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NCCN Clinical Practice Guidelines in Oncology™

Cancer-Related Fatigue

V.1.2009

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NCCN Guidelines Panel Disclosures

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Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

Summary of the Guidelines Updates

Summary of major changes in the 1.2009 version of the Cancer-Related Fatigue guidelines from the 1.2008 version include:

(FT-4)

- **Assessment of treatable contributing factors: A new bullet was added "Medication side effects profile (ie, sedation)".**

(FT-5)

- **General Strategies for Management of Fatigue; Energy conservation: "Nap time" was changed from 45 to 20-30 minutes. (Also for FT-6 and FT-7)**
- **Nonpharmacologic (Also for FT-6 and FT-7):**
  - **Activity enhancement; Caution:**
    - **"Fever" was changed to "Fever or active infection"**
  - **Psychosocial interventions:**
    - **Cognitive behavioral therapy (CBT) has a new corresponding footnote that states, "A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and facilitate psychological adjustment."**
    - **Stress management, Relaxation and Support groups were designated as "category 1" recommendations.**
  - **"Sleep therapy" changed to "CBT for sleep".**

(FT-7)

- **Nonpharmacologic; Activity enhancement:**
  - **"Optimize level of activity" was changed to "Optimize level of activity with careful consideration of the following constraints". The constraints are listed as "Bone metastases, Immunosuppression/neutropenia, Thrombocytopenia, Anemia, Fever, and Assessment of safety issues (ie, risk of falls, stability)."**
  - **The panel removed "Consider referral to rehabilitation: physical therapy, occupational therapy, physical medicine" as a recommendation.**

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Cancer-Related Fatigue

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.

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STANDARDS OF CARE IN CHILDREN/ADOLESCENTS AND ADULT CANCER-RELATED FATIGUE MANAGEMENT

- 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 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.
- 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.
- 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.
- Quality of fatigue management should be included in institutional continuous quality improvement (CQI) 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.

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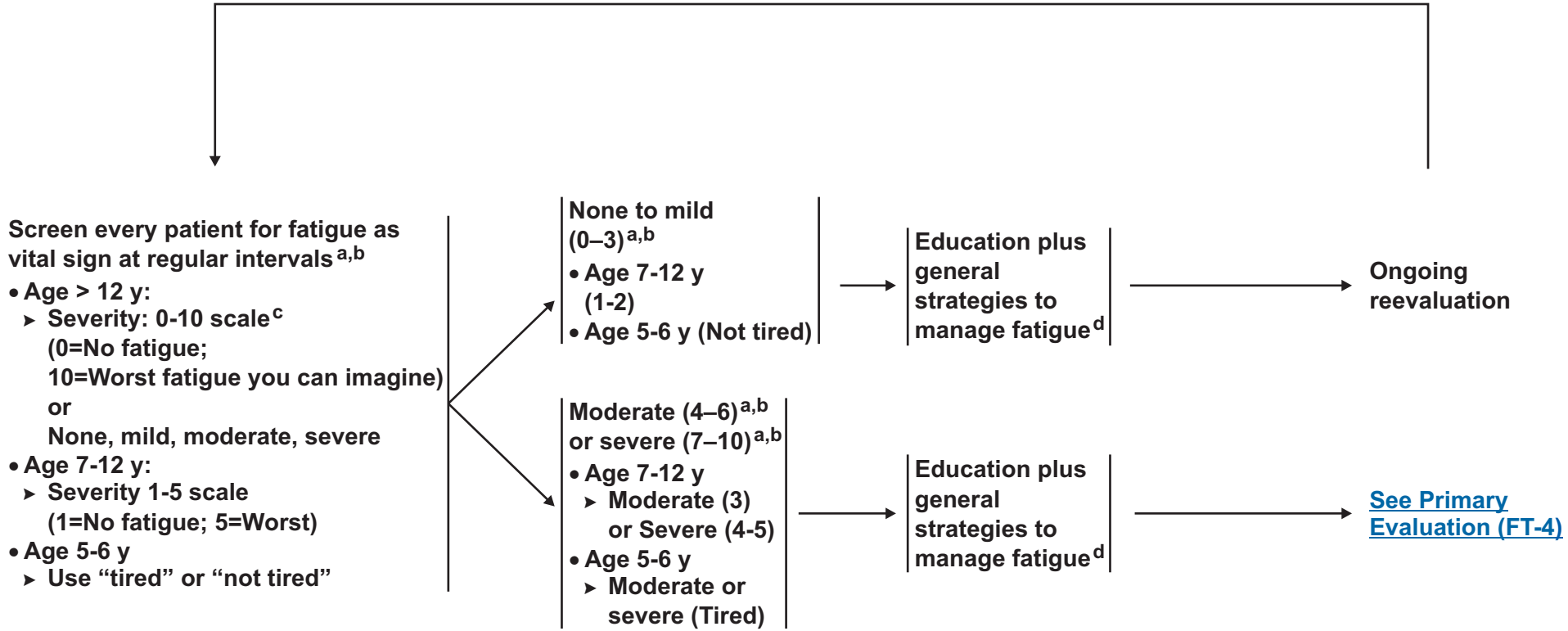
Cancer-Related Fatigue

SCREENING



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

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

[c] 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. Journal of Pain and Symptom Management 2008; 35(1): 20-30.

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

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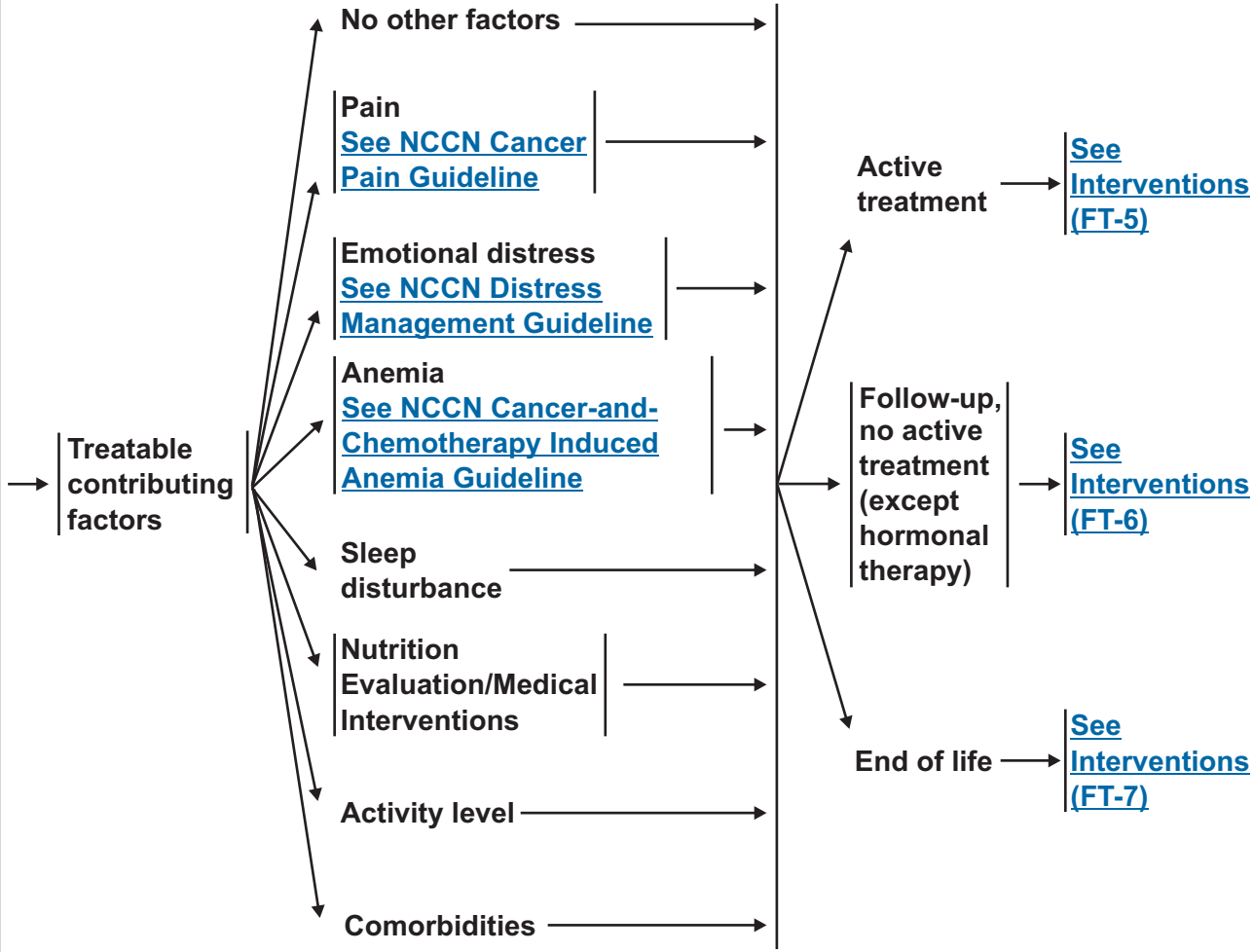
Cancer-Related Fatigue

PRIMARY EVALUATION FATIGUE SCORE: MODERATE OR SEVERE
Age > 12 y (4-10), Age 7-12 y (3-5), or Age 5-6 y (Tired)

PATIENT CLINICAL STATUS

Focused history
- Disease status and treatment
  - Rule out recurrence or progression
  - Current medications/medication changes
  - Prescription/OTCs and supplements
- Review of systems
- In-depth fatigue history
  - Onset, pattern, duration
  - Change over time
  - Associated or alleviating factors
  - Interference with function

Assessment of treatable contributing factors:
- Pain
- Emotional distress
  - Depression
  - Anxiety
- Anemia
- Sleep disturbance (eg, obstructive sleep apnea, restless leg syndrome, narcolepsy, insomnia)
- Nutrition Assessment
  - Weight/caloric intake changes
  - Fluid electrolyte imbalance: sodium, potassium, calcium, magnesium
- Activity level
  - Decreased activity
  - Decreased physical fitness
- Medication side effects profile (ie, sedation)
- Comorbidities
  - Infection
  - Cardiac dysfunction
  - Pulmonary dysfunction
  - Renal dysfunction
  - Hepatic dysfunction
  - Neurologic dysfunction
  - Endocrine dysfunction (hypothyroidism, hypogonadism, adrenal insufficiency)



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Cancer-Related Fatigue

INTERVENTIONS FOR PATIENTS ON ACTIVE TREATMENT[e]

Patient/Family Education and Counseling

Information about known pattern of fatigue during and following treatment
- Reassurance that treatment-related fatigue is not necessarily an indicator of disease progression

→

General Strategies for Management of Fatigue

- Self-monitoring of fatigue levels
- Energy conservation
  - Set priorities
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Labor-saving devices
  - Postpone nonessential activities
  - Limit naps to 20-30 minutes or less so as to not interfere with night-time sleep quality
  - Structured daily routine
  - Attend to one activity at a time
- Use distraction (eg, games, music, reading, socializing)

→

SPECIFIC INTERVENTIONS

Nonpharmacologic[f]

- Activity enhancement (category 1)
  - Maintain optimal level of activity
  - Consider initiation of exercise program
  - Consider referral to rehabilitation: physical therapy, occupational therapy & physical medicine
  - Caution:
    - Bone metastases
    - Immunosuppression/neutropenia[g]
    - Thrombocytopenia
    - Anemia
    - Fever or active infection
    - Limitations secondary to metastases or other illnesses
- Psychosocial interventions
  - Cognitive behavioral therapy (CBT)[h] (category 1)
  - Stress management (category 1)
  - Relaxation
  - Support groups (category 1)
- Attention-restoring therapy (eg, nature) (See MS-9)
- Nutrition consultation
- CBT for sleep (See MS-10)
  - Sleep restriction
  - Sleep hygiene
  - Stimulus control

Pharmacologic

→

- Consider psychostimulants[i] (methylphenidate or modafanil) after ruling out other causes of fatigue
- Treat for anemia as indicated (See NCCN Cancer-and-Chemotherapy Induced Anemia Guidelines)
- Consider sleep medication

→ Repeat evaluation See (FT-4)

[e] See Discussion for information on differences between Active treatment, Long term follow-up, and End-of-life treatment. (See MS-1)

[f] Interventions should be culturally specific and tailored to the needs of patients and families because not all patients may be able to integrate these options due to variances in individual circumstances and resources. (Sahler OJZ, Varni JW, Fairclough DL, et al. Problem-Solving Skills Training for Mothers of Children with Newly Diagnosed Cancer: A Randomized Trial. Journal of Developmental & Behavioral Pediatrics. 23(2):77-86, April 2002)

[g] Concern is with environment. Limit activity to environments where risk of infection is low.

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

[i] Pharmacological interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. There is more evidence for methylphenidate and less for modafinil. These agents 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 cancer patients.

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Cancer-Related Fatigue

INTERVENTIONS FOR PATIENTS ON LONG-TERM FOLLOW-UP[e]

Patient/Family Education and Counseling

Information about known pattern of fatigue during and following treatment
- Self-monitoring of fatigue levels

→

General Strategies for Management of Fatigue

- Energy conservation
  - Set priorities
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Labor-saving devices
  - Postpone nonessential activities
  - Limit naps to 20-30 minutes or less so as to not interfere with night-time sleep quality
  - Structured daily routine
  - Attend to one activity at a time
- Use distraction (eg, games, music, reading, socializing)

→

SPECIFIC INTERVENTIONS

Nonpharmacologic[f]

- Activity enhancement (category 1)
  - Maintain optimal level of activity
  - Consider initiation of exercise program
  - Consider referral to rehabilitation: physical therapy, occupational therapy, physical medicine
  - Caution:
    - Late effects of treatment (eg, cardiomyopathy)
- Psychosocial interventions (category 1)
  - CBT[h] (category 1)
  - Stress management (category 1)
  - Relaxation
  - Support groups (category 1)
- Attention-restoring therapy (eg, nature) (See MS-9)
- Nutrition consultation
- CBT for sleep (See MS-10)
  - Sleep restriction
  - Sleep hygiene
  - Stimulus control

→

Pharmacologic[j]

- Consider psychostimulants[i] (methylphenidate or modafanil) after ruling out other causes of fatigue
- Treat for anemia as indicated (See NCCN Cancer-and-Chemotherapy Induced Anemia Guidelines)
- Consider sleep medication

→ Repeat evaluation See (FT-4)

[e] See Discussion for information on differences between Active treatment, Long term follow-up, and End-of-life treatment. (See MS-1)

[f] Interventions should be culturally specific and tailored to the patients and families because not all patients may be able to integrate these options due variances in individual circumstances and resources. (Sahler OJZ, Varni JW, Fairclough DL, et al. Problem-Solving Skills Training for Mothers of Children with Newly Diagnosed Cancer: A Randomized Trial. Journal of Developmental & Behavioral Pediatrics. 23(2):77-86, April 2002)

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

[i] Pharmacological interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. There is more evidence for methylphenidate and less for modafinil. These agents 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 cancer patients.

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

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INTERVENTIONS FOR PATIENTS AT THE END OF LIFE[e,k]

Patient/Family Education and Counseling

Information about known pattern of fatigue during and following treatment
- Expected end-of-life symptom
- May vary in intensity

→

General Strategies for Management of Fatigue

- Energy conservation
  - Set priorities
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Labor-saving and assistive devices
  - Eliminate nonessential activities
  - Limit naps to 20-30 minutes or less so as to not interfere with night-time sleep quality
  - Structured daily routine
  - Attend to one activity at a time
  - Conserve energy for valued activities
- Use distraction (eg, games, music, reading, socializing)

→

SPECIFIC INTERVENTIONS

Nonpharmacologic[f,j]

- Activity enhancement
  - Optimize level of activity with careful consideration of the following constraints:
    - Bone metastases
    - Immunosuppression/ neutropenia[g]
    - Thrombocytopenia
    - Anemia
    - Fever or active infection
    - Assessment of safety issues (ie, risk of falls, stability)
- Psychosocial interventions (category 1)
  - CBT[h]
  - Stress management
  - Relaxation
  - Support groups
- Attention restoring therapy (eg, nature) (See MS-9)
- Nutrition consultation
- CBT for sleep (See MS-10)
  - Sleep restriction
  - Sleep hygiene
  - Stimulus control

→

Pharmacologic

- Consider psychostimulants[i] (methylphenidate or modafanil) after ruling out other causes of fatigue
  - Consider corticosteroids (prednisone or dexamethasone)
- Treat for anemia as indicated (See NCCN Cancer-and-Chemotherapy Induced Anemia Guidelines)
- Consider sleep medication

→ Repeat evaluation See (FT-4)

[e] Discussion for information on differences between Active treatment, Long term follow-up, and End-of-life treatment. (See MS-1)

[f] Interventions should be culturally specific and tailored to the needs of patients and families because not all patients may be able to integrate these options due to variances in individual circumstances and resources. (Sahler, O J Z., Varni, JW, Fairclough, D L, Butler R W, et al. Problem-Solving Skills Training for Mothers of Children with Newly Diagnosed Cancer: A Randomized Trial. Journal of Developmental & Behavioral Pediatrics. 23(2):77-86, April 2002)

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[k] Also See NCCN Palliative Care Guidelines.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Fatigue is a common symptom in patients with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biological response modifiers.[1-10] The problem, which affects 70% to 100% of cancer patients, has been exacerbated by the increased use of fatigue-inducing multimodal treatments and dose-dense, dose-intense protocols.[11] In patients with metastatic disease, the prevalence of cancer-related fatigue exceeds 75%, and cancer survivors report that fatigue is a disruptive symptom months or even years after treatment ends.[12-21] The distinction between tiredness, fatigue, and exhaustion has not been made consistently, despite conceptual differences.[22,23] 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, for most patients, can generally be managed by medications.[24,25]

Fatigue in cancer patients has been under-reported, under-diagnosed, and under-treated. Persistent cancer-related fatigue affects quality of life (QOL), as cancer patients become too tired to participate fully in the roles and activities that make life meaningful.[16,26-28] 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 cancer patients who are cured of their malignancy but have continued fatigue.[29] Despite biomedical literature documenting this entity, it is often difficult for patients with cancer-related fatigue 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.

Despite the prevalence of cancer-related fatigue, the exact mechanisms involved in its pathophysiology are unknown. Proposed mechanisms include abnormal accumulation of muscle metabolites, production of cytokines,[30] changes in neuromuscular function,[31] abnormalities in adenosine triphosphate (ATP) synthesis, serotonin dysregulation, and vagal afferent activation.[32,33] Limited evidence supports these proposed mechanisms, and much of the research to date has focused on correlates of fatigue.

To address the important problem of cancer-related fatigue, the NCCN convened a panel of experts. The NCCN Cancer-Related Fatigue Guideline, first published in 2000[34] and updated annually (see www.nccn.org), synthesizes the available research and clinical experience in this field as well as provides recommendations for patient care.

Defining Cancer-Related Fatigue

The panel defines cancer-related fatigue as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning (FT-1). Compared with the fatigue experienced by healthy individuals, cancer-related fatigue is more severe, more distressing,[12,35] and less likely to be relieved by rest.[36] In terms of the defining characteristics, it is important to note the subjective sense of tiredness reported by the patient. As with pain, the clinician must rely on patients' descriptions of their fatigue and accompanying distress. Fatigue that interferes with usual functioning is another substantial component of the definition for cancer-related fatigue and the source of much distress for patients.[7,37,38] Investigations have documented a significant effect of fatigue on physical functioning during cancer treatment, and it is uncertain whether patients regain full functioning when treatment is over.[39,40]

Standards of Care for Assessment and Management

The panel developed Standards of Care for Cancer-Related Fatigue Management (FT-2), using the NCCN Adult Cancer Pain Guidelines, NCCN Pediatric Cancer Pain Guidelines, and the NCCN Distress Management Guidelines as exemplar models. These fatigue standards represent the best level of care for the assessment and management of fatigue in cancer patients, including children, adolescents and adults, and should provide guidance for health care professionals as they implement the guideline in their respective institutions and clinical settings. The overall goal of the standards and guideline is to ensure that all cancer patients with fatigue are identified as well as treated promptly and effectively.

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 by self-report. The history and physical examination, laboratory data, and descriptions of patient behavior by family members, especially in children, are important sources of additional information.

Fatigue should be screened, assessed, and managed for most patients according to clinical practice guideline. This guideline provides "best care" information based on current evidence to support treatment.[41] Patients should be screened for the presence and severity of fatigue at their initial clinical visit, at appropriate intervals during and/or following 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.[42]

Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner. Implementation of the guideline for fatigue is best managed by an interdisciplinary institutional committee, including medicine, nursing, social work, physical therapy, and nutrition.[43] 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 institutional settings is necessary if professionals are to become skilled in managing fatigue.

Cancer-related fatigue should be included in clinical health outcome studies, and the NCCN Panel recommends that assessment of fatigue levels be included in outcomes research. Quality of fatigue management should be included in institutional continuous quality improvement (CQI) projects. Institutions can make faster progress in implementing the guidelines if they monitor adherence and progress with the guidelines. Medical care contracts should include

reimbursement for the management of fatigue whether the patient needs referral to a physical therapist, dietitian, or the institution's symptom management service. In addition, 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 incorporates the following phases: screening, primary evaluation, intervention, and re-evaluation. During the first phase, the health care professional must screen for fatigue, determine its presence or absence, and assess its intensity level. If the intensity level is moderate to severe, the health care professional is directed to conduct a more focused history and physical examination during the primary evaluation phase of the algorithm. This phase includes an in-depth fatigue assessment and an evaluation of 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 treatable 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 Cancer-Related Fatigue Guidelines.

After the evaluation phase, the guideline delineates a set of interventions for the amelioration of fatigue based on the patient's clinical status (ie, active cancer treatment, long-term follow-up, or end of life). Education and counseling are believed to be central to the effective management of fatigue. Additional interventions are nonpharmacologic and pharmacologic; however, in many instances a combination of approaches must be used. Finally, the algorithm calls for re-evaluation, leading to an iterative loop in fatigue screening and management.

Screening

The first phase of the algorithm emphasizes screening of every patient for the presence or absence of fatigue (FT-3). If fatigue is present, a quantitative or semiquantitative assessment should be performed and documented. For example, on a 0 to 10 numeric rating scale (zero = no fatigue and 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.[44,45] The fatigue scale for children is simplified; thus, young children (age 5-6 years) may be asked if they are "tired" or "not tired." Valid and reliable instruments are available to measure fatigue in children and adolescents.[3,46-48] If the screening process determines that fatigue is absent or at a mild level, the patient and family should receive education about fatigue and common strategies for managing it. Periodic re-screening and re-evaluation are recommended; for inpatients this should be carried out daily and for outpatients at subsequent routine and follow-up visits. It should be emphasized that survivors or patients who have been taken off treatment must still be monitored for fatigue, because fatigue may exist beyond the period of active treatment.[12,15,49]

Currently, screening is not systematic or effective in many practice settings for various reasons, which often include patient or family barriers and clinician barriers.[50] 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. Also, patients do not want to be perceived as complaining and, therefore, may not mention fatigue. Or, they may assume that they just have to live with fatigue, because they believe there is no treatment for it. Health care professionals may not initiate a discussion about fatigue for many of the same reasons. First, clinicians may not recognize that fatigue is a problem for the patient. Fatigue, as a symptom, has been unrecognized and untreated. Conversely, medical advances have led to better control

over the more noticeable or less-subtle acute symptoms of nausea, vomiting, and pain. Researchers have begun to document not only the prevalence and incidence of fatigue but also how it significantly disrupts a patient's QOL.[51-53] Second, health care professionals may not be aware that there are effective treatments for fatigue. In addition, the underlying pathophysiology and mechanisms of fatigue have not been elucidated.

Given these barriers, screening for cancer-related fatigue 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 addition, 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; however, the spouse, parents, or other family members may be more cognizant of these changes and the effect of fatigue. An appendix to this manuscript provides additional information and resources to assist in the selection of instruments to measure cancer-related fatigue.

Using the numeric rating scale (ie, 0 to 10 scale), fatigue studies in cancer patients have revealed a marked decrease in physical functioning at the level of 7 or higher.[44,54] The authors of an international study on fatigue in breast and prostate cancer patients evaluated and compared fatigue-intensity levels with scores from the MOS-SF-36 Physical Functioning Subscale.[45] The study documented a dramatic decrease in physical functioning when fatigue intensity levels were at level 7. Based on these validated levels of intensity, the panel believes that this rating scale can be used as a guide in practice settings and decision-making.

Primary Evaluation Phase [Fatigue Score: moderate-to-severe (4-10)]

Focused History and Physical Examination

When fatigue is rated as moderate to severe, with a score 4-10, a more focused history and physical examination should be conducted as part of the primary evaluation phase (FT-4). A component of this evaluation is an assessment of the patient's current disease status, the type and length of treatment as well as its capacity to induce fatigue, and the patient's response to treatment. If possible, it should be determined whether the fatigue is related to a recurrence of malignancy for those patients assumed to be disease-free or related to a progression of malignancy for those patients with underlying disease. This is often an important factor causing patients with fatigue to seek further evaluation. If the fatigue is determined not to be related to disease recurrence, informing patients and family members will substantially reduce their anxiety levels.

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[55] that includes evaluation of aspects of fatigue onset, pattern, duration, change over time, associated or alleviating factors, and interference with function. Physical, emotional, and cognitive symptoms may be associated with fatigue. The health care professional must evaluate fatigue's effect on normal functioning and its effect on the patient's 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 should also include the patient's self assessment of the causes of fatigue.

Assessment of Treatable Contributing Factors

As part of this focused evaluation, the panel identified seven factors that are often causative elements in the fatigue experience and, therefore, should be specifically assessed. These factors include pain, emotional distress, sleep disturbance, anemia, nutrition, activity level, medication side effects profile (ie. sedation), and other comorbidities.

Appropriate assessment of pain along with emotional distress and institution of effective treatment are essential. Descriptive studies have shown that, in adults as well as in children, fatigue seldom occurs by itself and that it more commonly clusters with sleep disturbance, emotional distress (eg, depression, anxiety), or pain.[7,56-59]

Fatigue and depression have been documented as concurrent symptoms in cancer patients. In 987 lung cancer patients, Hopwood and Stephens[60] documented depression in 33% and that fatigue was an independent predictor of depression in this group. Newell and colleagues[61] found fatigue was the most commonly experienced and debilitating physical symptom for 201 oncology patients; about 25% of these patients also experienced depression. In 457 patients with Hodgkin's disease, Loge and colleagues[62] found that 26% had fatigue for 6 months or longer (defined as fatigue "cases") and that fatigue correlated moderately with depression (r = .41). Fatigue cases had higher levels of depression than non-cases. Visser and Smets[63] studied the relationship between fatigue and depression in 308 adults in Amsterdam who were treated as outpatients with radiation therapy for cure or control of cancer. They concluded that fatigue and depression were independent conditions with different patterns over time: fatigue increased over the course of treatment but depression decreased. Fatigue was not predictive of depression, and depression did not predict fatigue in this sample.

Sleep disturbances are a neglected problem in oncology[64] and may range from hypersomnia to insomnia.[65,66] Sleep disturbances are prevalent in 30% to75% of patients with cancer.[67] Several studies have shown that fatigued cancer patients in active treatment spend increased time resting and sleeping but that their pattern of sleep is often severely disrupted.[68,69] When sleep disturbances are present, the patient should be assessed for depression, because this is a common manifestation.[70] 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 (ie, thyroid, estrogen, testosterone), therefore, obstructive sleep apnea should also be evaluated.

Studies have shown fatigue's association with anemia in cancer patients and its amelioration with erythropoietin. Patients should undergo a nutritional assessment to evaluate weight gain and loss, caloric intake changes, impediments to nutritional intake, and fluid and electrolyte imbalances. Weight and weight changes should be carefully noted. The health care provider should also review and discuss changes in caloric intake with the patient. If there are substantial abnormalities, a consultation with a nutrition expert may be appropriate. Often fatigue symptoms can be improved by improving dietary intake, with appropriate caloric exchanges. Imbalances in sodium, potassium, calcium, and magnesium serum levels are often reversible and, with appropriate supplementation, may improve 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 activity level, including changes in exercise or activity patterns and the influence of deconditioning. This assessment is important when formulating a treatment plan that may include exercise. 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? Exercise has been beneficial in lowering fatigue levels in certain populations of cancer patients.[71-73] 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 levels of activities, which gradually increase over a period of 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. In addition, recent medication changes should be noted. Medications and medication interactions may contribute to worsening of fatigue. For example, certain cardiac medications (such as beta-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 subsequently improve fatigue.

Non-cancer comorbidities may contribute substantially to symptoms of fatigue in the cancer patient. The status of each comorbidity must be reviewed in conjunction with the present treatment management of that comorbidity. If the comorbidity is not optimally managed, it may be necessary to further evaluate and improve that 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 infection as well as cardiac, pulmonary, renal, hepatic, neurologic, and endocrine dysfunction (including hypothyroidism, hypogonadism or adrenal insufficiency). Canaris and colleagues[74] noted the high incidence of thyroid dysfunction in normal individuals and in patients receiving thyroid medications; they suggested that more attention must be given to thyroid problems in both the general and cancer-patient populations. Development of hypothyroidism occurs after radiation therapy for Hodgkin's disease and other non-Hodgkin's lymphomas, head and neck cancers, and breast cancer, as well as after total body irradiation in bone marrow transplantation. Also, 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 often seen in patients with advanced cancer. A recent cross-sectional pilot study by Strasser and colleagues[75] explored whether hypogonadism contributes to fatigue in men with advanced cancer. The results of the study indicate that abnormally low levels of testosterone are associated with fatigue. However, additional research with larger samples 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, long-term follow-up with no active treatment except hormonal therapy, or end of life) should be determined, because it will influence cancer-related fatigue management and treatment strategies. However, some general treatment guidelines apply across all clinical categories.[76]

If any of the eight treatable contributing factors discussed above is identified during the primary evaluation phase, it should be treated as an initial approach to fatigue management. NCCN clinical practice guidelines are also available to guide the treatment of pain (see NCCN Adult Cancer Pain Guidelines and NCCN Pediatric Cancer Pain Guidelines), distress (see NCCN Distress Management Guidelines), and anemia (see NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines). Treatment of sleep disturbances, nutritional alterations, and physical deconditioning are discussed under "Nonpharmacologic Interventions" for the three levels of clinical status.

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 cancer patients[50] but is particularly essential for patients beginning potentially fatigue-inducing treatments (such as radiation, chemotherapy, or biotherapy), before the onset of fatigue (FT-5). Patients should be informed that if fatigue does occur, it may be a consequence of the treatment and not necessarily an indication that the treatment is not working or that the disease is progressing. Daily self-monitoring of fatigue levels in a treatment log or diary can be helpful.

In addition to education, the panel recommends counseling for patients about general strategies (energy conservation and distraction) useful in coping with fatigue. Energy conservation encompasses a common sense approach that helps patients to prioritize and pace activities, and to delegate less essential activities.[77] 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 the patient to ascertain peak energy periods.[78] The fatigued patient can then plan activities accordingly. A multisite clinical trial of energy conservation in 296 patients receiving cancer treatment by Barsevick and colleagues[79] reported significantly lower fatigue in those receiving the experimental intervention. Some participants in descriptive studies have suggested that activities designed to distract (eg, games, music, reading, socializing) are helpful in decreasing fatigue, although the mechanism is unknown.[80,81]

Nonpharmacologic Management

Of the specific nonpharmacologic interventions during active cancer treatment, activity enhancement (category 1) and psychosocial interventions (category 1) have the strongest evidence base for treating fatigue; however, attention-restoring therapy, dietary management, and sleep therapy all have some supporting evidence.[82]

Activity Enhancement.

In cancer patients, the adverse effects of therapy results in decreased activity and physical performance. Although there are a number of factors that contribute to the decline in functionality, fatigue is one of the major contributors. Mustian and colleges[83] 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 Index (ADLs). 753 patients were enrolled (64% female). 85.4% and 79.3 % of patients reported fatigue after the first and second cycles of chemotherapy respectively. The mean severity of fatigue was 5.0 for the first cycle and 4.7 for the second cycle (scale 0-10, 10 = severe fatigue). Cancer-related fatigue interfered with all ADLs in the majority of 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 both evaluate the feasibility of interventions to increase physical activity during and after therapy, and to explore the impact of increased activity upon cancer-related fatigue, quality of life, 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 manuscript. However, many of these studies have specifically evaluated the effect of increased activity upon cancer-related fatigue, and several meta-analyses have been conducted over the past five years to provide a comprehensive evaluation of the impact of increased activity upon cancer-related fatigue.

The two most recent analyses provide a clear picture of the current status of this area of investigation. Kangas and colleagues[84] reported the results of 19 articles that reported the effectiveness of physical exercise on fatigue-related outcomes. 17 studies were randomized controlled trials (RCT) of which 17 trials reported fatigue outcome and 10 reported vigor/vitality outcomes. None of the trials required that patients have a specified a level of fatigue at the time of study entry. 35% of studies demonstrated an improvement in fatigue and 30% demonstrated an improvement in vigor/vitality. For fatigue, the weighted pooled mean effect size was -0.42 (95% CI, -0.599 to -0.231) and for vigor/vitality -0.69 (95% CI, 0.43 to 0.949). Thus, the effect size for fatigue was felt to be "on the edge of moderate" and clinically significant, while the effect size for vigor/vitality was moderate to large. Of interest, no significant difference in effect size was noted between studies using different fatigue outcome measures. Exercise interventions had a stronger effect when administered during therapy as opposed to after therapy was completed. Overall, patients with breast cancer derived greater benefit than those with other malignancies. A 2008 Cochrane analysis[85] reported the results of 28 RCTs that investigated the effect of exercise on CRF. 19 studies included patients with a specific cancer diagnosis while 9 included various cancers. The majority of cancer specific trials investigated breast cancer patients (n=16). 13 studies investigated home-based or unsupervised exercise programs, 16 investigated supervised, institutional programs. Interventions ranged from three to 32 weeks with an average of 12 weeks. 18 studies reported outcome measures beyond the endpoint of the intervention. Overall, exercise was more effective in relieving fatigue than the control intervention (SMD -0.23; 95% CI, -0.33 to -0.13). The exercise intervention was statistically more effective than the control arm both during (SMD -0.18, 95%CI-0.32 to -0.05) and after therapy (SMD -0.37; 95% CI, -0.49 to -0.23). An improvement in fatigue was noted in patients with breast cancer and prostate cancer. No improvement was noted in the single study for colorectal cancer or multiple myeloma.

It is reasonable to encourage all patients to engage in a moderate level of physical activity during and after cancer treatment. Currently there is not sufficient evidence to recommend a specific amount of physical activity for cancer populations. The US Surgeon General recommends 30 minutes of moderate activity most days of the week for all populations.[86] Some observational and interventional studies have suggested that cancer patients who engage in at least 3-5 hours of moderate activity per week may experience better outcomes and have fewer side effects of therapy, including fatigue.[71,72,87-91]

Some patients may require referrals to exercise specialists such as physical therapy, physical medicine or rehabilitation for assessment and an exercise prescription. The American College of Sports Medicine has recently developed a certification program for cancer rehabilitation that is available for exercise professionals who specialize in care of cancer populations.

Specific issues that should trigger a referral for physical therapy:

- Patients with comorbidities (such as cardiovascular disease or COPD)
- Recent major surgery
- Specific functional or anatomical deficits (such as decreased range of motion due neck dissection for head and neck cancer)
- Substantial deconditioning

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

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

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

Psychosocial Interventions.
Patients should be counseled about stress management and methods for dealing with depression and anxiety, which are commonly associated with fatigue during cancer treatment.[92] Although a strong correlation exists between emotional distress and fatigue, the precise relationship is not clearly understood. Both depression and anxiety may be characterized by fatigue, but it is also evident that high levels of fatigue may cause emotional distress when valued roles and activities are affected. Preliminary evidence in a recent study suggests that the relationship between fatigue and depression in cancer patients is mediated by functional status.[93]

Studies testing interventions to reduce stress and to increase psychosocial support in cancer patients have shown reductions in fatigue levels, usually measured as a component of mood state.[94-99] The interventions have included education,[96,97,99] support groups,[94,98,100] individual counseling,[95,101] a comprehensive coping strategy,[100,102] stress management training,[103] and a tailored behavioral intervention.[39] The studies were randomized controlled trials, with good experimental designs and adequate sample sizes, and included various cancer populations; thus, the level of evidence for using these psychosocial interventions to treat fatigue is category 1. However, in many of these studies, fatigue was a secondary endpoint measured by a single item or a subscale of an instrument to measure emotional distress.

Attention-restoring Therapy.
Attention-restoring therapy is another type of nonpharmacologic intervention. Attentional fatigue, which is an aspect of the sensory dimension of fatigue, has been defined as a decreased capacity to concentrate or to direct attention during stressful or demanding situations.[104] Cimprich developed and tested attention-restoring interventions in women with breast cancer.[105-107] Patients who received these interventions displayed improved concentration and problem solving on neurocognitive tests and returned earlier to work after surgery compared with control individuals.[105] When the intervention was begun before surgery, the experimental group showed greater preoperative to postoperative recovery of capacity to direct attention.[106] Bird watching and sitting in the park are examples of experiences in natural environments that have a restorative influence on cancer patients.

Nutrition Consultation.
Many cancer patients 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.[108] Adequate hydration and electrolyte balance are also essential in preventing and treating fatigue.

Sleep Therapy.
Cancer patients 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.[109] Non-pharmacological interventions to improve sleep quality have been organized into four general types of therapies that include cognitive-behavioral, complementary, psycho-education/information and exercise therapies.[110] These interventions are designed to optimize sleep quality and some have also been shown to decrease fatigue.[111]

There are numerous cognitive behavioral therapies (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 same time each night, and maintaining a regular rising time each day. Stimulus control also includes getting out of bed after 20 minutes if unable to fall asleep, both when first going to bed and when awakening during the night.[112] Sleep restriction includes avoiding long or late afternoon naps and limiting total time in bed.[113] Sleep hygiene includes 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 (e.g, dark, quiet, and comfortable). These strategies were employed 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.[114] For children with cancer, a consistent bedtime and routine, a conducive environment, and presence of security objects (such as blankets and toys) are effective measures.

A number of published studies[115-117] support the conclusion that cognitive-behavioral therapy interventions designed to optimize sleep quality in cancer patients may also improve fatigue. Two randomized clinical trials of patients in the survivorship phase after cancer treatment who reported chronic insomnia resulted in positive effects on both sleep and fatigue after 4-5 weekly behavioral therapy sessions.[118-120] Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.[115,116] Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.[114,117] The American Academy of Sleep Medicine has recommended three specific therapies for chronic insomnia in healthy individuals: relaxation training, cognitive behavior therapy, and stimulus control therapy.[121] AASM has also published clinical guidelines for the management of chronic insomnia in adults.[122]

CBT therapies are often combined with complimentary therapies to relax the individual such as breathing control, progressive muscle relaxation, and guided imagery techniques. Complementary therapies such as massage therapy,[123-125] yoga,[126-128] muscle relaxation,[129,130] and mindfulness-based stress reduction[131-134] have been evaluated in pilot studies; the preliminary data suggest that they may be effective in reduction of fatigue in cancer patients. Cohen and Fried[135] compared a control group, a cognitive behavioral, and a relaxation and guided imagery intervention and reported means of fatigue and sleep difficulties fell in both intervention groups, but were only significantly different in the relaxation and guided imagery group.

Pharmacologic Interventions

Though a wide variety of pharmacologic options are available to improve sleep quality, there is little empirical evidence 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 a recent FDA warning regarding potential risks of sedative-hypnotics drugs that include severe allergic reactions and complex sleep-related behaviors, including sleep-driving.[136] A table summarizing the medications commonly used to promote sleep is provided at the National Cancer Institute PDQ web-site.[137] Prescribing considerations with 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 cytochrome p450 isoenzyme system. Increased public and professional education regarding sleep, sleep disturbances, and daytime consequences of sleep loss are recommended.

There is some evidence for pharmacologic therapy as a fatigue treatment. A recent meta-analysis of ten studies concluded that the treatment of anemia during chemotherapy with erythropoietin resulted in a reduction of fatigue (see the NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines).[138] Studies on a selective serotonin reuptake inhibitor paroxetine showed no influence by this antidepressant on fatigue in patients receiving chemotherapy.[139,140] Antidepressants are not recommended to lower fatigue.

The psychostimulant, methylphenidate, has been evaluated for its effect on cancer-related fatigue. The reader is referred to more information about the use of psycho-stimulants to modify fatigue in the General Strategies for Management of Fatigue - Pharmacologic Interventions section (see MS-15).

Interventions for Patients on Long-Term Follow-Up (FT-6)

More than 9 million U.S. people now living have a history of cancer. Of the approximately 1,437,180 persons in the United States who will be diagnosed with cancer in 2008, 66% are expected to survive at least 5 years.[141] These improvements in survival have led to efforts to enhance symptom management, QOL, and overall functioning of individuals entering long-term follow-up after cancer treatment. As previously mentioned, fatigue is an acute effect of cancer or treatment, but it can also be a long-term or late effect.[142,143] Patients may continue to report unusual fatigue for months or years after treatment cessation.[12-15,17-21]

Researchers have suggested that such fatigue may be due to persistent activation of the immune system[13,144] or to other factors, such as late effects of treatment on major organ systems.[144] 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[145] and range from 33% to 53% when other criteria (such as a score of 4 or more on the 0 to 10 fatigue scale) are used.[146] In contrast to these findings, Canadian and U.S. 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.[147] As a consequence, what constitutes valid incidence and prevalence rates in disease-free patients requires more study.

In general, most research reports to date are limited by their cross-sectional designs,[25,52,143,145,148-150] lack of comparison groups,[25,52,150] heterogeneous samples,[145,151] use of differing fatigue scales, small sample sizes,[144] varying baseline survivorship definitions (ie, time since diagnosis versus time since treatment cessation), and different mean survivorship durations. These design issues make it difficult to reach conclusions about the effect of fatigue's prevalence, incidence, duration, associated risk factors, and QOL. Additionally, most fatigue studies of post-treatment disease-free patients have been conducted in Caucasian, English-speaking breast cancer,[13,144,148] and peripheral stem cell or bone marrow transplant patients[151,152] with few exceptions.[17,19,21]

The cause of fatigue in post-treatment disease-free patients is unclear and probably multifactorial.[153] One cross-sectional comparative study investigated fatigue and physiologic biomarkers of immune system activation in 20 breast cancer survivors who were fatigued (a mean of 5 years since diagnosis) and in 20 non-fatigued survivors.[144] Fatigued

survivors had significantly higher serum markers (interleukin-1 receptor antagonist [IL-1ra], soluble tumor necrosis factor type II [sTNF-RII], and neopterin) and lower cortisol levels when compared with non-fatigued survivors. Significantly higher numbers of circulating T lymphocytes that also correlated with elevated serum IL-1ra levels suggesting that persistent fatigue in survivors may be caused by a chronic inflammatory process involving the T-cell compartment.[13]

Other risk factors associated with fatigue in post-treatment disease-free patients include pretreatment fatigue, anxiety and depression levels,[154] physical level activities,[155,156] coping methods and cancer-related stressors, comorbidities,[157] type of malignancy, prior treatment patterns, and treatment late effects. For example, in one Norwegian study, a small proportion of long-term disease-free cancer patients who had pre-existing coronary artery disease had 30% higher fatigue levels compared with controls. In another Norwegian study that investigated fatigue in Hodgkin's disease survivors in remission for more than 5 years, higher fatigue levels were documented in those who had pulmonary dysfunction.[146] In these survivors, the prevalence of chronic fatigue was 2 to 3 times higher than in survivors who did not have such impairment. No significant correlations in this study were found between fatigue and cardiac sequelae as measured by echocardiography, exercise testing, and chest radiography.[146] Prior treatment patterns may affect the survivor's fatigue. For example, in a study of 322 post-treatment disease-free breast cancer patients, the highest fatigue scores occurred in women who had received previous combination therapy versus other forms of treatment.[150] 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 it is critical that exercise be individualized to the survivors abilities to prevent exacerbation of cancer treatment toxicities.[155,156]

Education and Counseling of Patient and Family

Patients who are completing treatment and entering the phase of long-term follow-up 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,[12,15] most patients experience a gradual decrease in fatigue and return of energy to normal levels.[14,147] Regular self-monitoring of fatigue levels is helpful to document the decrease of fatigue that normally occurs after treatment. Oncology care providers should continue to screen regularly for fatigue during follow-up visits.

Nonpharmacologic Management

Specific interventions recommended to manage fatigue during active cancer treatment are also recommended for disease-free patients on long-term follow-up.[76]

Activity Enhancement.

Activity enhancement is a category 1 recommendation. Improving strength, energy, and fitness through regular exercise, even a moderate walking exercise program, has been shown to facilitate the transition from patient to survivor, decrease anxiety and depression, improve body image, and increase tolerance for physical activity.[158] However, if the patient is significantly deconditioned, weak, or have 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 cancer-related fatigue, exercise has the best evidence to support its effectiveness.[76,159-166]

Psychosocial interventions.

Psychosocial interventions, including CBT, stress management, and support groups are category 1 recommendations.[39,94-99,101-103] Additional details on these interventions are provided in the preceding pages in the section on Psychosocial interventions for patients on Active Treatment.

Additional Nonpharmacological Approaches.

Attention-restoring therapy, sleep therapy,[110] family interaction, and nutritional therapy are all helpful for fatigue management in this population as well.

Pharmacologic Interventions

Cause-specific pharmacologic therapy may include hypnotics as a possible short-term treatment for insomnia; If indicated, anemia should also be treated (see NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines). Whether psychostimulants are useful for treating fatigue in disease-free patients on long-term follow-up has not been reported, although psychostimulants, such as methylphenidate, can be considered after ruling out other causes of fatigue.

Interventions for Patients at the End of Life (FT-7)

Although the assessment and management of fatigue at the end of life parallels the general principles of this guideline, there are a few issues that 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.[167] 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 come on suddenly.[51,168]At the end of life, most research has demonstrated that cancer patients 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%).[169] In a large sample of adults (N = 1000) receiving palliative care, Walsh and colleagues[170] noted that individuals with advanced cancer had multiple symptoms. Pain was the most prevalent (84% of patients), followed by easy fatigue (69%), weakness (66%), and lack of energy (61%). Walsh and Rybicki[171] cluster-analyzed 25 symptoms in 1000 consecutive admissions to a palliative care program and found seven symptom clusters. The fatigue cluster included easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, and taste changes. There is also the possibility, suggested by Given and colleagues,[37,172] that pain and fatigue together could have a synergistic effect that worsens the overall symptom experience in elderly cancer patients.Children with advanced cancer also experienced multiple symptoms at the end of life, most commonly fatigue, pain, and dyspnea.[173]

Education and Counseling of Patient and Family

Individuals with advanced cancer and their caregivers need information about the management of symptoms, including fatigue,[174] with specific information related to the disease trajectory.[175,176] This includes information about the causes, patterns, and consequences of fatigue during treatment for advanced cancer and at the end of life.

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 interfere increasingly with usual activities.[168] Families need to be apprised of this problem so they can begin planning for it. In addition, fatigue is likely to have increasing effect on emotional well-being.[168,173] 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 a great deal of suffering from it.[173]

In a case study of 15 adults with advanced disease, Krishnasamy found that fatigue resulted in substantial regret, sadness, and sense of loss due to the deterioration of one's health.[168] Mystakidou and colleagues[177] reported that patient desire for a hastened death was predicted by feeling sad, 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 those with a low likelihood of long-term survival.[173] Although there is no effective therapy for some causes of fatigue and other symptoms, treatment of those more amenable to therapy could help to relieve suffering.[76]

General Strategies for Management of Fatigue

Energy conservation is a self-care strategy for individuals with advanced cancer and their caregivers.[79] Energy conservation is defined as the deliberately planned management of one's personal energy resources to prevent their depletion. The goal of energy conservation is to maintain as balance between rest and activity during times of high fatigue so that valued activities can be maintained. Energy conservation strategies include priority setting, delegating activities of lesser importance, pacing oneself, taking extra rest periods, and planning high-energy activities at times of peak energy. It may also include the use of labor-saving devices (such as a bedside commode, walker, raised toilet seat, energy-saving appliances, and grabbing tools). 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 fatigue may increase at end of life, individuals may choose to be active despite failing health. There is some evidence that exercise is beneficial to individuals with incurable cancer and short life expectancy. A group exercise program was pilot-tested in 63 Norwegian palliative care outpatients.[178] The program consisted of two 50-minute sessions twice a week for six weeks. A combination of strength building, standing balance, and aerobic exercise was used. The exercise participants had less physical fatigue and increased walking distance. There were no adverse effects of exercise although 46% of the 63 participants did not complete the program.

A small pilot study was conducted to evaluate an exercise program for nine individuals with advanced cancer enrolled in a home hospice program.[179] A physical therapist guided participants in the selection of several activities (such as walking, performing arm exercises with resistance, marching in place, and 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. There was also a trend 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 (category 1), attention-restoring therapy, sleep therapy, family interaction, and nutritional therapy are also helpful to this population.

A 12-week exercise program tested on 82 men with locally advanced or metastatic prostate cancer was compared to a wait-list control group (N = 73). The men in the exercise group reported less interference of fatigue with daily activities and better quality of life. 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[180] summarized weight-bearing precautions for bone metastases as well as exercise guidelines for adults with solid tumors and hematological cancers; older cancer survivors; and individuals with cancer-related fatigue. They also

recommended an exercise protocol for multiple myeloma that incorporated aerobic, resistance, and flexibility exercises.

Pharmacologic Interventions

There continues to be interest in using psychostimulant drugs for cancer patients at the end of life although studies have had mixed results. In a meta-analysis of two studies (n=264) comparing methylphenidate to placebo the active drug was found to be effective in reducing fatigue.[138] However neither study had a large effect size and one study showed both arms had a positive treatment effect and no superiority over placebo. In addition, methylphenidate has side effects including headache and nausea that have been reported as minor. A more recent clinical trial of d-threo-methylphenidate to prevent fatigue during radiotherapy for brain tumors did not demonstrate efficacy for the drug in preventing fatigue.[181] Other studies of fatigued breast cancer survivors,[182] advanced cancer patients,[183] and HIV patients[184] have shown positive results for this drug.

Another psychostimulant, dexamphetamine (10 mg twice daily for 8 days), was evaluated for fatigue in patients with advanced cancer.[185] The results of a randomized controlled clinical trial showed tolerance of the drug and short-term improvement in fatigue at the second day, but no long-term benefit by the end of the 8-day study. The overall study results for psycho-stimulants show that additional randomized controlled trials are needed before a definitive recommendation can be made.

The wakefulness promoting agent, modafinil, has been approved by the Food and Drug Administration for use in narcolepsy, but it does not have an indication for fatigue in cancer patients. However, in recent small studies, modafinil shows some promise for management of cancer-related fatigue. Morrow et al[186] conducted an open label study of modafinil for 82 breast cancer survivors with persistent fatigue. The dose was 200 mg per day for one month. Eighty-three percent reported reduced of fatigue, 10% had no improvement, and 7% dropped out of the study. In a randomized pilot study of 16 adults with brain tumors, Kaleita and colleagues[187] titrated the modafinil dose from 100 mg to 600 mg (optimal dose) for 13-17 days and concluded that modafinil was a safe and effective treatment for fatigue. A case report of modafinil showed improvements in daytime wakefulness and normalization of the sleep-wake cycle in 2 adult patients with advanced cancer.[188] However, no randomized controlled clinical trials have been published. Common side-effects include those related to the stimulating effects of the medication. Therefore, the panel does not believe there is sufficient evidence at this time to recommend wakefulness enhancing drugs for cancer patients who have moderate or severe fatigue and recommends that more research be done in this area.

In addition to psycho-stimulants, there has been interest in the progestational agent, megestrol acetate (MA) to improve fatigue as well as appetite and well being.[189] A study comparing MA with dexamethasone showed that MA had fewer side effects than dexamethasone.[190] A systematic review paper demonstrated the safety and efficacy of MA for cancer patients.[191] However, a systematic review and meta-analysis of four studies[192-195] revealed no benefit of progestational steroids compared with placebo for treatment of cancer-related fatigue.[138]

It has been proposed that micronutrient deficiency could be responsible for increased fatigue in advanced cancer patients. Some chemotherapy agents such as ifosfamide and cisplatin cause a urinary loss of carnitine.[196] Carnitine is a micronutrient involved in the production of energy at the cellular level[197] that has been shown to be deficient in people who are chronically ill. Advanced cancer patients are at risk for carnitine deficiency because of decreased intake and increased renal loss. L-carnitine supplementation has been examined in three small open label studies examining safety and dose-finding.[198]

This preliminary, work showed some promise for L-carnitine in fatigue management. A subsequent clinical trial was conducted with a double blind phase followed by an open label phase.[199] The planned intent-to-treat analysis showed no significant improvement in serum l-carnitine levels or fatigue. However, an exploratory analysis with adherent patients only using data from both the double blind and open label phases of the study reversed the primary result. Based on the positive findings of the exploratory analysis, the investigators recommended a larger randomized clinical trial to examine efficacy of this agent.

Re-Evaluation Phase

Because fatigue may arise at many points in the course of a patient's disease and treatment, ongoing re-evaluation 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 Cancer-Related Fatigue Guidelines 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.

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. At this point, the patient is assessed for 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 any of these conditions are present, they should be treated according to practice guidelines, with referral to other care professionals as appropriate, and the patient's fatigue should be re-evaluated regularly. If none of the factors are present or if the fatigue is unresolved, selection of appropriate fatigue management and treatment strategies is done within the context of the patient's clinical status: (ie, receiving active cancer treatment, disease-free long-term follow-up, or care at the end of life). Management of fatigue is cause-specific when conditions known to cause fatigue can be identified and treated. When specific causes of fatigue cannot be identified and corrected, nonpharmacologic and pharmacologic treatment of the fatigue should still be done.

Nonpharmacologic interventions may include a moderate exercise program to improve functional capacity and activity tolerance, psychosocial programs to manage stress and increase support, attention-restoring therapies to decrease cognitive alterations and improve mood state, energy conservation to maintain energy, and nutritional and sleep interventions for patients with disturbances in eating or sleeping. Pharmacologic therapy may include drugs, such as antidepressants for depression or erythropoietin for anemia. A few clinical reports of the use of psychostimulants suggest the need for further research on these agents as potential treatment modalities in managing fatigue.

Effective management of cancer-related fatigue involves an informed and supportive oncology care team that assesses patients' fatigue levels regularly, counsels and educates patients regarding strategies for coping with fatigue,[200] and uses institutional experts for referral of patients with unresolved fatigue.[43] 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.[201,202]

Appendix

Fatigue Measurement

A resource to facilitate selection of instruments to measure fatigue

Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. The Lancet 2003;262:640-650.
(This resource provides a detailed description of six scales frequently used in cancer patients to measure fatigue.)

Jacobsen PB. Assessment of fatigue in cancer patients. J Natl Cancer Inst Monogr 2004; 32: 93-97.
(Includes factors to consider in selecting a fatigue measure.)

Meek PM, Nail LM, Barsevick A, et al. Psychometric testing of fatigue instruments for use with cancer patients. Nurs Res 2000;49:181-190.
(Study evaluates psychometric properties of several commonly used fatigue measures.)

National Cancer Institute. Fatigue (PDQ) Health Professional Version (11/18/05). Retrieved from http://www.nci.nih.gov/cancertopics/pdq/supportivecare/fatigue/healthprofessional/
(Gives citation links to nine commonly used scales to measure fatigue.)

Oncology Nursing Society. Measuring oncology nursing-sensitive patient outcomes: Fatigue evidence-based summary (June 22, 2004). Retrieved from http://onsopcontent.ons.org/toolkits/evidence/Clinical/Summaries.shtml
(Provides two detailed tables summarizing scale descriptions and psychometric properties for 13 scales.)

Piper BF. Measuring fatigue. In: Frank-Stromborg M, Olsen SJ, eds. Instruments for clinical health-care research. 3rd ed. Boston, Ma: Jones & Bartlett. 2004:538-553.
(Provides four detailed tables that summarize scale descriptions and psychometric propoerties for all fatigue scales that have been developed to date including single item and multiple item, single dimension scales and multidimensional scales.)

Wu HS, McSweeney M. Measurement of fatigue in people with cancer. Oncol Nurs Forum 2001;28:1371-1384.
(Qualitative review of commonly used fatigue measures.)

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