
CHAPTER 3

Cancer-Related Fatigue

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THE PROBLEM

Cancer-related fatigue (CRF) is a prevalent and disabling symptom experienced by both cancer patients and cancer survivors. It is a multifaceted condition characterized by diminished energy and an increased need to rest, disproportionate to any recent change in activity level, and accompanied by a range of other characteristics, including generalized weakness, diminished mental concentration, insomnia or hypersomnia, and emotional reactivity.¹ Decrements in physical, social, cognitive, and vocational functioning,^{2,3} adverse mood changes,⁴ sleep disturbances,⁵ treatment noncompliance⁶ and emotional and spiritual distress for both the patient and family members⁷ are among the consequences of CRF.

Despite this degree of distress and functional loss associated with CRF, screening, evaluation, and treatment for CRF in clinical settings remain suboptimal. Reasons for this shortcoming may include clinicians' failure to offer interventions, patients' lack of awareness of effective treatments for fatigue, a desire on patients' part to treat fatigue without medications, and a tendency to be stoic about fatigue to avoid being labeled as a "complainer" or risk having the dose of anticancer treatment reduced.⁸

Although many different definitions of CRF have been proposed, the National Comprehensive Cancer Network (NCCN) defines CRF as a distressing, persistent, and subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.⁹ The clinical expression of CRF is multidimensional, making evaluation of a patient experiencing fatigue challenging.

An inherently subjective condition, fatigue may be experienced and reported differently by each individual.

One qualitative study of fatigue underscored the fact that the cancer fatigue experience is unlike any other fatigue individuals have previously experienced, and suggested that its unpredictability and refractoriness to self-management strategies contribute to the distress associated with CRF.¹⁰ Personality and coping style may also influence the experience of CRF.¹¹ Some patients identify the main features of their fatigue as a loss of efficiency, mental foginess, inertia, and failure of sleep to be restorative, while others describe an excessive need to rest, the inability to recover promptly from exertion, and muscle heaviness and weakness. Further research is needed to determine whether these represent variable features of fatigue, suggest the presence of fatigue subtypes, or are the cause or sequelae of fatigue.¹² Efforts continue to be directed toward clarifying the defining features of fatigue, and determining how CRF may be distinguished from syndromes such as depression, cognitive dysfunction, or asthenia that have overlapping symptoms^{13,14} or that may share neurophysiologic mechanisms.^{15,16}

The varying estimates of the prevalence of CRF may be due in part to the fact that investigators use varying case definitions of cancer-related fatigue.¹⁷ Progress in evaluating the effectiveness of new therapies for CRF is also hindered by the absence of a precise definition of the level of fatigue that must be present to define eligibility for trial participation. Establishing criteria for a diagnosis of cancer-related fatigue—that is, a case definition—will allow us to define clinically significant fatigue, will enable better classification of patients with CRF, and will facilitate comparisons across studies and populations.

Consensus criteria for a diagnosis of cancer-related fatigue syndrome were initially proposed in 1998¹ and are provided in Table 3-1. Based on these criteria, CRF is of a markedly different quality and severity from ordinary fatigue,

TABLE 3-1

International Classification of Diseases (10th Edition) ICD-10 Criteria for Cancer-Related Fatigue

Six (or more) of the following symptoms have been present every day or nearly every day during the same two-week period in the past month, and at least one of the symptoms is (A1) significant fatigue.

- A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
- A2. Complaints of generalized weakness or limb heaviness
- A3. Diminished concentration or attention
- A4. Decreased motivation or interest to engage in usual activities
- A5. Insomnia or hypersomnia
- A6. Experience of sleep as unrefreshing or nonrestorative
- A7. Perceived need to struggle to overcome inactivity
- A8. Marked emotional reactivity (e.g., sadness, frustration, irritability) to feeling fatigued
- A9. Difficulty completing daily tasks attributed to feeling fatigued
- A10. Perceived problems with short-term memory
- A11. Post-exertional malaise lasting several hours
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.
- D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium

Source: Cella, D., Peterman, A., Passik, S., Jacobsen, P., & Breitbart, W. (1998). Progress toward guidelines for the management of fatigue. *Oncology (Williston Park)*, 12(11A), 369–377.(1) Used with permission.

adversely impacts function, and is unrelieved by rest or sleep. It is also accompanied by symptoms such as an increasing need for rest, limb heaviness, diminished concentration, inertia, emotional lability, and post-exertional malaise. One must also be fairly certain that the underlying cause is cancer or its treatment. These criteria have been subjected to only limited empiric testing,¹⁸ and more than one case definition may ultimately be needed to capture the features of clinically significant fatigue in varying populations.¹²

INCIDENCE

Fatigue is one of the most commonly reported symptoms experienced by patients receiving treatment for cancer, and it often persists beyond the conclusion of active treatment and at the end of life.^{19,20} Depending on how CRF is defined and measured and the clinical characteristics of the population under study (e.g., tumor site, phase stage on the cancer continuum, and type of anticancer therapy), prevalence estimates range from 25% to 99%.^{20–24} Across all cancer types, fatigue was ranked as the most important symptom or concern in a survey of more than 500 patients and nearly 100 clinicians.²⁵ Longitudinal and comparative studies indicate that persistent fatigue may also be a significant problem for cancer survivors, even those free of disease.^{26,27} In the setting of advanced cancer, almost 60% of patients experience

fatigue, with one-fourth reporting severe fatigue.²⁸ Fatigue may occur as an isolated symptom, or as one component within a cluster of other symptoms, including depression, pain, sleep disturbance, and menopausal symptoms.^{29–34}

ETIOLOGY

For a majority of patients, cancer and its treatment will be associated with the development of CRF, although patterns of fatigue onset, severity, daily fluctuations, and resolution vary widely depending on the type of treatment, and the site and stage of the underlying disease. Fatigue is reported in association with radiation, chemotherapy, hematopoietic stem cell transplantation, hormonal treatment, and biologic and molecularly targeted agents in patients receiving treatment in both outpatient and inpatient settings.^{20,21,35–39} However, few direct relationships between treatment-related variables such as dose intensity, radiation fractionation schedule, and time since treatment completion have been seen.¹⁹ Associations between the occurrence or severity of CRF and demographic variables such as gender, age, marital status, and employment status have also not been consistently identified.⁴⁰

Direct and indirect biobehavioral mediators of CRF in patients on cancer treatment include pro-inflammatory cytokine release, anemia, mood disturbances, alterations in muscle metabolism, sarcopenia, hypothalamic-pituitary-adrenal

(HPA)-axis dysregulation, fluid and electrolyte disturbances, and deconditioning. Other potential etiologic factors for CRF include anxiety, depression, and psychological distress; concurrent symptoms such as pain and nausea/vomiting; sleep disturbances; cardiopulmonary, hepatic, or renal dysfunction; infection; malnutrition; and the side effects of drugs that act on the central nervous system, such as benzodiazepines and narcotics.^{4,39–43} A number of metabolic and endocrine disorders can exacerbate CRF, including hypothyroidism, hypogonadism, adrenal insufficiency, hypercalcemia, hypomagnesemia, and dehydration.⁴² Cancer anorexia-cachexia and their resultant protein-calorie malnutrition lead to increased proteolysis in skeletal muscles, producing muscle wasting, weakness/asthenia, and reduced endurance.

PATHOPHYSIOLOGY

The pathophysiology of CRF likely involves the interaction of several biobehavioral mechanisms.^{16,47} Accumulating evidence points to gene polymorphisms,⁴⁸ altered circadian rhythmicity,⁴⁹ and immune dysregulation and pro-inflammatory cytokine activity^{50,51} as pathophysiologic mechanisms underlying CRF. Cancer and treatment-emergent side effects contribute to dysregulation of the HPA axis, adversely affecting the secretion of corticotrophin-releasing hormone.⁵¹ Changes in this essential neuro-endocrine hormonal milieu can impair several aspects of sleep, including

depth of sleep, slow-wave sleep, rapid-eye-movement sleep, and waking.⁵² These adverse changes in sleep architecture act together with psychological stressors to produce significant sleep disturbances in patients with cancer⁵³ and may thereby contribute directly or indirectly to CRF.

Alterations in skeletal muscle energy metabolism have also been postulated to be a cause of CRF.⁵⁴ Accumulation of metabolites, deprivation of nutrients, and the disruption of mitochondrial synthesis of adenosine-5'-triphosphate (ATP) or diminished oxygen delivery to muscle cells can all affect skeletal muscle energy metabolism, thereby influencing the ability of the muscle to perform mechanical work. It is through these and other mechanisms that cancer, cancer treatment, and treatment-emergent side effects such as anemia or cachexia alter skeletal muscle energy metabolism and reduce the capacity for muscle contraction.^{39,55}

SYMPTOM ASSESSMENT

RISK FACTORS

Although CRF is experienced by patients almost universally across the continuum from diagnosis, through treatment, survivorship, and end of life, there is individual variability in its time course, severity, and extent to which it causes distress and interferes with daily activities. Risk factors for CRF^{19,39,44–46} that may account for this variability are summarized in Table 3-2.

TABLE 3-2

Risk Factors for CRF
• Advanced/metastatic disease or cancer recurrence
• Cancer treatment (chemotherapy, radiation, surgery, biologic agents, hormonal agents, molecularly targeted agents)
• Anemia
• Neutropenia
• Hypothyroidism
• Adrenal Insufficiency
• Hypogonadism
• Infection
• Malnutrition
• Depletion of vitamins B1, B6 and B12
• Electrolyte disturbances (calcium, magnesium, phosphorus)
• Cardiopulmonary, hepatic or renal dysfunction
• Sarcopenia, asthenia, deconditioning
• Proinflammatory cytokine expression associated with generalized inflammation
• Medications with sedating side effects (eg. narcotics, anxiolytics, antiemetics, antidepressants), or medications with fatigue as part of the side effects profile (e.g. beta-blockers) of medications
• Concurrent symptoms (eg. pain, dyspnea, nausea, diarrhea, urinary frequency)
• Impaired sleep quality
• Psychological distress (depression, anxiety)

SELF-ASSESSMENT

The etiology and clinical expression of CRF are multidimensional. An inherently subjective condition, fatigue may be experienced and reported differently by each individual. Qualitative studies of fatigue underscore the fact that the cancer fatigue experience is unlike any other fatigue individuals have previously experienced,¹⁰ and patients emphasize that its unpredictability and refractoriness to self-management strategies that were previously effective make it a particularly distressing symptom. Personality and coping style may also influence the experience of CRF.¹¹ As noted earlier, some patients complain of a loss of efficiency, mental fogging, inertia, and inability of sleep to have restorative effects, while others describe an excessive need to rest, the inability to recover promptly from exertion, and muscle heaviness and weakness. Efforts continue to be directed toward clarifying the defining features of fatigue,⁵⁶ and determining how CRF may be distinguished from syndromes such as depression, cognitive dysfunction, or asthenia that have overlapping symptoms^{13,14,57–61} or may share neurophysiologic mechanisms.^{15,62} Despite its complex etiology and often multifactorial presentation, fatigue may be defined quite simply as a persistent and subjective sense of tiredness that interferes with usual functioning.⁹

There are two aspects to symptom evaluation in the patient at risk for or experiencing CRF: (1) screening at regular intervals of all patients to identify the presence of CRF and gauge its severity, and (2) in patients with moderate or severe CRF, evaluating the characteristics, consequences, and potential contributing factors.

Brief screening measures for CRF are sensitive and can be applied efficiently in clinical settings to identify patients who could benefit from further evaluation.^{63,64} The NCCN guidelines⁹ recommend that every patient be screened for the presence of fatigue (yes/no). If present, CRF should be assessed quantitatively on a 0–10 scale (0 = no fatigue and 10 = worst fatigue imaginable). Those patients with a score of 4 or higher should be further evaluated by history and physical examination. Routine screening should occur at regular intervals during and following cancer treatment. Additional questions that may be useful in screening are provided in Figure 3-1.

Although a single-item measure may provide efficient screening for fatigue, evidence suggests that such measures do not fully capture all the dimensions of fatigue.⁶⁵ There is general consensus that the experience of fatigue can be separated into a sensory dimension (e.g., fatigue severity, persistence), a physiological dimension (e.g., leg weakness, diminished mental concentration), an affective dimension (e.g., sadness, loss of self-esteem), and a behavioral dimension (e.g., reduction in the performance of needed or valued activities). Multidimensional fatigue measures provide information about this full range of characteristics beyond fatigue presence and intensity. Measures available to evaluate

CRF include (1) multi-item scales that assess fatigue as a unidimensional construct (e.g., presence, severity, interference, distress); (2) instruments designed specifically to evaluate CRF from a multidimensional perspective (e.g., physical, behavioral, and affective components of fatigue); and (3) single items or subscales measuring relevant aspects of the fatigue experience that have been drawn from existing measures of quality of life, psychosocial adjustment, mood or self-reported health status.⁴⁵ More than 20 self-report measures have been developed to measure fatigue in patients with cancer.^{66–69} Examples of unidimensional measures of fatigue include the Functional Assessment of Cancer Therapy Fatigue (FACT-F),⁷⁰ Brief Fatigue Inventory,⁷¹ Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale,¹⁴ and the fatigue subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C-30).⁷² Multidimensional measures of fatigue include the Multidimensional Fatigue Inventory,⁷³ Multidimensional Fatigue Symptom Inventory,⁷⁴ and Piper Fatigue Scale.⁷⁵ Measures of health, symptoms, emotional distress, or mood state such as the Medical Outcomes Study Short Form-36 (SF-36),⁷⁶ Profile of Mood States,⁷⁷ Rotterdam Symptom Checklist,⁷⁸ Brief Symptom Inventory,⁷⁹ and Symptom Distress Scale⁸⁰ also include single items that address fatigue or have subscales that reflect fatigue, vigor, or vitality.

To efficiently gather data to explore the factors that may contribute to CRF—specifically, sleep disturbance, distress, inactivity, and concurrent medications—the NCCN has recently proposed the Fatigue and Contributing Factors Inventory.⁸¹ A new outcome measure to evaluate the construct of self-efficacy for fatigue management has also been recently developed and tested.⁸² This measure may be useful in effectiveness studies of interventions that target self-efficacy, and in research to identify the mechanisms through which fatigue interventions exert their effects on intermediate and distal clinical outcomes.

When selecting a measure of fatigue, it is important to keep in mind that other descriptors of fatigue such as weakness, tiredness, or lack of vigor may not necessarily be equated with fatigue.⁸³ Considerations of reliability, validity, responsiveness to change, recall period, respondent burden, translation in multiple languages, and the availability of normative values to aid interpretation should guide decisions about the utility of a measure for specific clinical or research purposes.⁸⁴

OBJECTIVE ASSESSMENT

History

As outlined in Table 3-3, a detailed history of the patient with CRF includes the presence, intensity, and pervasiveness of fatigue, its course over time, the factors that exacerbate or relieve fatigue, and the impact of fatigue on

1. In the past week, on a scale of 0 to 10, what is the 'worst' fatigue you have experienced?

None Worst

0 1 2 3 4 5 6 7 8 9 10

2. On how many days in the past week have you felt somewhat to quite fatigued?

None 1–2 days 3–5 days More than 5 days

Within the past week, to what extent has fatigued interfered with:

	Not at all	A little bit	Somewhat	Quite a bit	Very much
3. Performing the activities you need or want to do.....	0	1	2	3	4
4. Relationships with other people.....	0	1	2	3	4
5. Mood.....	0	1	2	3	4

6. Have you been experiencing any of the following symptoms during the past 7 days? Select all that apply:

I have no symptoms

Pain Nausea Poor Appetite Difficulty Sleeping

Shortness of Breath Difficulty moving around

Problem with Bowels Other

7. Would you like to discuss your fatigue with a member of your healthcare team?

No Yes

FIGURE 3-1

Screening Questions for CRF.

functioning and psychological distress. The consequences of CRF on mood, self-esteem, and the ability to perform activities of daily living; fulfill valued roles as a parent, spouse, and worker; and relate to family and friends are also evaluated. Inquiring about the self-management interventions the patient has tried for fatigue, including their effectiveness, can be helpful in tailoring recommendations for fatigue management.

A comprehensive history in a patient with CRF identifies etiologic or potentiating factors (as summarized in Table 3-3) that may contribute to CRF, including sleep disturbance, emotional distress, and uncontrolled symptoms.

The medication profile should also be reviewed to identify specific classes of medications (including over-the-counter medications) with a sedative side-effect profile. Medications with a sedating side-effect profile may include opioid analgesics, sedative-hypnotic agents such as secobarbital, benzodiazepines such as lorazepam, and anxiolytics such as buspirone. A number of antidepressant agents, antiemetics, antihistamines, and anticonvulsant agents (e.g., gabapentin, phenobarbital, tegretol) also have the potential to produce sedation, daytime sleepiness, and fatigue. Certain cardiac medications such as beta blockers may contribute to fatigue by causing bradycardia, while corticosteroids may

TABLE 3-3

Comprehensive Assessment of CRF

Severity

- On a scale of 0–10 where zero is no fatigue and 10 is the worst fatigue imaginable, how severe has your fatigue been in the past 7 days:
- Would you say that your fatigue is mild, moderate or severe?

Persistence/Frequency/Temporal Features

- When did the fatigue start? _____
- Frequency of fatigue: ____ days during past week or hours per day _____

Factors Associated with Fatigue

- What makes your fatigue better?
- What makes your fatigue worse?
- Does rest relieve your fatigue?
- Do you feel weak?
- Do you have any trouble sleeping?
- Do you have daytime sleepiness (likely to doze off during quiet activities such as reading, watching TV, sitting quietly after lunch)?
- Do you have other symptoms such as pain, difficulty breathing, nausea and vomiting?
- Do you experience anxiety? If yes, how often?
- Do you feel discouraged, blue or sad? If yes, how often?
- Do you feel bored? If yes, how often?

Interference/Distress

- As a result of fatigue, to what extent have you:
 - limited your social activity,
 - had difficulty getting things done
 - felt like fatigue was making it difficult to maintain a positive outlook
- To what extent does fatigue interfere with relationships or fulfilling responsibilities at work or in the home?

Self-Management

- What do you do to help with fatigue or manage fatigue?
- Have you discussed your fatigue with anyone on your health care team?
- Have you ever been given any recommendations for managing your fatigue?

cause fatigue by disrupting sleep or by creating proximal muscle weakness. Coadministration of multiple agents with sedative, cardiac, or sleep-disrupting side effects may significantly compound fatigue symptoms.

Physical Assessment and Diagnostic Evaluation

Physical examination of the patient with CRF may include clinical muscle strength testing; performance-based measures of physical function^{2,85} such as the 6-minute walk, timed-up and go, and grip strength; and auscultation of heart and lung for adventitious sounds.

Diagnostic evaluation in the patient with CRF is directed toward identifying the presence of hypothyroidism, hypogonadism, adrenal insufficiency, cardiomyopathy, pulmonary dysfunction, anemia, neutropenia, and electrolyte imbalance, as these conditions may cause or amplify CRF. Appropriate diagnostic tests will aid in determining whether disease progression or recurrence could be among the causes of fatigue.

DEGREES OF TOXICITY

The standard grading system for adverse events in cancer clinical trials is the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v.4.0).⁸⁶ Now in its fourth version, CTCAE toxicities are graded by healthcare providers, based on the clinician's review of systems, physical examination, and review of laboratory and diagnostic studies. One of every eight adverse events included in the NCI CTCAE is a symptom or a side effect that could be validly and efficiently collected by direct patient report. Currently, research staff identify and grade toxicities that are reflected by the clinical staff in the health record, even though studies have demonstrated that health professionals tend to underestimate the onset, duration, and severity of symptoms such as fatigue and pain, compared to patients' own accounts.^{87,88} Staff-based adverse event reporting also generally occurs at clinic visits, so adverse

events that occur between visits may be missed. As a result of these gaps, we often lack a full understanding of the spectrum of toxicities associated with a new agent or a new regimen.⁸⁹ This incomplete picture of treatment-associated toxicities hinders the drug development process, and may restrict optimal treatment of toxicities for individual patients.

In response to these challenges, the NCI has recently developed the Patient Reported Outcomes—Common Terminology Criteria for Adverse Events (PRO-CTCAE). PRO-CTCAE comprises a psychometrically robust set of questionnaire items evaluating the presence, severity, and interference with usual activities of 81 symptoms drawn from the CTCAE.⁹⁰ The overall goal of PRO-CTCAE is to enhance the quality of adverse event data reporting in clinical trials, represent the patient perspective, and improve detection of potentially serious adverse events.⁹¹ Incorporating the patient’s self-report into the toxicity evaluation also has the potential to improve patients’ satisfaction and communication with their clinicians and foster early detection of potentially serious adverse events.⁹² PRO-CTCAE toxicity assessment and CTCAE grading for CRF are presented in Figure 3-2.

SYMPTOM MANAGEMENT STRATEGIES

THERAPEUTIC APPROACHES

Because fatigue typically has several different causes in any one patient, a multicomponent, individually tailored treatment plan is essential. Open communication between the patient, family, and caregiving team will facilitate discussion about the experience of fatigue and its effects on daily life, and promote collaborative goal setting. Deliberative selection

of management strategies and tailoring of the program based on the patient’s current level of energy, attention, motivation, and phase in the cancer continuum are important considerations, as at least one study suggests that too intensive or demanding programs may actually worsen CRF.⁹³

General supportive care recommendations for patients with fatigue include encouraging consumption of a balanced diet with adequate intake of fluid, calories, protein, carbohydrates, fat, vitamins, and minerals, and balancing rest with physical activity and attention-restoring activities such as exposure to natural environments and pleasant distractions such as music.⁹

There have been more than 190 empiric studies of pharmacologic and nonpharmacologic interventions to reduce or manage CRF, and several meta-analyses or systematic reviews are available.^{94–104} For some interventions, there is strong and consistent evidence to support their effectiveness, while for other interventions only preliminary effectiveness data drawn from single-arm trials in small samples are available. Evidence-based interventions for CRF are summarized in Table 3-4.

Expert consensus indicates that patients with fatigue should be evaluated for potentially treatable etiologic factors contributing to fatigue, and managed as indicated.⁹ Examples of such factors include endocrinopathies (e.g., hypothyroidism, hypogonadism, adrenal insufficiency), cardiopulmonary dysfunction, impaired sleep quality, medications with fatigue or sedation as side effects (e.g., opiates, antidepressants, antiemetics, antihistamines), deconditioning, asthenia, sarcopenia, and concurrent symptoms such as pain, nausea, or depression.

Deconditioning related to decreased activity is common among patients with cancer, and can cause or intensify fatigue from other causes. Meta-analyses of randomized trials support the benefits of exercise in the management of

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days...

1. FATIGUE, TIREDNESS OR LACK OF ENERGY				
What was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe
How much did FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST INTERFERE with your usual or daily activities?				
<input type="radio"/> Not at all	<input type="radio"/> A little bit	<input type="radio"/> Somewhat	<input type="radio"/> Quite a bit	<input type="radio"/> Very much

FIGURE 3-2

Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) Fatigue Items

TABLE 3-4

Evidence-Based Interventions to Manage Cancer-Related Fatigue

Evaluate All Patients For Fatigue

- Screen all patients for fatigue at regular intervals: On a scale of 0–10 where zero is no fatigue and 10 is the worst fatigue imaginable, how would you rate your fatigue over the past 7 days?
- If moderate (4–6) or severe (7–10), evaluate onset, pattern, duration, change over time, contributing factors, interference with function, and self-management strategies, and develop a tailored fatigue plan

Exercise

- After appropriate medical clearances, recommend a program of physical activity such as walking, stretching, and cycling. Patient should begin with 5–10 minutes twice daily, and increase the time by 1 minute a day. They should avoid temptation to overdo in exercise, but rather strive for consistency
- Consider referral to physical therapy, occupational therapy, exercise physiologist, or psychiatrist to develop, tailor, and sustain an exercise program

Improve Sleep Quality

- Provide behavioral interventions to improve sleep (eg. go to bed only when sleepy and at approximately the same time each night; maintain a regular rising time each morning; avoid daytime napping, create a bedtime routine, avoid stimulants such as caffeine after noon, and eat dinner at least 3 hours before bedtime etc)

Energy Conservation and Activity Management

- Instruct patient in energy conservation and activity management:
 - Set priorities to reduce or eliminate tasks that are less important
 - Schedule a daily routine to ensure pacing of activities and balance of rest and activity
 - Delegate or use labor-saving devices
 - Schedule activities for times of peak energy and mental concentration

Interventions to Manage Stress and Mood Disturbances

- Maintain open communication among patient, family and health care professional about fatigue, its effects on daily life
- Offer information and referrals to counseling or support groups
- Consider treatment with an antidepressant for fatigue with depressive symptoms
- Teach diversional and relaxation techniques

Other Interventions

- Evaluate for treatable causes of fatigue (hypothyroidism, hypogonadism, adrenal insufficiency, cardiopulmonary dysfunction) and manage as indicated
- Optimize the management of concurrent symptoms (pain, depression, dyspnea)
- Consider referrals for structured rehabilitation, psychosocial and stress management interventions, or cognitive-behavioral therapy for sleep
- Consider massage, acupuncture, mindfulness-based stress reduction
- Consider levocarnitine supplementation or ginseng
- Consider treatment with a psychostimulant

Patient and Family Education about Fatigue

- Offer anticipatory guidance about possible patterns of fatigue onset occurrence (eg. at nadir, with conclusion of radiotherapy, in association with muscle weakness/deconditioning, distress, excess activity, impaired sleep quality, sedating medications)
- Encourage patient to differentiate facets of the fatigue experience (fatigue, tiredness, weakness, cognitive slowing)
- Explain the multifactorial causes of fatigue including:
 - Side effects of treatment
 - Psychosocial stressors
 - Concurrent symptoms
 - Imbalance of rest and activity
 - Insufficient sleep
 - Inadequate nutrition
 - Muscle weakness/deconditioning
 - Sedating/fatiguing side effects of medications
 - Proinflammatory cytokine release
 - Anemia/neutropenia

TABLE 3-4

Evidence-Based Interventions to Manage Cancer-Related Fatigue (Continued)

- Explain that fatigue can develop or worsen as a direct result of treatment, and that this does not necessarily indicate that a treatment is ineffective or that the disease is progressing.
- Suggest a journal, log or diary of activities, fatigue severity, associated feelings/symptoms, and an evaluation of self-care actions
- Develop and tailor an individualized plan for fatigue management
- Inform patient and family that interventions such as energy conservation, exercise, relaxation and stress management, psychosocial support, and measures to optimize sleep quality and reduce concurrent symptoms have been shown to be effective in limiting the severity of fatigue during treatment
- Teach energy conservation strategies and principles of cognitive-behavioral self-management to improve sleep quality, and provide coaching to integrate these into daily patterns
- Affirm the benefits of open communication between patient, family and caregiving team to facilitate discussions about the experience of fatigue and its effects on daily life
- Encourage attention restoring activities such as exposure to natural environments, and pleasant distractions such as music
- Provide information concerning the importance of a balanced diet with adequate intake of fluid, calories, protein, carbohydrates, fat, vitamins, minerals

fatigue during and following cancer treatment for patients with breast cancer, with solid tumors, or undergoing hematopoietic stem cell transplantation, although effect sizes are generally small and positive results for the outcome of fatigue have not been observed consistently across studies.^{98,105–110} The exercise modalities that have been tested differ in content (walking, cycling, swimming, resistive exercise, or combined exercise), frequency (ranging from two times per week to two times daily), intensity (with most programs at 50% to 90% of the estimated VO_2 maximum heart rate), degree of supervision (fully supervised group versus self-directed exercise), and duration (from 2 weeks to 1 year). The type, intensity, and duration of physical exercise most beneficial in reducing fatigue at different stages of disease and treatment are not known,^{107,108,111} and more research is needed to systematically assess the safety of exercise (both aerobic exercise and strength training) in cancer subpopulations. Patients require specific guidance about how to begin, maintain, and advance an exercise program. Referral to a rehabilitation professional such as physical therapist or an exercise trainer can be helpful in providing specific and detailed recommendations about the type, intensity, and frequency of exercise in which the patient should engage; in strengthening motivation and adherence; and in recommending advancements in the exercise program as functional capacity improves.

Several trials^{112–115} and a systematic review¹¹⁶ suggest that structured rehabilitation programs result in statistically significant and sustained improvements in fatigue, particularly in patients who have completed treatment and are in the survivorship phase. The rehabilitation interventions studied were multicomponent interventions consisting of a structured combination of intensive exercise, physical training, sports, psychoeducation, and physical modalities such as massage, mud packs, and manual lymph drainage. In some studies, these therapies were delivered over the course of a several-week inpatient rehabilitation hospital stay.

A growing body of evidence that includes several adequately powered randomized controlled trials suggests that educational interventions and psychological support play an important role in supporting positive coping in patients with fatigue.¹¹⁷ Effective psychoeducational and self-management interventions include anticipatory guidance about patterns of fatigue, tailored recommendations for self-management of fatigue through activity/exercise and improved sleep hygiene, coaching to enhance motivation and empower self-care and active coping, and praise and encouragement to promote self-efficacy and augment feelings of control.

Energy conservation and activity management (ECAM) is a self-management intervention that teaches patients to apply the principles of energy conservation and activity management and provides coaching to integrate these activities into their daily lifestyle. ECAM has been found to have a modest but significant effect in a large, multisite randomized controlled trial (RCT) in patients (predominantly with breast cancer) initiating chemotherapy or radiation and in a small pilot study using historical controls^{118,119}; however, a recent study did not find significant effects on fatigue outcomes when an energy and sleep self-management intervention was tested in patients receiving chemotherapy.¹²⁰

Cognitive-behavioral interventions designed to improve sleep quality also have demonstrated a beneficial effect on fatigue.^{121,122} These interventions to improve sleep quality can be delivered individually or in a group setting, and include relaxation training, sleep consolidation strategies (avoiding long or late-afternoon naps, limiting time in bed to actual sleep time), stimulus control therapy (going to bed only when sleepy, using the bed/bedroom for sleep and sexual activities only, lying down and getting up at a consistent time, avoiding caffeine and stimulating activity in the evening), and strategies to reduce cognitive-emotional arousal (keeping at least an hour to relax before going to bed, establishing a pre-sleep routine to be used every night).

Cognitive-behavioral therapy (CBT) to treat fatigue and manage concurrent symptoms such as pain or depression has been shown to have beneficial effects on CRF.⁹⁹ Although outcomes of a randomized controlled trial of CBT for cancer pain in 131 patients demonstrated improvement in the outcomes of pain, the differences in fatigue were not statistically significant.¹²³ However, three RCTs ($n = 200$ cancer patients with major depressive disorder¹²⁴; $n = 83$ cancer survivors with fatigue¹²⁵; $n = 45$ women with metastatic breast cancer¹²⁶) and a small case series ($n = 6$ women with metastatic breast cancer¹²⁷) demonstrated that a CBT intervention targeted to fatigue and other symptoms resulted in statistically significant improvements in fatigue.

The use of erythropoiesis-stimulating agents (ESAs) to correct anemia characterized by a hemoglobin level less than 10 g/dL may result in increased vigor and diminished fatigue.^{128–131} In contrast, only limited evidence supports the contention that erythropoietin improves fatigue outcomes when anemia is less severe. A target hemoglobin level of 11–12 g/dL is associated with the greatest gains in fatigue and other quality of life outcomes.¹³¹ While both epoetin and darbepoetin are generally well tolerated, the use of these agents specifically for the management of fatigue must be considered in light of safety issues including a small increased risk of thrombotic events, hypertension, and pure red cell aplasia, and theoretical concerns that ESAs may support or extend tumor growth in certain disease tumor types.^{132,133} Overall, better-quality evidence is needed to unequivocally support the use of ESAs solely to improve patient-reported outcomes such as fatigue. National clinical practice guidelines^{134–136} and the recommendations of the Food and Drug Administration (FDA) should guide decisions about patient monitoring, treatment thresholds, dose reductions, treatment initiation and discontinuation, and the use of supplemental iron in patients receiving ESAs.

Paroxetine, donepezil, bupropion, methylphenidate, and modafinil have been evaluated for their effectiveness in reducing fatigue during and following cancer treatment. Several recent systematic reviews have concluded that only two pharmacologic treatments for CRF—treatment with psychostimulants (methylphenidate and dexamethylphenidate) and the wakefulness-promoting agent modafinil—are supported by evidence from adequately designed randomized trials.^{97,101,102} Although additional evidence is needed, modafinil at a dose of 100 mg bid may be effective in treating fatigue and improving daytime wakefulness and cognitive function in patients during and following cancer treatment.^{137–140} Randomized placebo-controlled trials of antidepressants do not appear to have a direct effect on fatigue outcomes, although improvement in mood has been seen.^{97,141} In contrast, two small trials have demonstrated a trend toward a possible benefit for paroxetine in treating fatigue in two distinct subpopulations: women experiencing hot flashes and patients receiving interferon alpha.¹⁴¹

Several trials suggest that levocarnitine supplementation in patients who have low serum carnitine levels^{142–145} and treatment with ginseng¹⁴⁶ are potentially efficacious in treating cancer-related fatigue. Levocarnitine is a naturally occurring amino acid that plays a vital role in the metabolism of fat by the mitochondria, and is thought to be essential for muscle contraction and endurance.¹⁴⁷ Systemic carnitine depletion is characterized by fatigue and muscle weakness, and has been described in association with cancer and its treatment.^{148,149} Although interpretation of the results of the studies of levocarnitine or ginseng supplementation is complicated by small sample sizes, and in the case of levocarnitine by the absence of a double-blinded randomized controlled design, results are intriguing. The antioxidant effects of levocarnitine supplementation on treatment outcomes in patients receiving radiotherapy or chemotherapy also warrant further study.^{150,151}

Complementary therapies such as yoga, relaxation, healing touch, massage, a mindfulness-based stress reduction intervention, acupuncture, acupressure and several combined modality interventions that include aromatherapy, lavender footsoak, and reflexology have demonstrated preliminary evidence of effectiveness in the management of CRF.¹⁵² The design of these studies was open label and/or uncontrolled, with no random assignment, and with sample sizes that were extremely small, making it difficult to draw firm conclusions about efficacy. Of note, the studies evaluating acupuncture and the combined aromatherapy, footsoak, and reflexology intervention included patients with advanced cancer and at the end of life. If found to be effective in larger RCTs, these approaches may offer treatment options for patients with advanced cancer and those at the end of life for whom other fatigue interventions such as exercise may not be feasible.

In summary, although we have made gains in identifying interventions that are effective for this distressing symptom, the causative factors for CRF are distinct, and treatment approaches are evolving and largely empiric. The intervention approach for each patient is symptom oriented, and must be individualized and regularly revised. A multimodal approach that includes exercise, psychoeducational interventions, efforts to manage concurrent symptoms, and interventions to improve sleep quality, together with judicious use of medications such as modafinil, methylphenidate, and complementary therapies such as relaxation, massage, healing touch, or acupuncture, has the potential to improve clinical outcomes in CRF. An algorithm for fatigue screening, evaluation, and management is offered in Figure 3-3.

NURSING IMPLICATIONS

CRF outcomes sensitive to nursing intervention include a reduction in fatigue severity and improvements in the psychological distress and functional interference associated with fatigue. Other outcomes that reflect the effects of nursing

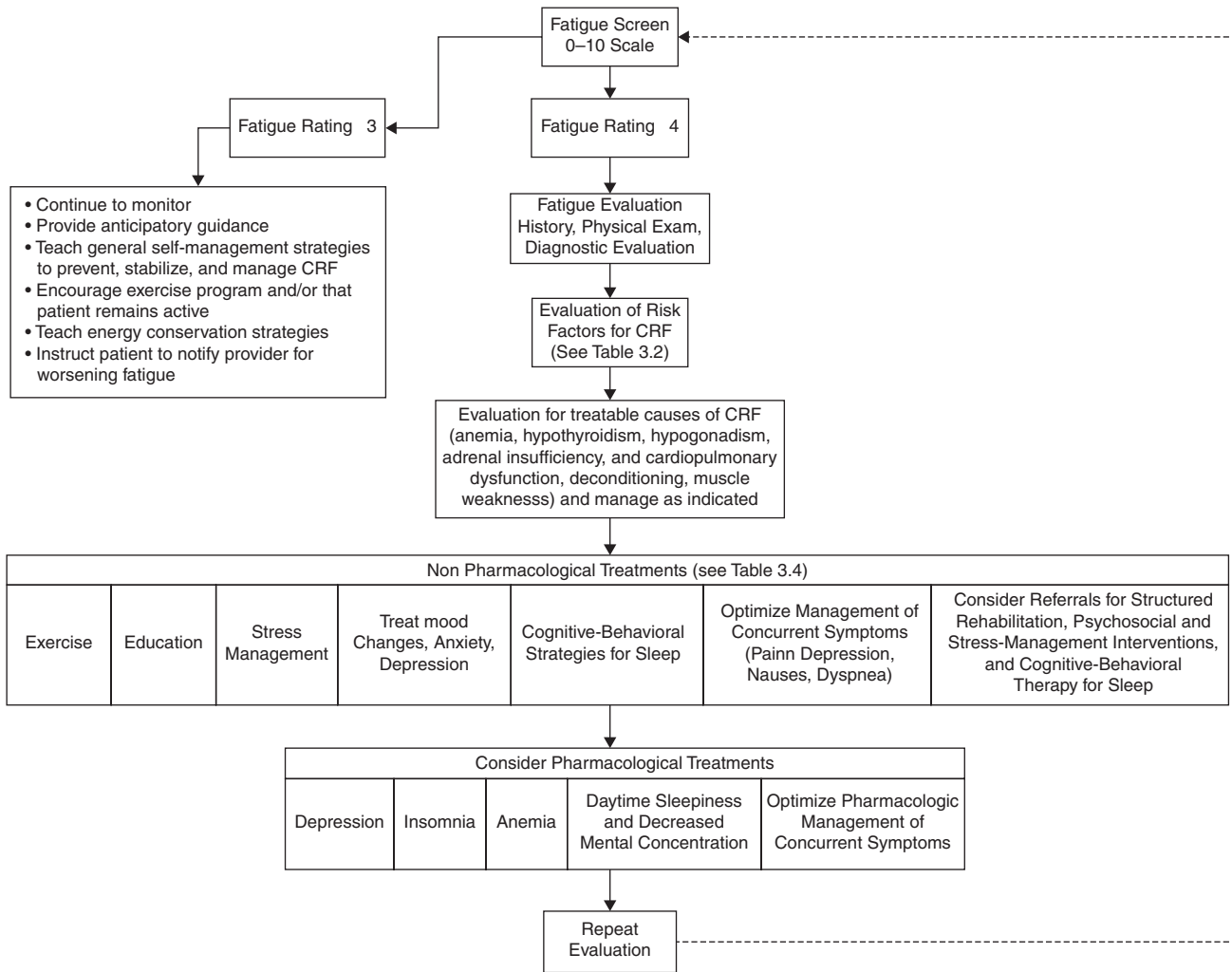


FIGURE 3-3
Algorithm for Fatigue Screening, Evaluation and Management.

intervention include adequate knowledge of strategies for effective self-management, and self-efficacy for fatigue management. In some clinical situations (e.g., patients undergoing hematopoietic stem cell transplant or beginning a course of radiation therapy), reduction in fatigue severity, associated distress, and interference will not be achievable. In these circumstances, the clinical goal is to stabilize worsening of the fatigue severity, distress, and interference that would be expected across the course of treatment. Process outcomes that reflect implementation of an effective fatigue management program include that (1) all patients with cancer are screened for fatigue during each encounter with the health-care team while on active treatment and during long-term follow-up, and (2) in patients with moderate to severe fatigue, the health record documents the factors that contribute to cancer fatigue (concurrent symptoms, emotional distress, sleep disturbances, anemia, nutritional alterations, inactivity/

deconditioning, and comorbidities such as hypothyroidism and cardiomyopathy) and the management plan to address these issues. Evidence-based guidelines to support the achievement of these outcomes have been published by the NCCN⁹ and by the Oncology Nursing Society.¹⁵²

PATIENT SELF-CARE

Evidence suggests that across the continuum from diagnosis, to treatment, survivorship, and the end of life, implementation of clinical guidelines and self-management interventions may reduce barriers to effective fatigue management,^{153,154} contribute to reductions in fatigue severity, and improve the distress associated with CRF. A self-care guide that can be shared with patients to strengthen their knowledge of effective fatigue self-management is provided in Appendix 3A.

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Fatigue

Patient Name: _____

Symptom and Description

Fatigue is a common problem for patients during and often for many months following cancer treatment. It is one of the most difficult side effects of treatment and can be hard to describe to others. The symptoms of fatigue are different than “feeling tired.” Fatigue can begin suddenly; it can affect all of your regular activities; naps may not help; and fatigue can be physically and emotionally draining on the patient as well as the family. General weakness may occur with a heavy feeling in your arms or legs, decreased ability to concentrate, trouble sleeping, and/or irritability. People sometimes think that patients with fatigue are just being lazy or depressed.

Many factors can contribute to the fatigue that a person with cancer experiences. Sudden changes in feelings of fatigue may mean that there is a serious problem. Slower, gradual development of fatigue can limit your ability to do everyday activities and enjoy life.

If you are experiencing this type of extreme tiredness, begin by speaking to your nurse or doctor about it. A few simple tests, including a blood count to check for anemia or infection, thyroid function tests, and a physical examination, will help your health provider find some causes that are treatable. Fatigue can be managed with a plan just for you and the factors that may be causing your fatigue.

Here are some ideas to think about:

Exercise

- With permission from your healthcare team, begin a program of physical activity such as walking, stretching, and cycling. Begin with 5–10 minutes twice daily, and increase the time by 1 minute per day. Do not be tempted to overdo the exercise, but be consistent.
- A moderate amount of exercise may help improve your energy level. Find a friend to walk with; he or she can encourage you to get out when you are tempted to stay in. An exercise trainer or physical therapist can also help with strengthening and building muscles and improving flexibility and balance.
- Think about asking your healthcare provider to refer you to physical therapy, occupational therapy, or an exercise specialist (such as a physiologist or physiatrist) to plan your own exercise program.

Gain Information about Fatigue

- Learn more about fatigue, and educate your family so they can be supportive.
- Consider the possible patterns of when fatigue occurs (e.g., related to muscle weakness/deconditioning, distress, excess activity, poor sleep quality, medications that make you sleepy) to see what makes fatigue better or worse.
- Learn the different aspects of the fatigue experience (fatigue, tiredness, weakness, cognitive slowing).
- Keep a journal or diary of activities, severity of fatigue, your feelings, symptoms, and the results of your self-care actions.

Improve Sleep Quality and Quantity

- Try to get undisturbed sleep. Go to bed at a regular time each day and follow a regular routine. The routine will begin to serve as a signal to your body that it is time for sleep.
- If you wake up at night because of pain or other symptoms, ask your doctor or nurse if your medication schedule can be changed to allow more hours of sleep at night.
- Try other activities rather than napping. Taking a daytime nap is almost a guarantee that you will have trouble sleeping at night. Try activities such as meditation, massage, or yoga instead. These activities can also help you avoid sleep troubles by reducing the anxiety and stress that play a part in sleep difficulties.

Energy Conservation and Activity Management

Energy conservation means looking at your daily routines to find ways to reduce the amount of effort needed to perform certain tasks and stopping other tasks. Sometimes switching rest periods with activities throughout the day can help. Although not every technique will work for you, these are suggestions that you can consider:

- Set priorities to reduce or stop tasks that are less important. Sort out the really important activities from those that can wait.
- Schedule a daily routine to help you balance rest and activity.
- Ask others to do some tasks such as laundry or meals or use labor-saving devices such as a robotic vacuum cleaner.
- Schedule activities for times of peak energy and mental concentration.
- Keep a journal to learn your energy patterns.
- Do not do jobs that need not be done every day, such as making beds.
- Ask your healthcare team about an occupational therapy evaluation to teach you energy-saving strategies.
- Keep a list of tasks that need to be done near your phone. When a neighbor, family member, or friend asks what they can do to help, tell them!

Seek Help in Managing Stress, Symptoms, and the Ups and Downs of the Cancer Experience

- Maintain open communication with family, friends, and healthcare professionals about fatigue and its effects on daily life.
- Ask your nurse or doctor if your fatigue or the other symptoms that are adding to your fatigue might be helped with medication.
- Make your team aware of the effects of your tiredness on your daily life.
- Consider joining a support group or talking with a counselor.

Phone Numbers

Nurse: _____ Phone: _____

Physician: _____ Phone: _____

Other: _____ Phone: _____

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