SUMMARY

Background: Many cancer patients suffer from cancer-related fatigue (CRF) both during and after their treatment. CRF can arise at any point in the course of the disease and can be either self-limited or persistent, sometimes for years. It gives rise to a vicious circle of impaired physical performance, avoidance of exertion, inactivity, inadequate physical recovery, helplessness, and depressed mood. Its hallmarks are tiredness, exhaustion, and lack of energy; it can impair performance so severely that the patient is unable to work. It is associated with increased mortality. Cancer patients are hardly ever systematically asked about the symptoms and signs of CRF. The stress and impairments that it produces are often inadequately appreciated, and the opportunities for treatment often neglected.

Method: Selective review of the pertinent literature, including published guidelines from Germany and abroad.

Results: The pathogenesis of CRF is complex, involving an interaction of somatic, emotional, cognitive, and psychosocial factors, with a highly variable pattern of clinical expression. Clinical history-taking plays a key role in diagnostic assessment. Depressive disorders must be considered in the differential diagnosis. Many randomized trials and meta-analyses have documented the efficacy of pharmacological and non-pharmacological treatments for CRF.

Conclusion: Cancer-related fatigue is a serious problem that impairs patients physically, mentally, and socially. Physicians need to know how to recognize and treat it.

► Cite this as:

A wide variety of complex diagnostic and therapeutic techniques that have arisen through advances in modern oncology now enable more frequent cures, or at least longer survival and a better quality of life, for patients with cancer. Unfortunately, however, for many patients this also means that they will have to endure arduous treatment regimens, and in addition may suffer long term sequelae subsequent to their illness and its treatment.

Fatigue, lack of energy, exhaustion, and impaired physical performance are among the most common symptoms in cancer patients and can have severe physical, emotional, and social effects. The syndrome of fatigue and exhaustion in cancer patients is commonly described as “cancer-related fatigue” (CRF) by oncologists around the world (1).

Learning objectives
In this article, we discuss the following aspects of CRF:
- clinical features,
- epidemiology,
- etiology and pathogenesis,
- diagnostic evaluation and differential diagnosis, and
- pharmacological and non-pharmacological treatments of CRF.

Methods
This article is based on a selective review of the pertinent literature (retrieved by searches in the Cochrane Library, Embase, and Medline), also taking account of the guidelines of the National Comprehensive Cancer Network (NCCN, [2]) and the German College of General Practitioners and Family Physicians (Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin [DEGAM], [3]), as well as a consensus statement of
The European Association for Palliative Care (EAPC, [4]).

Clinical features
The multifarious manifestations of CRF include feelings of exhaustion and lack of energy, loss of drive and personal interests, and impaired memory and concentration. The affected patients vary widely in their manner of expressing and describing the problems that they experience. Qualitative studies have shown that the clinical features are highly individual, and hardly any two patients are alike (5, e1). Typically, no clear relation exists between the symptoms and whatever activities immediately precede them; moreover, unlike normal fatigue and exhaustion, CRF often fails to improve, or does so only slightly, after rest or sleep (6). Many patients also suffer from pain, sleep disturbances, and emotional distress, including anxiety and depression (7–9) (Box 1).

Among all symptoms that tend to affect cancer patients in particular—e.g., pain, sleep disturbances, lack of appetite, or nausea—those of CRF are perceived as most distressing (e2, e3). CRF markedly impairs the quality of life and the physical performance ability of many of the affected patients (10, e3, e4).

Multiple prospective studies have shown an association of the manifestations of CRF with shorter survival and increased mortality (e5, e6). CRF can arise at any point in the course of the disease: It may be an early symptom even before the cancer is diagnosed, or it may arise during the treatment, long after the treatment is over, or when the disease recurs or progresses. Its symptoms may be temporary, but they may also persist, remaining present in some cases for years after the end of treatment (e7). The worse the symptoms of CRF are during the treatment phase (chemotherapy and/or radiotherapy), the more likely they are to persist or recur once the treatment is over (e8).

Effects
Depending on the course and severity of the underlying disease, the effects of CRF can range from temporary indisposition to inadequate coping with everyday life and social withdrawal (e9) all the way to the inability to perform one’s job and earn a living, leading to economic hardship for the patient and an additional economic burden for society at large (e10, e11). Thus, CRF clearly poses a problem not only for the patients themselves, but also for the persons around them (e12).

Many studies have shown that physicians generally fail to ask cancer patients systematically about the symptoms and signs of CRF. Therefore, the treating teams often do not realize the extent of stress and impairment caused by CRF and consequently underestimate the need for treatment (11, 12). There are reasons for inadequate communication about CRF on both sides of the physician–patient relationship. Patients may not volunteer information about the symptoms of CRF for fear of seeming to complain too much, or they may think these are “normal” side effects of their disease and its treatment. They may also fear that such symptoms herald a recurrence of cancer, or that mentioning them could delay treatment (e13, e14). On the other hand, treating teams may miss the opportunity to communicate appropriately about CRF because of time pressure or because of inadequate acquaintance with the diagnosis and treatment of CRF (11). Not least, both the treating physician(s) and the patient’s family and friends may wrongly compare the patient’s symptoms with their own everyday fatigue and fail to take the manifestations of CRF seriously (e15, e16).

Prevalence
When interpreting epidemiological figures about cancer-related fatigue (CRF), one must bear in mind that CRF is not a single nosological entity, even though it is characterized by a typical constellation of

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<th>BOX 1</th>
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<tr>
<td><strong>Clinical features of cancer-related fatigue</strong></td>
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<tr>
<td>• CRF involves a vicious circle of diminished physical performance, inactivity, avoidance of effort, absence of regeneration, helplessness, and depressed mood.</td>
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<td>• The more severe the symptoms of CRF are during cancer treatment, the more likely they are to persist or recur afterward.</td>
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<td>• The following are risk factors for CRF:</td>
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<tr>
<td>– pain</td>
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<td>– nausea</td>
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<td>– pre-existing depressive disorders</td>
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Risk factors for cancer-related fatigue
– Pain
– Nausea
– Pre-existing depressive disorder
– Other emotional disturbances and stressors

A vicious circle
The worse the symptoms of CRF are during the treatment phase (chemotherapy and/or radiotherapy), the more likely they are to persist or recur once the treatment is over.
symptoms and signs. In epidemiological studies, the frequency of CRF is often gauged with the aid of self-assessment questionnaires. Those that include items about the various dimensions of CRF (somatic, affective, and cognitive), such as the Multidimensional Fatigue Inventory (MFI), are considered the “gold standard” (e17). In reality, however, many different types of questionnaires are used, and the thresholds for the assignment of a diagnosis of CRF vary widely as well, with the result that the reported prevalence figures are distributed over a wide range. In a recent longitudinal study of CRF in a representative sample of cancer patients in Germany, symptoms of fatigue and exhaustion that were markedly worse than those of a control group of healthy individuals (as measured on the “general fatigue” subscale of the MFI) were found in 32% of patients on their admission to the hospital, 40% on discharge, and 36% six months later (13). In a further study by Kuhnt et al., 48% of patients still had symptoms of and signs of CRF—and 12% had very severe signs and symptoms of CRF—two years after completing their initial treatment (e18). Studies in other countries have yielded comparable findings (e19–e21).

Etiology and pathogenesis

All explanatory models of the causes and mechanisms of fatigue and exhaustion proceed from the assumption of a complex, multifactorial process. The causes and mechanisms of CRF may be associated with the tumor itself or with its treatment, or indeed with a potential genetic predisposition, an accompanying physical or mental illness, or behavioral and environmental factors (14, 15). Thus, a wide range of possible causes and influences—somatic, affective, cognitive, and psychosocial—that often cannot easily be separated from one another share cancer-related fatigue as a final common pathway. The following underlying pathophysiological factors are discussed in the literature:

- Dysregulation of inflammatory cytokines (e22–e25),
- A disturbance of hypothalamic regulatory circuits (e26–e28),
- Changes in the CNS serotonergic system (e29, e30),
- A disturbance of circadian melatonin secretion and the sleep-wake rhythm (e31–e33), and
- Gene polymorphisms for regulatory proteins of oxidative phosphorylation, signal transduction in B cells, the expression of pro-inflammatory cytokines, and catecholamine metabolism (e34–e37).

The causes of reduced physical performance ability, which is a common problem, are thought to lie in changes in the cortical and spinal sensorimotor centers (e38), in energy metabolism, and in the process of muscular activation (e39).

Diagnostic evaluation

According to the NCCN guideline, all cancer patients should be directly asked about symptoms of fatigue and exhaustion at regular intervals during their treatment and their further follow-up (2). The use of a visual analogue scale is recommended for recording the intensity of symptoms in the week leading up to the moment of inquiry (0 = no fatigue; 10 = worst fatigue you can imagine). A reported intensity of 4 or above is taken as the threshold value for further diagnostic assessment. The use of visual analogue scales is also recommended for assessing the degree to which CRF impairs the patient in various areas of everyday life; values of 5 and above are taken to imply a severe limitation of the patient’s
Cancer-related fatigue can be an expression of (pre-existing) depression and can also be a cause of depression. The two-question test for depressive disorders should be administered as part of the diagnostic assessment, as CRF may be an expression of pre-existing depression.

**The two-question test for depressive disorders**

The two-question test consists of the following questions:

- “In the last month, have you often felt dejected, sad, depressed, or hopeless?”
- “In the last month, have you gotten much less pleasure than usual out of the things that you normally like to do?”

With regard to the differential diagnosis of CRF, physicians are often faced with the important task of determining its possible relationship to a depressive disorder. The symptoms of fatigue and exhaustion have been found to be correlated with those of depressivity in nearly all studies that have addressed the question.
**Differential diagnosis**
The possible presence of a depressive disorder must be investigated.

**Treatment**
The causes of the patient's symptoms can be treated both pharmacologically and non-pharmacologically.
(8); this is hardly surprising, as easy fatigueability and a lack of drive are considered to be among the main symptoms of depressive disorders. Nonetheless, according to the findings of two studies, only about one-third of persons suffering from severe CRF also have major depression, as defined by the DSM-IV (e41, e42). In clinical practice, a depressive disorder that may underlie CRF can be detected rapidly and sensitively with two questions (e43): If the patient answers both questions affirmatively, a depressive disorder is very likely to be present and therefore merits further, specialized diagnostic evaluation (Box 2).

Clinical experience with CRF patients indicates that many of them have no identifiable somatic or psychosocial cause for their symptoms. Physicians must beware of writing off the symptoms of CRF as “illegitimate” solely because of this. Rather, it is precisely this fact that makes it all the more important for the physician to take the patient’s symptoms and stresses seriously, and to show a readiness to talk about them and treat them. Repeated follow-up—even weeks or months after initial evaluation—often reveals additional information that may help establish or confirm a diagnosis (3).

**Treatment**

In most cases, CRF must be treated in the absence of a clearly diagnosed cause, but with the knowledge of a number of potential contributing factors (Figure 3). The treatment should be initiated early, to prevent CRF from turning into a chronic problem (e8). Multiple treatment approaches should be jointly applied, with an orientation toward the individual pattern of physical, mental, and cognitive symptoms, the extent of functional impairment, and the patient’s own conceptualization of the problem. The important persons in the patient’s life should also be included in treatment planning (e44).

The central goals of treatment are:

- alleviating any factors that may be worsening the patient’s CRF,
- offering individualized help so that the patient can cope with the symptoms and stresses of CRF,
- activating the patient’s strengths and resources,
- and working toward a shared biopsychosocial conception of the situation that takes its many different aspects into account.

As a first step, the patient should be comprehensively informed about CRF and given appropriate counseling. Many patients are unaware that there is such a thing as CRF and cannot understand why they are so exhausted—especially if they seem to have achieved cure. Many patients find that the people around them cannot understand the problem either. Just knowing that their symptoms have a name and can be treated can give patients a large measure of emotional support and hope.

### Initiation of Treatment

Treatment should be initiated early to prevent chronification.

### The central goals of treatment

- Alleviate factors that worsen CRF
- Help the patient cope with symptoms & stresses
- Activate the patient’s strengths and resources
- Maintain a biopsychosocial view
relief (e45). It is also important to tell patients that CRF need not have a bad outcome (e46). The physician can alleviate or prevent fears of prolonged and intractable fatigue by discussing CRF prophylactically before the treatment of the tumor is begun (e8).

All of the suggestions below for treating CRF with medications, or with non-pharmacological measures, are derived from randomized controlled trials and/or summaries of such trials in review articles and meta-analyses. They thus correspond to evidence levels 1 and 2 of the Oxford Centre for Evidence-Based Medicine.

Non-pharmacological treatments
There are many ways to alleviate the symptoms and stresses of CRF without recourse to medications.

The findings of two recent meta-analyses and numerous randomized controlled trials enable us to recommend certain specific psychosocial interventions and special types of physical exercise (16, 17).

Psychosocial interventions—The main interventions of this type that can alleviate CRF include cognitive behavioral therapeutic approaches (16, 17, e47); psychoeducation and directed, topical counseling (16, 17); energy conservation and activity management; and methods for the promotion and reinforcement of regeneration (17, e48, e49) (Table 1).

While behavioral therapy (including cognitive behavioral therapy) and so-called mindfulness-based stress reduction (MBSR) are specialized techniques that must be carried out by trained experts, the remaining interventions can be incorporated into routine general medical practice, as long as the necessary infrastructure is available.

Energy conservation and activity management are intended to help patients economize with their physical resources, e.g., by doing only the most important tasks themselves, resting at appropriate intervals, and planning time for pleasant diversions (e.g., going to the movies, meeting friends, or listening to music).

Psychoeducation and topical counseling are important elements of a supportive treatment plan. Directed cognitive behavioral therapeutic approaches have proven particularly useful (17, e47); the aim of such approaches is to illuminate the relationship of the physical symptoms with the way they are subjectively assessed (e.g., as “unpleasant” versus “catastrophic”), the resulting emotional states (e.g., worry versus despair), and patterns of behavior. Patients should be helped to understand that an appropriate assessment of the physician–patient relationship
Psychoeducational interventions and topic-centered counseling are important elements of a supportive treatment plan.

Physical exercise
Strength and endurance training helps the patient escape from the vicious circle of physical inactivity, deconditioning, and rapid exhaustion; it can be recommended to all patients with CRF, as long as no contraindications are present.

### BOX 4

**Contraindications to exercise in patients with cancer**

- **Absolute contraindications**
  - acute illnesses
  - acute worsening or decompensation of chronic illness
  - fever above 38°C
  - pain
  - inadequately controlled arterial hypertension

- **Relative contraindications**
  - anemia (hemoglobin below 8 g/dL)
  - thrombocytopenia, coagulopathy
  - bone metastases
  - accompanying illnesses such as coronary heart disease, occlusive peripheral arterial disease, arterial hypertension, diabetes mellitus, arthrosis
  - administration of cytostatic agents on the same day
  - mediastinal/cardiac radiation therapy
  - flu-like symptoms under immunotherapy
  - epilepsy

*modified from Refs. (22, e80)
the situation can improve their quality of life. Cognitive behavioral therapy and MBSR can also alleviate the hypersomnia and insomnia that often accompany CRF (2). In addition, they can equip the patient with ways to cope with the illness and the consequences of its treatment and limit emotional distress in the form of fears, mood shifts, and so forth.

**Physical exercise**—Strength and endurance training programs help the patient escape from the vicious circle of physical inactivity, deconditioning, and rapid exhaustion; they can be recommended to all patients with CRF (18, e50), as long as no contraindications are present (Box 3). The German Society for Sports Medicine and Prevention (Deutsche Gesellschaft für Sportmedizin und Prävention) and the German Cancer Society (Deutsche Krebsgesellschaft) have issued guidelines for training and exercise programs for cancer patients (19).

Ideally, medically prescribed physical exercise sessions should take place several times per week, with daily endurance exercises and twice-weekly exercises to improve strength. Each training session should last 30 to 45 minutes (20) (Box 4). From the patient’s point of view, there are often multiple hindrances to the implementation of an ideal exercise program of this type, which should, in the best case, be continued for life: These include physical limitations, lack of interest, and purported lack of opportunity (e51). The physician should detect any such hindrances by directed history-taking and endeavor to overcome them with appropriate counseling or behavioral therapeutic approaches, so that physical exercise becomes a regular part of the patient’s daily routine. It is useful to encourage patients to do their own favorite types of physical exercise and to adapt the intensity and duration of each training session to their current capabilities and illness situation, with a gradual increase over four to six weeks (21). At the end of this period, the degree of physical exertion during exercise should not exceed 70% to 80% of the patient’s maximal capacity (maximal heart rate or maximal force). Strength training should generally take place in a facility where it can be overseen by a physical therapist or physician, while moderate endurance training can be introduced as part of routine clinical practice. Effective training involves elevating the heart rate to 70% to 80% of maximum. As a rule, exercise should not be so vigorous as to make the patient short of breath (22).

**Pharmacotherapy**

Medications with various mechanisms of action are used to treat CRF, including psychostimulants, phytotherapeutic agents, growth factors, and corticosteroids. Trials of antidepressants to date have not yielded any improvement in CRF (e52). It follows that these should be used only if there is clear evidence for, or a definitive diagnosis of, a depressive disorder.

In the following sections, we will discuss only those forms of treatment whose safety and efficacy have been studied in randomized controlled trials, corresponding to evidence levels 1 and 2 in the scheme of the Oxford Centre for Evidence-Based Medicine (Table 2).

**Hematopoietic growth factors**—The administration of erythropoiesis-stimulating agents (ESA) can relieve CRF in anemic patients undergoing chemotherapy (e53). The expected treatment effect is seen in only a minority of patients, as most patients with CRF are not anemic (e52, e54, e55). A meta-analysis of individual patient data indicated that the administration of ESA during chemotherapy is associated with higher mortality, and that ESA elevate the frequency of thrombotic and thromboembolic events (e56); thus, the benefits and risks of treating CRF with ESA must be critically weighed in every case (e57).

**Psychostimulants**—The psychostimulants methylphenidate (MP) and modafinil (MF) can relieve CRF (23–25). In Germany, these medications may only be given off-label, or in the setting of a clinical trial, to

**BOX 3**

**Calculation of the maximal heart rate, according to Lagerström (Ref. [15])**

- In the acute-care hospital: 180 minus age in years
- In the rehabilitation phase, for endurance sports such as cycling and rowing: 220 minus age
- In the rehabilitation phase, for non-strength-oriented sports such as swimming and jogging: 220 minus 2/3 of age

These are only rules of thumb; beware of demanding excessive effort from patients!
treat CRF. They are potentially useful especially for patients with severe CRF that has not responded satisfactorily to other forms of treatment. They can only be given in the absence of contraindications such as poorly controlled arterial hypertension, symptomatic coronary heart disease, arrhythmia, or epilepsy (for methylphenidate), or psychosis and severe affective disorders (for modafinil).

Methylphenidate has been found to relieve moderate-to-severe CRF significantly better than placebo in patients with advanced prostate cancer (e58) and gynecological tumors (e59) (Table 2). A retrospective analysis of trial data suggests that methylphenidate is most effective for patients with severe CRF; that the D-(+) form of methylphenidate is more effective than other forms; and that patients who already benefit from the drug in the first few days of treatment will benefit more from it overall (e60).

The findings of a recent study imply that modafinil is only effective against severe CRF (e61) (Table 2). In any case, in the past year, the European Medicines Agency (EMA) has restricted its use to the treatment of adults with excessive sleepiness, because of the occurrence of psychiatric manifestations and cutaneous reactions (erythema multiforme, Stevens-Johnson syndrome).

Corticosteroids—In palliative situations, corticosteroids can temporarily improve CRF.

**Thyreoliberin**

The findings of an initial randomized trial suggest that intravenously administered thyreoliberin (thyrotropin-releasing hormone [TRH]) may be a safe and effective way to treat CRF.

**Ginseng**

The results of scientific studies permit the tentative conclusion that both *Panax quinquefolius* and *Panax ginseng* may effectively alleviate CRF.
patients’ physical activity (e62). Therefore, the National Comprehensive Cancer Network (NCCN) and the European Association for Palliative Care (EAPC) recommend considering corticosteroids for use in such situations, but for a limited time only, in view of the risk that steroid-induced myopathy might worsen CRF with prolonged use (2, 4).

**Thyreoliberin**—The findings of an initial randomized trial suggest that intravenously administered thyreoliberin (thyrotropin-releasing hormone [TRH]) may be a safe and effective way to treat CRF (e63). In this trial, the patients’ manifestations of exhaustion improved within a few hours of treatment, and the improvement was sustained for several days (Table 2). In Germany, however, TRH preparations are approved only for diagnostic purposes, not for treatment.

**Phytotherapeutic agents**—Ginseng is traditionally given to treat states of exhaustion of all kinds (e64). American ginseng (*Panax quinquefolius*) (e65) and Asian ginseng (*Panax ginseng C.A. Meyer*) (e66) have both been studied scientifically; the results permit the tentative conclusion that both may be effective against CRF (Table 2). In Germany, *Panax ginseng* preparations are approved for the treatment of states of exhaustion (e67).

Regarding the putative efficacy of guarana (*Paullinia cupana*), there is initial positive evidence from a randomized trial, in which guarana improved CRF in women undergoing chemotherapy for breast cancer (e68) (Table 2). The main active ingredient of guarana is caffeine; in the trial just cited, the dose of guarana that was given contained about the same amount of caffeine as two cups of strong coffee, but caffeine is said to be released more slowly from guarana than from coffee (e69).

### Conflict of interest statement

Prof. Weis has received honoraria for lectures at symposia sponsored by the following pharmaceutical companies: Novartis, Roche, Astra Zeneca, and Ipsen.

PD Dr. Rüffer owns stock in Sanofi Aventis and serves as an advisor for Hexal.

PD Dr. Dimeo has received reimbursement of travel and accommodation expenses from Chugai and Amgen and lecture honoraria from Pfizer, Amgen, and Chugai. He has received money from Pfizer for a research project that he initiated.

Dr. Horneber has received lecture honoraria from Novartis.

Dr. Fischer states that she has no conflict of interest.

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**Guarana**

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The CME unit “Functional Bowel Disorders in Adults” (issue 5/2012) can be accessed until 16 March 2012. For issue 13/2012, we plan to offer the topic “Insect Stings: Clinical Features and Management.” Solutions to the CME questionnaire in issue 1–2/2012: Kiefer M, Unterberg A: The Differential Diagnosis and Treatment of Normal-Pressure Hydrocephalus.
Solutions: 1c, 2a, 3e, 4d, 5e, 6b, 7a, 8a, 9e, 10b
Please answer the following questions to participate in our certified Continuing Medical Education program.
Only one answer is possible per question. Please select the answer that is most appropriate.

**Question 1**
Which of the following may be a manifestation of cancer-related fatigue?
- a) Impaired memory and concentration
- b) Recurrent tension headache
- c) Tremor and altered gait
- d) Lymphadenopathy and skin irritation
- e) Ptosis and diplopia

**Question 2**
What initial laboratory tests are useful for differential diagnosis in patients who first present with symptoms of cancer-related fatigue?
- a) EBV, borrelia, hepatitis viruses, M. tuberculosis, herpes viruses
- b) Complete blood count, adrenocortical hormones, tumor markers
- c) Vitamins, selenium, vitamin D, magnesium, manganese, heavy metals
- d) Blood count, electrolytes, glucose, transaminases, γ-GT, CRP, TSH
- e) Serotonin, cortisol, melatonin, cytokines, catecholamines

**Question 3**
Roughly what percentage of patients with severe CRF meet the DSM-IV criteria for major depression?
- a) Less than 5%
- b) ~ 10%
- c) ~ 30%
- d) ~ 50–80%
- e) More than 80%

**Question 4**
What temporal relation does CRF have to cancer?
- a) CRF usually arises before cancer is diagnosed.
- b) CRF usually arises after diagnosis and before the initiation of treatment.
- c) CRF usually arises immediately after the end of chemotherapy.
- d) CRF usually arises after the completion of radiotherapy.
- e) CRF can arise at any point in the course of cancer and its treatment.

**Question 5**
Which of the following is a known risk factor for CRF?
- a) Emotional stress
- b) Irritable bowel syndrome
- c) Fibromyalgia
- d) Migraine
- e) Disturbances of impulse control

**Question 6**
Which of the following statements from the patient points to CRF as the leading element of the differential diagnosis?
- a) “All my muscles hurt all the time. I have continuous cramping pain.”
- b) “When I come home from shopping, I am so tired that I have to lie down.”
- c) “I can hardly fall asleep any more, because so many things are going through my head.”
- d) “I have no appetite any more; then again, I can hardly keep any food down, either.”
- e) “Every little thing makes me upset now. I feel totally stressed out.”

**Question 7**
Which of the following absolutely contraindicates physical exercise in a patient with CRF?
- a) Anemia with a hemoglobin concentration below 8 g/dL
- b) Bone metastases
- c) Accompanying illnesses such as coronary heart disease, diabetes mellitus, and arthritis
- d) Fever above 38°C
- e) Flu-like symptoms under immunotherapy

**Question 8**
What percentage of maximum capacity (i.e., maximum heart rate or maximum force) is the recommended upper limit of exercise for CRF patients doing physical exercise?
- a) 50%
- b) 60%
- c) 70%
- d) 80%
- e) 90%

**Question 9**
What non-pharmacological intervention is suitable for the treatment of patients with CRF?
- a) Qigong
- b) Cognitive behavioral therapy
- c) Whole foods diet
- d) Relax zone massage
- e) Kinesiology

**Question 10**
Which of the following preparations is approved in Germany for the treatment of states of exhaustion?
- a) Mistletoe
- b) Paroxetine
- c) Panax ginseng
- d) St. John’s wort oil
- e) Methylphenidate
Cancer-Related Fatigue
Epidemiology, Pathogenesis, Diagnosis, and Treatment

Markus Horneber, Irene Fischer, Fernando Dimeo,
Jens Ulrich Rüffer, Joachim Weis

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