4-2020

Fatigue in Primary Care: Doctor, Why Am I So Tired?

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Thomas Jefferson University

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Fatigue in primary care: Doctor, Why Am I So Tired?

NINA MINGIONI, MD FACP
Learning Objectives

- Identify top causes of fatigue in primary care
- Develop an evidence-based approach to assessing a patient with fatigue
- Reflect on the evidence for available screening tools for fatigue
Doctor, why am I so tired all the time?

43-year-old woman presents to you with the chief complaint of “Doctor, I am run down all the time.”
Definition of fatigue

Multiple ones exist!

Are definitions relevant?

Does duration matter?

Table 1. Definitions of Fatigue.²,7,8

<table>
<thead>
<tr>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive decline in the ability to activate the muscle voluntarily</td>
</tr>
<tr>
<td>Progressive loss of ability to generate MVC during or following</td>
</tr>
<tr>
<td>repeated or sustained muscle contraction</td>
</tr>
<tr>
<td>Loss of force generation during a task</td>
</tr>
<tr>
<td>Difficulty in initiating or sustaining voluntary activity</td>
</tr>
<tr>
<td>Mismatch between expended effort and actual performance or</td>
</tr>
<tr>
<td>exhaustion</td>
</tr>
<tr>
<td>Reduced force production (weakness)</td>
</tr>
<tr>
<td>Loss of exercise capacity (reduced endurance)</td>
</tr>
<tr>
<td>Increased sense of effort or overperception of force</td>
</tr>
<tr>
<td>Decreased power (reduced velocity of muscle contraction)</td>
</tr>
<tr>
<td>Loss of peak force (torque) &gt;50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perception of the feeling to be cognitively fatigued after performing</td>
</tr>
<tr>
<td>demanding cognitive activities that involve concentration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor cortex failure to recruit muscle, particularly loss of high</td>
</tr>
<tr>
<td>threshold motor units</td>
</tr>
<tr>
<td>Reduced central drive from increased inhibitory interneuron input to</td>
</tr>
<tr>
<td>the cortex</td>
</tr>
<tr>
<td>Central conduction block from demyelination of neurons</td>
</tr>
<tr>
<td>Increased negative feedback from muscle afferents via type 3 + 4</td>
</tr>
<tr>
<td>sensory neurons</td>
</tr>
<tr>
<td>Loss of positive feedback from muscle spindle type 1 sensory</td>
</tr>
<tr>
<td>afferents</td>
</tr>
<tr>
<td>Poor coordination of motor unit firing</td>
</tr>
<tr>
<td>Delayed conduction and impairment of dynamic recruitment</td>
</tr>
<tr>
<td>Changes in synergistic muscle contraction to net force</td>
</tr>
<tr>
<td>Loss of coherence between CNS motor neurons</td>
</tr>
<tr>
<td>Changes in joint mobility from spasticity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive decline in MVC produced by a muscle</td>
</tr>
<tr>
<td>Progressive loss of MVC or decline in MVC during a task</td>
</tr>
<tr>
<td>Sense of exhaustion and lack of energy to perform repeated or</td>
</tr>
<tr>
<td>sustained muscle contractions during a task</td>
</tr>
<tr>
<td>Long-lasting reduction in the activity to contract and to exert force</td>
</tr>
<tr>
<td>Incapacity to maintain the required or expected force</td>
</tr>
<tr>
<td>Diminished ATP production due to deconditioning</td>
</tr>
<tr>
<td>Disuse muscle atrophy secondary to inactivity</td>
</tr>
<tr>
<td>Muscle atrophy due to loss of innervation</td>
</tr>
</tbody>
</table>

Abbreviations: ATP, adenosine triphosphate; CNS, central nervous system; MVC, maximal voluntary contraction.
Fatigue

- Feeling down
- Decreased exercise tolerance
- Weakness
- Lack of energy
- Sleepiness
- Dyspnea on Exertion
Fatigue
Sleepiness
Dyspnea on Exertion
Weakness
Lack of energy
Decreased exercise tolerance

Good history is key!
### Most common (identifiable) causes of fatigue

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Depression</th>
<th>Thyroid Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary Disease</td>
<td>Sleep apnea</td>
<td>Side effects of medications and supplements</td>
</tr>
</tbody>
</table>
Start with open-ended questions…

”Tell me more about this”

“Please describe to me what that means”
Then explore more specifically
Start with sleep

What time do you go to sleep on a typical night?
How long does it take you to fall asleep?
Do you wake up at night? Why? How many times?
When do you wake up?
How do you feel when you wake up in the morning?
Then ask about the day

- How much effort does it take to get out of bed and get moving?
- Do you get sleepy throughout the day?
- How likely are you to fall asleep during quiet activities, such as sitting down and reading a book or watching TV?
- How is your energy level throughout the day?
- How’s your mood?
Assess exercise tolerance

Are you able to keep active?

What happens when you exert yourself?
Assess impact on life

What do you enjoy?
What hobbies do you have?
Have you been able to enjoy your normal day-to-day activities?
Other review of systems

- Weight changes
- Bleeding/pica
- Dyspnea
- Edema
- Bowel changes
Physical Exam

- Vital signs
- Conjunctiva
- Oropharynx
- Neck
- Cardiopulmonary exam
- Abdominal exam
- Strength testing
Mallampati Classification

Class 1  Class 2  Class 3  Class 4

Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnea?: The Rational Clinical Examination systematic review. JAMA. 2013;310(7):731-741.
Also important

Medication/supplement review

PHQ-9
Common illness scripts

- Anemia
- Depression
- Thyroid Disease
- Cardiopulmonary Disease
- Sleep apnea
Anemia: Fatigue and...

Dyspnea, dizziness, decreased exercise tolerance

May be more prevalent in younger menstruating women or those at risk for malabsorption

Pica is commonly associated (ice, clay, dirt, starch)

- Prevalence varies
- OR 2.4

ANEMIA

Probability

Decrease

-45%  -30%  -15%

Increase

+15%  +30%  +45%

LRs

0.1  0.2  0.5  1  2  5  10

Absence of palmar pallor

Conjunctival rim pallor
Palmar crease pallor
Palmar pallor
Pallor at any site
Facial pallor
Sleep disorders: fatigue and...

Need for naps throughout the day
Naps improve fatigue
Sleepiness during quiet activities
Patient with obesity

DDx: Sleep apnea, insufficient sleep, sleep latency disorders
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal choking/gasping</td>
<td>52%</td>
<td>84%</td>
<td>3.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Morning headache</td>
<td>22%</td>
<td>85%</td>
<td>1.5</td>
<td>0.92</td>
</tr>
<tr>
<td>Reported apnea</td>
<td>80%</td>
<td>42%</td>
<td>1.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>50%</td>
<td>61%</td>
<td>1.3</td>
<td>0.81</td>
</tr>
<tr>
<td>Snoring</td>
<td>90%</td>
<td>19%</td>
<td>1.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Mallampati class 3 or 4</td>
<td>55%</td>
<td>65%</td>
<td>1.6</td>
<td>0.68</td>
</tr>
<tr>
<td>Overall clinical impression</td>
<td>58%</td>
<td>67%</td>
<td>1.7</td>
<td>0.67</td>
</tr>
<tr>
<td>STOP-Bang Questionnaire</td>
<td>93%</td>
<td>35%</td>
<td>1.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>
### STOP-Bang Questionnaire

Please answer the following questions by checking “yes” or “no” for each one

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring (Do you snore loudly?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiredness (Do you often feel tired, fatigued, or sleepy during the daytime?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed Apnea (Has anyone observed that you stop breathing, or choke or gasp during your sleep?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Blood Pressure (Do you have or are you being treated for high blood pressure?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (Is your body mass index more than 35 kg per m²?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Are you older than 50 years?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck Circumference (Is your neck circumference greater than 40 cm [15.75 inches]?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Are you male?)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Score 1 point for each positive response.

Scoring interpretation: 0 to 2 = low risk, 3 or 4 = intermediate risk, ≥ 5 = high risk.
Hypothyroidism: fatigue and...

- Weight gain
- Edema
- Dry skin
- Goiter
- Family history
<table>
<thead>
<tr>
<th>Finding</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cool and dry skin</td>
<td>16</td>
<td>97</td>
<td>4.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Coarse skin</td>
<td>29-61</td>
<td>74-95</td>
<td>3.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Peri orbital puffiness</td>
<td>53-91</td>
<td>21-81</td>
<td>NS</td>
<td>0.6</td>
</tr>
<tr>
<td>Puffiness of wrists</td>
<td>39</td>
<td>86</td>
<td>2.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Hair loss of eyebrows</td>
<td>29</td>
<td>85</td>
<td>1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Pretibial edema</td>
<td>78</td>
<td>31</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hypothyroid speech</td>
<td>37</td>
<td>93</td>
<td>5.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Slow pulse rate</td>
<td>29-43</td>
<td>89-98</td>
<td>4.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Enlarged thyroid</td>
<td>46</td>
<td>84</td>
<td>2.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Delayed ankle reflexes</td>
<td>48</td>
<td>86</td>
<td>3.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Slow movements</td>
<td>87</td>
<td>13</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
Cardiac disease: fatigue and...

Women are more likely than men have Acute Coronary Syndrome with no chest pain or discomfort (37% vs 27%)

Approximately 60% of all patients with Unstable Angina report unusual fatigue

Fatigue does NOT generally occur in isolation as the only symptom of ACS

- Look for associated symptoms
- Look for risk factors


Depression: fatigue and...

Depressed mood and anhedonia are key features

At least 5 symptoms present most days for at least 2 weeks

Depressed people are twice as likely to feel fatigue and people with no depression

People with fatigue are twice as likely to also have depression as people with no fatigue

# Patient Health Questionnaire - 9

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

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**For Office Coding**

0 + _____ + _____ + _____

Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th>Difficulty Level</th>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
Medications as a cause of fatigue

- Beta-blockers
- Anti-histamines
  - 1st generation
  - 2nd generation
- Narcotics
- Muscle relaxants
- Sedatives/hypnotics
- Benzodiazapines
- Gabapentin/Pregabalin
- Venlafaxine
- Tricyclic antidepressants
- Additive effects!!!
Supplements as a cause of fatigue

ST. JOHN’S WART

VALERIAN ROOT

SAW PAMETTO

OTHERS?

MEDICATION/SUPPLEMENT INTERACTION

What if there is no clear syndrome?
Are there labs that each patient with fatigue should get?

The Low Yield of Physical Examinations and Laboratory Investigations of Patients With Chronic Fatigue

T J Lane, D A Matthews, P Manu

Abstract

Fatigue is a common symptom but guidelines for its appropriate evaluation are lacking. The authors prospectively studied 100 adults with a chief complaint of fatigue lasting at least 1 month in order to determine the diagnostic contribution of physical examinations and laboratory investigations. The evaluations were performed in the specialized clinic of a faculty practice. Physical examinations produced diagnostic information in 2% of patients, and laboratory investigations elucidated the cause of fatigue in 5% of patients. Structured follow-up evaluations after an average interval of 10 months failed to reveal any new organic causes for the fatigue symptom. Minor laboratory abnormalities were relatively common but did not contribute to the diagnostic process and did not seem to influence the clinical outcome. The authors conclude that the traditional medical evaluation of patients complaining of chronic fatigue has a low yield in discovering treatable physical disorders.
Are there labs that each patient with fatigue should get?

Usefulness of a Standard Battery of Laboratory Tests in Investigating Chronic Fatigue in Adults

A Valdini, S Steinhardt, E Feldman
Affiliations + expand
PMID: 2632306 DOI: 10.1093/fampra/c6.4.286

Abstract
Twenty-two adults with chronic fatigue were studied to determine the clinical usefulness of commonly applied laboratory tests. Subjects with the chief complaint of fatigue persisting for more than one year were followed for an average of seven months at a university family health centre. During this time a group of commonly recommended tests were carried out and the patients had repeated physical examinations. Physical diseases and laboratory abnormalities were few, and patients with abnormal values and active problems were followed until their fatigue resolved or their abnormalities reverted to normal following therapy. The study demonstrated that the presence of an abnormal laboratory result in a fatigued individual does not necessarily indicate the cause of fatigue. A psychiatric history was also performed and patients were tested with the symptom check list 90-R (SCL-90-R), a 90-item psychological symptom check list. Seven patients were receiving psychotherapy when they enrolled in the study. Two additional subjects entered therapy after the start of the study. Results on the symptom check list for the study group were largely abnormal, with a majority scoring in the highest quartile for depression, paranoid ideation and psychotism. It is concluded that the investigation of patients with fatigue which has lasted for longer than one year should focus on psychological causes. In this group of patients laboratory abnormalities are not useful in guiding evaluation or treatment for their fatigue.
What if there is no clear syndrome

- CBC
- BMP
- LFT
- TSH
Consider Ferritin testing

In non-anemic menstruating women with unexplained fatigue and low ferritin levels iron supplementation improved fatigue.

Consider no-cost interventions

PHQ-9 Questionnaire

STOP-Bang Questionnaire
Other considerations

Make sure they are up to date on age-appropriate screening

- Cancer screening
- Hepatitis C if born between 1945 and 1965
- HIV screening is recommended in all adults by USPSTF
What about other labs?
**ESR/CRP**

**CRP**
mild elevations of CRP are common

significant elevations are consistent with bacterial infections

drops quickly once treated

**ESR**
ESR>100 mm/hour: PPV>90% for an identifiable cause of marked ESR elevation

can take weeks to return to normal

Clinical suspicion for disease

Check ESR/CRP

ESR/CRP Results

HIGH

LOW

HIGH SUSPICION FOR SERIOUS UNDERLYING ILLNESS

MODERATE

HIGH

LOW

NOT HELPFUL

LOW

RULE OUT SERIOUS UNDERLYING ILLNESS

LOW
Vitamin D Deficiency can be associated with:
- Muscle weakness
- Type II muscle fiber atrophy
- Accelerated sarcopenia

So:
- Might be appropriate to order if some has muscular weakness
- Not clearly associated with non-specific fatigue
- Consider screening if at risk
Vitamin B12 Deficiency:

• Neuropsychiatric symptoms WITHOUT anemia or macrocytosis (28%)
  ◦ paresthesia, sensory loss, ataxia, dementia, and psychiatric disorders

• Macrocytosis with or without anemia

• NO isolated fatigue


T3 and T4

Many conditions cause decrease in total T3 and T4, but FREE T3 and T4 are relatively stable

Central hypothyroidism
- Normal TSH, low T4
- Usually due to hypopituitarism
- Symptoms can be same as primary hypothyroidism but are frequently milder due to co-existing hormonal deficiencies
- 1000 times LESS common than primary hypothyroidism

70% of adolescents and adults with EBV infections present with Infectious Mononucleosis

90-95% of adults are eventually EBV seropositive

Association between EBV and Chronic Fatigue Syndrome is questionable

◦ In prospective studies, 7-13% of adults reported fatigue 6 months after an acute EBV infection.

Severe fatigue is common in rheumatologic disease (35-57%).

Diagnosis of any rheumatologic disease is based on a specific syndrome alone with suggestive serologies and is never based on serology alone.

Celiac disease is common (1% of general population)

Fatigue is common in patients with celiac disease
  - Prevalence 8-100% in various studies
  - No clear evidence that fatigue improves on gluten-free diet

Patients with celiac disease usually have more than fatigue as a presenting symptom

No evidence that patients with chronic fatigue are more likely to have celiac disease


Mold testing

Mold can cause legitimate medical ailments
- Allergic diseases
- Hypersensitivity pneumonitis
- Dermatologic infections
- Sepsis in immunocompromised

Toxic Mold Syndrome: fact or fiction?
- Syndrome of headache, fatigue, difficulty concentrating, myalgias, memory loss, mood changes
- Mycotoxins: no evidence, no plausible mechanism
- No FDA approved testing

Untreated “stage 3” Lyme disease syndrome is oligoarthritis and neuroborreliosis

- these have defined symptoms

After treatment of Lyme disease, systemic symptoms can linger

- no evidence that indicates persistent infection
- No evidence that giving more antibiotics is helpful

“Chronic” Lyme Disease?

- Poorly defined syndrome of various atypical symptoms
- No objective clinical symptoms of recognized Lyme syndromes
- Usually negative testing
What NOT to order routinely

- Vitamin D
- Vitamin B12
- T3, T4
- Lyme testing
- EBV Titers
- Celiac panel
- Rheumatologic testing
What if no cause is found?
Does diet matter?

Maybe!

High-protein high-fat low-carb diets result in less skeletal muscle glycogen stores than high-carb diet.

Depletion of muscle glycogen results in decrease in exercise tolerance.
Does my patient have occult malignancy?

No literature to support that fatigue is the only symptom of malignancy

Making sure patient is up-to-date on age-appropriate recommended cancer screening is reasonable.
Does my patient have fibromyalgia?

Diffuse pain is a central for diagnosis

Severe fatigue is common

Common co-occurrence with inflammatory conditions (central sensitization)
Does my patient have Myalgic Encephalomyelitis?

Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS)

Overwhelming fatigue not improved by rest

Prominent post-exertional malaise

Unrefreshing sleep

Cognitive impairment OR orthostatic intolerance

Summary

- Good history is key!
- Illness scripts drive the work-up
- Labs: CBC, BMP, LFT, TSH
- Consider Ferritin
- Do not over-order tests
- Clinical follow up is important