



## **Intro**

First, some definitions.

Generally, fatigue is defined as feeling exhausted during or after activity, or as a feeling of not having enough energy to even start activities.

You want to try to distinguish this from related complaints like daytime sleepiness or objective weakness, which might steer you down a different path.

Acute fatigue is fatigue lasting less than a month. This will often be secondary to an acute medical condition like the flu, or a change in life circumstances, like a new job. In these cases you might pick up an identifiable cause on history pretty quickly, and the fatigue itself may require little or no further evaluation.

Sub-acute or chronic fatigue is usually defined as lasting one to six months or longer. When the cause isn't obvious, or when you get into this sub-acute to chronic timeline, then you'll often need to dig a little deeper.

There are no specific Canadian guidelines on how to approach fatigue, so our approach is a mashup of those from several sources.

## **Objective One**

**In all patients complaining of fatigue, include depression in the differential diagnosis.**

This varies by source, but on average about a quarter of patients presenting with unexplained fatigue will have a form of depression. Use your SIGECAPs and your PHQ-9.

**Or, to keep your review of systems tight, start with a PHQ-2 first, and if positive move on to the more thorough PHQ-9. A brief recap, the PHQ-2 focuses on just two questions:**



Over the **last 2 weeks**, how often have you been bothered by the following problems?

Not at all

Several days

More than half the days

Nearly every day

1. Little interest or pleasure in doing things

<input type="radio"/> 0	<input type="radio"/> +1	<input type="radio"/> +2	<input type="radio"/> +3
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2. Feeling down, depressed or hopeless

<input type="radio"/> 0	<input type="radio"/> +1	<input type="radio"/> +2	<input type="radio"/> +3
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But consider other psychiatric conditions on your differential as well, such as eating disorders, anxiety disorders or somatization.

And don't forget to ask about substance use. Alcohol, marijuana and opioids can all contribute to fatigue, particularly when there is overuse or dependency. Ask about stimulants too, such as cocaine and methamphetamines.

## Objective Two

**Ask about other constitutional symptoms as part of a systematic approach to rule out underlying medical causes in all patients complaining of fatigue.**

On history, your OPQRST can be helpful. Patients who fatigue with exertion or particular activities may be more likely to have a medical condition.

Whereas “tired all the time” (air quotes), or having fatigue that does not improve with rest, is more often associated with psychological conditions, medication side effects or substance use.

Sleep is obviously important. You want to know about the quality and length of sleep, and whether sleep is restful. Symptoms like snoring or apnea should make you think about obstructive sleep apnea. Daytime sleepiness can also point to sleep apnea or to another primary sleep disorder.

In terms of your review of systems and physical exam, a systems-based approach can be helpful because the differential is so broad. [And it also helps you ensure you don't miss the big red flags for underlying disease.](#) For example:



- B symptoms like weight loss, fevers and night sweats and signs like lymphadenopathy should make you consider malignancy.
- Fever should of course also make you consider various infections, such as mononucleosis or endocarditis, depending on the other associated signs and symptoms.
- Ask about dyspnea and chest pain, and examine the heart and lungs to look for signs of diseases like congestive heart failure or COPD.
- Ask about heat or cold intolerance, and weight change, and look for signs like bradycardia or tachycardia, skin changes, or goiters that could point to thyroid disease.
- And ask about morning stiffness and diffuse muscle pain, and do skin and MSK exams to look for rheumatological conditions like polymyalgia rheumatica, rheumatoid arthritis, or fibromyalgia.

<u>Condition</u>	<u>Symptoms</u>	<u>Physical findings</u>	<u>Supportive diagnostic studies</u>
<u>Cardiopulmonary</u>			
<u>Congestive heart failure</u>	<u>Dyspnea on exertion, orthopnea, leg swelling</u>	<u>S3 gallop, inspiratory rales, elevated jugular venous distension, peripheral edema</u>	<u>Chest radiograph, echocardiogram</u>
<u>Chronic obstructive pulmonary disease</u>	<u>Dyspnea, chronic cough, sputum production</u>	<u>Evidence of hyperinflation, wheezing, rales</u>	<u>Chest radiograph</u>
<u>Sleep apnea</u>	<u>Snoring, interrupted breathing during sleep</u>	<u>Obesity, hypertension</u>	<u>Sleep study</u>
<u>Endocrinologic/metabolic</u>			
<u>Hypothyroidism</u>	<u>Cold intolerance, weight gain, constipation, dry skin</u>	<u>Bradycardia, goiter, slow deep tendon reflex relaxation phase</u>	<u>Thyroid function tests</u>



<u>Hyperthyroidism</u>	<u>Heat intolerance, weight loss, diarrhea, moist skin</u>	<u>Tachycardia, goiter, ophthalmopathy</u>	<u>Thyroid function tests</u>
<u>Chronic renal disease</u>	<u>Nausea/vomiting, mental status changes, decreased urine</u>	<u>Hypertension, peripheral edema</u>	<u>Renal function tests/ serum electrolytes</u>
<u>Chronic hepatic disease</u>	<u>Abdominal distention, gastrointestinal bleeding</u>	<u>Jaundice, palmar erythema, gynecomastia, splenomegaly, evidence of ascites</u>	<u>Hepatic function tests</u>
<u>Adrenal insufficiency</u>	<u>Weight loss, salt craving, gastrointestinal complaints</u>	<u>Hypotension, hyperpigmentation, vitiligo</u>	<u>Morning cortisol/ACTH, ACTH stimulation test</u>
<u>Electrolyte abnormalities</u>			
<u>Hyponatremia</u>	<u>Nausea, malaise, cognitive dysfunction</u>	<u>Generally normal exam</u>	<u>Serum sodium level</u>
<u>Hypercalcemia</u>	<u>Anorexia, polydipsia/polyuria, nausea</u>	<u>Generally normal exam</u>	<u>Serum calcium/albumin levels</u>
<u>Hematologic/neoplastic</u>			
<u>Anemia</u>	<u>Dizziness, weakness, palpitations, dyspnea</u>	<u>Tachycardia, pallor</u>	<u>Complete blood count</u>
<u>Occult malignancy</u>	<u>Weight loss, localized symptoms may be present depending upon type</u>	<u>Variable</u>	<u>Variable depending upon type</u>
<u>Infectious diseases</u>			

<u>Mononucleosis syndrome</u>	<u>Fever, sore throat, tender lymph nodes</u>	<u>Fever, exudate pharyngitis, tender cervical adenopathy</u>	<u>Complete blood/differential count, monospot</u>
<u>Viral hepatitis</u>	<u>Fever, nausea/vomiting, abdominal discomfort</u>	<u>Fever, jaundice, tender hepatomegaly</u>	<u>Hepatic function tests, viral hepatitis serologies</u>
<u>HIV infection</u>	<u>Weight loss, variable localized complaints</u>	<u>Variable physical findings</u>	<u>HIV serology</u>
<u>Subacute bacterial endocarditis</u>	<u>Fever/chills, night sweats, myalgias</u>	<u>Fever, new (regurgitant) murmur, peripheral manifestations</u>	<u>Blood cultures, echocardiogram</u>
<u>Tuberculosis</u>	<u>Fever/chills, night sweats, fatigue, weight loss</u>	<u>Cough, chest pain, dyspnea, hemoptysis</u>	<u>PPD/gamma-interferon assay, chest radiograph</u>
<u>Rheumatologic</u>			
<u>Fibromyalgia</u>	<u>Chronic diffuse muscle pain</u>	<u>Multiple "tender points" on palpation</u>	<u>None</u>
<u>Polymyalgia rheumatica</u>	<u>Aching/morning stiffness of shoulders, neck, and hips</u>	<u>Decreased range of motion of shoulders, neck, and hips</u>	<u>Erythrocyte sedimentation rate</u>
<u>Psychological</u>			
<u>Depression</u>	<u>Sad mood, anhedonia, altered sleep, cognitive dysfunction</u>	<u>Generally normal exam</u>	<u>Screening test (eg, PHQ-2, PHQ-9)</u>
<u>Anxiety disorder</u>	<u>Generalized nervousness, panic attacks, phobias</u>	<u>Tachycardia, muscle tension</u>	<u>Screening test (eg, GAD-7)</u>



<u>Somatization disorder</u>	<u>Multiple chronic constitutional and localized complaints</u>	<u>Generally normal exam</u>	<u>Screening test (eg, SSS-8)</u>
<u>Medication toxicity*</u>			
	<u>Variable</u>	<u>Generally normal exam</u>	<u>None</u>
<u>Substance use¶</u>			
	<u>Variable</u>	<u>Generally normal exam</u>	<u>None</u>

\* Benzodiazepines, antidepressants, muscle relaxants, first-generation antihistamines, beta-blockers, opioids, GABA analogues.

¶ Alcohol, marijuana, opioids, cocaine/other stimulants.

## Objective Three

**Exclude adverse effects of medication as the cause in all patients complaining of fatigue.**

Ask about both prescriptions and over the counter medications, vitamins and supplements.

Common culprits include benzodiazepines, antidepressants, muscle relaxants, first-generation (and sometimes second-generation) antihistamines, beta-blockers, opioids, and GABA analogues.

When patients have renal or hepatic impairment, consider whether they could be developing toxicity with their medications and ensure proper dose adjustments.

Environmental exposure to toxins like lead or arsenic are way less common these days, but still worth thinking about, especially if relevant to the patient's occupation or home environment.



## Objective Four

**Avoid early, routine investigations in patients with fatigue unless specific indications for such investigations are present.**

Your physical exam and history should guide your investigations. This includes making sure any age-specific cancer and medical screening tests – like FIT testing, mammograms, A1Cs, all that stuff - are up to date.

And consider whether your patient has specific risk factors that should prompt particular testing - for example, if your patient has a life-long history of smoking or strong family history of particular cancers, then extra screening might be appropriate.

Serologic screening for conditions like HIV or Hepatitis B and C are not appropriate to do routinely for everyone - but consider doing them if your patient has never had them done before at all, or if they engage in activities that put them at an increased risk.

Ok. But what if your patient's screening is already up to date and your assessment hasn't revealed any specific indications for labs or imaging? Can't I just order everything but the kitchen sink and hope I find the answer?

There isn't much evidence on this – but if your pre-test probability for a particular condition is already low, investigations are unlikely to be helpful. The few studies we found suggest labs affect management or clarify the cause of fatigue in only about 5 to 8% of patients!

A Systematic Review in 2016 in BMC Family Practice found that a presenting complaint of tiredness led to a diagnosis of:

- anaemia in 2.8% of cases
- malignancy in 0.6% of cases
- serious somatic disease in 4.3% of cases
- and depression in **18.5%** of cases.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5072300/>

In acute fatigue, if you've already determined that your patient has a likely underlying cause that doesn't require further investigations, then it's reasonable to trial treatment or conservative management first, as appropriate. If your patient has depression, treat the depression!



All that said, most sources do still recommend a few routine labs, *especially* if symptoms persist beyond a few weeks.

Consider ordering a CBC and differential, chemistries like electrolytes, a random glucose and hemoglobin A1c, calcium, renal and hepatic function tests, and a TSH – these will rule out your most common secondary causes, like anemia, and some more serious conditions like cancer.

Some sources would also recommend considering a CRP, a Vitamin B12, a urinalysis and pregnancy tests, but again, mileage will vary.

Ok. But now what if these all come back normal, and there are no other localized findings? Then can I start looking for zebras?

Well, then there is not much evidence that repeating tests will be helpful, unless something in the patient's presentation changes. And if those basic labs are normal, there is *no* good evidence for going fishing for rare immunological conditions or vitamin deficiencies.

This means you don't need to go ordering tests like an ANA, or Lyme serologies, or Vitamin D levels, unless you've really got a good reason.

Though we didn't find good Canadian sources for this, Australian Family physician published a document regarding investigations for Fatigue in Primary Care. We will link to this and the shownotes include a pathway they recommend, which is very much as we just review, as well as some red flags to look for that should prompt further investigations.

<https://www.rcpa.edu.au/getattachment/17c38096-b72f-4f30-82d8-5426b93ee623/Investigating-fatigue.aspx>

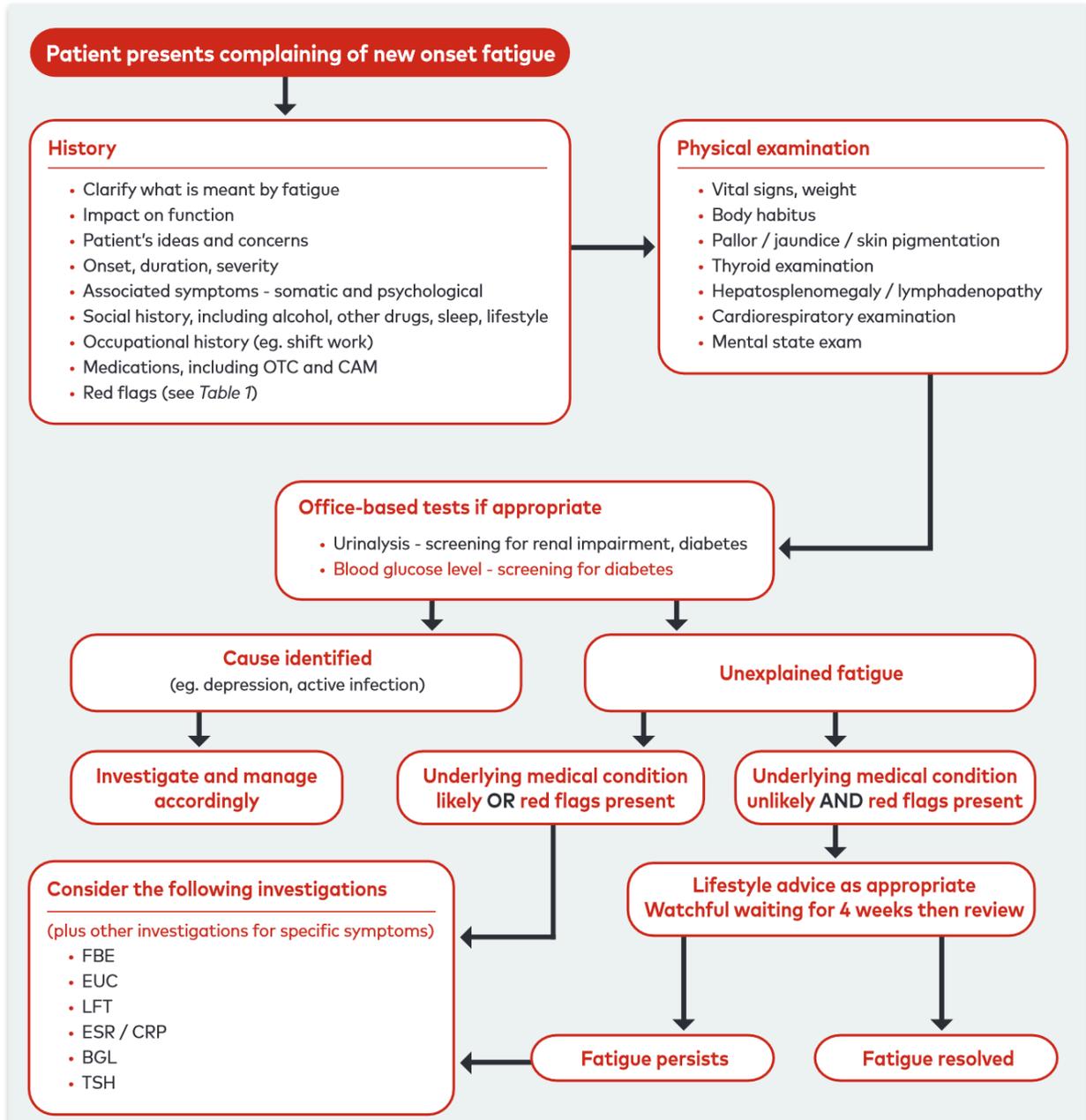
**Table 1: RED FLAGS THAT RAISE SUSPICION OF SERIOUS UNDERLYING DISEASE<sup>†</sup>**



Red flags	Examples of potential serious underlying disease
Unintentional weight loss	<ul style="list-style-type: none"> <li>• Malignancy</li> <li>• HIV infection</li> <li>• Diabetes mellitus</li> <li>• Hyperthyroidism</li> </ul>
Abnormal bleeding	<ul style="list-style-type: none"> <li>• Anaemia</li> <li>• Gastrointestinal malignancy</li> </ul>
Shortness of breath	<ul style="list-style-type: none"> <li>• Anaemia</li> <li>• Heart failure</li> <li>• Chronic obstructive pulmonary disease</li> </ul>
Lymphadenopathy	<ul style="list-style-type: none"> <li>• Malignancy</li> </ul>
Fever	<ul style="list-style-type: none"> <li>• Hidden infection or abscess</li> </ul>
Concurrent cardiovascular, gastroenterological, neurological or rheumatological symptoms	<ul style="list-style-type: none"> <li>• Autoimmune disease e.g. rheumatoid arthritis</li> <li>• Malignancy</li> <li>• Coeliac disease</li> <li>• Multiple sclerosis</li> </ul>
Recent onset of fatigue in a previously well older patient	<ul style="list-style-type: none"> <li>• Malignancy</li> <li>• Anaemia</li> <li>• Renal failure</li> <li>• Diabetes mellitus</li> </ul>

<sup>†</sup> Adapted from the Australian Family Physician 2014.<sup>9</sup>

**Figure 1. Guidelines for the investigation of fatigue<sup>†</sup>**



## Objective Five



**Given patients with fatigue in whom other underlying disorders have been ruled out, assist them to place, in a therapeutic sense, the role of their life circumstance in their fatigue.**

On average, only about two-thirds of primary care patients with chronic fatigue will receive a specific diagnosis to explain it. For that other third, it's important to acknowledge their fatigue as real even when you can't find a medical explanation.

Exploring the psychosocial factors and behaviours that may be at play can help your patients recognize the causes of their fatigue, which is also the first step to potentially address them. If fatigue becomes chronic, it's also important to consider the diagnosis of Chronic Fatigue Syndrome, which we will talk about in the next objective.

Sleep is a key place to start.

Are they getting enough sleep? Patients may need to prioritize making enough time in their day for sleep, and may need some coaching on good sleep hygiene. These are things like getting up at the same time every day, reducing exposure to screens before bed, and avoiding caffeine, alcohol or eating too much later in the day.

In some cases, cognitive behavioural therapy for insomnia or pharmacotherapy may also be appropriate. Although in practice I've never had any luck getting patients to take me up on going for formal CBTi, this is something that you can sometimes sneak into your office visit.

Sleep can be a particular struggle for shift workers, who often struggle with altered sleep wake cycles and may require a combination of behavioural changes and medications to get their sleep back on track.

Other areas to explore could include work stress and work hours, interpersonal relationships and risk factors for domestic violence, financial stressors, or caregiver responsibilities.

Some of these aspects can be challenging to address or will be outside your scope as a family doctor. But once you and your patient have recognized them as contributing, you can at least look to make appropriate referrals or loop them in with services like social work that might be helpful.



## Objective Six

**In patients whose fatigue has become chronic, manage supportively, while remaining vigilant for new diseases and illnesses.**

‘Chronic fatigue’ is defined as lasting over 6 months. It’s important to distinguish ongoing secondary fatigue that’s due to another condition, from both idiopathic chronic fatigue and chronic fatigue syndrome (CFS - also known as myalgic encephalomyelitis/Chronic fatigue syndrome, or ME/CFS).

Chronic fatigue syndrome is one of those conditions where we still have a very poor understanding of the pathophysiology or cause, nor is there a specific or sensitive test to diagnose it.

TOP (Towards Optimized Practice) has a great set of guidelines on CFS which we will link to in the show notes for more details. [It is considered an uncommon cause of chronic fatigue - but while there is not a lot of good data on the prevalence in Canada, the guidelines suggest prevalence may be as high as 1.4% in Canadians over the age of 12.](#)

A key feature on history that should make you consider CFS is:

- pathological fatigue and post-exertional malaise that is out of proportion to the level of exertion, and
- that takes more than 24 hours to recover.

[It is often associated with a precipitating cause like a flu-like illness, but it can come on gradually. It’s also important to realize that the severity of CFS can range from mild \(able to work with effort\) to severe \(essentially bedbound\).](#)

There are several tools for diagnosing CFS in the literature. The [Toward Optimized Practice \(TOP\)](#) guidelines recommend the validated Canadian Consensus Criteria as the most specific to help you distinguish CFS from psychiatric conditions - they are pretty detailed, so we will include the complete criteria in the show notes. But in brief, a patient with CFS will have at least:

- a 6-month history (3 months in children) of the following:
  - fatigue,
  - post-exertional malaise or fatigue,
  - sleep dysfunction and pain;



- they also need two or more categories of neurological or cognitive manifestations, such as
  - confusion,
  - impaired concentration,
  - information processing difficulties or word finding issues,
  - disorientation, or
  - perceptual and sensory disturbances),
- and at least one symptom from at least two other categories of symptoms (these include autonomic, immune and neuroendocrine symptoms).

Typically the physical exam is normal. Patients often feel febrile, but rarely have an elevated temperature. Painful lymph nodes, especially cervical lymph nodes, are also common, but there is rarely true lymphadenopathy. And although patients often experience sore joints and muscles, on exam there is not typically any swelling or erythema, and studies like biopsies and EMGs are normal.

In terms of supportive management, any ongoing fatigue of any etiology can lead to high levels of health care utilization and disability. It's important to realize that patients can be sicker than they look.

Regardless of the etiology, again, super important to start by acknowledge fatigue as real and trying to build that therapeutic relationship.

Many symptoms associated with fatigue are common to CFS and other chronic conditions, and can often be treated similarly, although there are some particular considerations - check out those TOP guidelines for more details on treating CFS specifically.

In general, if you think there's a medical reason for their fatigue – like heart failure – then you should monitor their symptoms while treating the underlying condition to see if the fatigue improves. If not, then you need to consider other causes and potentially repeat your initial evaluation.

You also want to continue to support patients to address those life circumstances we talked about in Objective Five.



For patients with overlapping depressive symptoms, it may be reasonable to trial an antidepressant, even if they do not meet criteria for a major depressive disorder. First line options would include SSRIs and SNRIs.

Cognitive behavioural therapy and group therapies can be helpful in helping patients understand their fatigue symptoms and work towards achieving personal goals. This can be particularly helpful for patients with overlapping symptoms of depression or anxiety.

For some patients, especially those in which you suspect some degree of physical deconditioning, exercise therapy may also be beneficial.

And finally, remain vigilant for new diseases. Changes in symptoms or signs should prompt you to reconsider your original diagnosis, as underlying disease processes may declare themselves over time.

Annnnd, that's it for \*yaawwn\* fatigue. I think I'm ready for a nap.

## **Outro babble**

## **Referenced Works**

TOP (toward's optimized practice) 2016 guidelines for myalgic encephalomyelitis / chronic fatigue syndrome: <https://actt.albertadoctors.org/CPGs/Pages/Myalgic-Encephalomyelitis-Chronic-Fatigue-Syndrome.aspx>

UpToDate: approach to the adult patient with fatigue .  
<https://www.uptodate.com/contents/approach-to-the-adult-patient-with-fatigue>

Rosenthal TC, Majeroni BA, Pretorius R, Malik K. Fatigue: an overview. *Am Fam Physician*. 2008 Nov 15;78(10):1173-9. PMID: 19035066.

Sugarman JR, Berg AO. Evaluation of fatigue in a family practice. *J Fam Pract*. 1984;19(5):643-647.

Jacques Cornuz, Idris Guessous and Bernard Favrat

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## Figures

### 1. ME/CFS Symptom Checklist

<u>Symptoms</u>	<u>Description of Symptom</u>
<b>Pathological fatigue</b> Yes No	<b>A significant degree of new onset, unexplained, persistent or recurrent physical and/or mental fatigue that substantially reduces activity levels and which is not the result of ongoing exertion and is not relieved by rest.</b>
<b>Post-exertional malaise &amp; worsening of symptoms</b> Yes No	<b>Mild exertion or even normal activity is followed by malaise: the loss of physical and mental stamina and/or worsening of other symptoms. Recovery is delayed, taking more than 24 hours.</b>
<b>Sleep problems</b> Yes No	<b>Sleep is un-refreshing: disturbed quantity – daytime hypersomnia or nighttime insomnia and/or disturbed rhythm – day/night reversal Rarely there is no sleep problem</b>
<b>Pain</b> Yes No	<b>Pain is widespread, migratory or localized: myalgia; arthralgia (without signs of inflammation); and/or headache – a new type, pattern or severity</b>  <b>Rarely there is no pain</b>
<b>Two neurocognitive symptoms</b> Yes No	<b>Impaired concentration, short term memory or word retrieval; hypersensitivity to light, noise or emotional overload; confusion; disorientation; slowness of thought; muscle weakness; ataxia</b>



<p>At least one symptom from two of these categories:</p> <p>a) Autonomic</p>	<p><b>a) Autonomic:</b></p> <p>Orthostatic intolerance – neutrally-mediated hypotension (NMH); postural orthostatic tachycardia (POTS); light headedness; extreme pallor; palpitations; exertional dyspnea; urinary frequency; irritable bowel syndrome (IBS); nausea</p>
<p>Yes No b) Neuroendocrine</p> <p>Yes No</p> <p>c) Immune</p> <p>Yes No</p>	<p><b>b) Neuroendocrine:</b></p> <p>Low body temperature; cold extremities; sweating;</p> <p>intolerance to heat or cold; reduced tolerance for stress; other symptoms worsen with stress; weight change; abnormal appetite</p>
	<p><b>c) Immune:</b></p> <p>Recurrent flu-like symptoms; sore throats; tender lymph nodes; fevers; new sensitivities to food, medicines, odors or chemicals</p>

2. Causes of subacute and chronic fatigue - reproduced from UpToDate ([Causes of subacute and chronic fatigue](#))