Cancer-Related Fatigue: Guidelines for Evaluation and Management

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ABSTRACT

Fatigue is a highly prevalent condition among cancer patients. Although most cancer patients report that fatigue is a major obstacle to maintaining normal daily activities and quality of life, it is seldom assessed and treated in clinical practice. Few studies have explored its epidemiology, possible etiologies, or management. Cancer-related fatigue, which recently was accepted as a diagnosis in the International Classification of Diseases 10th Revision—Clinical Modification, reduces physical, psychological, and social functioning and results in significant distress for patients and caregivers. Adequate evaluation of fatigue must do more than simply assess severity. The assessment should clarify other characteristics, determine the degree to which fatigue interferes with the activities of daily living, and identify potential causes, including the underlying disease, disease treatments, intercurrent systemic disorders, psychological disorders, and other conditions. Possible primary therapies include modification of the patient’s drug regimen, correction of metabolic abnormalities, and pharmacologic treatments for anemia (e.g., epoetin alfa), depression, or insomnia. Other symptomatic interventions include specific drug treatments, exercise, modification of activity and rest patterns, cognitive therapies, sleep hygiene approaches, and nutritional support. Pharmacologic approaches, which are supported by limited studies and growing clinical experience, include psychostimulant drugs, corticosteroids, and possibly other therapies. Although additional research is needed to further identify the causes and corresponding treatment of fatigue, practitioners should routinely assess and treat patients who may benefit from currently identified interventions, because fatigue can profoundly undermine the quality of life of patients with cancer.

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INTRODUCTION

Fatigue has been identified by patients with cancer as a major obstacle to normal functioning and a good quality of life [1]. It is a nearly universal symptom in patients undergoing primary antineoplastic therapy or treatment with biologic response modifiers and is extremely common in populations with persistent or advanced disease [1-12].

Given the prevalence and impact of cancer-related fatigue, there have been remarkably few studies of the phenomenon. Its epidemiology has been poorly defined, and the variety of clinical presentations remains anecdotal. The existence of discrete fatigue syndromes linked with predisposing factors or potential etiologies has not been confirmed, and clinical trials to evaluate putative therapies for specific types of cancer-related fatigue are almost entirely lacking.

It is important to begin to characterize the phenomenon of cancer-related fatigue and offer guidelines for management. Increased awareness will encourage better assessment and consideration of available therapeutic options. Management will improve as new research clarifies the prevalence and nature of the problem, yields validated assessment tools, and evaluates specific treatment strategies. This review discusses the clinical aspects of cancer-related fatigue and offers strategies to assist in the management of this undertreated condition.

DEFINITION, PREVALENCE, AND CAUSES OF FATIGUE

Patients and practitioners can generally differentiate “normal” fatigue experienced by the general population from clinical fatigue associated with cancer or its treatment. The term “asthenia” has been used to describe fatigue in oncology patients but has no specific meaning apart from the more common term. Fatigue is an inherently subjective and multidimensional condition. It may be described in terms of a variety of characteristics (e.g., severity, distress, temporal

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features) and specific impairments (e.g., lack of energy, weakness, somnolence, difficulty concentrating). Criteria have been needed to define this clinically relevant syndrome. Recently, cancer-related fatigue was accepted as a diagnosis in the International Classification of Diseases 10th Revision–Clinical Modification. Fatigue may be characterized as a multidimensional phenomenon that develops over time, diminishing energy, mental capacity, and the psychologic condition of cancer patients (Table 1) [13]. Fatigue is also linked with lethargy, malaise, and asthenia in the revised National Cancer Institute (NCI) Common Toxicity Criteria (CTC). These classifications may enhance awareness of fatigue and improve reporting of the condition.

Cancer-related fatigue is extremely prevalent. A recent population-based survey of 419 randomly selected patients observed that 78% experienced fatigue, which was defined as debilitating tiredness or loss of energy at least once each week; the majority of these patients reported that fatigue had either significantly (31%) or somewhat (39%) affected their daily routine [1]. In a cross-sectional survey of 151 ovarian cancer patients, the prevalence of fatigue was 69%, and approximately half of affected patients described the condition as highly distressing [11]. Other surveys of patients with metastatic disease suggest that the prevalence in this setting exceeds 75% [11, 14-18].

Numerous surveys have associated the occurrence of fatigue with specific treatments [3-6, 19-23]. These surveys suggest that fatigue commonly occurs after surgery, chemotherapy, radiotherapy, or immunotherapy. Prevalence rates of fatigue as high as 96% have been reported in conjunction with chemotherapy and radiotherapy [5], and severe fatigue is almost universal with the use of biologic response modifiers, including α-interferon and the interleukins [19, 23, 24].

When fatigue is primarily related to a treatment, there is a generally a clear temporal relationship between the condition and the intervention [21, 25-27]. In patients receiving cyclic chemotherapy, for example, fatigue often peaks within a few days and declines until the next treatment cycle. During a course of fractionated radiotherapy, fatigue is often cumulative and may peak after a period of weeks. Occasionally, fatigue persists for a prolonged period beyond the end of chemotherapy or radiotherapy.

The relationships between fatigue and demographic characteristics, physiologic factors, and psychosocial factors are not well defined. The specific mechanisms that precipitate or sustain the syndrome are unknown. Fatigue may represent a final common pathway to which many predisposing or etiologic factors contribute (Table 2) [29-35]. The pathophysiology in any individual may be multifactorial. Proposed mechanisms include abnormalities in energy metabolism related to increased requirements (e.g., due to tumor growth, infection, fever, or surgery); decreased availability of metabolic substrate (e.g., due to anemia, hypoxemia, or poor nutrition); or the abnormal production of substances that impair metabolism or normal functioning of muscles (e.g., cytokines or antibodies). Other proposed mechanisms link fatigue to the pathophysiology of sleep disorders and major depression. There is no clear evidence in support of any of these mechanisms, and further research is needed.

**Table 1. Proposed criteria for cancer-related fatigue [13]**

| The following symptoms have been present every day or nearly every day during the same 2-week period in the past month: |
| ▲ Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level |
| ▲ Plus five (or more) of the following: |
| ▲ Complaints of generalized weakness or limb heaviness |
| ▲ Diminished concentration or attention |
| ▲ Decreased motivation or interest in engaging in usual activities |
| ▲ Insomnia or hypersomnia |
| ▲ Experience of sleep as unrefreshing or nonrestorative |
| ▲ Perceived need to struggle to overcome inactivity |
| ▲ Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued |
| ▲ Difficulty completing daily tasks attributed to feeling fatigued |
| ▲ Perceived problems with short-term memory |
| ▲ Post-exertional malaise lasting several hours |

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer-related therapy. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

**Fatigue is a multidimensional phenomenon that develops over time, diminishing energy, mental capacity, and the psychologic condition of cancer patients.**
to develop a therapeutic strategy (Table 3). A comprehensive assessment includes a description of fatigue-related phenomena, a physical examination, and a review of laboratory and imaging studies. These data may allow plausible hypotheses concerning pathogenesis, which in turn may suggest appropriate treatment strategies.

Patients may describe fatigue in terms of decreased vitality or lack of energy, muscular weakness, dysphoric mood, somnolence, impaired cognitive functioning, or some combination of these disturbances. Although this variability suggests the existence of fatigue subtypes, this has not yet been empirically confirmed. Regardless, the patient’s history should clarify the spectrum of complaints and attempt to characterize features associated with each component. This information may suggest specific etiologies (e.g., depression) and influence the choice of therapy. Neurologic and psychologic evaluations also may help further clarify potential etiologies of fatigue in some patients.

Other characteristics are similarly important. Onset and duration, for example, distinguish acute and chronic fatigue. Acute fatigue has a recent onset and is anticipated to end in the near future. Chronic fatigue has persisted for a prolonged period (weeks to months, or longer) and is not expected to remit soon. Patients perceived to have chronic fatigue typically require a more intensive evaluation, as well as a management approach focused on both short- and long-term goals. Other important descriptors of fatigue include its severity, daily pattern, course over time, exacerbating and palliative factors, and associated distress.

To measure fatigue severity, consistent use of a simple unidimensional scale, such as a verbal rating scale (none, mild, moderate, severe) or a numeric scale (for example, a 0-10 scale, where “0” equals no fatigue and “10” equals the worst fatigue imaginable, or a 0-4 scale, as applied in the NCI CTC) are useful for monitoring changes over time [36]. Other unidimensional scales include the fatigue subscale of the Profile of Mood States [37], linear analog scales (linear analog scale assessment [LASA]) [38], and single items incorporated into symptom checklists [39-41].

Multidimensional fatigue assessment, which captures multiple characteristics and manifestations of fatigue and its impact on function, is more informative than the measurement of severity alone. In the practice setting, when time for evaluation is limited, the routine use of three simple questions may help assess fatigue severity and impact over time [36]:

▲ Are you experiencing any fatigue?
▲ If yes, how severe has it been, on average, during the past week, using a 0-10 scale?
▲ How is the fatigue interfering with your ability to function?

Validated multidimensional questionnaires provide a more sophisticated alternative for practice, or, more commonly, for use in research settings [12, 22, 36, 42-47].

**Multidimensional Assessment Tools**

The first validated multidimensional instrument was the Piper Fatigue Self-Report Scale. This scale addresses the severity, distress, and impact of fatigue using a 41-item
questionnaire administered as either a series of LASA or numeric scales [36]. It was developed to assess fatigue in patients receiving radiotherapy. It is both reliable and valid in this population and may also be used to assess cancer patients who are not receiving radiotherapy. Efforts continue to further refine it [48].

A 20-item scale that evaluates well-being associated with fatigue and anemia has been developed as a module of a general quality of life instrument known as the Functional Assessment of Cancer Therapy (FACT) [12, 42, 43]. The fatigue, or fatigue and anemia, subscales of this module can be used alone as brief, reliable, and valid assessments. Using this questionnaire, an association between fatigue and anemia was demonstrated in a large survey of cancer patients in community settings. Patients with hemoglobin values >12 g/dL reported significantly less fatigue, fewer nonfatigue anemia symptoms, better physical and functional well-being, and a higher overall quality of life than those with hemoglobin values ≤12 g/dL [49].

Other validated multidimensional instruments are available [9, 44-47]. The Fatigue Symptom Inventory, for example, has been used in a series of studies that evaluated the severity and impact of treatment-related fatigue [44]. Investigators or clinicians who seek a detailed assessment of fatigue should review the items in these questionnaires and select the instrument that captures the fatigue-related phenomena of greatest interest.

Assessment of Related Constructs

An assessment of cancer-related fatigue also should include consideration of broader concerns, including global quality of life, symptom distress, and the goals of care. Fatigue may be only one of numerous factors that influence quality of life. Among these factors are progressive physical decline, psychological disorders, social isolation, financial concerns, and spiritual distress. Optimal care of the cancer patient includes a broad assessment of these factors and should be directed toward maintaining or enhancing quality of life.

The concept of global symptom distress is useful in characterizing patients who often have multiple symptoms concurrently [39-41]. Fatigue, pain, and psychological distress are the most prevalent symptoms across varied cancer populations [41]. Patients who report fatigue should be queried about the presence of other symptoms and the degree to which fatigue predominates as a cause of distress.

The goals of care guide all therapeutic decision making. Specific treatments may or may not be appropriate depending on the degree to which the preeminent goals relate to prolonging life, improving function, or providing comfort alone.

Management Strategies

A successful strategy should ameliorate fatigue within a broader approach to patient care. Education of the patient regarding the nature of fatigue, options for therapy, and anticipated outcomes is an essential aspect of the therapy. Unfortunately, results of a recent survey indicate that fatigue is seldom discussed by patients and their oncologists [1].

Treatment of Underlying Causes

As an initial approach to cancer-related fatigue, efforts should be made to correct potential etiologies, if possible and appropriate. Anemia frequently is a major factor in the development of cancer-related fatigue. Anecdotaly, transfusion therapy for severe anemia often has been associated with substantial improvement in fatigue. Until the early 1980s, red blood cell transfusions were administered empirically when hemoglobin concentrations fell below 10 g/dL [55, 56] and were the primary treatment for cancer-related and chemotherapy-induced anemia. At that time, concern about the safety of the blood supply related to potential transmission of the human
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Patient with cancer-related fatigue

Evaluation of fatigue
Assess characteristics/manifestations
- Severity
- Onset, duration, pattern, and course
- Exacerbating and palliative factors
- Distress and impact
- Manifestations may include:
  - Lack of energy
  - Weakness
  - Somnolence
  - Impaired thinking
  - Mood disturbance

Assess Related Constructs
- Overall quality of life
- Symptom distress
- Goals of care

Evaluation of predisposing factors/etiologies
Physiologic
- Underlying disease
- Treatments
- Intercurrent disease processes (e.g., infection, anemia, electrolyte disturbance or other metabolic disorder, neuromuscular disorder)
- Sleep disorder
- Possible polypharmacy
  - Psychological
  - Mood disorder
  - Stress

Management of fatigue
- Establish reasonable expectations
- Plan to assess repeatedly

Correction of potential etiologies
Symptomatic therapies

Depression or pain
- Antidepressants
  - Selective serotonin-reuptake inhibitors
  - Secondary amine tricyclics
  - Bupropion
- Analgesics

Anemia
- Exclude common causes of anemia
  - Iron deficiency
  - Bleeding
  - Hemolysis
  - Nutritional deficiency
  - Severe anemia
  - Transfuse
- Mild to moderate anemia
  - Consider epoetin alfa
    - 10,000 units subcutaneously 3 times weekly
  - Evaluate after 4 weeks:
    - If increase in Hgb is ≥1 g/dL, continue therapy
    - If increase in Hgb is <1 g/dL, increase dosage to 20,000 units 3 times weekly.
    - If no response, discontinue epoetin alfa
  - Provide supplemental iron as necessary

Sleep disorder
- Sleep hygiene
- Careful use of hypnotics

Other conditions
- Correct fluids/electrolytes
- Calcium, thyroid, or corticosteroid replacement
- Give oxygen
- Treat infection
- Reduce or eliminate nonessential medications

Pharmacologic treatment
- Psychostimulants
  - Methylphenidate
  - Pemoline
  - Dextroamphetamine
- Low-dose corticosteroids
  - Dexamethasone
  - Prednisone

Nonpharmacologic treatment
- Patient education
- Exercise
- Modify activity and rest patterns (sleep hygiene)
- Stress management and cognitive therapies
- Adequate nutrition and hydration

Fatigue nonresponsive to other interventions
- Empiric trial of antidepressant
  - Selective serotonin-reuptake inhibitors
  - Secondary amine tricyclics
  - Bupropion
- Empiric trial of amantadine

Figure 1. Algorithm for the evaluation and management of cancer-related fatigue.
immunodeficiency virus prompted clinicians to alter their treatment approach [56, 57]. Without an alternative to transfusion, treatment of mild or moderate anemia was generally avoided until hemoglobin concentrations declined to more severe levels (7-8 g/dL) or the patient experienced signs and symptoms of severe anemia [55, 58]. As reticence to treat anemia increased, it was less often reported as an adverse sequela in published chemotherapy trials and received less attention in the medical literature overall.

New data demonstrate an association between chemotherapy-induced mild-to-moderate anemia and both fatigue and quality-of-life impairment. For example, combined data from 413 patients in three randomized, placebo-controlled trials of epoetin alfa, the recombinant form of human erythropoietin, reveal that treated patients experienced a significant increase in hematocrit, a reduced need for transfusion, and a significant improvement in overall quality of life. Those patients with an increase in hematocrit of >6% also demonstrated significant improvement in energy level and daily activities [59]. Additional studies in patients treated with chemotherapy and radiation therapy for a variety of hematologic and solid tumors confirm that epoetin alfa has positive effects on hemoglobin levels [60-63].

Two large, prospective, nonrandomized, multicenter community trials evaluated the effectiveness of epoetin alfa in anemia associated with cancer chemotherapy [64, 65]. In the more recent trial, Demetri et al. assessed the effectiveness of epoetin alfa as an adjunct to chemotherapy in more than 2,000 cancer patients undergoing cytotoxic chemotherapy [64]. Patients received epoetin alfa 10,000 units three times weekly for a maximum of 16 weeks. If the increase in hemoglobin level was <1.0 g/dL at four weeks, the dose was increased to 20,000 units three times weekly. Quality-of-life parameters were assessed with LASA and the FACT-Anemia instruments. Over time, patients experienced significant improvements in energy level, activity level, functional status, and overall quality of life; these improvements were independent of antitumor response and were significantly correlated with hemoglobin levels. These results were similar to the findings in the previous large, community-based study by Glaspy et al. [65].

**Symptomatic Approaches**

**Pharmacologic Treatments**

The pharmacologic therapies for fatigue associated with medical illness have not been rigorously evaluated in controlled trials. Nonetheless, there is evidence to support the use of several drug classes. Psychostimulants, such as methylphenidate, pemoline, and dextroamphetamine, have been well studied for the treatment of opioid-related somnolence and cognitive impairment [66], and depression in the elderly and medically ill [67-69]. There are no controlled studies of these drugs for cancer-related fatigue, but empiric administration may yield favorable results in some patients.

Clinical response to one drug does not necessarily predict response to the others, and sequential trials may be needed to identify the most beneficial therapy. Methylphenidate has been more extensively evaluated in the cancer population than other stimulant drugs and often is the first drug administered. Pemoline has less sympathomimetic activity than other psychostimulants but has a low risk of severe hepatotoxicity compared with similar agents [70]. It is available in a chewable formulation that can be absorbed through the buccal mucosa for patients who are unable to swallow or take oral medications.

Adverse effects associated with the psychostimulants include anorexia, insomnia, tremulousness, anxiety, delirium, and tachycardia. To ensure safety, slow and careful dose escalation should be undertaken to minimize potential adverse effects. A regimen of methylphenidate, for example, usually begins with a dose of 5-10 mg once or twice daily (morning and, if needed, midday). If tolerated, the dose is increased. Most patients appear to require less than 60 mg per day, but some require much higher doses.

Extensive anecdotal observations and very limited data from controlled trials [71, 72] support the use of low-dose corticosteroids in fatigued patients with advanced disease and multiple symptoms. Dexamethasone and prednisone are most commonly used. There have been no comparative trials.

The selective serotonin-reuptake inhibitors, secondary amine tricyclics (e.g., nortriptyline and desipramine), or bupropion are sometimes associated with the experience of increased energy that appears disproportionate to any change in mood. For this reason, these agents also have been tried empirically in nondepressed patients with fatigue. Given the limited experience in the use of these drugs for this indication, an empiric trial should be considered only in severe and refractory cases.

Amantadine has been used to treat fatigue in patients with multiple sclerosis, but it has not been studied in other

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**Despite the high prevalence in the cancer population, depression is often underdiagnosed, and, consequently, undertreated.**

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patient populations. This drug is usually well tolerated, and an empiric trial may be warranted in selected patients with severe refractory cancer-related fatigue.

**Nonpharmacologic Interventions**

Nonpharmacologic approaches for the management of cancer-related fatigue are largely supported by favorable anecdotal experience (Table 4). Patient preferences should be considered in the selection of one or more of these approaches.

Education about fatigue greatly benefits some patients [73–77]. There are large individual differences in patients’ preferences for information, however, and efforts to educate should be directed at the patients’ educational level and readiness to learn. The use of a patient diary may help the clinician and patient discern a pattern to the fatigue or identify specific activities that are associated with increased levels. This information may be useful in developing a management plan that modifies specific activities and incorporates appropriate periods of rest [27]. For example, some patients identify a pattern that suggests the utility of scheduled brief rest periods during the day.

Some patients benefit from education about sleep hygiene. Sleep hygiene principles should be tailored to the individual patient and might include the establishment of a specific bedtime and wake time, and routine procedures prior to sleep [78]. Patients also should be instructed to avoid stimulants and central nervous system depressants prior to sleep [78]. Regular exercise performed at least 6 h before bedtime may improve sleep, whereas napping in the late afternoon or evening may worsen it.

Exercise may be beneficial in relieving fatigue [25, 77, 79-81]. This may be counterintuitive to patients, and considerable education may be needed to foster cooperation with an exercise program. There are no data that clarify the most appropriate exercise program for cancer patients with fatigue. In general, exercise should be individualized, considering such factors as the patient’s age and medical condition. Anecdotally, the type of exercise that appears to be most beneficial involves rhythmic and repetitive movement of large muscle groups such as walking, cycling, or swimming. The exercise program should be initiated gradually and should include a light-to-moderate workout several days a week.

Anxiety, difficulties in coping with cancer or its treatment, or sleep disturbances may contribute to fatigue. Anxiety, difficulties in coping with cancer or its treatment, or sleep disturbances may contribute to fatigue and may be ameliorated using stress reduction techniques or cognitive therapies, such as relaxation therapy, hypnosis, guided imagery, or distraction. Some patients find distraction (e.g., listening to music) or other cognitive techniques to be particularly effective when the symptom is associated with attention deficits [82, 83]. Referral to a psychologist for counseling and training in stress management techniques or cognitive therapies may be warranted in some patients.

Cancer and its treatment also can interfere with dietary intake. With aggressive approaches to management, patients’ weight, hydration status, and electrolyte balance should be monitored and maintained to the extent possible [84]. Regular exercise may improve appetite and increase nutritional intake. Referral to a dietician for nutritional guidance and suggestions for nutritional supplements may be useful.

**Summary**

Despite the high prevalence and distress associated with fatigue, there have been few studies of this condition, and relatively little is known about its epidemiology, etiologies,
pathogenesis, and management. With growing interest in palliative care, however, there is recognition of fatigue as an important issue for research and treatment guideline development [13]. Oncologists, as well as the entire medical team, must become more aware of this problem, its impact on patient quality of life, and the various strategies that may be helpful in its treatment. Although further research is needed, many patients could benefit from more comprehensive evaluation and greater use of available interventions for cancer-related fatigue.

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