

Continuing Medical Education

Fatigue as the Chief Complaint

Epidemiology, Causes, Diagnosis, and Treatment

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Summary

Background: Fatigue is a main or secondary reason for 10–20% of all consultations with a primary care physician.

Methods: This review is based on pertinent publications retrieved by a comprehensive, selective literature search on the epidemiology, etiology, and diagnostic evaluation of fatigue as a leading symptom of disease, as well as on the treatment of its common causes. Information was also included from the literature search we conducted for the German clinical practice guideline on fatigue that was issued by the German College of General Practitioners and Family Physicians (*Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin, DEGAM*).

Results: Fatigue can be due to any of a broad spectrum of diseases, including decompensation of already known conditions. Sleep disorders and sleep-related disorders of breathing, depression (18.5%), and excessive psychosocial stress are the most common causes of persistent fatigue. Previously undiagnosed cancer is a rare cause, accounting for only 0.6% of cases (95% confidence interval [0.3; 1.3]). Anemia and other organic causes are rare as well (4.3% [2.7; 6.7]). Investigations beyond the history, physical examination, and simple laboratory tests are needed only in the presence of additional symptoms or findings. If the diagnosis remains unclear, watchful waiting and regularly scheduled follow-up help prevent an excessive focus on somatic causes, leading to overdiagnosis. Irrespective of specific causes, psychoeducative and psychotherapeutic approaches should be discussed with the patient, as well as an individually adapted exercise program.

Conclusion: The work-up of fatigue as a chief complaint should be guided by investigating common and/or potentially dangerous disorders. Since the latter are rare, an exclusively somatic focus should be avoided in order to prevent overdiagnosis.

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In 2018, a 27-year-old woman was employed by the Hamburg Consumer Advice Center to be a simulated patient with persistent fatigue, presenting herself to the primary care practices of 28 randomly chosen general practitioners and internists. The quality of history-taking, physical examination, diagnosis, counseling, and the physician-patient relationship in the initial patient interview was assessed on the basis of the S3 guideline for fatigue issued by the German College of General Practitioners and Family Physicians (*Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin, DEGAM*).

In the overall assessment, 14.3% of the physicians were judged as “very good,” but another 14.3% were “deficient.” 18%, 32%, and 21.4% were “good,” “satisfactory,” and “adequate,” respectively (1). Other studies, too, have shown that fatigue, a symp-

tom that patients commonly report, is among those that often cause diagnostic difficulties in routine clinical practice, and that physicians perceive as difficult (2–4).

Learning objectives

In view of the commonness of fatigue as a chief complaint, and the difficulties physicians face in its evaluation, this article is intended to help the reader do the following:

- learn a rational, evidence-based, somatic and psychosocial diagnostic and therapeutic approach to patients complaining of fatigue in primary care;
- know the common causes of fatigue as a chief complaint, its dangerous but treatable causes, and its rarer causes

Frequency

Fatigue is the main reason or a secondary reason for 10–20% of patient consultations in primary care.

Causes

A wide range of medical problems and decompensation processes of underlying diseases can cause fatigue. Sleep disorders, sleep-related respiratory disorders, depression, and psychosocial stress are the main causes of persistent fatigue.

- be able to apply the proper strategy of care for patients whose initial evaluation has not yielded any explanation for fatigue.

Methods

This CME article is based on a comprehensive selective literature search on the epidemiology, etiology, and diagnostic evaluation of fatigue as a chief complaint, as well as the treatment of its more common causes. The search was for publications from the years 2015 to 2019. In the Medline and Scopus databases, the searching terms “fatigue,” “tiredness,” “primary care,” “general practice,” “family medicine,” “Allgemeinmedizin,” and/or “Primaerarzt” were used; in the Cochrane Database of Systematic Reviews and the Cochrane Database of Clinical Trials, the searching terms were “fatigue” and “tiredness,” without any restriction to primary care. In the Current Content database, the search additionally included the tables of contents of German-language medical publications from the years 2015 to 2019. The comprehensive literature searches performed by the authors for the current edition of the German S3 guideline on fatigue (5) (searching period, up to July 2015) were also incorporated in this review, as were links to further publications.

Definition and types of fatigue

There is no uniform, generally accepted definition of fatigue. In one proposed definition of fatigue, it is described as a symptom that cannot be relieved by the usual strategies of restoring energy, and that impairs, to a variable degree, the individual’s ability to carry out his or her usual daily activities (6). These usual strategies include taking more time to rest and sleep, and reducing or eliminating potential sources of excessive stress. Patients describe fatigue as listlessness, lack of energy, exhaustion, tiredness, early fatigability, sleepiness, a tendency to fall asleep during the day, physical weakness, or a feeling of running on empty (7). Fatigue must be distinguished from muscle weakness, e.g., due to myopathy or a neurological disorder, and from daytime sleepiness, which already leads to the onset of sleep during normal everyday activities. Fatigue lasting longer than six months is called chronic fatigue.

Fatigue is associated with mental, physical, and occupational impairment (e1, e2) as well as with an elevated rate of accidents (e3, e4). Fatigue is subjectively the most bothersome symptom for approximately 60% of cancer patients (e5, e6). Sufferers may describe various qualitative components of fatigue:

emotional (loss of interest and motivation), cognitive (lessened mental activity and performance), behavioral (lessened productivity), and physical (e.g., muscle weakness).

Chronic fatigue syndrome (CFS), recently renamed “systemic exertion intolerance disease” (SEID), is a syndrome that has been defined in various ways, without any uniform etiology, and with varying diagnostic criteria. According to most definitions, it involves fatigue for at least 6 months and at least four to six accompanying symptoms, such as increased tiredness after exertion, sleep disturbance, muscle and joint pain, head and neck pain, cognitive impairment, orthostatic disturbances, and marked restriction of everyday activities not attributable to any other specific disease (e7, e8). Moreover, the symptoms tend to worsen with stress. The efficacy of exercise training and cognitive behavior therapy in patients with this syndrome is debated (8). Its prevalence in the population is less than 2% (9, 10), and less than 2% of patients seen in doctors’ practices complaining of fatigue have chronic fatigue syndrome (11). The diagnostic and therapeutic recommendations with regard to this syndrome require an independent discussion and will not be dealt with any further in this article.

Epidemiology

Because of variable study methods, figures on the prevalence of fatigue in European countries other than Germany vary from 22 to 38% (e9, e10, e11); in Germany, they vary from 20% to approximately 60%, depending on the study methods and the age group in question (e12, e13). In three representative cross-sectional studies of women and men aged 18-60 in western Germany, the prevalence of at least moderately severe fatigue was 37.3% in 1975, 20.1% in 1994, and 21.9% in 2013 (12). In 1995, 31% of persons over age 16 who participated in an Allensbach survey said that they sometimes, or often, suffered from fatigue (e14). The prevalence of fatigue rises with age, and women are generally more severely affected (13-15). Persons suffering from fatigue visit a physician when, from their own point of view, the disturbance cannot be adequately explained, the impairment due to fatigue no longer seems acceptable, or the individual’s compensatory strategies are no longer effective.

Estimates of the prevalence of fatigue among patients in primary care vary widely because of differences in the mode of data collection (active asking vs.

Effects

Fatigue is associated with emotional, physical, and occupational impairment and with an elevated rate of accidents. It is the most distressing symptom in approximately 60% of cancer patients.

Epidemiology

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patient-driven), the variable duration of fatigue required for inclusion in the statistics, and the heterogeneous definitions of fatigue itself. It can be concluded, however—despite the high variability among studies—that fatigue is the main reason for consulting a doctor in 2–8% of outpatient consultations. In other studies, the prevalence is as high as 10–20%, when fatigue as a main or secondary reason for the consultation is included in the statistics (16).

Diagnostic evaluation

Fatigue has a wide variety of potential biological, psychological, and social causes, and direct causality cannot always be clearly established. Interactions between these factors are important as well, as are the effects of treatment, the exhaustion of psychosocial compensatory strategies (taking more time to rest and sleep, eliminating potential stressors), and physical inactivity. The following aspects must be considered in the differential diagnosis:

Mental illness

Fatigue can arise in the setting of mental disturbances, above all depression, anxiety disorders, functional somatic conditions such as irritable bowel syndrome and fibromyalgia, and psychosocial stress. Approximately 75% of patients with depression (17) and somatoform disorders (18) suffer from fatigue. Socio-economic factors such as low income, low educational level, and occupational stress play a role as well (19).

Cancer

Fatigue is present, and often very distressing, in 65% of cancer patients (20), nearly all of whom have other clinical evidence of their underlying malignancy (e15). If a patient complains of fatigue without any further clinical evidence of cancer, then an underlying malignancy is a very unlikely cause; in our opinion, there is no indication for a diffuse diagnostic search for such a condition (5, 11, e16).

Anemia, iron deficiency

There is only a weak association between low hemoglobin concentrations and fatigue. Reportedly, iron administration can lessen fatigue in premenopausal women who have a ferritin value below 20 µg/mL and a low normal hemoglobin concentration. However, a Cochrane Review led to no clear conclusions on which to base a recommendation (21).

Differential diagnostic considerations

Mental illness, cancer, anemia, iron deficiency, endocrine disorders, infections, liver diseases, chronic somatic diseases, sleep disorders, and sleep-related respiratory disorders.

Endocrine disorders

Overt thyroid dysfunction, diabetes mellitus, and the premenstrual syndrome can all cause fatigue. Nonetheless, thyroid hormone administration does not improve fatigue in patients with subclinical hypothyroidism whose TSH values are below 10 mIU/L (e17).

Infectious diseases and liver diseases

Viral respiratory infections, mononucleosis, *Giardia* infections (22, 23) and other infections (24) are important causes of fatigue. In patients with these conditions, further causative factors are usually present, including treatment side effects, sleep disturbances, anxiety, and depression, if the symptoms persist for many weeks (5). Long-term data are currently lacking with regard to fatigue as a chief complaint in the aftermath of COVID-19 infection, as are relevant studies in patients who had only mild to moderate COVID-19 symptoms and did not need to be hospitalized, as well as in asymptomatic, PCR-positive persons. Patients with hepatitis often suffer from fatigue, as do patients with other serious liver diseases, yet liver disease is a very rare cause of fatigue in patients who have no other evidence of such a disease in their history, physical examination, or laboratory findings.

Chronic somatic diseases

Fatigue is a very common and very distressing symptom of many chronic somatic diseases (5), including congestive heart failure, multiple sclerosis, Parkinson's disease, residual deficit of stroke, rheumatoid arthritis, sarcoidosis, cancer (many types), chronic renal insufficiency, postoperative states, and nycturia due to prostatic hyperplasia (e18). These diseases, if present, are nearly always known to be so, and they must be considered a likely cause of the patient's fatigue. Severe fatigue with exhaustion is a risk factor for coronary heart disease (25); in women, it can be a harbinger of myocardial infarction (e19).

Sleep disturbances and sleep-related respiratory disorders

26.5% of patients seen in general medical practices have primary insomnia as defined in the DSM-IV (impaired sleep of at least four weeks' duration, with significant social or functional impairment; not due to narcolepsy, a breathing-related or circadian rhythm sleep disorder, a parasomnia, or substance use or abuse) (26). Fatigue and sleep disturbances often have a common cause, such as depression, psychosocial stress, a painful condition, or a somatic disease. Chronic allergic

Frequency in primary care, as defined in the DSM-IV

26.5% of patients in general medical practices have primary insomnia as defined in the DSM-IV (impaired sleep for at least four weeks, with significant social or functional impairment; not due to narcolepsy, a breathing-related or circadian rhythm sleep disorder, a parasomnia, or substance use or abuse).

rinitis can also impair sleep and cause daytime fatigue by impairing nasal breathing (e20). Obstructive sleep apnea is associated with impaired wakefulness, tiredness, depression, accidents (27), and arterial hypertension.

Drugs and psychotropic substances

The ingestion of drugs and/or psychotropic substances may be related to a chief complaint of fatigue. Causative agents include antidepressants and anti-histamines, benzodiazepines, antipsychotic drugs, antihypertensive drugs, opiates, antiparkinsonian drugs, interferon, antiviral drugs, cytostatic drugs, and substance abuse disorders, particularly alcoholism (e21).

Environmental influences

Types of environmental influence that have been discussed as possible causes of fatigue, though nearly always without adequate evidence (28), include hydrocarbon compounds, amalgam, sick building syndrome (SBS), multiple chemical sensitivity, and electromagnetic hypersensitivity syndrome. There is, at most, a vague correlation between amalgam and fatigue among persons providing dental care (e22). Studies on SBS provide no data on fatigue in control groups, and potential confounders such as workplace dissatisfaction are difficult to evaluate (e23). Studies of electromagnetic hypersensitivity syndrome are impaired by flawed methods, nocebo effects, and other illnesses in the study subjects (e24).

Other causes

Abdominal surgery in particular can lead to fatigue lasting for weeks or months, presumably by multiple mechanisms (e25). Hydrocarbon poisoning caused 648 deaths in Germany in 2015; milder, nonlethal intoxication can cause fatigue, among other manifestations (e26). The relation between celiac disease and fatigue is unclear. A diagnostic evaluation for celiac disease is indicated only if further manifestations are present (abdominal discomfort, anemia, altered liver function tests). Lack of exercise is a reputed cause of fatigue (15), but it remains unclear how often it is truly the main cause.

The diseases listed in *Table 1*, most of which have other symptoms, have been linked to fatigue, but their rare occurrence as a cause of fatigue in the primary care setting has not been studied systematically. They should only be considered in case of concrete suspicion; the evaluation not a differential-diagnostic

TABLE 1

Rare causes of fatigue (usually accompanied by other symptoms) (5)

Type of disease	Rare causes of fatigue
Endocrine	<ul style="list-style-type: none"> • Addison's disease (e27) • Conn syndrome/Cushing syndrome (e28) • pituitary deficiency (e29)
Metabolic	<ul style="list-style-type: none"> • Gilbert's disease • hypercalcemia (e30, e31)
Infectious	<ul style="list-style-type: none"> • tuberculosis • toxoplasmosis • brucellosis • malaria, other tropical diseases • AIDS, borreliosis/Lyme disease (e32)
Inflammatory	<ul style="list-style-type: none"> • systemic lupus erythematosus (e33)
Cardiac	<ul style="list-style-type: none"> • endocarditis
Neurological	<ul style="list-style-type: none"> • brain tumor (e34) • multiple sclerosis (e35) • prior head injury (e36)
Psychiatric	<ul style="list-style-type: none"> • schizophrenia (e37)

checklist to be worked through in patients with fatigue of undetermined cause. For further information, see the links in *eBox 1*.

The diagnostic approach

Fatigue can be considered the final common pathway of a multitude of biological, psychological, and social disturbances that are often not clearly distinguishable from one another. A biopsychosocial approach is, therefore, in order, and it should be borne in mind that, frequently, more than one mechanism is at work.

Patients seen in general medical practice with primarily unexplained fatigue have the following conditions in the following frequencies (means and 95% confidence intervals, from a systematic review) (11): anemia, 2.8% [1.6; 4.8]; cancer, 0.6% [0.3; 1.3]; serious somatic disease (including anemia and cancer, because the studies are highly variable in the clinical definitions and methods employed), 4.3% [2.7; 6.7]; depression, 18.5% [16.2; 21.0]. Further relevant conditions include sleep disturbances and sleep-related breathing disturbances, post-infectious states, and substance abuse, particularly alcohol abuse, as has been shown in other studies as well (29, e38).

The recommended basic test battery (*Table 2*) comprises, independently of the age of the patient: history-taking and physical examination focused on

Obstructive sleep apnea and rhinitis

Chronic allergic rhinitis can also impair sleep and cause daytime fatigue by impairing nasal breathing. Obstructive sleep apnea is associated with impaired wakefulness, tiredness, depression, accidents, and arterial hypertension.

The diagnostic approach

Fatigue can be considered the final common pathway of many biological, psychological, and social disturbances that are often not clearly distinguishable from one another. A biopsychosocial approach is, therefore, in order, and often more than one mechanism is at work.

TABLE 2

The basic diagnostic evaluation of fatigue (e41)*

History		
<ul style="list-style-type: none"> • symptom characteristics, differentiation from somnolence • associated complaints • fatigue new/unusual • impairment in everyday life • the patient's own conception of the cause and treatment of fatigue • symptoms of depression and anxiety 	<ul style="list-style-type: none"> • somatic history • sleep: duration, quality, changes from personal norm, (habitually) insufficient sleep • body weight, changes in weight • cardiac, respiratory, gastrointestinal, urogenital, and central nervous system function • drugs, psychotropic substances • post-infectious state, chronic disease 	<ul style="list-style-type: none"> • social, familial, occupational situations • exposure to chemicals or noise • similar symptoms in family members, friends, or coworkers • snoring, falling asleep at the wheel
Physical examination		
<ul style="list-style-type: none"> • depending on positive findings in the history 	<ul style="list-style-type: none"> • if the history does not arouse suspicion of any particular physical illness: abdomen, heart, circulation, airways, skin and mucous membranes, lymph nodes; muscle bulk, strength, and tone; proprioceptive reflexes 	
Laboratory testing		
<ul style="list-style-type: none"> • depending on positive findings in the history and physical examination 	<ul style="list-style-type: none"> • if there is no evidence of any particular physical illness: fasting blood sugar, complete blood count, erythrocyte sedimentation rate/CRP, transaminases/γ-GT, TSH (creatinine only if there is evidence of renal disease, or in the presence of risk factors such as hypertension, diabetes, nephrotoxic drugs) 	<ul style="list-style-type: none"> • further laboratory testing only if the history or physical examination arouses suspicion of a particular condition • ferritin measurement in premenopausal women with normal history, physical examination, and basic laboratory tests

*These recommendations are also given in the DEGAM guideline.

potential causes of fatigue, particularly sleep disturbances, major changes in body weight, dysfunction of the cardiac, respiratory, gastrointestinal, urogenital, and central nervous systems, intake of drugs and psychoactive substances, problems in the patient's social, familial, or occupational setting, chemical exposures or excessive exposure to noise, similar symptoms in family members or co-workers, snoring, falling asleep at the wheel, and (habitual) sleep deficit. Targeted laboratory testing should include blood sugar, complete blood count, erythrocyte sedimentation rate/CRP, transaminases or γ -GT, and TSH. The patient should also fill out a fatigue questionnaire, such as the one found in the accompanying information for patients in the DEGAM guideline on fatigue (e39). In particular, the question about the patient's own ideas about the cause of fatigue (e40) often yields plausible explanations and important information about the patient's expectations and fears, which the physician must know in order to establish effective communi-

cation with the patient. If the basic evaluation yields evidence of a specific illness, further testing is indicated. In premenopausal women whose basic evaluation is negative, the ferritin concentration should be measured as well.

Many patients presenting with fatigue as their chief complaint suffer from depression or anxiety disorders or have a history of infection. These conditions should be asked about specifically. Screening questions for current depression are: In the last four weeks, have you felt dejected, melancholic, or hopeless? Have you had less interest in, or enjoyment from, activities that you are ordinarily interested in or enjoy (e42)?

Analogous screening questions for anxiety disorders are: In the last four weeks, have you suffered from nervous tension / fearfulness / a feeling of being emotionally out of balance? Have you been worried about many different things, or suffered from anxiety attacks (e43)? Positive answers to any of these

Relevant sleep disorders

Relevant conditions include sleep disturbances and sleep-related breathing disturbances, post-infectious states, and substance abuse, particularly alcohol abuse, as has been shown in other studies as well.

Premenopausal women

In premenopausal women whose basic evaluation is negative, the ferritin concentration should be measured as well.

questions call for further evaluation, and, in depressed patients, the potential risk of suicide must be assessed.

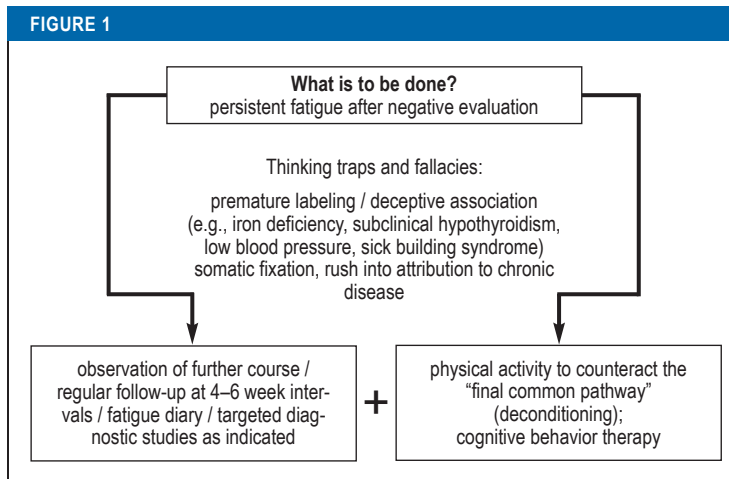
In patients with evidence of sleep disturbances, the following things should be determined: Does the patient have greater difficulty falling asleep, or a worse quality of sleep, than in the normal situation for him or her? Is sleep hygiene inadequate, does the patient have too little time to sleep, or is sleep prevented by situational factors (pain, psychosocial stress, noise, shiftwork)? The suspicion of a sleep-related respiratory disorder (SRRD) is aroused if the patient reports snoring, respiratory pauses in sleep observed by others, and falling asleep at the wheel of a car or any other manifestation of unavoidable, involuntary falling asleep in the daytime. If the patient also has a high STOP-BANG score (number of items from a list of eight: snoring, tiredness, observed apnea, high blood pressure or body-mass index [BMI], age, neck circumference, and gender) (e44), or a high score on the somewhat more practical and probably equally useful GOAL questionnaire (which has only four items: male gender, obesity with a BMI ≥ 30 , age ≥ 50 years, loud snoring) (30), evaluation by a specialist in sleep medicine is indicated. A STOP-BANG score of 0–2 implies a low probability of moderate to severe obstructive sleep apnea, while a score of 5–8 implies a high probability. In the intermediate range (3–4 points), further criteria are needed. A GOAL score of 2 or above implies a high probability of sleep apnea.

The history and physical examination enable classification into the following three categories (Figure 1):

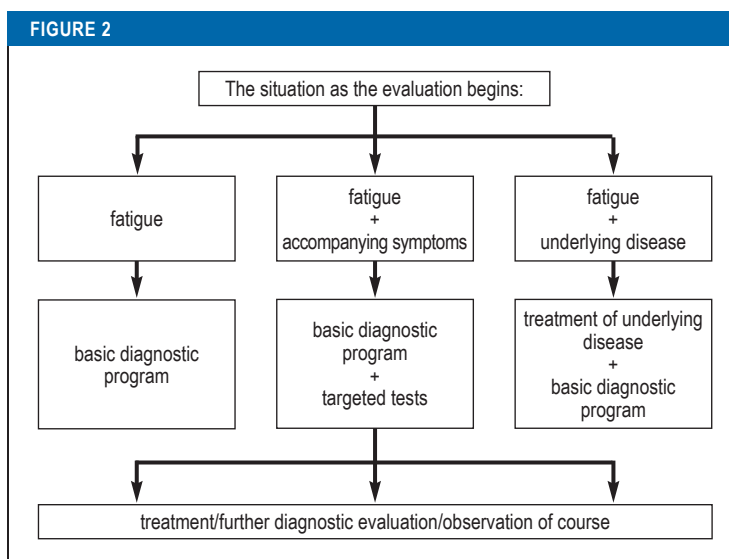
- Fatigue as the chief complaint without any known underlying illness or relevant accompanying manifestations. The history and physical examination should be complemented by a basic laboratory test battery and a patient questionnaire.
- Fatigue with the simultaneous presence of further manifestations requiring evaluation. Targeted additional studies are indicated.
- Fatigue in the known presence of an underlying disease that might be the reason for fatigue. In addition to the evaluation and treatment of the underlying disease, the basic evaluation program outlined in Table 2 should be used to investigate a potential fatigue-inducing second illness, or the patient's inability to compensate for the known underlying illness. If drug-induced fatigue is suspected, the drug in question can be switched to another agent after an individualized risk-benefit

Sleep-related respiratory disorder

The suspicion of a sleep-related respiratory disorder (SRRD) is aroused if the patient reports snoring, respiratory pauses in sleep observed by others, and falling asleep at the wheel of a car or any other manifestation of unavoidable, involuntary falling asleep in the daytime.



Thinking traps and fallacies about fatigue as the chief complaint



Diagnostic pathways for patients with fatigue as the chief complaint

assessment. Temporary reexposure to the original drug may be helpful to confirm the diagnosis.

If the cause of fatigue remains unknown after initial laboratory testing and (possibly) further technical studies, the strategy from then on is one of expectant observation, with regular follow-up every four to six weeks. A ferritin level should be measured in premenopausal women, but other additional laboratory tests

When to obtain a specialized sleep study

A high STOP-BANG score (snoring, tiredness, observed apnea, high blood pressure or BMI, age, neck circumference, and gender) or GOAL score (male gender, obesity with a BMI ≥ 30 , age ≥ 50 years, loud snoring) indicates that evaluation by a specialist in sleep medicine is indicated.

TABLE 3

The treatment of diseases that cause fatigue

Type of disease and treatment	Results, differences in effect strength ¹ [95% confidence intervals]
Anxiety, generalized	
SSRI and SNRI (e48, 37)	As first-line therapy, vs. placebo: SSRI: g = 0.33 (limits: 0.26–0.39), SNRI: g = 0.36 (limits: 0.29–0.42) (e49); Pp d: SSRI: 3.48 [3.18; 3.78], SNRI: 2.47 [2.09; 2.84] (e50)
CBT (e51, 37)	Strong effect compared to waiting list: d = 1.23 [1.02; 1.45], weak to moderate effect compared to routine treatment and placebo: d = 0.57 [0.20; 0.94] (effect strengths of individual CBT pooled over all anxiety disorders) (e50)
Panic disorder	
CBT and psychodynamic therapy (e52, 37)	Best long-term treatment outcome of all psychological therapies. Pp individual CBT: d = 1.24 [1.10; 1.39]; Pp psychodynamic therapy: d = 0.97 [0.58; 1.36] (e50)
Depression	
Antidepressants (38)	More effective than placebo against major depression: odds ratios of 21 antidepressants vs. placebo range from 1.37 [1.16; 1.63] to 2.13 [1.89; 2.41] (e53)
Exercise therapy (38)	Only moderate effect: SMD compared to no treatment –0.62 [–0.81; –0.42], no significant effect in high-quality studies: –0.18 [–0.47; 0.11] (e54)
Behavior therapy (38)	Similar efficacy to other forms of psychotherapy: response rate of BT vs. all other forms of psychotherapy: risk reduction 0.97 [0.86; 1.09] (e55)
Insomnia	
Antidepressants (39)	Doxepin pooled with imipramine vs. placebo, for improved sleep quality: SMD –0.39 [–0.56; –0.21] (e56)
Antihistamines (39)	Inadequate evidence
Antipsychotic drugs (39)	Inadequate evidence
Benzodiazepines and benzodiazepine receptor agonists (39) ²	Improvement of sleep parameters: benzodiazepines: g for TST: 0.64 [0.12; 1.16], for SOL: –0.76 [–1.28; –0.24] benzodiazepine receptor agonists: g for TST: 0.52 [0.33; 0.71], for SOL: –0.46 [–0.61; –0.31] (e57)
Melatonin (39)	Generally not recommended because of low efficacy
Phytotherapeutic drugs (39)	No improvement to moderate improvement of sleep quality
CBT (39) ³	CBT is recommended as the first line of treatment for adults of any age. CBT vs. placebo: Hedges' g: 1.07 [0.10; 2.05] (e58)
Chronic obstructive pulmonary disease (COPD)	
Complex rehabilitation (exercise training and psychological counseling) after a COPD exacerbation (e59)	Good evidence for improvement of fatigue-related quality of life Fatigue domain: mean difference 0.81 [0.16; 1.45] (e60)
Congestive heart failure	
Exercise training (e61, e62)	Questionable improvement of quality of life
Behavior therapy (relaxation, meditation, and guided imagery) (e63, e64)	Potential benefit with regard to quality of life
Neurological diseases (residual deficit after stroke, multiple sclerosis, Parkinson's disease, other)	
Exercise training (e65, e66)	May lessen fatigue
CBT (e65, e66)	May lessen fatigue
Pharmacotherapy (e65, e66)	Individual decision in the absence of convincing evidence
Somatiform disorders	
Newer-generation antidepressants (30)	Compared to placebo (with very low study quality) moderately effective against somatic symptoms (SMD –0.91, [–1.36; –0.46]), anxiety (SMD –0.88, [–1.81; 0.05]), depression (SMD –0.56, [–0.88; –0.25]) (e67) ⁴
Cancer	
Exercise training (40)	Moderate improvement of CRF: mean weighted effect size (WES) = 0.30 [0.25; 0.36] (e68)
CBT (40)	Moderate improvement of CRF: mean weighted effect size (WES) = 0.37 [0.28; 0.47] (e68)
Psychological interventions overall (40)	Moderate improvement of CRF: mean weighted effect size (WES) = 0.27 [0.21; 0.33] (e68)
Pharmacotherapy (40)	Very little improvement of CRF: mean weighted effect size (WES) = 0.09 [0.00; 0.19] (e68)

BT, behavior therapy; CRF, cancer-related fatigue; CBT, cognitive behavior therapy; d, Cohen's d; g, Hedges' g; SMD, standardized mean difference; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor; TST, total sleep time; SOL, sleep onset latency; WES, weighted effect size; Pp, pre-post

¹ In general, effect strengths (Cohen's d, Hedges' g) of > 0.2 are considered weak, > 0.5 as moderate, and > 0.8 as strong. The effect strengths presented here for COPD, neurological diseases and cancer are with respect to fatigue as a symptom of these conditions; the strengths presented for the other diseases are with respect to the overall disease process.

² This can be offered if CBT is insufficiently effective or not feasible. Beware of the risk of tolerance and dependence, no information on daytime fatigue

³ Risk of daytime fatigue and somnolence in sleep restriction therapy

⁴ The potential benefit must be weighed against the risk of side effects.

or ancillary studies further on in the patient's course are indicated only if there are positive findings or specific clinical evidence. The risk of an underlying illness in an early stage is not completely ruled out, but is thought to be no higher in such patients than in the population at large (11, 29, e16), and the low diagnostic yield must be weighed against the stress and risk of diffuse, untargeted diagnostic testing. Current evidence suggests that such testing does not, in general, improve patient outcomes. Rather, it elevates the risk of false-positive findings, overdiagnosis, which can derail the proper care of the patient. The risk of the patient's focusing or fixating on a putative somatic disease as the cause of fatigue (e45, 31) is also increased if prolonged diagnostic efforts are made—perhaps lasting several weeks—to rule out somatic causes, while psychological matters are not discussed at all. Dreiholz describes somatic fixation as “a cyclic process in which all the patient's symptoms, signs, problems, and illnesses are considered purely somatic processes by the patient and/or the primary care physician, while the psychosocial aspects of the symptoms or illnesses are overlooked and disregarded, whether consciously or not” (e46) (Figure 2).

A further risk is that irrelevant changes will be assigned too much importance and labeled the cause of fatigue. Deceptive associations of this kind are most likely in patients who suffer from a known underlying disease, manifest isolated laboratory changes such as mild iron deficiency or subclinical hypothyroidism, or are subject to dubious environmental influences. Conversely, the overall clinical picture must always be borne in mind so that a relevant disease will not be overlooked in the presence of only mild laboratory abnormalities.

Treatment and management

Disease-specific treatment should be given if such a treatment is possible and indicated, and its effect on fatigue should be documented: for example, antidepressant therapy and the treatment of anemia, heart failure, diabetes mellitus, neurological diseases, sleep disturbances, and pain. If fatigue remains unexplained, or if there is evidence of relevant psychosocial stress, the clinical approach should be one of expectant observation for somatic and psychological causes, with regular follow-up at four- to six-week intervals, as appropriate for the individual patient. The physician should counsel the patient empathetically and communicate openly, so that the patient can be

motivated to change his or her behavior in order to modify unmanageable (or, in some cases, insufficient) physical and psychosocial challenges. Problem-oriented cognitive behavior therapy is useful in some cases as well. Keeping a symptom diary can be useful (32) as a basis for discussions about symptoms, impairments, and the associated feelings and conceptions. This therapeutic approach accords with the recommendations of the DEGAM guideline on fatigue cited above; the corresponding evidence levels and recommendation strengths can be found in the guideline.

Psychoeducative measures to inform the patient about the disease process and the appropriate way of dealing with it by assuming personal responsibility, thus strengthening patient resources (e47), with the aid of accompanying materials (e39), are useful for dealing with excessive (or insufficient) challenges in everyday life, as well as for patients with sleep disturbances or cancer (33). For patients with many different types of underlying condition or disease, behavior therapy (34) or symptom-oriented activating measures lessen fatigue and improve overall well-being (35, 36). An appropriately adapted program of physical activation lessens fatigue and counteracts physical deconditioning (Table 3), as discussed in the Case Illustration (eBox 2).

Overview

The common causes of fatigue include the following, some of which are both preventable and dangerous: psychosocial problems, depression, anxiety disorders, sleep disorders, and sleep-related respiratory disorders. Patients with an unremarkable history, physical examination, and basic laboratory test battery are highly unlikely to be suffering from anemia, cancer, thyroid dysfunction, or other somatic diseases as the cause of their fatigue.

Aspects that must be considered include known underlying illnesses, drug and substance intake, and health risks. Additional diagnostic studies should only be performed in case of well-founded clinical suspicion. The etiology, course, and optimal treatment of chronic fatigue syndrome are still unclear.

The further management of patients with fatigue as their main symptom is characterized by causally directed as well as symptomatic treatment, empathetic patient counseling, expectant observation, and regularly scheduled follow-up.

Laboratory tests

Patients whose initial laboratory tests and ancillary studies do not reveal the cause of their fatigue are treated with a watchful waiting strategy, with follow-up every four to six weeks.

Psychoeducation

Psychoeducative measures to inform the patient about the disease process and how to deal with it by assuming personal responsibility, thus strengthening patient resources, are useful for dealing with excessive (or insufficient) challenges in everyday life.

Conflict of interest statement

Prof. Donner-Banzhof has a personal relationship with GSK.

The other authors state that they have no conflict of interest.

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► **Supplementary material**

eReferences, eBoxes:
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Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

You decide how to plan your continuing medical education on the basis of the frequency and dangerousness of the reasons your patients come to see you. In your primary care practice, you have approximately 50 direct physician-patient contacts every day.

How many times a day, on average, will you see a patient with fatigue/exhaustion as their chief complaint?

- a) zero to one time; b) one to four times;
- c) seven times; d) ten times;
- e) fifteen times

Question 2

A previously healthy 26-year-old woman studying physical education is working toward the completion of her thesis and expects to be taking her practical and oral final examinations ten weeks from now. She reports having suffered from exhaustion of progressive severity over the past six weeks. In your physical examination, you note very pale conjunctivae.

What serum laboratory test should be obtained in addition to the basic laboratory test battery?

- a) aldosterone; b) cortisol
- c) ferritin; d) LDL cholesterol
- e) tetrahydrocannabinol

Question 3

Mr. F., a 22-year-old bank employee who lost his father in a fatal automobile accident six months ago, reports having suffered from marked fatigue and lack of energy for the past four months. You suspect depression as the main cause.

Which of the following, if the patient states he has suffered from it for several weeks, would tend to confirm your preliminary diagnosis?

- a) marked anxiety
- b) lack of enjoyment
- c) elevated sense of his own worth
- d) altered senses of taste and smell
- e) nervous tension

Question 4

You are pursuing the differential diagnosis of fatigue in your patient Mr. K., a very obese 65-year-old man.

Which of the following is highly consistent with a sleep-related respiratory disorder?

- a) symptom duration more than three months
- b) symptom duration more than six months
- c) falling asleep during everyday activities
- d) high stress on the job
- e) a markedly elevated TSH level

Question 5

Mr. O., a 44-year-old warehouse worker, consults you because of severe fatigue. You suspect obstructive sleep apnea as the cause.

Which of the following symptoms or findings is most consistent with your suspicion?

- a) diminished breathing sounds in sleep
- b) observed respiratory pauses during sleep
- c) a BMI value below 25
- d) a trend to low blood pressure
- e) nycturia at least twice per night

Question 6

Patients with somatic diseases may suffer from fatigue as a direct result of their underlying condition, or else by way of dysfunctional emotional adaptation processes or treatment side effects.

Approximately 65% of patients with which of the following diseases suffer from fatigue and exhaustion?

- a) low blood pressure; b) urinary urge incontinence;
- c) hyperthyroidism; d) cancer;
- e) celiac disease

Question 7

You have not been able to find the cause of longstanding fatigue in your patient Ms. K., a 38-year-old single mother, despite comprehensive history-taking, physical examination, basic laboratory testing, and the use of a patient questionnaire.

Which of the following is a reasonable next step?

- a) measurement of borreliosis antibodies
- b) having the patient keep a symptom diary and following up regularly
- c) laboratory testing for environmental toxins
- d) test administration of levothyroxine
- e) biplanar chest x-ray

Question 8

Ms. S., a 43-year-old kindergarten teacher, complains of fatigue over the past two months, impairing her everyday activities. There is no known underlying disease, and the history and physical examination reveal no evidence of any somatic condition.

Which of the following laboratory tests is a component of the recommended basic battery?

- a) test for borreliosis; b) purine level
- c) melatonin level; d) TSH value
- e) vitamin D level

Question 9

Mr. N. is a 34-year-old software developer who has been suffering from fatigue for four months. You have conducted a diagnostic evaluation according to the basic evaluation program and have come to the conclusion that he has an anxiety disorder.

Which of the following treatments would be appropriate for him?

- a) analytically oriented psychotherapy
- b) trial therapy with methylphenidate
- c) cognitive behavior therapy
- d) having the patient spend 1 hour longer in bed each night
- e) ordering a beta-mimetic drug p.r.n.

Question 10

Long-lasting fatigue carries the risk of physical deconditioning. What measure do you order to prevent this?

- a) anaerobic interval training three times a week
- b) trace element and dietary supplement administration
- c) an individualized physical activation program
- d) the injection of a cortisone depot preparation once every four weeks
- e) 45-minute rest periods around noon every weekday

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Supplementary material to:

Fatigue as the Chief Complaint

Epidemiology, Causes, Diagnosis, and Treatment

by Peter Maisel, Erika Baum, and Norbert Donner-Banzhoff

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eBOX 1

Internet addresses (last checked on 20 February 2021)

- **Patient history questionnaires:**
[www.degam.de/files/Inhalte/Leitlinien-Inhalte/Dokumente/DEGAM-S3-Leitlinien/053-002_Leitlinie%20Muedigkeit/Zusatzmodule%20Beratung%20\(Aerzte\)_2011/053-002z_-Anamnesefragebogen_22-1-2018.pdf](http://www.degam.de/files/Inhalte/Leitlinien-Inhalte/Dokumente/DEGAM-S3-Leitlinien/053-002_Leitlinie%20Muedigkeit/Zusatzmodule%20Beratung%20(Aerzte)_2011/053-002z_-Anamnesefragebogen_22-1-2018.pdf)
- **DEGAM guideline on fatigue:**
www.awmf.org/uploads/tx_szleitlinien/053-002l_S3_Muedigkeit_2018-06.pdf
- **Family practice notebook:**
www.fpnotebook.com/fpnmvccore/searchBs2013?qu=fatigue
- **Patient information:**
www.degam.de/zusatz_m%C3%BCdigkeit.html
- **Patient information on exercise training (“Bring your life back into swing”):**
www.degam.de/files/Inhalte/Leitlinien-Inhalte/Dokumente/DEGAM-S3-Leitlinien/053-024_Risikoberatung%20kardiovaskul.%20Praevention/053-024PI_Bewegung_A4.pdf
- **Progressive muscle relaxation (the Jacobson technique):**
 Instructions with or without music: www.tk.de/techniker/magazin/life-balance/aktiv-entspannen/progressive-muskelentspannung-zum-download-2021142
- **Cancer-associated fatigue:**
www.esmo.org/guidelines/supportive-and-palliative-care/cancer-related-fatigue
- **Extensive patient information, advice, and further health information from the IQWiG:**
www.gesundheitsinformation.de
- **Free medical and scientific search engines and databases:**
 searching terms: fatigue, tiredness, Müdigkeit (automatic translation):
 Cochrane Library: www.cochranelibrary.com
 Epistemonikos: www.epistemonikos.org
 Google-Scholar: www.scholar.google.de
 Livivo: www.livivo.de/app?LANGUAGE=de
 PubMed: www.pubmed.ncbi.nlm.nih.gov
 Tripdatabase: www.tripdatabase.com

eBOX 2

Case Illustration

Mr. F., a 32-year-old barber, complains to his family physician of fatigue and exhaustion of approximately ten weeks' duration. He states that he no longer even wants to go jogging, despite having been an enthusiastic endurance athlete until now. He has hardly ever been ill before, except for minor injuries. He is experiencing considerable stress at the moment, as he will soon be taking an examination for an important professional qualification that will enable him to set up his own barber shop. His history is otherwise positive only for difficulty falling asleep at night. In response to screening questions about anxiety and depression, he reports having suffered from nervous tension in the past four weeks, but no further symptoms. On physical examination, his blood pressure is 118/76 mmHg, height 188 cm, weight 78 kg. The skin, mucous membranes, heart, lungs, abdomen, renal beds, limbs, and basic neurological examination are normal. In the DEGAM patient questionnaire on fatigue, Mr. F. notes that his symptoms are associated with the above-mentioned stresses in his everyday life. Laboratory findings: hemoglobin 14.2 g%, normal complete blood count, ESR 7/14 mm, TSH 2.3 mU/L, ALT 18 U/L, γ GT 20 U/L, fasting blood sugar 96 mg%. Assessment and plan: Discussing the findings, the physician and the patient agree that his fatigue and exhaustion are probably due to the stress of his upcoming professional examination and his plan to go into business for himself in the near future. There is no evidence of any serious somatic or psychological disorder. They determine that Mr. F. will seek help with business planning from the Chamber of Industry and Commerce and resume jogging in order to reduce stress and keep fit. He also obtains a CD from his health insurance company with audio instructions on the Jacobson technique of progressive muscle relaxation. He is told to contact the physician in four weeks to report back on his condition, or at any time until then in case any warning symptoms or signs should arise.