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Cancer-Related Fatigue, Version 2.2015:

Clinical Practice Guidelines in Oncology

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Abstract

Cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. It is one of the most common side effects in patients with cancer. Fatigue has been shown to be a consequence of active treatment, but it may also persist into posttreatment periods. Furthermore, difficulties in end-of-life care can be compounded by fatigue. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer-Related Fatigue provide guidance on screening for fatigue and recommendations for interventions based on the stage of treatment. Interventions may include education and counseling, general strategies for the management of fatigue, and specific nonpharmacologic and pharmacologic interventions. Fatigue is a frequently underreported

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.
All recommendations are category 2A unless otherwise noted.
Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

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Disclosures for the NCCN Cancer-Related Fatigue Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.
Individual disclosures for the NCCN Cancer-Related Fatigue Panel members can be found on page 1039. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)
These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

complication in patients with cancer and, when reported, is responsible for reduced quality of life. Therefore, routine screening to identify fatigue is an important component in improving the quality of life for patients living with cancer.

Overview

Fatigue is a common symptom in patients with cancer. It is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biologic response modifiers.[1–3] According to a survey of 1569 patients with cancer, fatigue is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.[4,5] In patients with metastatic disease, the prevalence of cancer-related fatigue (CRF) exceeds 75%.[6–9] Using a cutpoint of 4 or higher for moderate fatigue and 7 or higher for severe fatigue on a 0- to 10-point scale, moderate to severe fatigue was reported by 983 of 2177 patients (45%) who were undergoing active outpatient treatment, and 150 of 515 survivors (29%) experiencing complete remission from breast, prostate, colorectal, or lung cancer.[10] Cancer survivors report that fatigue is a disruptive symptom experienced months or even years after treatment ends.[11–18] The distinction between tiredness, fatigue, and exhaustion has not been made in practice, despite conceptual differences.[19,20] Patients perceive fatigue to be the most distressing symptom associated with cancer and its treatment, more distressing even than pain or nausea and vomiting, which can generally be managed using medications.[21]

Fatigue in patients with cancer has been under-reported, underdiagnosed, and undertreated. Persistent CRF affects quality of life (QOL), because patients become too tired to fully participate in the roles and activities that make life meaningful.[13,22] Health care professionals have been challenged in their efforts to help patients manage this distressful symptom and to remain as fully engaged in life as possible. Because of the successes in cancer treatment, health care professionals are now likely to see patients with prolonged states of fatigue related to the late effects of treatment. Disability-related issues are relevant and often challenging, especially for patients with cancer who are cured of the malignancy but have continued fatigue.[23] Despite biomedical literature documenting this entity, it is often difficult for patients with CRF to obtain or retain disability benefits from insurers. Health care professionals should advocate for patients who require disability benefits, and educate insurers about this issue.

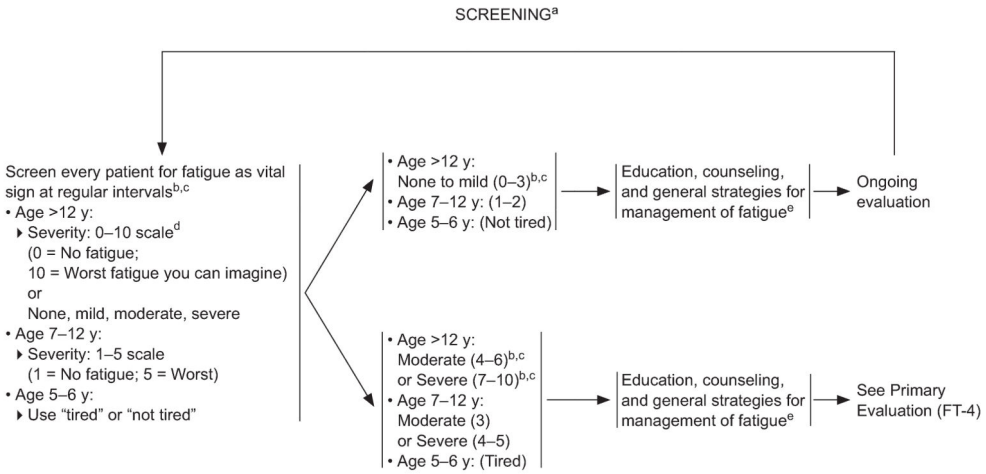
DEFINITION OF CANCER-RELATED FATIGUE

Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.

STANDARDS OF CARE FOR CANCER-RELATED FATIGUE IN CHILDREN/ADOLESCENTS AND ADULTS

- Fatigue is rarely an isolated symptom and most commonly occurs with other symptoms, such as pain, distress, anemia, and sleep disturbances, in symptom clusters. Therefore, patients should be screened for multiple symptoms that may vary according to diagnosis, treatment, and stage of disease.
- Fatigue is a subjective experience that should be systematically assessed using patient self-reports and other sources of data.
- Fatigue should be screened, assessed, and managed according to clinical practice guidelines.
- All patients should be screened for fatigue at their initial visit, at regular intervals as a vital sign during and following cancer treatment, and as clinically indicated.
- Fatigue should be recognized, evaluated, monitored, documented, and treated promptly for all age groups, at all stages of disease, prior to, during, and following treatment.
- Patients and families should be informed that management of fatigue is an integral part of total health care and that fatigue can persist following treatment.
- Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner.
- Implementation of guidelines for fatigue management is best accomplished by interdisciplinary teams who are able to tailor interventions to the needs of the individual patient. Consider referral to an appropriate specialist or supportive care provider.
- Educational and training programs should be implemented to ensure that health care professionals have knowledge and skills in the assessment and management of fatigue.
- Cancer-related fatigue should be included in clinical health outcome studies as an independent variable and potential moderator of outcome.
- Quality of fatigue management should be included in institutional continuous quality improvement projects.
- Medical care contracts should include reimbursement for the management of fatigue.
- Disability insurance should include coverage for the continuing effects of fatigue.
- Rehabilitation should begin with the cancer diagnosis.

FT-1
FT-2



[a]See Discussion Appendix for screening resources (available online, in these guidelines, at NCCN.org).

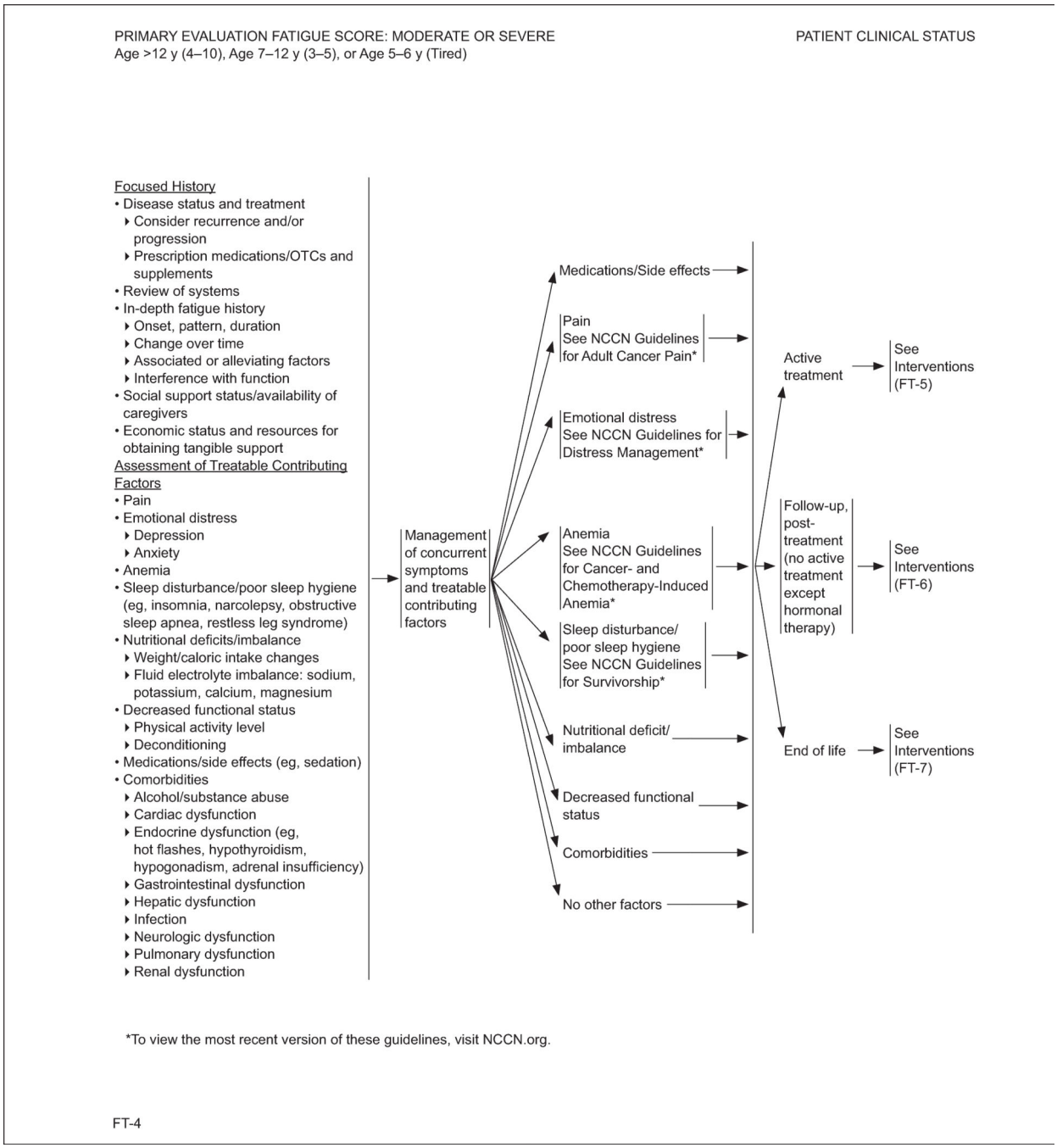
[b]Recommended screen and re-evaluation: "How would you rate your fatigue on a scale of 0–10 over the past 7 days?"

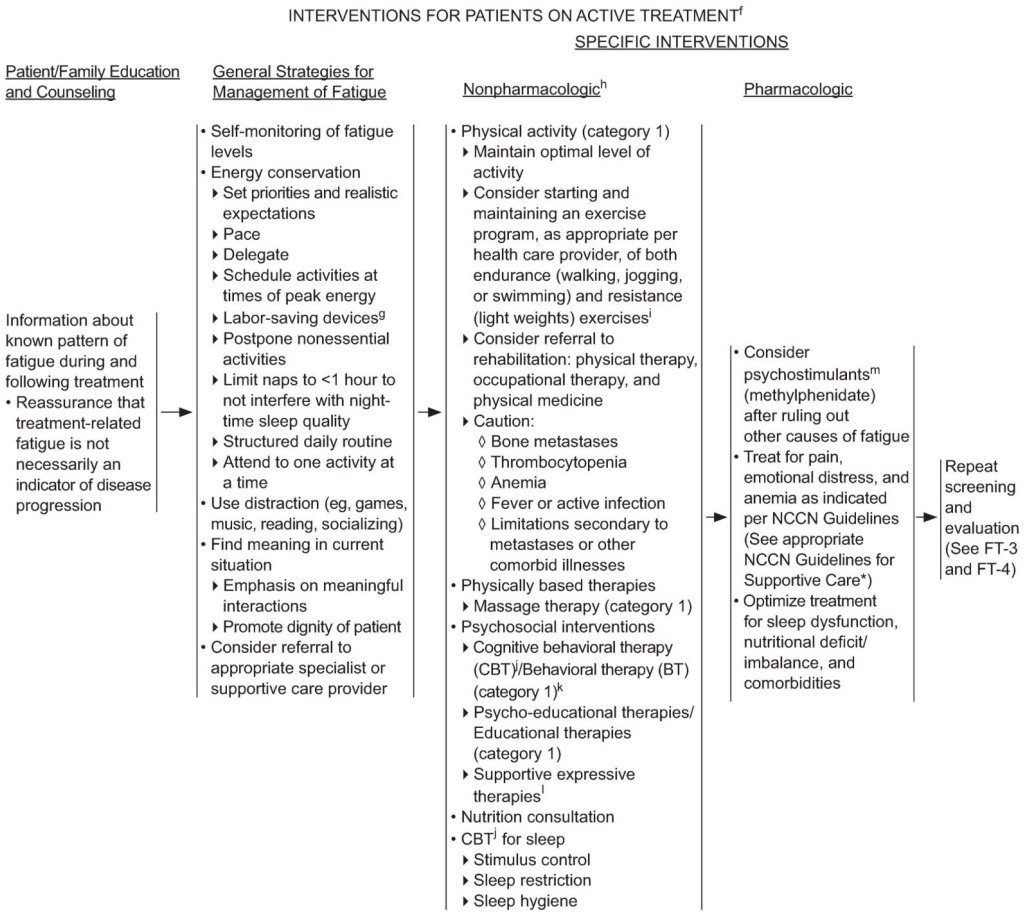
[c]Fatigue scale for children is simplified: Use "tired" or "not tired" as screen for young children (age <6 or 7 y).

[d]Butt Z, Wagner LI, Beaumont JL, et al. Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. J Pain Symptom Manage 2008;35:20-30.

[e]See "Patient/Family Education and Counseling" and "General Strategies for Management of Fatigue" based on clinical status: Active Treatment (FT-5), Post-Treatment (FT-6), and End of Life (FT-7).

FT-3





*To view the most recent version of these guidelines, visit NCCN.org.

[f]See Discussion for information on differences between active treatment, post-treatment, and end-of-life treatment.

[g]Examples include use of reachers for grasping items beyond arm's length, sock aids for pulling on socks, rolling carts for transporting items, escalators and elevators for traveling between building floors, and electrical appliances for performing common household tasks (eg, opening cans).

[h]Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources.

[i]See NCCN Guidelines for Survivorship (SE-3*).

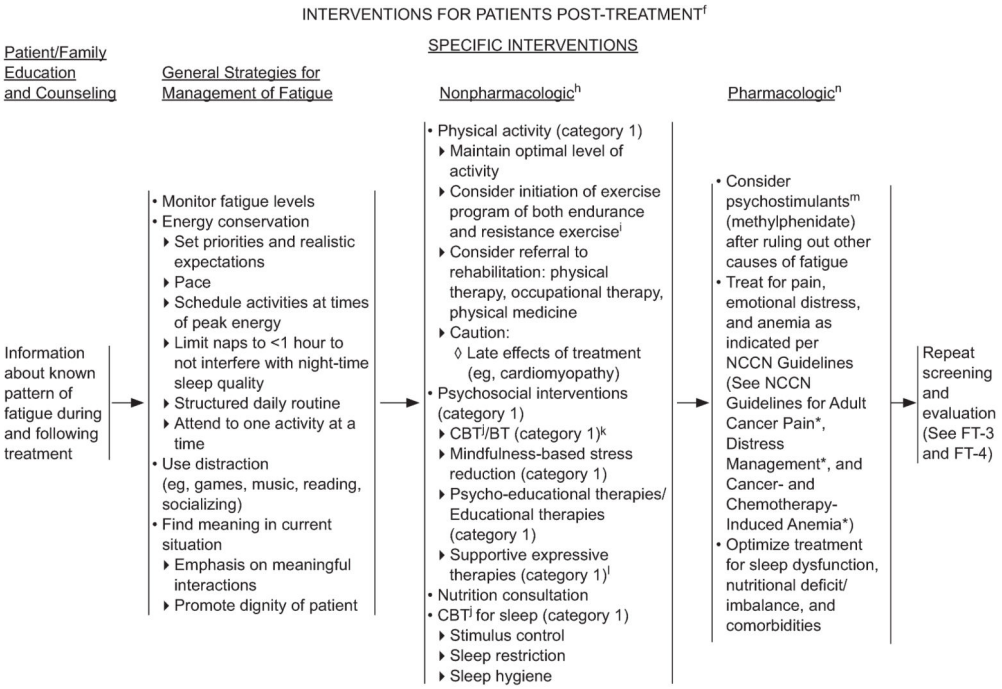
[j]A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and behaviors and to facilitate psychological adjustment.

[k]CBT/BT influences thoughts and promotes changes in behavior; it includes relaxation strategies.

[l]Supportive expressive therapies (eg, support groups, counseling, journal writing) facilitate expression of emotion and foster support from one or more people.

[m]Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in patients with cancer.

FT-5



*To view the most recent version of these guidelines, visit NCCN.org.

[f]See Discussion for information on differences between active treatment, post-treatment, and end-of-life treatment. (See MS-1)

[h]Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources.

[i]See NCCN Guidelines for Survivorship (SE-3*).

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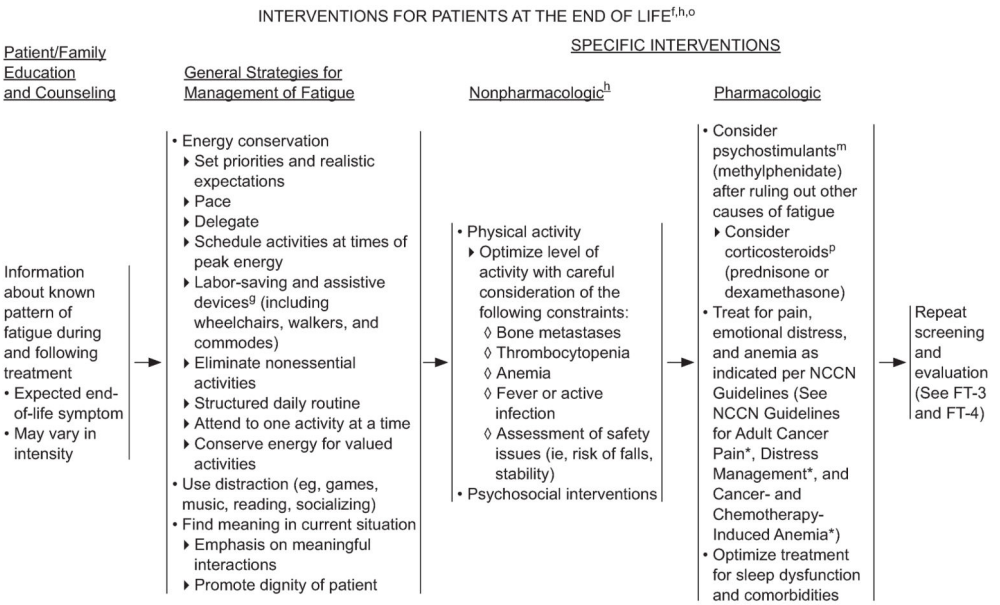
[m]Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in patients with cancer.

[n]Adjustment of current treatments for pain, sleep disturbances, and other symptoms and comorbidities, including drugs. Nonpharmacologic management of pain may be considered, such as palliative radiation, nerve blocks, or epidural management.

FT-6



Despite the prevalence of CRF, the specific mechanisms involved in its pathophysiology are unknown. Proposed mechanisms include proinflammatory cytokines,[24–26] hypothalamic-pituitary-adrenal (HPA) axis dysregulation,[24] circadian rhythm desynchronization,[27] skeletal muscle wasting,[28] and genetic dysregulation[29]; however, limited evidence supports these proposed mechanisms.

To address the important problem of CRF, NCCN convened a panel of experts. The NCCN Guidelines for Cancer-Related Fatigue, first published in 2000[30] and updated annually,

synthesize the available research and clinical experience in this field and provide recommendations for patient care.

Defining Cancer-Related Fatigue

The panel defines CRF as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Compared with the fatigue experienced by healthy individuals, CRF is more severe, more distressing, and less likely to be relieved by rest. In terms of the defining characteristics, the subjective sense of tiredness reported by the patient is important to note. As with pain, the clinician must rely on the description of fatigue and accompanying distress provided by the patient. Fatigue that interferes with usual functioning is another substantial component of the definition for CRF and the source of much distress for patients.[31] Investigations have documented a significant effect of fatigue on physical functioning during cancer treatment, and whether patients regain full functioning when treatment is complete is uncertain.[32,33]

Standards of Care for Assessment and Management

The panel developed the Standards of Care for CRF Management using the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adult Cancer Pain and for Distress Management as exemplar models (see “Standards of Care for Cancer-Related Fatigue in Children/Adolescents and Adults,” page 1014 [FT-2]; to view the most recent versions of all NCCN Guidelines, visit NCCN.org). These fatigue standards represent the best level of care for the assessment and management of fatigue in patients with cancer, including children, adolescents, and adults, and should provide guidance for health care professionals as they implement these guidelines in their respective institutions and clinical settings. The overall goal of the standards and guidelines is to ensure that all patients with cancer experiencing fatigue are identified and given prompt, effective treatment.

The first standard recognizes fatigue as a subjective experience that should be systematically assessed using patient self-reports and other sources of data. Because it is a symptom that is perceived by the patient, fatigue can be described most accurately through self-report. The history and physical examination, laboratory data, and descriptions of patient behavior provided by family members, especially regarding children, are important sources of additional information.

Fatigue should be screened, assessed, and managed in most patients according to the clinical practice guidelines. The NCCN Guidelines provide “best care” information based on current evidence to support treatment.[34] Patients should be screened for the presence and severity of fatigue at their initial clinical visit, at appropriate intervals during and after cancer treatment, and as clinically indicated. Screening should identify fatigue. Patients and families should be informed that managing fatigue is an integral part of total health care. All patients should receive symptom management. Furthermore, if patients cannot tolerate their cancer treatment or if they must choose between treatment and QOL, control of their disease may be diminished.[35]

Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner. The guidelines for fatigue are best implemented by an interdisciplinary institutional committee, including experts in medicine, nursing, social work, physical therapy, and nutrition.[36] The panel recognizes that education and training programs are needed to prepare oncology experts in fatigue management. These are now being offered, but much more attention to these programs within the institutional setting is necessary if professionals are to become skilled in managing fatigue. Variation exists among institutions regarding which professional disciplines and staff can provide appropriate specialized consultation for fatigue. Therefore, in addition to implementation of fatigue treatment guidelines, health care providers should familiarize themselves with the type of supportive care staff available at their institution.

The NCCN Panel recommends that assessment of CRF levels be included in outcomes research. Quality of fatigue management should be included in institutional continuous quality improvement projects. Institutions can make faster progress in implementing these guidelines if they monitor adherence and progress with the recommendations. Medical care contracts should reimburse for managing fatigue, including referrals to a physical therapist, dietitian, or the institution's symptom management service. Disability insurance should include coverage for the continuing effects of fatigue that lead to persistent disability. Rehabilitation should begin with a cancer diagnosis and should continue even after cancer treatment ends.

Guidelines for Evaluation and Treatment

The general schema of the fatigue algorithm defines 4 phases: screening, primary evaluation, intervention, and reevaluation. During the first phase, the health care professional must screen for fatigue and, if present, assess the intensity level. If the intensity level is moderate to severe, the health care professional is directed during the primary evaluation phase of the algorithm to conduct a more focused history and physical examination. This phase also includes an in-depth fatigue assessment and an evaluation of concurrent symptoms and contributing factors frequently associated with fatigue, and can be treated as an initial step in managing fatigue. If, however, a patient either does not have one of these trea contributing factors or continues to have moderate to severe fatigue after treatment of the factors, the health care professional should recommend additional treatment based on the NCCN Guidelines for CRF.

After the evaluation phase, the guidelines delineate a set of interventions for the amelioration of fatigue based on clinical status (ie, active cancer treatment, posttreatment, end of life). Education and counseling are believed to be central to the effective management of fatigue. Additional interventions that are both nonpharmacologic and pharmacologic may be introduced; in many instances a combination of approaches must be used. The treatment of fatigue is continuous and, as indicated by the reevaluation of patients, leads to an iterative loop of fatigue screening and management. Regardless of whether a patient demonstrates moderate to severe fatigue, health care professionals should continue to monitor for fatigue both throughout and after treatment, because fatigue symptoms have been shown to persist

for years. Although no studies have evaluated the long-term treatment of fatigue, it should be assessed and measures should be taken to reduce its impact on QOL.

Screening

The first phase of the algorithm emphasizes the screening of every patient for the presence or absence of fatigue. If fatigue is present, a quantitative or semiquantitative assessment should be performed and documented. For example, on a 0 to 10 numeric rating scale (0 = no fatigue; 10 = worst fatigue imaginable), mild fatigue is indicated as a score of 1 to 3, moderate fatigue as 4 to 6, and severe fatigue as 7 to 10. The evaluation of fatigue in children may be simplified to a scale of 1 to 5 and modified even further in young children (age 5–6 years) who may be asked more simply if they are “tired” or “not tired.”[2,37–39] If the screening process determines that fatigue is absent or at a mild level, the patient and family should receive education and common management strategies for fatigue. Periodic rescreening and reevaluation are recommended. Inpatients should be screened daily and outpatients should be screened at subsequent routine and follow-up visits. Survivors and patients who have completed treatment must still be monitored for fatigue, because fatigue may exist beyond the period of active treatment.[40]

Valid and reliable instruments are available to measure fatigue in children, adolescents, and adults (Table 1, available online, in these guidelines, at NCCN.org [MS-23]); however, the effectiveness of these methods is limited without adequate implementation. Currently, screening is not systematic or effective in many practice settings for various reasons, which often include patient or family barriers and clinician barriers. For example, patients may not want to bother their health care professional in the clinic or office or when they are hospitalized. Patients are also concerned that if they report high levels of fatigue, they might have their treatment altered. Patients do not want to be perceived as complaining, and therefore may not mention fatigue. Or, they may assume that they must live with fatigue, because they believe there is no treatment for it.

Health care professionals may not start a discussion about fatigue for many of the same reasons. First, clinicians may not recognize that fatigue is a problem for the patient. As a symptom, fatigue has been unrecognized and untreated, whereas medical advances have led to better control over the more noticeable or less subtle acute symptoms of nausea, vomiting, and pain. More recently, researchers have begun to document the prevalence and incidence of fatigue, correlating these data with the degree of disruption to QOL.[41–43] Second, health care professionals may not be aware that effective treatments are available for fatigue despite a lack of knowledge about the underlying pathophysiology and mechanisms.

Given these barriers, screening for CRF must be emphasized. Clinical experience with fatigue assessment has shown that some patients cannot put a numeric value on their fatigue. Consequently, some patients may need to rate fatigue as mild, moderate, or severe. In some circumstances, other sources of data must be used. For example, the patient may not be aware that fatigue has negatively affected his or her life; the spouse, parents, or other family members may be more cognizant of these changes and the effect of fatigue in the patient.

Using the numeric rating scale (ie, 0–10), fatigue studies in patients with cancer have revealed a marked decrease in physical functioning at the level of 7 or higher.[44] In another study, ratings of symptom interference guided the selection of numeric rating cutpoints for the levels of mild, moderate, and severe fatigue. Interference levels on the MD Anderson Symptom Inventory (MDASI) scale were found to be well differentiated with the cutpoints for mild, moderate, or severe fatigue.[10] Based on these validated levels of fatigue intensity, the panel believes that the numeric rating scale can be used as a guide in practice settings and decision-making.

Primary Evaluation Phase

Focused History and Physical Examination

When fatigue is rated as moderate to severe, with a score of 4 to 10, a more focused history and physical examination should be conducted as part of the primary evaluation phase outlined in the algorithm. One component of this evaluation is an assessment of the patient's current disease status, which encompasses the type and length of treatment, its capacity to induce fatigue, and the patient's response to treatment (see "Primary Evaluation," page 1016 [FT-4]). If possible, clinicians should determine whether the fatigue is related to a recurrence of the malignancy for those patients assumed to be disease-free or whether it is related to a progression of the malignancy for patients with underlying disease. This is often an important factor causing patients with fatigue to seek further evaluation. If clinicians determine that the fatigue is not related to disease recurrence, informing patients and family members will substantially reduce their anxiety levels. In addition to cancer treatment, clinicians should be aware of any other prescription or over-the-counter medications and supplements the patient is taking.

As part of a focused history, a review of systems should be completed. This review may be helpful in determining the various organ systems affected and in directing the physical evaluation and diagnostic workup. Another component of the focused history is an in-depth fatigue assessment that includes evaluation of several aspects of fatigue: onset, pattern, duration, change over time, associated or alleviating factors, and interference with function. Other physical, emotional, and cognitive symptoms may be associated with fatigue. The health care professional must evaluate the effect of fatigue on normal functioning, including effects on daily living or enjoyable activities. Because fatigue is a subjective condition involving a combination of symptoms and is experienced and reported differently by each person, it is important that the in-depth assessment includes the patient's self-assessment of the causes of fatigue.

The panel also recognized the important role of social support throughout the course of cancer treatment and survivorship (reviewed by Given et al[45]). Fatigue is a major cause of functional dependence for patients with cancer, especially among the elderly.[46] Besides assisting with daily living, caregivers provide cancer-specific support, such as monitoring treatment side effects, aiding in fatigue and pain management, and administering medicine.[47] The availability of dependable caregivers can significantly impact the functional, emotional, and financial capacity of a patient coping with cancer and pursuant

fatigue. A support network also can be provided when the patient lacks the economic and supportive resources to obtain tangible support.

Assessment of Concurrent Symptoms and Treatable Contributing Factors

As part of this focused evaluation, the NCCN Panel identified factors that are often causative elements in the fatigue experience and, therefore, should be specifically assessed. These factors include pain, emotional distress, sleep disturbance, poor sleep hygiene, anemia, nutrition, activity level, medication side effects profiles, alcohol/substance abuse, and co-morbidities.

Descriptive studies have shown that, in adults and children, fatigue seldom occurs alone; it more commonly clusters with sleep disturbance, poor sleep hygiene, emotional distress (eg, depression, anxiety), or pain.[48–51] Assessment of pain along with emotional distress and institution of effective treatment are essential. In a randomized controlled trial (RCT) of 152 patients with advanced cancer, protocol patient-tailored treatment of the accompanying physical symptoms was coordinated by a nurse and resulted in a higher impact on fatigue than standard oncologic care.[52]

Fatigue and depression have been documented as concurrent symptoms in patients with cancer. Hopwood and Stephens[53] documented depression in 33% of 987 patients with lung cancer and found that fatigue was an independent predictor of depression in this group. In 457 patients with Hodgkin's disease, Loge et al[54] found that 26% of patients had fatigue for 6 months or longer (defined as fatigue "cases") and that fatigue correlated moderately with depression (r=.41).

Sleep disturbances are a neglected problem in oncology[55] and may range from hypersomnia to insomnia.[56,57] Sleep disturbances are prevalent in 30% to 75% of patients with cancer.[58] Several studies have shown that patients with cancer experiencing fatigue during active treatment spend increased time resting and sleeping but that their pattern of sleep is often severely disrupted. When sleep disturbances are present, the patient should be assessed for depression, because this is a common manifestation.[59] Patients may benefit from evaluation and education to improve sleep quality. In addition, sleep apnea can develop as a consequence of cancer treatment in the settings of surgery affecting the upper airway, changes in body composition, and alterations in hormone status (eg, thyroid, estrogen, testosterone); therefore, obstructive sleep apnea should also be evaluated.

Poor sleep hygiene behaviors are frequent in patients with cancer. Factors that contribute to poor sleep hygiene include poor individual habits, a poor sleep environment, or an inability to decompress before bedtime. Habits that may be an issue include deviating from a regular sleep schedule, napping during the daytime, and ingesting caffeine, alcohol, or high-sugar foods before bed. An environment conducive to sleep should be dark, quiet, and comfortable to improve sleep quality. Positive sleep hygiene habits include sleeping in a dark room and engaging in activities to reduce stress before bedtime, such as reading, journaling, yoga, meditation, or listening to quiet music. Although all patients should be aware of factors that hinder sleep hygiene, younger patients are especially prone to some of these factors, including late-night gaming, TV watching, computer and cell phone use, and social media

use in the hours that interfere with sleep. Both adults and school-aged patients should also be assessed for anxiety that may arise from work or school and the concern of falling behind.

Patients should undergo a nutritional assessment to evaluate weight gain and loss, caloric intake changes, impediments to nutritional intake, anemia, and fluid and electrolyte imbalances. Weight and weight changes should be carefully noted. The health care provider should review and discuss changes in caloric intake with the patient. If there are substantial abnormalities, consultation with a nutrition expert may be appropriate. Often fatigue symptoms can be lessened through improving anemia and modifying dietary intake with appropriate caloric exchanges. Imbalances in sodium, potassium, calcium, iron, and magnesium serum levels are often reversible and, with appropriate supplementation, may reduce fatigue. Nutritional intake may be affected by nausea, vomiting, loss of appetite, food disinterest, mucositis, odynophagia, bowel obstruction, diarrhea, and constipation.

Patients with moderate to severe fatigue should be queried about their functional status, including changes in exercise or activity patterns and the influence of deconditioning. Can patients accomplish normal daily activities? Can they participate in formal or informal exercise programs? What is the amount and frequency of exercise? Has the patient modified exercise or other activity patterns since the development of fatigue? This assessment is important when formulating a treatment plan that may include exercise. Exercise has been beneficial in lowering fatigue levels in certain populations of patients with cancer.[60,61] However, before recommending an exercise program, the health care provider or exercise expert (eg, physiatrist, physical therapist) should assess the conditioning level of the patient. It is often difficult to convince fatigued patients that exercise will improve their symptoms. It may be best to begin with discussions and low-level activities, which gradually increase over time. This is especially important if the patient is significantly deconditioned.

Review of current medications (including over-the-counter, herbal, vitamins, and other supplements) is essential. Recent medication changes should also be noted. Medications and medication interactions may contribute to the worsening of fatigue. For example, certain cardiac medications (such as β-blockers) may elicit bradycardia and subsequent fatigue. Combinations of different classes of medications (such as narcotics, antidepressants, antiemetics, and antihistamines) may contribute to excessive drowsiness and increasing fatigue. It may be appropriate to delete or adjust the dose of medications to treat fatigue. In some cases, altering either the dosage or dosing interval of a medication may be sufficient to improve the condition.

During the examination, health care providers should also be alert for signs of alcohol or substance abuse. These detrimental habits can often lead to or aggravate other health problems, such as sleep disturbance, and result in fatigue.

Noncancer comorbidities may contribute substantially to symptoms of fatigue in patients with cancer. Therefore, the status of comorbidities must be reviewed in conjunction with the present treatment management strategies. If the comorbidity is not optimally managed, it may be necessary to further evaluate and improve management. For example, if a patient has

underlying congestive heart failure secondary to anthracycline cardiomyopathy and is experiencing symptoms of dyspnea and angina, fatigue may often be improved by stabilizing the condition and decreasing the frequency of episodes of congestive heart failure. This may entail introduction of new medications, titration of current medications, or both. It may also involve an invasive interventional assessment of the patient's cardiac status. Comorbidities that need review and assessment include cardiac, pulmonary, renal, gastrointestinal, hepatic, neurologic, and endocrine dysfunction (including hot flashes, hypothyroidism, hypogonadism, or adrenal insufficiency), and infection. Canaris et al[62] noted the high incidence of thyroid dysfunction in "normal" individuals and in patients receiving thyroid medications; they suggested that more attention be given to thyroid problems in both the general population and patients with cancer. Development of hypothyroidism occurs after radiation therapy for Hodgkin disease and other non-Hodgkin's lymphomas, head and neck cancers, and breast cancer, and after total body irradiation in bone marrow transplantation. Hypothyroidism has been noted in patients who have received interferon alfa-2b, aldesleukin (interleukin-2), L-asparaginase, and a multitude of combination chemotherapies. Hypogonadism is commonly seen in patients with advanced cancer. A recent cross-sectional pilot study by Strasser et al[63] explored whether hypogonadism contributes to fatigue in men with advanced cancer. Data indicate that abnormally low levels of testosterone are associated with fatigue. However, additional research in a larger patient population is needed to clarify the incidence of hypogonadism and its association with specific malignancies and neurotoxic chemotherapy.

Patient Clinical Status

After the primary fatigue evaluation is completed, the patient's clinical status (active cancer treatment, posttreatment with no active treatment except hormonal therapy, or end of life) should be determined because of its influence on CRF management and treatment strategies. However, some general treatment guidelines apply across all clinical categories.[64]

If any of the treatable contributing factors discussed earlier is identified during the primary evaluation phase, it should be treated as an initial approach to fatigue management. Other NCCN Guidelines are also available to guide supportive care, including those for Adult Cancer Pain, Distress Management, Cancer- and Chemotherapy-Induced Anemia, Antiemesis, and the Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit NCCN.org). Treatment of sleep disturbances, poor sleep hygiene, nutritional alterations, and physical deconditioning are discussed under "Nonpharmacologic Interventions" for patients on active treatment, posttreatment, or at end of life in the NCCN Guidelines for Survivorship and for Palliative Care (to view the most recent versions of these guidelines, visit NCCN.org).

Interventions for Patients on Active Treatment

Education and Counseling of Patient and Family

Education about fatigue and its natural history should be offered to all patients with cancer, but it is particularly essential for patients beginning potential fatigue-inducing treatments (such as radiation, chemotherapy, or biotherapy), before onset. Patients should be informed

that if fatigue does occur, it may be a consequence of the treatment and is not necessarily an indication that the treatment is not working or that the disease is progressing. This reassurance is important, because fear of progression is a main reason for the underreporting of fatigue. Daily self-monitoring of fatigue levels in a treatment log or diary can be helpful.

General Strategies for Management of Fatigue

In addition to education, the panel recommends counseling for patients about general strategies (energy conservation and distraction) that can be useful in coping with fatigue. Energy conservation is defined as the deliberately planned management of one's personal energy resources to prevent their depletion. It encompasses a common sense approach that helps patients set realistic expectations, prioritize and pace activities, and delegate less-essential activities.[65] Patients should be counseled that it is permissible to postpone all nonessential activities if they are experiencing moderate to severe fatigue. One useful plan is to maintain a daily and weekly diary that allows patients to ascertain peak energy periods and then plan activities accordingly within a structured routine. A multisite clinical trial of energy conservation in 296 patients receiving cancer treatment reported significantly lower fatigue in patients receiving the experimental intervention.[66] Some participants in the descriptive studies suggested that activities designed to distract (eg, games, music, reading, socializing) are helpful in decreasing fatigue, although the mechanism is unknown. Daytime naps can replenish energy, but it is advisable to limit these to less than an hour to avoid disturbing nighttime sleep. Patients may also use labor-saving techniques, such as wearing a bath robe instead of drying off with a towel, or using devices, including a walker, grabbing tools, and a bedside commode.

Emphasis should be given to finding meaning in the current situation, focusing on meaningful interactions, and promoting the dignity of the patient.

Nonpharmacologic Interventions

Of the specific nonpharmacologic interventions during active cancer treatment, physical activity (category 1), physically based therapies (category 1), and psychosocial interventions (category 1) have the strongest evidence base for treating fatigue; however, nutritional consultation and cognitive behavioral therapy (CBT) for sleep have some supporting evidence.[67] These interventions align with recommendations from the Oncology Nursing Society (ONS).[68–70] Both ASCO[71] and the pan-Canadian practice guidelines[72] used the ADAPTE method to take advantage of these existing guidelines (ie, NCCN, ONS) to enhance efficient production, reduce duplication, and promote the local update of quality guideline recommendations by their organizations.

Physical Activity—In patients with cancer, the adverse effects of therapy result in decreased activity and physical performance. Although several factors contribute to the decline in functionality, fatigue is one of the major contributors. Mustian et al73 conducted a study in patients receiving systemic chemotherapy to determine the impact of fatigue on physical function as measured by the Activities of Daily Living (ADLs) Index. Of the 753 patients enrolled, 64% were female. In the first and second cycles of chemotherapy, 85.4% and 79.3% of patients reported fatigue, respectively. The mean severity of fatigue was 5.0

for the first cycle and 4.7 for the second cycle (scale of 0–10, with 10 = severe fatigue). CRF interfered with all ADLs in most patients. Interference was moderate, and was noted to be higher in women, non-whites, and patients with metastatic disease.

A large number of small- to moderate-sized studies have been performed to evaluate the feasibility of interventions designed to increase physical activity during therapy, and to explore the impact of increased activity on CRF, QOL, treatment-related side effects, and other end points. A thorough review of the impact of physical activity on these varied outcomes is beyond the scope of this discussion. However, many of these studies have specifically evaluated the effect of increased activity on CRF, and several meta-analyses have been conducted in recent years to provide a comprehensive evaluation of the impact of increased activity on CRF.

The largest meta-analysis to date included 70 studies and 4881 patients with cancer during or after treatment.[74] Exercise reduced CRF by a mean effect of 0.32 (95% CI, 0.21–0.43) and 0.38 (95% CI, 0.21–0.54) during and after cancer therapy, respectively.[74] A 2012 Cochrane analysis included 56 randomized trials (n=4826), 36 of which were conducted among participants undergoing active cancer treatment.[75] Exercise resulted in a decrease in fatigue from baseline to 12 weeks' follow-up (standardized mean difference [SMD], −0.38; 95% CI, −0.57 to −0.18) or when comparing differences in follow-up scores at 12 weeks (SMD, −0.73; 95% CI, −1.14 to −0.31). Systematic reviews have correlated exercise with improvement in fatigue for patients with prostate cancer[76] and lymphoma,[77] and in those who have undergone hematopoietic cell transplant.[78] Other smaller analyses confirmed a significant effect of exercise intervention on fatigue.[79–83]

It is reasonable to encourage all patients to engage in a moderate level of physical activity during and after cancer treatment. Currently evidence is insufficient to recommend a specific amount of physical activity. The US Surgeon General recommends 30 minutes of moderate activity most days of the week for all populations.[84] Some observational and interventional studies have suggested that patients with cancer who engage in at least 3 to 5 hours of moderate activity per week may experience better outcomes and have fewer side effects of therapy, including fatigue.[60,85–89]

Patients may require referrals to exercise specialists (eg, physical therapist, physical medicine or rehabilitation specialist) for assessment and an exercise prescription. The American College of Sports Medicine recently developed a certification program for cancer rehabilitation that is available for exercise professionals who specialize in the care of patients with cancer. They also convened a roundtable discussion and published specific guidelines for physical activity testing and exercise programs for patients with cancer.[90]

Specific issues that should trigger a referral for physical therapy include:

- Patients with comorbidities (eg, cardiovascular disease or chronic obstructive pulmonary disease)
- Recent major surgery

- Specific functional or anatomic deficits (eg, decreased range of motion due to neck dissection in patients with head and neck cancer)
- Substantial deconditioning

Exercise interventions must be used with caution in patients with any of the following:

- Bone metastases
- Thrombocytopenia (low platelets)
- Anemia (low red blood cells)
- Fever or active infection
- Limitations secondary to metastasis or other co-morbid illnesses

The exercise program itself should be individualized based on the patient's age, gender, type of cancer, and physical fitness level. Consider cancer-specific exercise programs if available. The program should begin at a low level of intensity and duration, progress slowly, and be modified as the patient's condition changes.

Physically Based Therapies—Therapies performed on the patient by a therapist or layperson include acupuncture and massage therapy. Positive effects of acupuncture on fatigue have been reported in small samples and need to be confirmed with RCTs.91 These small trials were conducted during active non-palliative radiation therapy92,93 and postchemotherapy treatment.94,95 One RCT (n=230)96 and one retrospective review (n=1290)97 reported positive effects of massage therapy on fatigue during active therapy. A decade after these publications, the data remain limited; 2 systemic reviews suggest that acupuncture may have beneficial properties, although the studies acknowledge that a paucity of data makes it difficult to definitively evaluate the benefits.98,99 For further guidance on physical activity, see the NCCN Guidelines for Survivorship (to view the most recent version of these guidelines, visit NCCN.org).

Complementary Therapies—Complementary therapies, such as massage therapy,[96,97,100] yoga,[101–105] muscle relaxation, and stress reduction based on mindfulness,[106–108] have been evaluated alone or in combination with CBT approaches. The data suggest that these therapies may be effective in reducing fatigue in patients with cancer. Several recent RCTs have demonstrated that yoga intervention, compared with standard care, was effective in lowering CRF during radiotherapy[103] and in survivors.[101,104,105] However, most of the trials have been conducted in women with breast cancer, and more data are needed to establish the effectiveness of yoga in reducing fatigue in men and in individuals with other cancers.[102]

Psychosocial Interventions—Patients should be counseled about coping with fatigue and educated about anxiety and depression, which are commonly associated with fatigue during cancer treatment.109 Although a strong correlation exists between emotional distress and fatigue, the precise relationship is not clearly understood.

Studies testing interventions to decrease fatigue can be grouped as CBTs/behavioral therapy (BT), psychoeducational therapies/educational therapies, and supportive expressive therapies, based on review of 3 meta-analyses.[81,110,111] Of note, the categories in which interventions have been grouped are different in each of the meta-analyses and have been compared with the work reported by the ONS's Putting Evidence into Practice (PEP) initiative.[69,70,112] These studies can be categorized based on their primary outcome parameter: fatigue or other. In many studies, fatigue was a secondary end point measured by a single item or a subscale of an instrument designed to measure emotional distress, QOL, or general symptom burden. Furthermore, fatigue was not an eligibility requirement. In studies specifically designed to measure fatigue, no severity cutoff score was used. Thus, patients enrolled in these studies may or may not have had significant levels of fatigue, thereby limiting the potential impact of the intervention.

Current knowledge regarding CRF includes the following proposed mechanisms: 5-HT3 neurotransmitter deregulation, vagal afferent activation, alteration in muscle and adenosine triphosphate metabolism, HPA axis dysfunction, circadian rhythm dysfunction, and cytokine deregulation. Current psychosocial interventional studies may target one or more of these biologic mechanisms; however, most studies to date fail to identify the underlying targeted mechanism. The exception includes interventions aimed at increasing relaxation, thereby diminishing stress and activation of the HPA axis. Because of the inherent difficulty of conducting mechanistically based interventions, most studies to date have been designed to address educational and coping deficits in order to optimize the patient's ability to deal with this often debilitating symptom.

In addition to the issues noted earlier, outcome parameters used by investigators are highly variable. Currently published studies generally use patient's self-reporting exclusively as the outcome measure. Most studies do not reflect the impact of fatigue on function, report on fatigue-related behaviors, or use objective measures of functionality (eg, the 6-minute walk).

Several meta-analyses evaluated the impact of psychosocial interventions on CRF. Analyzing 41 studies on 3620 patients with cancer, Kangas et al[81] reported a weighted pooled mean effect of −0.31 for psychosocial interventions on fatigue. Goedendorp et al[110] reported that of 27 RCTs included in their analysis, 7 showed significantly reduced fatigue. Of interest, 80% of fatigue-specific interventions were effective, compared with 14% of nonspecific strategies. Jacobsen et al[111] analyzed 30 RCTs and found a significant effect for psychological interventions but not for activity-based programs. A meta-analysis by Duijts et al[80] reported that, like exercise programs, behavioral techniques, including cognitive therapy, relaxation techniques, counseling, social support, hypnosis, and biofeedback, are beneficial in improving fatigue among patients with breast cancer during and after treatment. Substantial data in the literature provide high-level evidence during active treatment for CBT/BT[106,113–116] and psychoeducational therapies/educational therapies.[32,67,117–124] Supportive expressive therapies (eg, in-person or online support groups, counseling, journal writing) may serve as an emotional outlet and as a support network. There is less-robust evidence for supportive expressive therapies during active treatment; therefore, their use is a category 2A recommendation.

Nutrition Consultation—Many patients with cancer have changes in nutritional status. Because cancer and treatment can interfere with dietary intake, nutrition consultation may be helpful in managing the nutritional deficiencies that result from anorexia, diarrhea, nausea, and vomiting.125 Adequate hydration and electrolyte balance are also essential in preventing and treating fatigue.

Sleep Therapy—Patients with cancer report significant disturbances in sleep patterns that could cause or exacerbate fatigue. Both insomnia and hypersomnia are common, with disrupted sleep as a common denominator. Nonpharmacologic interventions designed to improve sleep quality have been organized into 4 general types of therapies that include cognitive-behavioral, complementary, psychoeducation/information, and exercise therapies.[126] Some have also been shown to decrease fatigue.[112]

There are numerous types of CBT; the most frequently used include stimulus control, sleep restriction, and sleep hygiene. Stimulus control includes going to bed when sleepy, going to bed at approximately the same time each night, and maintaining a regular rising time each day. Getting out of bed after 20 minutes if unable to fall asleep, both when first going to bed and when awakening during the night, is a key aspect of stimulus control. Sleep restriction requires avoiding long or late afternoon naps and limiting total time in bed.[127] Techniques to promote a good night's sleep and optimal functioning the next day, such as avoiding caffeine after noon and establishing an environment that is conducive to sleep (eg, dark, quiet, comfortable) are components of sleep hygiene. These strategies were used in a pilot study with women during adjuvant breast cancer chemotherapy. Sleep/wake patterns remained consistent with normal values except for increased number and length of nighttime awakenings.[128] For children with cancer, a consistent bedtime and routine, an environment conducive for sleeping, and the presence of security objects (such as blankets and toys) are effective measures (see "Assessment of Concurrent Symptoms and Treatable Contributing Factors," page 1023).

Pharmacologic Interventions

Although a wide variety of prescription pharmacologic options are available to improve sleep quality, little empirical evidence exists for the use of these agents in patients with cancer, and their use may be associated with adverse side effect profiles. Clinicians need to be aware of the FDA warning regarding the potential risks associated with sedative-hypnotic drugs, including severe allergic reactions and complex sleep-related behaviors, including sleep-driving.[129] A table summarizing the medications commonly used to promote sleep is provided on the NCI Physician Data Query Web site.[130] Prescribing considerations for these classes of agents include increased likelihood of problems with daytime sleepiness, fatigue, withdrawal symptoms, dependency, rebound insomnia, problems with sleep maintenance, memory problems, anticholinergic symptoms, orthostasis, and the potential for drug-drug interactions involving the cytochrome p450 isoenzyme system. Increased public and professional education regarding sleep, sleep hygiene, sleep disturbances, and daytime consequences of sleep loss are recommended.

Some evidence supports pharmacologic therapy as a fatigue treatment, although a significant placebo response has been observed in a randomized trial.[131] Studies on the selective serotonin reuptake inhibitor paroxetine showed no influence by this antidepressant on fatigue in patients receiving chemotherapy.[132,133] Antidepressants are not recommended to reduce fatigue. See the relevant NCCN Guidelines for Supportive Care for details on the management of pain, emotional distress, emesis, and anemia (available at NCCN.org). Treatment for nutritional deficit or imbalance and co-morbidities may be optimized as indicated.

The psychostimulant methylphenidate has been evaluated for its effect on CRF, with mixed results in patients undergoing cancer therapy. A pilot study found a benefit in fatigue scores in 12 patients with melanoma undergoing interferon-based treatment compared with historical controls.[134] However, a randomized, placebo-controlled trial of d-threo-methylphenidate to prevent fatigue during radiotherapy for brain tumors did not demonstrate efficacy for the drug in preventing fatigue.[135] Similarly, an RCT of 57 women receiving adjuvant chemotherapy for breast cancer failed to show a difference between the active arm and placebo.[136] Most recently, Moraska et al[137] reported results of a double-blinded phase III trial, in which 148 patients, most of whom were receiving chemotherapy, were randomized to methylphenidate (54 mg/d) or placebo for 4 weeks. No difference in fatigue score was observed between the groups; however, a subset analysis found a benefit with the psychostimulant in patients with severe fatigue and/or advanced disease (P=.02). Analyzing 5 RCTs, Minton et al[138] attributed a significant benefit to psychostimulants in alleviating fatigue compared with placebo (z score=2.83; P=.005). Patients have reported minor side effects with methylphenidate, including headache and nausea.

The wakefulness-promoting nonamphetamine psychostimulant modafinil has been approved for use in narcolepsy. In a large RCT, Jean-Pierre et al[139] randomized 867 patients undergoing chemotherapy to 200 mg/d of modafinil or placebo. Of the 631 evaluable patients, 315 received modafinil and 316 received placebo. Improvement in fatigue was observed in patients with severe fatigue (P=.017), but not in those with mild or moderate fatigue. Toxicity was similar between the 2 arms. More recently, a phase III randomized, placebo-controlled trial measured the improvement in fatigue in patients with metastatic prostate or breast cancer undergoing docetaxel chemotherapy.[140] Fatigue was measured using the MDASI scale, and no statistically significant difference was seen between treatment arms (35.9 vs 39.6; 95% CI, −8.9 to 1.4; P=.15). An increase in toxicity was seen, with patients experiencing grade 2 or higher nausea and vomiting in the modafinil arm (45.4% vs 25%). Because of the limited number of studies and the marginal improvement in CRF in response to modafinil, it is not a recommended treatment.

The use of dietary supplements to alleviate the symptoms of fatigue has yielded mixed results. Although coenzyme Q10 and L-carnitine were evaluated and showed no benefit,[141,142] limited data may support the use of ginseng. In a phase III RCT of 364 patients experiencing cancer-related fatigue, improvement of symptoms was observed, as measured by the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), following treatment with 2000 mg of Wisconsin ginseng.[143] In the overall population, improvement at 4 weeks was not statistically significant (ginseng, 14.4 points; SD, 27.1, vs

placebo, 8.2 points; SD, 24.8; *P*=.07). However, at 8 weeks a statistically significant improvement (*P*=.003) was observed in patients receiving ginseng (20 points; SD, 27) versus patients given the placebo (10.3 points; SD, 26.1). Furthermore, improvement was greatest in patients undergoing active cancer treatment compared with those who had completed treatment. Statistical significance was observed at 4 weeks in the patients undergoing active treatment (*P*=.02) compared with the after-treatment group (*P*=.86), with an even greater improvement over placebo at 8 weeks (active treatment, *P*=.01 vs posttreatment, *P*=.07). These values were based on the percent change from baseline measured by the MFSI-SF.

After a review of the current literature, the NCCN Panel included consideration of the psycho-stimulant methylphenidate as a recommendation for treating fatigue in patients undergoing active cancer treatment when other causes of fatigue have been excluded. The data were not sufficient to support the recommendation for modafinil.

Interventions for Patients Posttreatment

More than 11 million US residents now living have a history of cancer. Of the approximately 1,658,370 persons in the United States who will be diagnosed with cancer in 2015, 68% are expected to survive at least 5 years.[144] These improvements in survival have led to efforts to enhance symptom management, QOL, and overall functioning of individuals posttreatment. As previously mentioned, fatigue can be an acute effect of cancer or treatment, but it can also be a long-term or late effect.[145] Patients may continue to report unusual fatigue for months or years after treatment cessation.[11,12,14–18] Researchers have suggested that such fatigue may be due to persistent activation of the immune system[11,146] or to other factors, including the late effects of treatment on major organ systems.[146] However, there are few longitudinal studies examining fatigue in long-term disease-free survivors.

Incidence and prevalence rates for fatigue in this population range from 17% to 21% when strict ICD-10 diagnostic criteria are applied,[147] and range from 33% to 53% when other criteria (such as a score of 4 or more on the 0–10 fatigue scale) are used.[148] In contrast to these findings, Canadian and US ovarian cancer survivors (n=100), who were diagnosed a mean of 7.2 years before the survey, reported equivalent energy levels when compared with the general population.[149] As a consequence, what constitutes valid incidence and prevalence rates in disease-free patients requires more study. Variation of prevalence rates in the literature likely reflects a lack of consistency in applying diagnostic criteria.[150]

Most research reports to date are limited by their cross-sectional designs,[42,145,147,151,152] lack of comparison groups,[42] heterogeneous samples,[147] differing fatigue scales, small sample sizes,[146] varying baseline survivorship definitions (ie, time since diagnosis vs time since treatment cessation), and different mean survivorship durations. These design issues make it difficult to reach conclusions about the prevalence, incidence, and duration of fatigue; the associated risk factors; and QOL. Additionally, most fatigue studies of posttreatment disease-free patients have been conducted in Caucasian, English-speaking patients with breast cancer,[11,146,151] and patients who have undergone peripheral stem cell or bone marrow transplant,[153,154] with few exceptions.[14,16,18]

The cause of posttreatment fatigue in patients who are disease-free is unclear and probably multi-factorial.[155] One cross-sectional comparative study investigated fatigue and physiologic biomarkers of immune system activation in 20 breast cancer survivors who were fatigued (mean, 5 years since diagnosis) and in 20 nonfatigued survivors.[146] Fatigued survivors had significantly higher serum markers (interleukin-1 receptor antagonist [IL-1ra], soluble tumor necrosis factor type II, and neopterin) and lower cortisol levels when compared with nonfatigued survivors. Significantly higher numbers of circulating T lymphocytes that correlated with elevated serum IL-1ra levels also suggest that persistent fatigue in survivors may be caused by a chronic inflammatory process involving the T-cell compartment.[11]

Other risk factors associated with posttreatment fatigue in patients who are disease-free include pre-treatment fatigue, anxiety and depression levels,[156] physical activity levels,[157,158] coping methods and cancer-related stressors, comorbidities, type of malignancy, prior treatment patterns, and treatment late effects. In a Norwegian study of Hodgkin disease survivors in remission for more than 5 years, higher fatigue levels were documented in those who had pulmonary dysfunction[148]; the prevalence of chronic fatigue was 2 to 3 times higher than in survivors without pulmonary dysfunction. No significant correlations were found between fatigue and cardiac sequelae as measured by echocardiography, exercise testing, and chest radiography.[148]

Prior treatment patterns may affect the fatigue. Women who had received radiation therapy had the lowest fatigue scores. Two studies testing the effects of physical activity interventions on fatigue in breast cancer survivors found that individualized, prescriptive exercise reduced fatigue. However, researchers emphasize that it is critical for exercise to be individualized to the survivor’s abilities to prevent exacerbation of cancer treatment toxicities.[157,158]

Education and Counseling of Patient and Family

Patients who are completing treatment and their families should be educated about the pattern and level of fatigue that can be expected during this period. Although a significant subset of patients continue to experience distressing levels of fatigue that interfere with function, most patients experience a gradual decrease in fatigue and return of energy to normal levels.[12,149] Regular monitoring of fatigue levels can document the decrease in fatigue that normally occurs after treatment. Health care providers should continue to screen patients regularly for fatigue during follow-up visits. Patients can benefit from general fatigue management strategies, including energy conservation and distraction. A focus on finding meaning in life should be an ongoing effort.

Nonpharmacologic Interventions

Specific interventions recommended to manage fatigue during active cancer treatment are also recommended for use in the posttreatment period in patients who are disease-free[64]; however, there are fewer studies of physically based therapies in post-treatment.

Physical Activity—Physical activity is a category 1 recommendation. Improving strength, energy, and fitness through regular exercise have been shown to facilitate the transition from patient to survivor, decrease anxiety and depression, improve body image, and increase tolerance for physical activity even in patients who implement a moderate walking exercise program. However, if the patient is significantly deconditioned, weak, or has relevant late effects of treatment (such as cardiopulmonary limitations), referral to a physiatrist or a supervised rehabilitation program may be indicated. Exercise should be recommended with caution in patients who have fever or remain anemic, neutropenic, or thrombocytopenic after treatment. Of the nonpharmacologic approaches for managing CRF, exercise has the best evidence to support its effectiveness.[64,159–163] A meta-analysis of 44 studies including 3254 cancer survivors concluded that exercise reduced fatigue, especially in programs that involved moderate-intensity resistance exercise among older cancer survivors.164 Further guidance on physical activity can be found in the NCCN Guidelines for Survivorship (to view the most recent version of these guidelines, visit NCCN.org).

Psychosocial Interventions—Psychosocial interventions, including CBT/BT, mindfulness-based stress reduction, psychoeducational therapies/educational therapies, and supportive expressive therapies are category 1 recommendations[80,107,108,117,119,155,165–168] (see “Interventions for Patients on Active Treatment,” page 1025).

Additional Nonpharmacologic Approaches—Nutritional consultation and CBT for sleep (category 1)[112,126] may be helpful for fatigue management during posttreatment. Several published studies[169–171] support the conclusion that CBT interventions designed to optimize sleep quality in patients with cancer may also improve fatigue. Positive effects on both sleep and fatigue after 4 to 5 weekly BT sessions have been reported in RCTs of patients who reported chronic insomnia in the survivorship phase after cancer treatment.[172–174] Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.[169,170] Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.[128,171] The American Academy of Sleep Medicine (AASM) has recommended 3 specific therapies for chronic insomnia in healthy individuals: relaxation training, CBT, and stimulus control therapy.[175] AASM has also published clinical guidelines for the management of chronic insomnia in adults.[176]

Pharmacologic Interventions

If indicated, anemia, pain, and emotional distress should be treated according to the NCCN Guidelines for Supportive Care (available at NCCN.org). Treatment may also be individually optimized as necessary for sleep dysfunction, nutritional deficit or imbalance, and comorbidities.

Some evidence supports the use of psychostimulants after cancer therapy. A 54% response rate to methylphenidate has been reported in a phase II trial of 37 patients with breast cancer in remission.[177] An RCT of 154 patients postchemotherapy also found an improvement in fatigue symptoms in the active arm.[178] Similar to patients receiving active treatment, modafinil has limited study data in patients posttreatment. Although pilot studies suggested

that modafinil may be associated with reduced fatigue,[179,180] the improved outcome did not hold in larger trials[140,181] (see “Interventions for Patients on Active Treatment,” page 1025). The panel agrees that methylphenidate may be considered after ruling out other causes of fatigue, but does not recommend the use of modafinil.

Interventions for Patients at the End of Life

Although the assessment and management of fatigue at the end of life parallels the general principles of this guideline, a few issues are specific to this population. Factors that have a greater likelihood of association with fatigue at the end of life include anemia, medication adverse effects and polypharmacy, cognitive impairment, adverse effects of recent treatment, and malnutrition.[182] Evaluating and correcting these contributing factors could reduce fatigue severity.

It is likely that fatigue will increase substantially as the disease progresses; however, patterns of fatigue are variable. For some adults, fatigue may be characterized as constant and unrelenting; for others, it is unpredictable and may occur suddenly.[41,183] At the end of life, most research has demonstrated that patients with cancer experience fatigue in the context of multiple symptoms. In a study of 278 Swedish adults admitted to a palliative care unit, 100% reported fatigue; other symptoms included pain (83%), dyspnea (77%), and appetite loss (75%).[184] In a large sample of adults receiving palliative care (N=1000), Walsh et al[185] noted that individuals with advanced cancer had multiple symptoms. Pain was the most prevalent (84%), followed by fatigue (69%), weakness (66%), and lack of energy (61%). Walsh and Rybicki[186] cluster-analyzed 25 symptoms in 1000 consecutive admissions to a palliative care program and found 7 symptom clusters. The fatigue cluster included easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, and taste changes. Given et al[31,187] postulate that pain and fatigue could have a synergistic effect that worsens the overall symptom experience in elderly patients with cancer. Children with advanced cancer also experienced multiple symptoms at the end of life, most commonly fatigue, pain, and dyspnea.[188]

Education and Counseling of Patient and Family

Individuals with advanced cancer and their caregivers need information about the management of symptoms, including fatigue.[189] This includes information about the causes, patterns, and consequences of fatigue during treatment for advanced cancer and end-of-life care.

Several major consequences of fatigue have been described, including its effect on functional status, emotional distress, and suffering. As fatigue escalates, it is likely to increasingly interfere with usual activities.[183] Families need to be apprised of this issue so they can plan accordingly. Fatigue is likely to have a significant effect on emotional well-being.[183,188] According to parents who cared for a child at the end of life, more than 90% of the children experienced fatigue and almost 60% experienced significant suffering from it.[188] In a case study of 15 adults with advanced disease, fatigue resulted in substantial regret, sadness, and sense of loss due to the deterioration of one’s health.[183] Mystakidou et

al[190] reported that a patient's desire for hastened death was predicted by feelings of sadness, a lack of appetite, pain, and fatigue.

Given the high prevalence of fatigue and other symptoms at the end of life, symptom management needs to be a major focus of care. Active commitment by the health care team to palliative care is critical when aggressive cancer therapy is given to patients with a low likelihood of long-term survival.[188] Interventions for fatigue should be initiated to relieve or diminish suffering, although it is recognized that some causes of fatigue cannot be assuaged.[64]

General Strategies for Management of Fatigue

Energy conservation is a self-care strategy for individuals with advanced cancer and their caregivers.[66] The goal of energy conservation is to maintain a balance between rest and activity during times of high fatigue so that valued activities can be maintained. Energy conservation strategies include setting priorities and realistic expectations, delegating activities of lesser importance, eliminating nonessential activities, pacing oneself, taking extra rest periods, and planning high-energy activities at times of peak energy. It may also include the use of assistive devices and labor-saving techniques. Distraction may also be helpful. Patients receiving palliative care should be allowed daytime naps as long as they do not disturb nighttime sleep. In a situation of escalating fatigue at the end of life, family members may wish to designate individuals to assume activities relinquished by the individual with cancer.

Nonpharmacologic Interventions

Although there is no category 1 evidence for non-pharmacologic interventions at the end of life, clinicians are encouraged to consider matching the patient with physical activity or psychosocial intervention as indicated. Psychosocial intervention at this stage may focus on meaning and dignity, and gaining acceptance of the limitations imposed by fatigue. It may include a reemphasis on meaningful family interactions that do not require high-level physical activity.[191] Sustaining a sense of meaning has been demonstrated to allow patients with cancer to endorse a high QOL despite significant symptoms.[192] Studies suggest that interventions aimed at sustaining or enhancing meaning and/or dignity can significantly reduce distress related to symptoms and improve overall QOL.[193–195]

Although fatigue may increase at end of life, some individuals may choose to be active despite failing health. Some evidence shows that exercise is beneficial to individuals with incurable cancer and a short life expectancy. A group exercise program was evaluated in a pilot study of 63 Norwegian outpatients receiving palliative care.[196] The program consisted of two 50-minute sessions twice a week for 6 weeks that combined strength building, standing balance, and aerobic exercise. The exercise participants had less physical fatigue and increased walking distance. There were no adverse effects of exercise, although 29 of the 63 participants did not complete the program due to sudden death, or for medical and social reasons.

A small pilot study was conducted to evaluate an exercise program for 9 individuals with advanced cancer enrolled in a home hospice program.[197] A physical therapist guided

participants in the selection of several activities (eg, walking, arm exercises with resistance, marching in place, dancing). These were performed at different times throughout the day on a schedule devised jointly by the therapist and participant. All participants were able to increase their activity level over a 2-week period without increased fatigue. A trend was seen toward increased QOL and decreased anxiety. Although more research is needed, enhanced activity shows promise as a fatigue management strategy at the end of life; psychosocial interventions, sleep therapy, family interaction, and nutritional therapy are also helpful.

Reports of fatigue from 82 men with locally advanced or metastatic prostate cancer who underwent a 12-week exercise program was compared with those from a wait-list control group (N=73). The men in the exercise group reported less interference of fatigue with daily activities and better QOL. They also demonstrated better upper and lower body muscle fitness. Body composition was not affected.

Based on a systematic review of 20 exercise studies relevant to fatigue and muscle wasting in multiple myeloma, Strong et al[198] summarized weight-bearing precautions for bone metastases and exercise guidelines for adults with solid tumors and hematologic cancers, older cancer survivors, and individuals with CRF. An exercise protocol for multiple myeloma that incorporated aerobic, resistance, and flexibility exercises was also recommended.

Pharmacologic Interventions

There continues to be interest in psychostimulant drugs for patients with cancer at the end of life, although studies have had mixed results. Methylphenidate has been shown to yield improvement in fatigue in patients with advanced cancer in 2 pilot studies.[199,200] However, 2 RCTs reported an improvement in fatigue in both the methylphenidate and placebo arms.[201,202] Another psychostimulant, dexamphetamine (10 mg twice daily for 8 days), was evaluated for fatigue in patients with advanced cancer.[203] The results of an RCT showed tolerance of the drug and short-term improvement in fatigue on the second day, but no long-term benefit by the end of the 8-day study. A recent RCT in patients with advanced non–small cell lung cancer (n=160) showed no significant improvement between patients treated with modafinil (n=75) versus placebo (n=85). Although well-tolerated, the mean score change between groups as measured by the FACT-F scale was not significant (0.20; 95% CI, −3.56 to 3.97).[181] Overall, methylphenidate may be considered with caution for selected terminal patients.

Evidence supports the effectiveness of corticosteroids (prednisone and its derivative, and dexamethasone) in providing short-term relief for fatigue and improving QOL.[204–207] An RCT in patients with advanced cancer demonstrated significant improvement of fatigue in patients receiving dexamethasone (n=43) compared with those receiving placebo (n=41) for 14 days (P=.008).[208] Improved outcome was determined from the FACT-F subscale as the primary end point. An assessment of overall QOL showed improvement at day 15 (P=.03) and in physical well-being measured at day 8 (P=.007) and day 15 (P=.002), as measured by the Edmonton Symptom Assessment Scale for physical distress. This study was effective as a short-term therapy, but the long-term effects were not evaluated.[208] Recently, in a second RCT investigating the effects of methylprednisone in patients with advanced cancer

receiving opium, fatigue was measured in patients given 16 mg of methylprednisone twice daily (n=26) versus patients in the placebo group (n=24).[209] Patients receiving methylprednisone experienced a 17-point improvement on the EORTC-QOL Questionnaire C30[210] compared with the 3-point decline recorded by the placebo group (–17 vs 3 points; *P*=.003).[209]

Given the toxicity associated with long-term use, consideration of steroids is restricted to the terminally ill, patients with fatigue and concomitant anorexia, and patients with pain related to brain or bone metastases. In addition, interest has been shown in the progestational agent megestrol acetate for improving fatigue. A systematic review demonstrated the safety and efficacy of megestrol acetate in treating cachexia for patients with cancer.[211] However, a second systematic review and meta-analysis of 4 studies revealed no benefit of progestational steroids compared with placebo for treatment of CRF (*z* score=0.78; *P*=.44).[138,212]

Treatment for sleep dysfunction, nutritional deficit, or comorbidities may be optimized to the specific needs of the patient and family along the illness trajectory, and clinicians are advised to refer to the appropriate NCCN Guidelines for Supportive Care (available at NCCN.org) for the management of pain, distress, and anemia in patients at the end of life. The NCCN Panel would like to emphasize that eating and nutrition should be tailored to the terminal patient's comfort and should not be forced on the patient, because nutritional decline is expected.

Reevaluation Phase

Because fatigue may arise at many points during the course of a patient's disease and treatment, ongoing reevaluation of the patient's status (with appropriate modifications and institution of new treatments) is an integral part of effective overall fatigue management.

Summary

The NCCN Guidelines for CRF propose a treatment algorithm in which patients are evaluated regularly for fatigue using a brief screening instrument and are treated as indicated by their fatigue level. Fatigue should be minimally evaluated with the scale outlined in the algorithm; however, there are additional tools for the measurement of fatigue that may be used to identify fatigue as appropriate (see Table 1; available online, in these guidelines, at NCCN.org [MS-23]).

Management of fatigue begins with primary oncology team members who perform the initial screening and either provide basic education and counseling or expand the initial screening to a more focused evaluation for moderate or higher levels of fatigue. The focused evaluation includes assessment of current disease and treatment status, a review of body systems, and an in-depth fatigue evaluation. In addition, the patient is assessed for the presence of treatable factors known to contribute to fatigue. If present, factors should be treated according to practice guidelines, with referral to other care professionals as appropriate, and the patient's fatigue should be reevaluated regularly. If none of the factors is present or if the fatigue is unresolved, appropriate fatigue management and treatment

strategies are selected within the context of the patient's clinical status (ie, active cancer treatment, posttreatment, end-of-life care). Management of fatigue is cause-specific when conditions known to induce fatigue can be identified and treated. When specific causes of fatigue cannot be identified and corrected, nonpharmacologic and pharmacologic treatment of fatigue should be initiated.

Nonpharmacologic interventions may include a moderate exercise program to improve functional capacity and activity tolerance; psychosocial programs to manage stress and increase support; implementation of energy conservation strategies; and nutritional and sleep interventions as appropriate. Pharmacologic therapy may include drugs used to treat comorbidities, such as levothyroxine. A recent update on the use of the psychostimulant methylphenidate suggests that it may provide some benefit.[213] A second agent that may be helpful for short-term use in advanced cancer is the corticosteroid methylprednisolone.[208,209,214] However, potential treatment modalities in managing fatigue require further research.

Effective management of CRF involves an informed and supportive oncology care team that assesses fatigue levels regularly, counsels and educates patients regarding strategies for coping with fatigue, and uses institutional experts for referral of patients with unresolved fatigue.[36] The oncology care team must recognize the many patient-, provider-, and system-related behaviors that can impede effective fatigue management. Reducing barriers by use of available resources and evidence-based guidelines increases benefits to patients experiencing fatigue.[215,216]

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Individual Disclosures of the NCCN Cancer-Related Fatigue Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Amy Alvarez-Perez, MD	None	None	None	6/26/15
Ann M. Berger, PhD, APRN	None	None	None	8/5/15
William S. Breitbart, MD	None	None	None	1/28/15
Kristen M. Carpenter, PhD	None	None	None	7/17/15
David Cella, PhD	None	Abbott Laboratories; Bayer HealthCare; Genentech, Inc.; Helsinn Pharma; and MOFFITT	None	6/12/15
Charles Cleeland, PhD	None	National Cancer Institute	Amgen Inc.; Bayer HealthCare; and Exelixis Inc.	4/29/15
Efrat Dotan, MD	MedImmune Inc.; OncoMed Pharmaceuticals; Biocompatibles; and Immunomedics Inc.	Ipsen pharmaceuticals	None	7/20/15
Mario A. Eisenberger, MD	Bayer HealthCare; Bristol-Myers Squibb Company; Genentech, Inc.; Merck & Co., Inc.; Medivation; Tokai Pharmaceuticals; and sanofiaventis U.S.	Bayer HealthCare; Bristol-Myers Squibb Company; and sanofiaventis U.S.	Bayer HealthCare; and sanofiaventis U.S.	4/27/15
Carmen P. Escalante, MD	Pfizer Inc.	None	None	7/2/15
Paul B. Jacobsen, PhD	On Q Health; and Pfizer Inc.	Onyx Pharmaceuticals, Inc.	Onyx Pharmaceuticals, Inc.	4/28/15
Catherine Jankowski, PhD	None	None	None	5/4/15
Thomas LeBlanc, MD, MA	Celgene Corporation; and Helsinn Therapeutics	Epi-Q	Boehringer Ingelheim GmbH; and Helsinn Therapeutics	4/27/15
Jennifer A. Ligibel, MD	None	None	None	11/10/14
Elizabeth Trice Loggers, MD, PhD	None	None	None	4/29/15
Belinda Mandrell, PhD, RN	None	None	None	4/28/15
Barbara A. Murphy, MD	None	Eisai Inc.	None	7/17/15
Oxana Palesh, PhD, MPH	National Cancer Institute; CPIC; Moffitt Cancer Center; NCI; and Vital Connect, Inc	None	None	6/19/15
William F. Pirl, MD	None	None	None	9/9/14
Steven C. Plaxe, MD[a]	Amgen Inc.; Jannsen Pharmaceutica Products, LP;	Ambrx; and Insys	insys	4/28/15

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
	Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; azaya; endocyte; Tesaro; and Pfizer Inc.			
Michelle B. Riba, MD, MS	None	None	None	4/27/15
Anna Roshal, MD				Pending
Hope S. Rugo, MD	None	None	Genomic Health, Inc.	8/28/14
Carolina Salvador, MD	None	None	None	7/10/15
Lynne I. Wagner, PhD	None	Gilead, Inc.	None	8/21/14
Nina D. Wagner-Johnston, MD	Celgene Corporation	Gilead	None	4/27/15
Finly J. Zachariah, MD	None	None	None	5/5/15

[a]The following of disclosed that they have an Employment/Governing Board, Patent, Equity, or Royalty conflict:

Steven C. Plaxe, MD: Abbott Laboratories; Bristol-Myers Squibb Company; and Pfizer Inc.

Courtney Smith, PhD, Scientist, NCCN, has disclosed that she has an Employment/Governing Board, Patent, Equity, or Royalty conflict with Johnson & Johnson and OPKO; she has a Spouse/Domestic Partner/Dependent Potential Conflict with Ethos Health Communications and Complete Healthcare Communications. The remaining NCCN Guidelines staff have no conflicts to disclose