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

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

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NINA MINGIONI, MD FACP

# Learning Objectives

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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.<sup>2,7,8</sup>

## General

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

## Mental

- Perception of the feeling to be cognitively fatigued after performing demanding cognitive activities that involve concentration

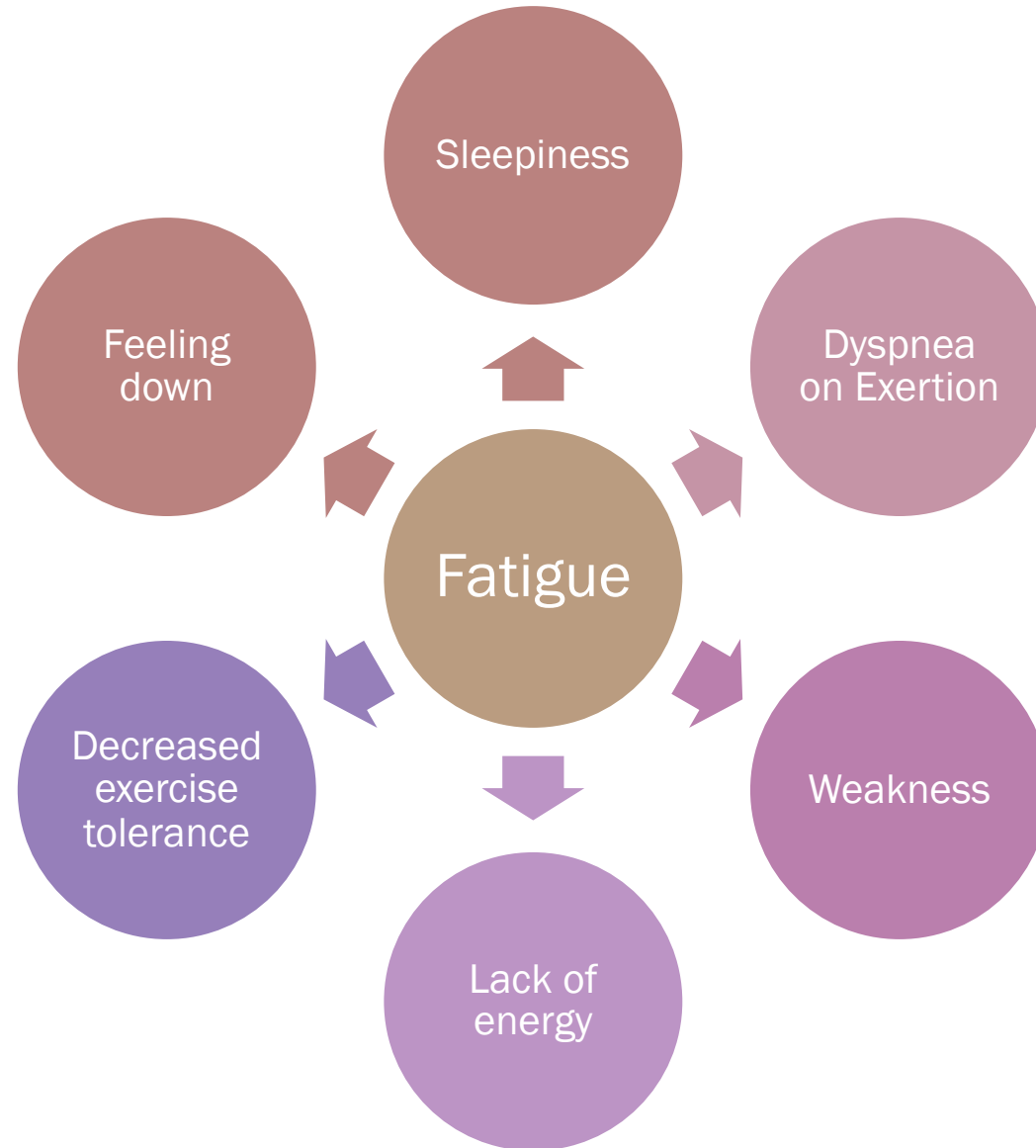
## Central

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

## Peripheral

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

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





# Most common (identifiable) causes of fatigue

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Anemia

Depression

Thyroid Disease

Cardiopulmonary  
Disease

Sleep apnea

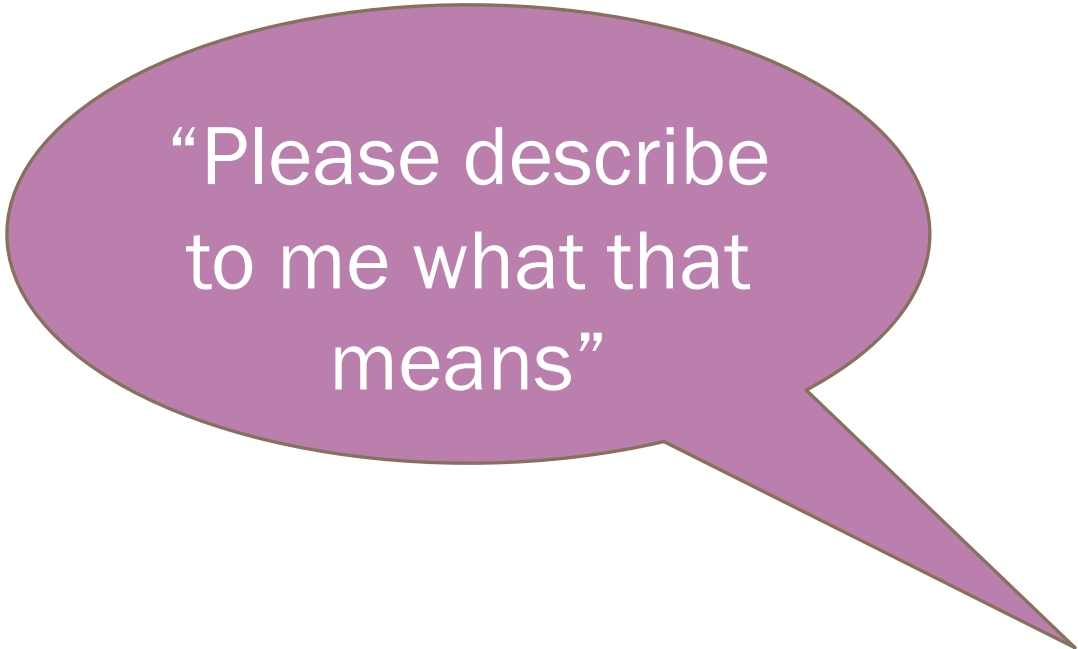
Side effects of  
medications and  
supplements

# Start with open-ended questions...

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"Tell me more about this"



"Please describe to me what that means"



Then explore more specifically

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# Start with sleep

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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

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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

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Are you able to keep active?

What happens when you exert yourself?



# Assess impact on life

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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



Also  
important

Medication/supplement review

PHQ-9

Anemia

Depression

Thyroid Disease

Cardiopulmonary  
Disease

Sleep apnea

Common illness scripts

# Anemia: Fatigue and...

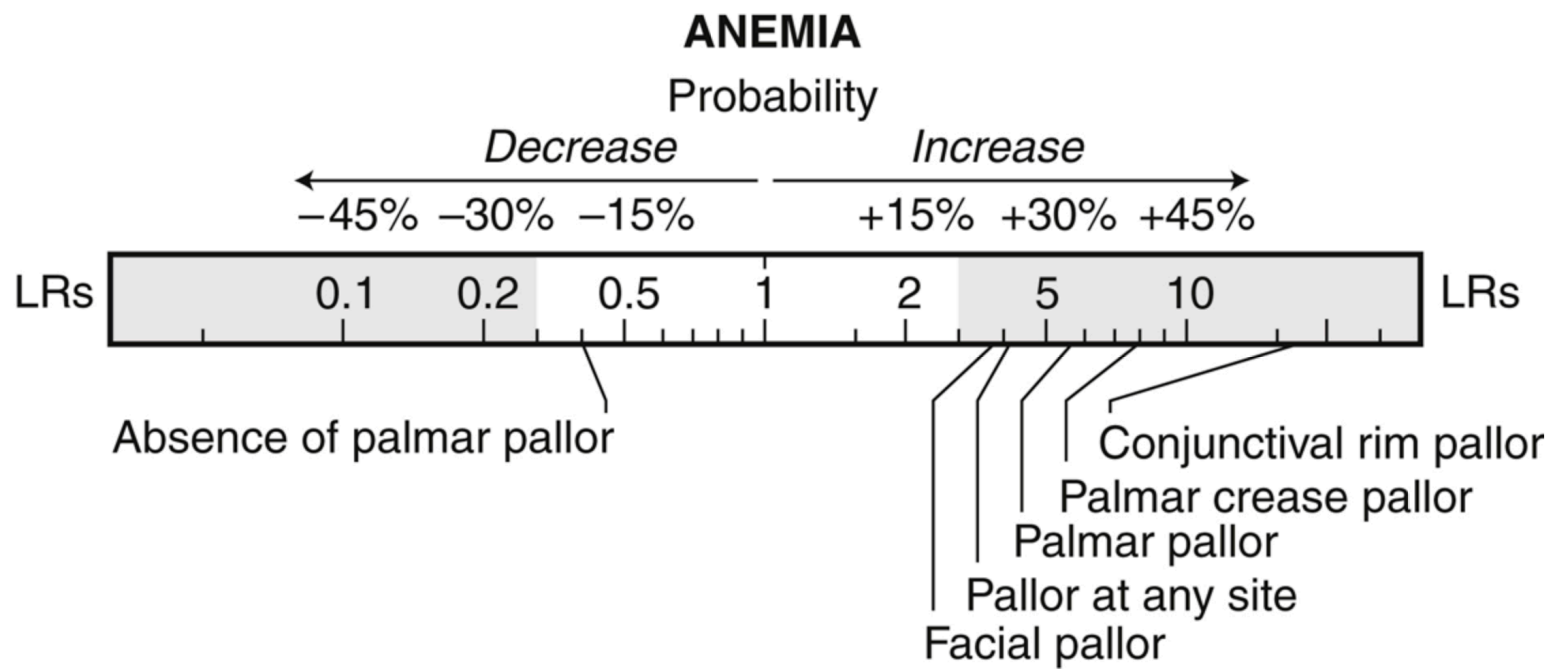
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Dyspnea, dizziness, decreased exercise tolerance

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



# Sleep disorders: fatigue and...

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Need for naps throughout the day

Naps improve fatigue

Sleepiness during quiet activities

Patient with obesity

DDx: Sleep apnea, insufficient sleep, sleep latency disorders

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Symptom	Sensitivity	Specificity	LR+	LR-
Nocturnal choking/gasping	52%	84%	3.3	0.57
Morning headache	22%	85%	1.5	0.92
Reported apnea	80%	42%	1.4	0.47
Excessive daytime sleepiness	50%	61%	1.3	0.81
Snoring	90%	19%	1.1	0.6
Mallampati class 3 or 4	55%	65%	1.6	0.68
Overall clinical impression	58%	67%	1.7	0.67
STOP-Bang Questionnaire	93%	35%	1.4	0.2

## STOP-Bang Questionnaire

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

	Yes	No
<b>S</b> noring (Do you snore loudly?)	<input type="checkbox"/>	<input type="checkbox"/>
<b>T</b> iredness (Do you often feel tired, fatigued, or sleepy during the daytime?)	<input type="checkbox"/>	<input type="checkbox"/>
<b>O</b> bserved Apnea (Has anyone observed that you stop breathing, or choke or gasp during your sleep?)	<input type="checkbox"/>	<input type="checkbox"/>
<b>H</b> igh Blood <b>P</b> ressure (Do you have or are you being treated for high blood pressure?)	<input type="checkbox"/>	<input type="checkbox"/>
<b>B</b> MI (Is your body mass index more than 35 kg per m <sup>2</sup> ?)	<input type="checkbox"/>	<input type="checkbox"/>
<b>A</b> ge (Are you older than 50 years?)	<input type="checkbox"/>	<input type="checkbox"/>
<b>N</b> eck Circumference (Is your neck circumference greater than 40 cm [15.75 inches]?)	<input type="checkbox"/>	<input type="checkbox"/>
<b>G</b> ender (Are you male?)	<input type="checkbox"/>	<input type="checkbox"/>

Score 1 point for each positive response.

Scoring interpretation: 0 to 2 = low risk, 3 or 4 = intermediate risk,  $\geq 5$  = high risk.

# Hypothyroidism: fatigue and...

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Weight gain

Edema

Dry skin

Goiter

Family history

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Finding	Sensitivity	Specificity	LR+	LR-
Cool and dry skin	16	97	4.7	0.9
Coarse skin	29-61	74-95	3.4	0.7
Periorbital puffiness	53-91	21-81	NS	0.6
Puffiness of wrists	39	86	2.9	0.7
Hair loss of eyebrows	29	85	1.9	NS
Pretibial edema	78	31	NS	NS
Hypothyroid speech	37	93	5.4	0.7
Slow pulse rate	29-43	89-98	4.2	0.7
Enlarged thyroid	46	84	2.8	0.6
Delayed ankle reflexes	48	86	3.4	0.6
Slow movements	87	13	NS	NS

# Cardiac disease: fatigue and...

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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

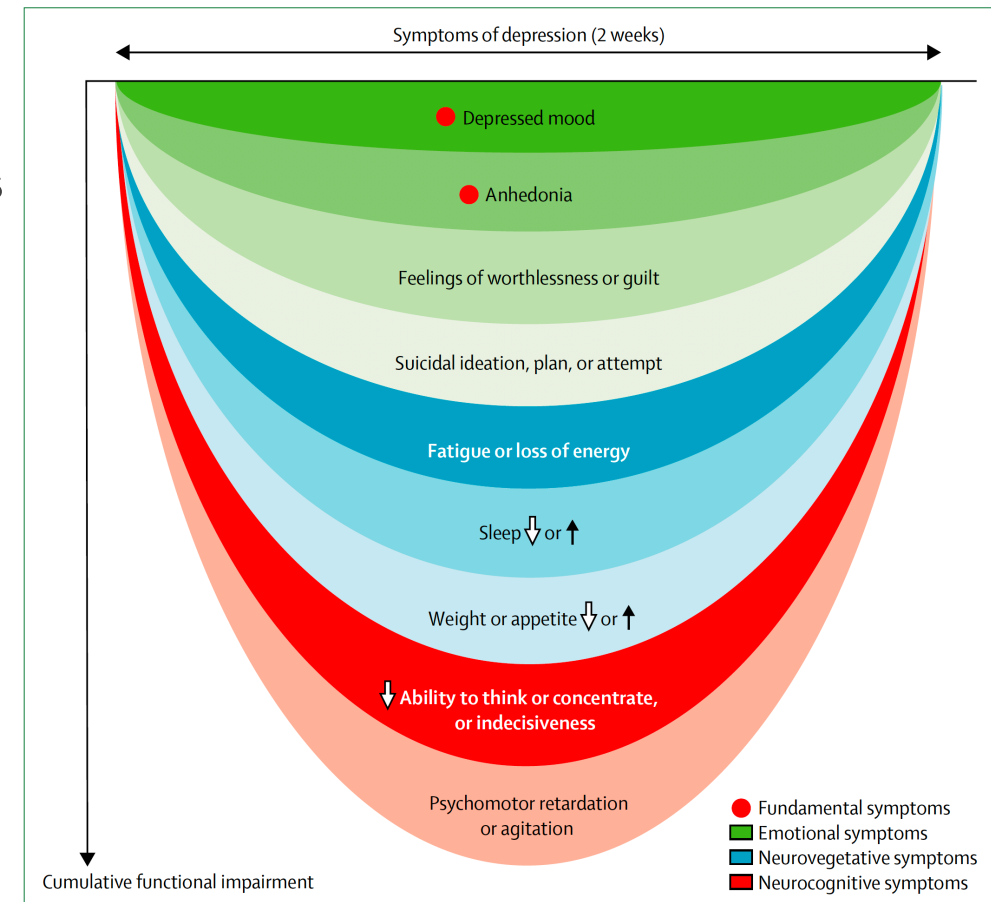
# Depression: fatigue and...

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 <u>last 2 weeks</u> , how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
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	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

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?

Not difficult  
at all  
☐

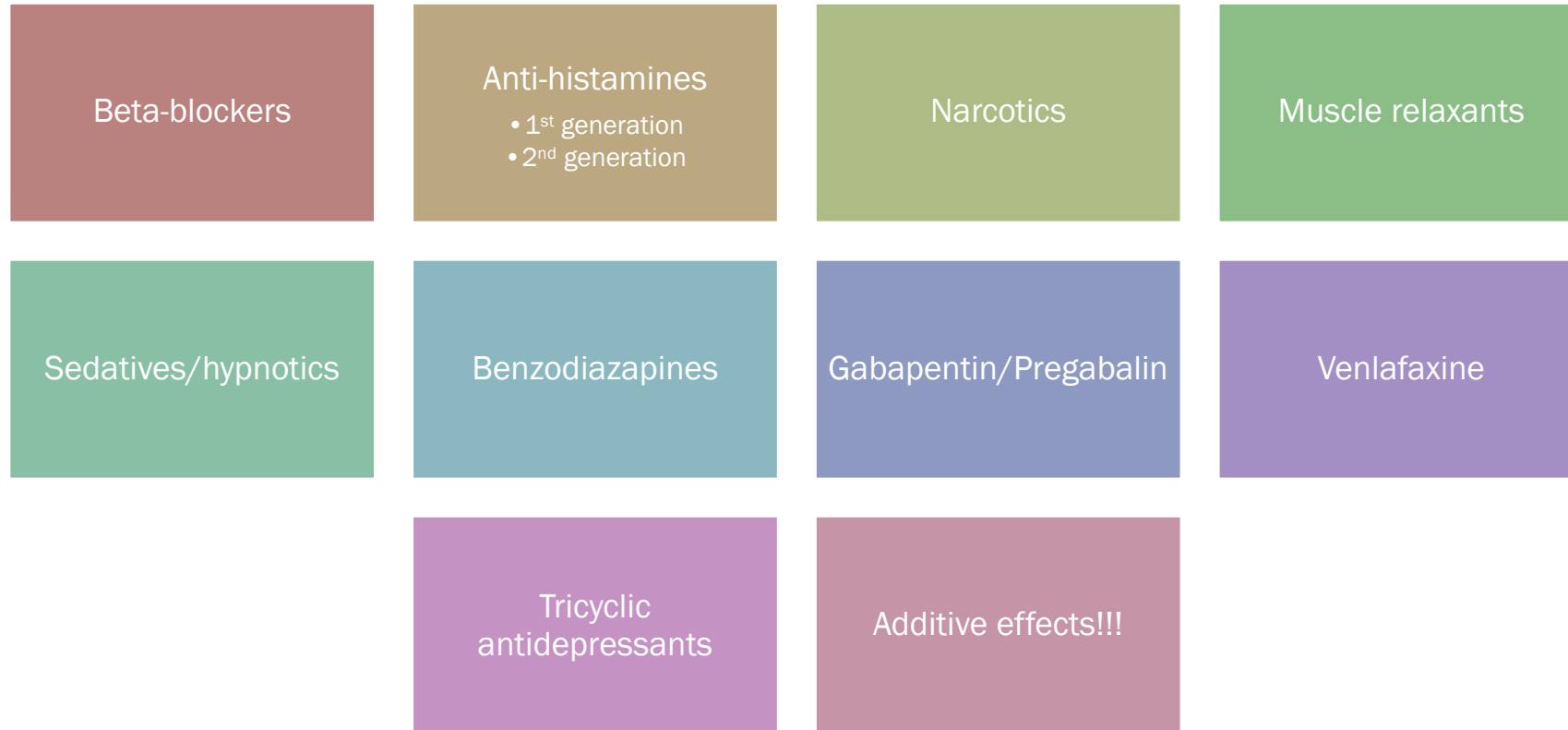
Somewhat  
difficult  
☐

Very  
difficult  
☐

Extremely  
difficult  
☐

# Medications as a cause of fatigue

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# Supplements as a cause of fatigue

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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?

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> [Am J Med Sci](#), 299 (5), 313-8 May 1990

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

[T J Lane](#)<sup>1</sup>, [D A Matthews](#), [P Manu](#)

Affiliations + expand

PMID: 2337122 DOI: [10.1097/00000441-199005000-00005](#)

### 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?

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> [Fam Pract](#), 6 (4), 286-91

Dec 1989

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

[A Valdini](#)<sup>1</sup>, [S Steinhardt](#), [E Feldman](#)

Affiliations + expand

PMID: 2632306 DOI: [10.1093/fampra/6.4.286](#)

### 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 psychoticism. 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

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

# Consider no-cost interventions

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PHQ-9 Questionnaire

STOP-Bang Questionnaire

# Other considerations

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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

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## CRP

mild elevations of CRP are common

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significant elevations are consistent with bacterial infections

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drops quickly once treated

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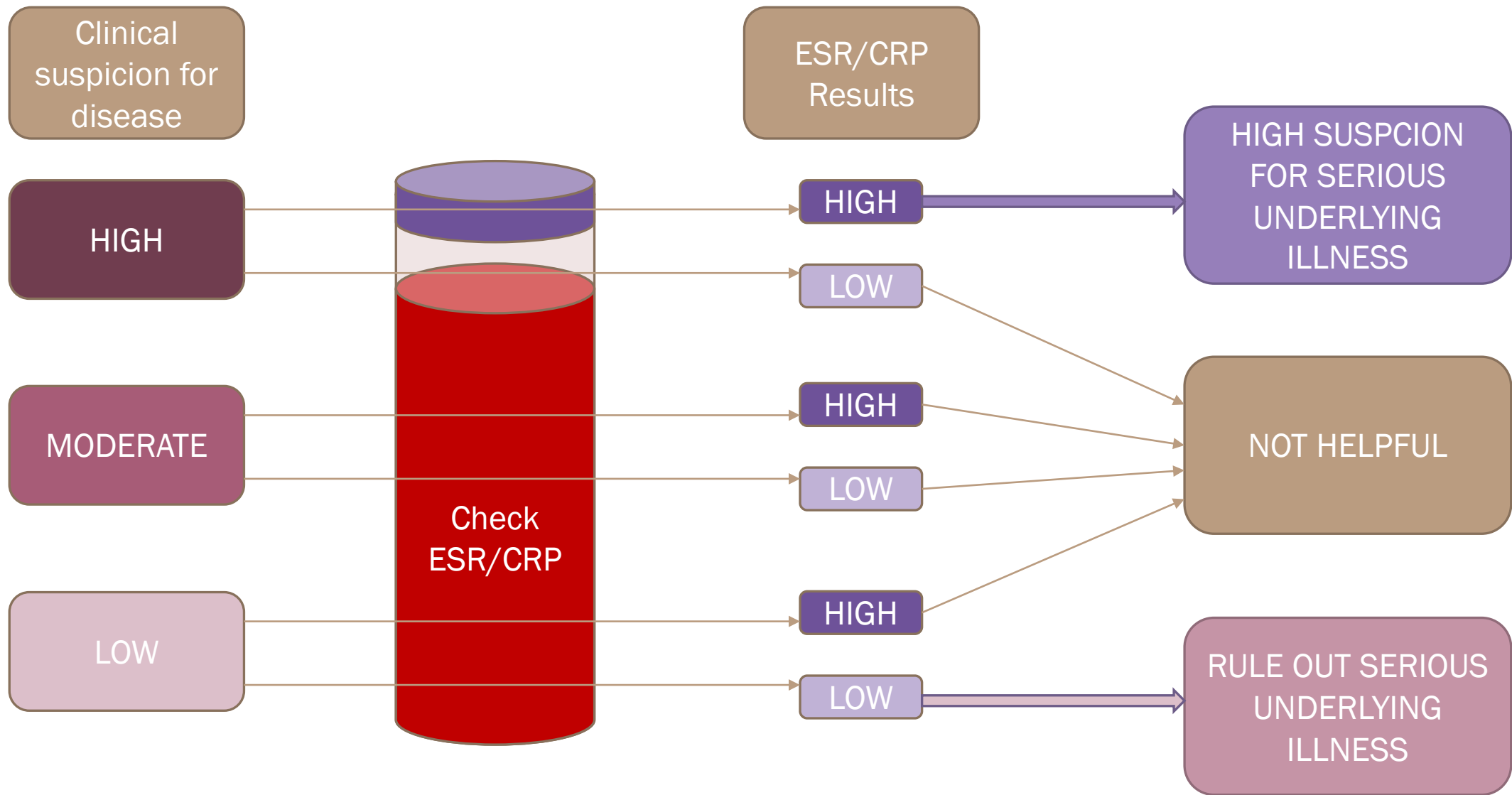
## ESR

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

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can take weeks to return to normal

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# Vitamin D

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

## 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

Stabler SP, Allen RH, Savage DG, Lindenbaum J. Clinical spectrum and diagnosis of cobalamin deficiency. *Blood*. 1990;76(5):871-881.

Lindenbaum J, Heaton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med*. 1988;318(26):1720-1728

# 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

# EBV Titers

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.

# Rheumatologic Testing

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 Testing

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

Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. *Eur J Gastroenterol Hepatol*. 2003;15(4):407-413.

Skowera A, Peakman M, Cleare A, Davies E, Deale A, Wessely S. High prevalence of serum markers of coeliac disease in patients with chronic fatigue syndrome. *J Clin Pathol*. 2001;54(4):335-336.

Skjellerudsveen BM, Omdal R, Grimstad T. Fatigue in celiac disease: A review of the literature. *JGH Open*. 2019;3(3):242-248.

# 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

# Lyme Titers

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

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Vitamin D

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Vitamin B12

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T3, T4

---

Lyme testing

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EBV Titers

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Celiac panel

---

Rheumatologic testing

What if no  
cause is  
found?

# Does diet matter?

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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?

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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?

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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?

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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