people presenting to primary care with tiredness as a complaint [[Morrison, 1980](#); [Kirk et al, 1990](#)], and on expert opinion in the published literature [[Cathebras et al, 1992](#); [Wessely, 2001](#); [BPAC NZ, 2006](#)].

### **Red flags**

- This recommendation is derived from a National Institute for Health and Clinical Excellence guideline on the diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy [[National Collaborating Centre for Primary Care, 2007](#)].

### **Easily missed diagnoses**

- This recommendation is derived from expert opinion in narrative reviews [[Morrison and Keating, 2001](#); [Murtagh, 2003](#); [Jones and Sleet, 2009](#); [Vaidya et al, 2009](#); [West et al, 2009](#)] and feedback from CKS expert reviewers.

### **Existing chronic illnesses, psychiatric history, and current or recent infections**

- This recommendation is based on:
  - Expert opinion from narrative reviews [[Godwin et al, 1999](#); [Rodriguez, 2000](#); [Simon, 2008](#)].
  - Evidence from a Canadian study that 93 people presenting to primary care with tiredness were significantly more likely to have a lifetime history of major depression or anxiety disorder compared with 593 controls [[Cathebras et al, 1992](#)].

## When should I refer an adult with tiredness?

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- **Referral to secondary care is likely to be required if a serious underlying physical cause is suspected or identified**, such as Addison's disease, coeliac disease, HIV, hepatitis B or C, malignancy, renal failure, or sleep apnoea (see the CKS topic on [Sleep apnoea](#)).
- **Refer adults (18 years of age or older) with symptoms suggestive of chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy (CFS/ME) to specialist CFS/ME services:**
  - Within 6 months of presentation, if symptoms are mild.
  - Within 3–4 months of presentation, if symptoms are moderate.
  - Immediately, if symptoms are severe.
- **Consider referring to secondary care those people with persistent, unexplained tiredness/fatigue *not* meeting the criteria for CFS/ME** if any of the following apply:
  - There is significant uncertainty regarding the presence of an underlying physical cause.
  - The person would benefit from the reassurance of a second opinion or from the thoroughness of a secondary care evaluation, and referral is not likely to reinforce unrealistic beliefs in a physical cause.
  - The person may benefit from access to the structured and multidisciplinary care delivered by specialist CFS/ME services, or from a secondary care opinion for occupational reasons or disability benefits.
- Children and young people 17 years of age or younger should be referred to paediatrics within 6 weeks of presentation, but are not included in the scope of this topic.

### Basis for recommendation

- The recommendations in relation to people with symptoms suggestive of chronic fatigue syndrome (CFS)/myalgic encephalomyelitis or encephalopathy (ME) are based on a National Institute for Health and Clinical Excellence guideline on the diagnosis and management of CFS/ME [[National Collaborating Centre for Primary Care, 2007](#)].
  - As well as comprehensive assessment, referral to specialist services provides access to cognitive behavioural therapy and graded exercise therapy, which NICE states are 'the interventions for which there is the clearest research evidence of benefit' in people with mild-to-moderate CFS/ME [[National Collaborating Centre for Primary Care, 2007](#)].

- The recommendation that referral may be required if any other serious underlying cause is suspected or identified is pragmatic.
- In the absence of published evidence, the recommendation on when to consider referral for people with persistent, unexplained tiredness/fatigue *not* meeting the criteria for CFS/ME is a compromise between the views of CKS expert reviewers, who were divided on the merits of referring this group of people to secondary care.

### What treatments should I consider for an adult with tiredness?

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- **Treat the underlying cause, if this is known.**
- **In women of child-bearing age with serum ferritin of 50 micrograms/L or less but without anaemia:**
  - Identify the cause and consider offering iron supplementation (80 mg/day elemental iron) for at least 4 weeks (off-label indication, based on limited evidence).
- **For all people with persistent unexplained fatigue**, including those with suspected chronic fatigue syndrome (CFS)/myalgic encephalomyelitis or encephalopathy (ME):
  - Try to establish a supportive therapeutic relationship.
  - Try to offer an understandable explanation for tiredness/fatigue that:
    - Absolves the person from blame but also offers ways for the person to take, or at least share, responsibility for managing the symptom.
    - Is linked clearly to the person's specific concerns.
    - Provides links between psychosocial and physical factors.
    - Try to broaden the person's perception of tiredness/fatigue so that psychosocial causes and solutions are validated and considered along with biomedical causes.
    - Identify and address modifiable psychological, social, and general health factors, including stress, work, personal relationships, pain, and alcohol.
- **For people meeting [criteria for CFS/ME](#) who have not yet been assessed by specialist CFS/ME services:**
  - Offer advice on sleep management.

- Provide general advice on sleep hygiene — see the section on [Good sleep hygiene](#) in the CKS topic on [Insomnia](#).
- Discourage excessive sleep and daytime sleeping or naps.
- In relation to activity, rest, and relaxation, advise:
  - Limiting the length of rest periods to 30 minutes at a time.
  - Introducing low level physical and cognitive activities (depending on the severity of symptoms).
  - Avoiding unsupervised, or unstructured, vigorous exercise.
  - Using relaxation techniques.
  - Advise a well-balanced diet.
  - Manage nausea by giving advice on eating little and often, snacking on dry starchy foods, and sipping fluids.
  - Use anti-emetic drugs only if nausea is severe.
- **For people with persistent unexplained fatigue (lasting 4 months or longer) who do *not* meet [criteria for CFS/ME](#):**
  - There is insufficient evidence to make any additional, clear recommendations, but the following treatment strategies may be considered:
    - Advise a balance between activity (including exercise) and rest.
    - Offer advice on sleep management — see the CKS topic on [Insomnia](#).
    - Consider offering referral for counselling or cognitive behavioural therapy, if services are available and the person is motivated and psychologically minded.
    - Consider referring to specialist CFS/ME services for a structured, multidisciplinary approach to management, to access specialist interventions such as cognitive behavioural therapy and supervised graded exercise therapy, or for a consultant opinion for occupational reasons or disability benefits.

### **Basis for recommendation**

#### **Treat the cause**

- This is a pragmatic recommendation.



## **Iron supplementation**

- There is limited [evidence](#) from one randomized, placebo-controlled trial in 144 people, sponsored by industry, that iron supplementation significantly reduces self-reported fatigue in women 18–55 years of age without anaemia presenting to primary care with fatigue [[Verdon et al, 2003](#)]. Only women with ferritin concentrations of 50 micrograms/L or less improved with treatment. These findings have not been confirmed in any subsequent trials, and CKS expert reviewers were divided over the appropriateness of recommending iron supplementation in this group of people.

## **Therapeutic relationship**

- This recommendation is based on expert opinion from narrative reviews and a Canadian guideline [[Ruffin and Cohen, 1994](#); [Godwin et al, 1999](#); [Dick and Sundin, 2003](#); [Moncrieff and Fletcher, 2007](#)].

## **Explanation**

- These recommendations are derived from a qualitative study on the effectiveness of GPs' explanations to provide reassurance (normalization) to 36 people with unexplained symptoms in UK primary care [[Dowrick et al, 2004](#)].
  - Consultations between 21 GPs and 36 people with unexplained medical symptoms were audio-taped.
  - Transcripts were analysed for recurring ways that normalizing statements were presented by GPs and responded to by patients.
  - The suggested methods for explanation are based on the findings of this study.

## **Try to broaden the person's perception of fatigue**

- These recommendations are based on expert opinion from narrative reviews [[Ruffin and Cohen, 1994](#); [Sharpe and Wilks, 2002](#); [Dick and Sundin, 2003](#); [Harvey and Wessely, 2009](#)].

## **Modifiable psychological, social, and general health factors**

- These recommendations are based on expert opinion from narrative reviews [[Ruffin and Cohen, 1994](#); [Harvey and Wessely, 2009](#)].

## **People meeting the criteria for chronic fatigue syndrome (CFS)/myalgic encephalomyelitis or encephalopathy (ME)**

- These recommendations are derived from the National Institute for Health and Clinical Excellence (NICE) guideline on the diagnosis and management of CFS/ME [[National Collaborating Centre for Primary Care, 2007](#)].

### People who do not meet the criteria for CFS/ME

- **Balance between activity and rest**

- This recommendation is based on expert opinion from narrative reviews [[Ruffin and Cohen, 1994](#); [Harvey and Wessely, 2009](#)].

- **Sleep management**

- This recommendation is pragmatic.

- **Counselling and cognitive behavioural therapy (CBT)**

- There is [evidence](#) from a randomized trial that, in people with severe fatigue for 4 months or longer and off work for 6–26 weeks, CBT delivered by a GP after 12 hours' training is no more efficacious than no active intervention [[Huibers et al, 2004a](#)].
- CKS found no trials in people with persistent, unexplained fatigue (not diagnosed as CFS/ME) that compared CBT or counselling, delivered by *qualified* practitioners, with no treatment or placebo treatment. However, there is [evidence](#) from a randomized trial that, in people with unexplained fatigue lasting 3–4 months or longer, CBT is equivalent to counselling [[Ridsdale et al, 2001](#)].
- Subsequently, it was reported that a better outcome was predicted by being psychologically minded and expressing, acknowledging, and accepting emotional distress [[Chalder et al, 2003](#); [Godfrey et al, 2007](#)]. The authors recommended that GPs should assess these factors before referring people for psychological treatments.
- Despite the findings of these studies, CBT is commonly recommended in narrative reviews for people with unexplained, persistent or chronic tiredness/fatigue [[Ruffin and Cohen, 1994](#); [Sharpe and Wilks, 2002](#); [Dick and Sundin, 2003](#)].
- **Graded exercise**
- CKS found no randomized, controlled trials in people with unexplained fatigue that have compared exercise with no treatment or placebo treatment, or compared one form of exercise with another.

- There is [evidence](#) from one randomized trial that graded exercise is equivalent to cognitive behavioural therapy in reducing unexplained fatigue that has been present for 3 months or longer [[Ridsdale et al, 2004](#)].
- **Referral to specialist CFS/ME services**
- This recommendation is based on comments from CKS expert reviewers.

## Prescriptions

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For information on contraindications, cautions, drug interactions, and adverse effects, see the electronic Medicines Compendium (eMC) (<http://emc.medicines.org.uk>), or the British National Formulary (BNF) ([www.bnf.org](http://www.bnf.org)).

## Iron preparations

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### Age from 18 years onwards

#### Ferrous sulphate tablets: 200mg (65mg iron) twice a day

Ferrous sulphate 200mg tablets  
 Take one tablet twice a day.  
 Supply 56 tablets.

**Age:** from 18 years onwards

**NHS cost:** £2.40

**OTC cost:** £4.20

**Licensed use:** no - off-label indication

**Patient information:** These tablets are usually well tolerated but may sometimes upset your stomach, causing sickness, heartburn, and possibly diarrhoea or constipation. These side effects should settle down with time, but if they are very troublesome at first you may reduce the dose to just one tablet each day. After 4 or 5 days, try increasing the number of tablets taken back up to twice a day. Taking the tablets with or after some food will also help reduce the side effects. This medicine may also colour your stools black. Keep these tablets out of the reach of children.

#### Ferrous fumarate tablets: 210mg (68mg iron) twice a day

Ferrous fumarate 210mg tablets  
 Take one tablet twice a day.  
 Supply 56 tablets.

**Age:** from 18 years onwards

**NHS cost:** £0.80

**OTC cost:** £1.42

**Licensed use:** no - off-label indication

**Patient information:** These tablets are usually well tolerated but may sometimes upset your stomach, causing sickness, heartburn, and possibly diarrhoea or constipation. These side effects should settle down with time, but if they are very troublesome try taking the tablets with or after some food to help reduce the side effects. Trying an alternative iron salt is another option. This medicine may also colour your stools black. Keep these tablets out of the reach of children.

#### Ferrous fumarate capsules: 305mg (100mg iron) once a day

Ferrous fumarate 305mg capsules  
 Take one capsule once a day.

Supply 28 capsules.

**Age:** from 18 years onwards

**NHS cost:** £0.50

**OTC cost:** £0.89

**Licensed use:** no - off-label indication

**Patient information:** These capsules are usually well tolerated but may sometimes upset your stomach, causing sickness, heartburn, and possibly diarrhoea or constipation. These side effects should settle down with time, but if they are very troublesome try taking the capsules with or after some food to help reduce the side effects. Trying an alternative iron salt is another option. This medicine may also colour your stools black. Keep these capsules out of the reach of children.

#### **Ferrous fumarate tablets: 322mg (100mg iron) once a day**

Ferrous fumarate 322mg tablets

Take one tablet once a day.

Supply 28 tablets.

**Age:** from 18 years onwards

**NHS cost:** £0.79

**OTC cost:** £1.39

**Licensed use:** no - off-label indication

**Patient information:** These tablets are usually well tolerated but may sometimes upset your stomach, causing sickness, heartburn, and possibly diarrhoea or constipation. These side effects should settle down with time, but if they are very troublesome try taking the tablets with or after some food to help reduce the side effects. Trying an alternative iron salt is another option. This medicine may also colour your stools black. Keep these tablets out of the reach of children.

#### **Ferrous gluconate tablets: 300mg (35mg iron) three times a day**

Ferrous gluconate 300mg tablets

Take one tablet three times a day.

Supply 84 tablets.

**Age:** from 18 years onwards

**NHS cost:** £2.10

**OTC cost:** £2.50

**Licensed use:** no - off-label indication

**Patient information:** These tablets are usually well tolerated but may sometimes upset your stomach, causing sickness, heartburn, and possibly diarrhoea or constipation. These side effects should settle down with time, but if they are very troublesome at first you may reduce the number of tablets you take each day to just one or two. After 4 or 5 days, try increasing the number of tablets taken back up to three a day. Taking the tablets with or after some food will also help reduce the side effects. This medicine may also colour your stools black. Keep these tablets out of the reach of children.