NCCN

Cancer-Related Fatigue

Clinical Practice Guidelines in Oncology

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NCCN Clinical Practice Guidelines in Oncology on Cancer-Related Fatigue

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, fatigue, chemotherapy, radiation therapy, bone marrow transplantation, carcinoma treatment, screening, evaluation, intervention (*JNCCN* 2010;8:904–931)

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.

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

Overview

Fatigue is a common symptom in patients with cancer and is nearly universal in those undergoing cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biologic response modifiers.^{1–10} The symptom is experienced by 70% to 100% of patients with cancer who undergo multimodal treatments and dose-dense, dose-intense protocols.¹¹ In patients with metastatic disease, the prevalence of cancer-related fatigue exceeds 75%. 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, despite conceptual differences.^{22,23} Patients perceive fatigue to be the most distressing symptom associated with cancer

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

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Disclosures for the NCCN Guidelines Panel for Cancer-Related Fatigue

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines on Cancer-Related Fatigue panel members can be found on page 931. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

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and its treatment, more distressing even than pain or nausea and vomiting, which, for most patients, can generally be managed with medications.^{24,25}

Fatigue in patients with cancer has been underreported, underdiagnosed, and undertreated. Persistent cancer-related fatigue affects quality of life (QOL), because patients become too tired to fully participate in the roles and activities that make their lives meaningful.^{16,26–28} Health care professionals have been challenged in their efforts to help patients manage this distressful symptom and 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 who are cured of their malig-

nancy but experience continued fatigue.²⁹ Despite biomedical literature documenting this entity, patients with cancer-related fatigue often have difficulty obtaining or retaining 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 specific mechanisms involved in its pathophysiology are unknown. Proposed mechanisms include proinflammatory cytokines,^{30–32} hypothalamic-pituitary-adrenal (HPA) axis dysregulation,³⁰ circadian rhythm desynchronization,³³ skeletal muscle wasting,³⁴ and genetic dysregulation.³⁵ Limited evidence supports these proposed mechanisms.

To address the important problem of cancer-related fatigue, the NCCN convened a panel of ex-

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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 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 after 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, before, during, and after 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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SCREENING

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

^bFatigue scale for children is simplified: use "tired" or "not tired" as screen for young children (age < 6 or 7 y).

^cButt 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.

^dSee "Patient/Family Education and Counseling" and "General Strategies for Management of Fatigue" based on clinical status: Active Treatment (page 909), Posttreatment (page 910), End of Life (page 911).

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 (e.g., 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 (i.e., sedation)
- Alcohol/substance abuse
- Comorbidities
 - Infection
 - Cardiac dysfunction
 - Pulmonary dysfunction
 - Renal dysfunction
 - Hepatic dysfunction
 - Neurologic dysfunction
 - Endocrine dysfunction (e.g., hot flashes, hypothyroidism, hypogonadism, adrenal insufficiency)

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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INTERVENTIONS FOR PATIENTS ON ACTIVE TREATMENT^e

SPECIFIC INTERVENTIONS

*To view the most recent version of these guidelines, please visit the NCCN Web site at www.NCCN.org.

^eSee Discussion for information on differences among active treatment, posttreatment, and end-of-life treatment.

^fInterventions should be culturally specific and tailored to the patients and families because not all patients may be able to integrate these options due to variations in individual circumstances and resources.

^gConcern is with environment. Limit activity to environments in which risk of infection is low.

^hA type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and facilitate psychological adjustment.

ⁱCBT/BT influences thoughts and promotes changes in behavior; it includes relaxation strategies.

^jSupportive expressive therapies facilitate expression of emotion and fosters support from one or more people.

^kPharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. More evidence exists 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 of psychostimulants have not been established in cancer patients.

INTERVENTIONS FOR PATIENTS POSTTREATMENT^e

SPECIFIC INTERVENTIONS

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

^eSee Discussion for information on differences among active treatment, posttreatment, and end-of-life treatment.
^fInterventions should be culturally specific and tailored to the patients and families because not all patients may be able to integrate these options due to variations in individual circumstances and resources.
^hA type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and facilitate psychological adjustment.
ⁱCBT/BT influences thoughts and promotes changes in behavior; it includes relaxation strategies.
^jSupportive expressive therapies facilitate expression of emotion and fosters support from one or more people.
^kPharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. More evidence exists 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 of psychostimulants have not been established in cancer patients.
^lAdjustment of current treatments for pain, sleep disturbances, other symptoms and comorbidities, including drugs. 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,l}

SPECIFIC INTERVENTIONS

Patient/Family Education and CounselingGeneral Strategies for Management of FatigueNonpharmacologic^fPharmacologic

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

^eSee Discussion for information on differences among active treatment, posttreatment, and end-of-life treatment.

^fInterventions 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 variations in individual circumstances and resources.

^gConcern is with environment. Limit activity to environments in which risk of infection is low.

^kPharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. More evidence exists 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 of psychostimulants have not been established in cancer patients.

^lAlso see NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Palliative Care.*

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perts. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Cancer-Related Fatigue, first published in 2000³⁶ and updated annually, synthesize the available research and clinical experience in this field and provide recommendations for patient care (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

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 (see page 906). Compared with the fatigue experienced by healthy individuals, cancer-related fatigue is more severe, more distressing,^{12,37} and less likely to be relieved by rest.³⁸ In terms of the defining characteristics, the subjective sense of tiredness reported by the patient is important to note. As with pain, clinicians must rely on patients' descriptions of their fatigue and accompanying distress.

Fatigue that interferes with usual functioning is another substantial component of cancer-related fatigue and the source of much distress for patients.^{7,39,40} Investigations have documented a significant effect of fatigue on physical functioning during cancer treatment, and whether patients regain full functioning after completion of treatment is uncertain.^{41,42}

Standards of Care for Assessment and Management

The panel developed standards of care for cancer-related fatigue management (see page 906), using the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Adult Cancer Pain and Distress Management as exemplar models (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). 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 guidelines is to ensure

that all cancer patients with fatigue are identified and 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 through self-report. The history and physical examination, laboratory data, and descriptions of patient behavior by family members, especially for children, are important sources of additional information.

Fatigue should be screened, assessed, and managed for most patients according to the clinical practice guidelines. These guidelines provide "best care" information based on current evidence to support treatment.⁴³ Patients should be screened for the presence and severity of fatigue at their initial clinical visit, at appropriate intervals during and/or 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, and all patients should undergo 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.⁴⁴

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 representatives from the fields of medicine, nursing, social work, physical therapy, and nutrition.⁴⁵ 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 is necessary within institutional settings if professionals are to become skilled in managing fatigue.

The panel recommends that assessment of cancer-related fatigue levels be included in outcomes research, and quality of fatigue management should be included in institutional continuous quality improvement projects. Institutions can implement the guidelines faster if they monitor adherence and progress regarding 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 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 reevaluation. During the first phase, the health care professional must screen for fatigue and, if present, 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 also 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 Guidelines on Cancer-Related Fatigue (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

After the evaluation phase, the guidelines delineate a set of interventions for the amelioration of fatigue based on the patient's clinical status (e.g., active cancer treatment, posttreatment, 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 reevaluation, 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 (see page 907). If fatigue is present, a quantitative or semiquantitative assessment should be performed and documented. For example, on a 0 to 10 numeric rating scale (with 0 indicating no fatigue and 10 indicating worst fatigue imaginable), mild fatigue is indicated by a score of 1 to 3, moderate by 4 to 6, and

severe by 7 to 10.^{46,47} 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.^{3,48–50}

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 its management. Periodic rescreening and reevaluation are recommended; this should be performed daily for inpatients, and at subsequent routine and follow-up visits for outpatients. Survivors or patients who have completed treatment must still be monitored for fatigue, because fatigue may exist beyond the period of active treatment.^{12,15,51}

Currently, screening is not systematic or effective in many practice settings for various reasons, which often include patient or family barriers and clinician barriers.⁵² 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. Additionally, many 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 no treatment exists.

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.^{53–55} Second, health care professionals may not be aware that effective treatments exist 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, patients may

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not be aware that fatigue has negatively affected their lives; however, spouses, parents, or their family members may be more cognizant of these changes and the effect of fatigue. Additional information and resources to assist in the selection of instruments to measure cancer-related fatigue are available online, in these guidelines, at www.NCCN.org (MS-18).

Using the numeric rating scale (i.e., 0–10 scale), fatigue studies in cancer patients have shown a marked decrease in physical functioning at the level of 7 or higher.^{46,56} The authors of an international study on fatigue in patients with breast and prostate cancer evaluated and compared fatigue intensity levels with scores from the Medical Outcomes Short-Form Survey Instrument physical functioning subscale.⁴⁷ 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

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 (see page 908). A component of this evaluation is an assessment of the patient's current disease status, the type and length of treatment and its capacity to induce fatigue, and the patient's response to treatment. If possible, whether the fatigue is related to a recurrence or progression should be determined. 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 of this will substantially reduce their anxiety levels.

A review of systems should be completed, which may help to determine the various organ systems affected, and to direct the physical evaluation and diagnostic workup. Another component of the focused history is an in-depth fatigue assessment⁵⁷ that includes evaluation of 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. Health care professionals 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, the in-depth assessment must 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 9 factors that are often causative elements of fatigue, and therefore should be specifically assessed: pain, emotional distress, sleep disturbance, anemia, nutrition, activity level, alcohol/substance abuse, medication side effects profile (i.e., sedation), and other comorbidities.

Descriptive studies have shown that, in adults and children, fatigue seldom occurs alone and that it more commonly clusters with sleep disturbance, emotional distress (e.g., depression, anxiety), or pain.^{7,58–61} Assessment of pain along with emotional distress and institution of effective treatment are essential.

Fatigue and depression have been documented as concurrent symptoms in cancer patients. Hopwood and Stephens⁶² documented depression in 33% of 987 patients with lung cancer and found that fatigue was an independent predictor of depression in this group. Newell et al.⁶³ found that fatigue was the most commonly experienced and debilitating physical symptom for 201 oncology patients, with approximately 25% of these patients also experiencing depression. In 457 patients with Hodgkin lymphoma, Loge et al.⁶⁴ found that 26% of patients had fatigue for 6 months or longer (defined as fatigue "cases") and that fatigue correlated moderately with depression ($r = .41$). Fatigue cases had higher levels of depression than non-cases. Visser and Smets⁶⁵ 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 did not predict depression, and depression did not predict fatigue in this sample.

Sleep disturbances are a neglected problem in oncology,⁶⁶ and may range from hypersomnia to insomnia.^{67,68} Sleep disturbances are prevalent in 30% to 75% of patients with cancer.⁶⁹ Several studies have shown that fatigued cancer patients undergoing active treatment spend increased time resting

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and sleeping but that their pattern of sleep is often severely disrupted.^{70,71} When sleep disturbances are present, the patient should be assessed for depression because this is a common manifestation.⁷² Patients may benefit from evaluation and education about improving 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 (e.g., thyroid, estrogen, testosterone). Thus, patients should also be evaluated for obstructive sleep apnea.

Studies have shown the association of fatigue 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. Health care providers should also review and discuss changes in caloric intake with patients. If substantial abnormalities are found, a consultation with a nutrition expert may be appropriate. Often, fatigue symptoms can be improved through 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.^{73–75} However, before recommending an exercise program, health care providers or exercise experts (e.g., physiatrist, physical therapist) should assess the conditioning level of their patients. Convincing fatigued patients that exercise will improve their symptoms is often difficult. It may be best to

begin with discussions and low levels of activities, which increase gradually. 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 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 (e.g., narcotics, antidepressants, antiemetics, antihistamines) may contribute to excessive drowsiness and increasing fatigue. Deleting or adjusting the dose of medications may be appropriate to treat fatigue. In some cases, altering either the dosage or the dosing interval of a medication may subsequently improve fatigue. During 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 contribute significantly to fatigue.

Noncancer comorbidities may contribute substantially to symptoms of fatigue in patients with cancer. The status of comorbidities must be reviewed in conjunction with the present treatment management strategies. If the comorbidity is not optimally managed, that management may need to be further evaluated and improved. 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, hepatic, neurologic, endocrine dysfunction (including hot flashes, hypothyroidism, hypogonadism, or adrenal insufficiency), and infection. Canaris et al.⁷⁶ noted the high incidence of thyroid dysfunction in normal individuals and patients taking thyroid medications; they suggested that more attention must be given to thyroid problems in both the general and cancer patient populations. Development of hypothyroidism

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occurs after radiation therapy for Hodgkin lymphoma and other non-Hodgkin's lymphomas, head and neck cancers, and breast cancer, and after total body irradiation in bone marrow transplantation. Also, hypothyroidism has been noted in patients who have undergone treatment with 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 et al.⁷⁷ 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 (e.g., active cancer treatment, posttreatment 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.⁷⁸

If any of the 9 treatable contributing factors is identified during the primary evaluation phase, it should be treated as an initial approach to fatigue management. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) are also available to guide the treatment of pain (see NCCN Guidelines on Adult Cancer Pain), distress (see NCCN Guidelines on Distress Management), and anemia (see NCCN Guidelines on Cancer- and Chemotherapy-Induced Anemia); to view the most recent versions of these guidelines, visit the NCCN Web site at www.NCCN.org. Treatment of sleep disturbances, nutritional alterations, and physical deconditioning are discussed in "Nonpharmacologic Interventions" for patients undergoing active treatment, posttreatment, or at the end of life.

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 patients⁵² but is particularly essential for patients beginning potentially fatigue-inducing treatments (e.g., radiation, chemotherapy, or biotherapy) before the onset of fatigue (see page

909). 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.⁷⁹ Patients should be counseled that they can 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.⁸⁰ The fatigued patient can then plan activities accordingly. In a multi-site clinical trial of energy conservation in 296 patients undergoing cancer treatment, Barsevick et al.⁸¹ reported significantly lower fatigue in those receiving the experimental intervention. Some participants in descriptive studies have suggested that activities designed to distract (e.g., games, music, reading, socializing) are helpful in decreasing fatigue, although the mechanism is unknown.^{82,83}

Nonpharmacologic Interventions: Of the specific nonpharmacologic interventions during active cancer treatment, activity enhancement (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 for sleep have some supporting evidence.⁸⁴

Activity Enhancement: In cancer patients, the adverse effects of therapy results in decreased activity and physical performance. Although several factors contribute to the decline in functionality, fatigue is one of the major contributors. Mustian et al.⁸⁵ conducted a study in patients undergoing systemic chemotherapy to determine the impact of fatigue on physical function as measured by the Activities of Daily Living Index (ADLs). Among 753 enrolled patients (64% women), 85.4% and 79.3 % 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 (on a scale of 0–10, with 10 indicating severe fatigue). Cancer-related fatigue interfered with all ADLs in most pa-

tients. 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 to increase physical activity during and after therapy, and to explore the impact of increased activity on cancer-related fatigue, 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 manuscript. However, many of these studies have specifically evaluated the effect of increased activity on cancer-related fatigue, and several meta-analyses have been conducted over the past 5 years to provide a comprehensive evaluation of the impact of increased activity on cancer-related fatigue.

The 2 most recent analyses clearly show the current status of this area of investigation. Kangas et al.⁸⁶ reviewed results of 19 articles that reported on the effectiveness of physical exercise on fatigue-related outcomes, of which 17 used a randomized controlled trial. Although 17 of the trials reported fatigue outcome, only 10 reported vigor/vitality outcomes. None of the trials required patients to have a specified a level of fatigue at study entry. Results showed a 35% improvement in fatigue and 30% improvement in vigor/vitality. The weighted pooled mean effect size was -0.42 (95% CI, -0.599 to -0.231) for fatigue and 0.69 (95% CI, 0.43 – 0.949) for vigor/vitality. Thus, the effect size for fatigue was believed to be “on the edge of moderate” and clinically significant, whereas the effect size for vigor/vitality was moderate to large. No significant difference in effect size was noted among 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 analysis⁸⁷ reported the results of 28 randomized controlled trials investigating the effect of exercise on cancer-related fatigue; 19 studies included patients with a specific cancer diagnosis, whereas 9 included those with various cancers. Most of the cancer-specific trials investigated patients with breast cancer ($n = 16$), with 13 studies investigating home-based or unsupervised exercise programs and 16 investigating supervised, institu-

tional programs. Interventions ranged from 3 to 32 weeks, with an average of 12 weeks. Eighteen studies reported outcome measures beyond the end point of the intervention. Overall, exercise was more effective in relieving fatigue than the control intervention (standardized mean difference [SMD], -0.23 ; 95% CI, -0.33 to -0.13). The exercise intervention was statistically more effective than the control intervention 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 and prostate cancers, whereas 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, no sufficient evidence exists to recommend a specific amount of physical activity for cancer populations. The U.S. Surgeon General recommends 30 minutes of moderate activity most days of the week for all populations.⁸⁸ Some observational and interventional studies have suggested that cancer patients who engage in at least 3 to 5 hours of moderate activity per week may experience better outcomes and experience fewer side effects, including fatigue.^{73,74,89–93}

Some patients may require referrals to exercise specialists in fields such as physical therapy, physical medicine, or rehabilitation 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 care of cancer populations.

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

- Patients with comorbidities (such as cardiovascular disease or chronic obstructive pulmonary disease)
- Recent major surgery
- Specific functional or anatomical deficits (e.g., decreased range of motion from 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)

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- 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.

Physically Based Therapies: Therapies performed by a therapist or lay person include acupuncture and massage therapy. Small trials have reported positive effects of acupuncture on fatigue, but these results must be confirmed in randomized controlled trials.⁹⁴ These small trials were conducted during active non-palliative radiation therapy^{95,96} and postchemotherapy.^{97,98} One randomized controlled trial (n = 230)⁹⁹ and one retrospective review (n = 1290)¹⁰⁰ reported positive effects of massage therapy on fatigue during active therapy.

Psychosocial Interventions: Patients should be counseled about coping and educated on how to deal with anxiety and depression, which are commonly associated with fatigue during cancer treatment.¹⁰¹ 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 cognitive behavioral therapies (CBT)/behavioral therapy (BT), psychoeducational therapies/educational therapies, and supportive expressive therapies. These groups were titled after reviewing 3 recent meta-analyses of the effects of these interventions on CRF.^{86,102,103} Notably, the categories in which interventions have been grouped are different in each of the meta-analyses and were compared with the work reported by the Oncology Nursing Society Putting Evidence into Practice.¹⁰⁴ These studies can be categorized based on their primary outcome parameter: fatigue or other. In many of these 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, in many of these studies, fatigue was not an eligibility requirement, and in the studies that were directed specifically of fatigue, no severity cut off score was used. Thus, patients enrolled in these studies may not have had significant levels of fatigue, thereby limiting the po-

tential impact of the intervention.

Current knowledge regarding cancer-related fatigue includes the following proposed mechanisms: 5-HT₃ neurotransmitter deregulation, vagal afferent activation, alteration in muscle and ATP metabolism, HPA axis dysfunction, circadian rhythm dysfunction, and cytokine deregulation. Current psychosocial interventional studies may target 1 or more of these biologic mechanisms; however, most studies 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 have been designed to address educational and coping deficits to optimize the patient's ability to deal with this often debilitating symptom.

In addition to these issues, outcome parameters used by investigators are highly variable. All currently published studies use patient self-report measurements exclusively as the outcome measure. Most studies do not reflect the impact of fatigue on function, report fatigue-related behaviors, or use objective measures of functionality (e.g., the 6-minute walk).

Substantial data in literature provide high-level evidence during active treatment showing benefit of CBT/BT^{105–111} and psychoeducational/educational therapies.^{41,84,102,103,112–121} Less evidence shows the benefit of supportive expressive therapies during active treatment, and therefore it was not rated as category 1 recommendation.¹²²

Nutrition Consultation: Many cancer patients experience 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.¹²³ 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 a common denominator.¹²⁴ Nonpharmacologic interventions to improve sleep quality have been organized into 4 general types of therapies that include cognitive-behavioral, complementary, psychoeducational/informational, and exercise therapies.¹²⁵ These interventions are de-

signed to optimize sleep quality, and some have also been shown to decrease fatigue.¹⁰⁴

Numerous types of CBT exist, and 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. 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.¹²⁶ Sleep restriction includes avoiding long or late afternoon naps and limiting total time in bed.¹²⁷ 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 used in a pilot study involving women undergoing 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.

Several published studies^{129–131} support the conclusion that cognitive-behavioral therapy interventions designed to optimize sleep quality in cancer patients may also improve fatigue. Results of 2 randomized clinical trials showed that patients in the survivorship phase after cancer treatment who reported chronic insomnia experienced positive effects on both sleep and fatigue after 4 to 5 weekly behavioral therapy sessions.^{132–134} Two smaller studies of patients with complaints of insomnia during the survivorship phase reported improved sleep and fatigue.^{129,130} Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.^{128,131} The American Academy of Sleep Medicine (AASM) has recommended 3 specific therapies for chronic insomnia in healthy individuals: relaxation training, cognitive behavior therapy, and stimulus control therapy.¹³⁵ AASM has also published clinical guidelines for the management of chronic insomnia in adults.¹³⁶

CBT therapies are often combined with complementary therapies, such as breathing control, progressive muscle relaxation, and guided imagery

techniques, to relax the individual. Complementary therapies, such as massage therapy,^{99,100,137} yoga,^{138–140} muscle relaxation,^{107,141} and mindfulness-based stress reduction,^{105,142–144} have been evaluated in pilot studies; preliminary data suggest that they may be effective in reducing fatigue in cancer patients. Cohen and Fried¹⁰⁶ compared cognitive-behavioral versus relaxation and guided imagery interventions, both versus a control group. They reported improved fatigue and sleep difficulties in both intervention groups, but were only significantly different in the relaxation and guided imagery group.

Pharmacologic Interventions: Although a wide variety of prescription pharmacologic options are available to improve sleep quality, little empiric evidence shows that the use of these agents in patients with cancer is associated with adverse side effect profiles. Clinicians must be aware of a recent FDA warning regarding potential risks associated with sedative-hypnotic drugs, including severe allergic reactions and complex sleep-related behaviors, including sleep-driving.¹⁴⁵ A table summarizing the medications commonly used to promote sleep is provided on the NCI Physician Data Query Web site (www.cancer.gov).¹⁴⁶ 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 interactions involving the cytochrome p450 isoenzyme system. Increased public and professional education regarding sleep, sleep disturbances, and daytime consequences of sleep loss are recommended.

Some evidence exists for pharmacologic therapy as a fatigue treatment. A recent meta-analysis of 10 studies concluded that the treatment of anemia during chemotherapy with erythropoietin resulted in a reduction of fatigue (see the NCCN Guidelines on Cancer- and Chemotherapy-Induced Anemia; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).¹⁴⁷ Studies on the selective serotonin reuptake inhibitor paroxetine showed that it had no influence on fatigue in patients undergoing chemotherapy.^{148,149} Antidepressants are not recommended for decreasing fatigue.

The psychostimulant methylphenidate has been evaluated for its effect on cancer-related fatigue. For

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more information about the use of psychostimulants for modifying fatigue see Pharmacologic Interventions, page 923.

Interventions for Patients Posttreatment

More than 11 million people now living in the United States have a history of cancer. Of the approximately 1,479,350 persons in the United States who were diagnosed with cancer in 2009, 66% are expected to survive at least 5 years.¹⁵⁰ These improvements in survival have led to efforts to enhance symptom management, QOL, and overall functioning of individuals posttreatment. Fatigue is an acute effect of cancer or treatment but can also be a long-term or late effect.^{151,152} Patients may continue to report unusual fatigue for months or years after treatment cessation.^{12–15,17–21} Researchers have suggested that this fatigue may be caused by persistent activation of the immune system^{13,153} or other factors, such as late effects of treatment on major organ systems.¹⁵³ However, few longitudinal studies have examined 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,¹⁵⁴ and range from 33% to 53% when other criteria are used (e.g., a score of ≥ 4 on the 0–10 fatigue scale).¹⁵⁵ In contrast to these findings, ovarian cancer survivors in Canada and the United States ($n = 100$) who were diagnosed a mean of 7.2 years before the survey reported equivalent energy levels when compared with the general population.¹⁵⁶ Therefore, what constitutes valid incidence and prevalence rates in disease-free patients requires more study.

In general, most research reports are limited by their cross-sectional designs,^{25,54,152,154,157–159} lack of comparison groups,^{25,54,159} heterogeneous samples,^{154,160} use of differing fatigue scales, small sample sizes,¹⁵³ varying baseline survivorship definitions (i.e., time since diagnosis vs. time since treatment cessation), and different mean survivorship durations. Because of these design issues, conclusions are difficult to reach about the effect of fatigue's prevalence, incidence, duration, associated risk factors, and QOL. Additionally, most fatigue studies of posttreatment disease-free patients have been conducted in Caucasian, English-speaking breast cancer patients^{13,153,157} and those who have undergone peripheral stem cell or bone marrow transplantation,^{160,161} with few exceptions.^{17,19,21}

The cause of fatigue in posttreatment disease-

free patients is unclear and probably multifactorial.¹⁶² One cross-sectional comparative study investigated fatigue and physiologic biomarkers of immune system activation in 20 breast cancer survivors experiencing fatigue (a mean of 5 years since diagnosis) and 20 nonfatigued survivors.¹⁵³ Fatigued survivors had significantly higher serum marker (interleukin-1 receptor antagonist [IL-1ra], soluble tumor necrosis factor type II [sTNF-RII], and neopterin) and lower cortisol levels when compared with nonfatigued survivors. Significantly higher numbers of circulating T lymphocytes 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 posttreatment disease-free patients include pretreatment fatigue; anxiety and depression levels;¹⁶³ physical level activities;^{164,165} coping methods and cancer-related stressors; comorbidities;¹⁶⁶ type of malignancy; prior treatment patterns; and late treatment effects. For example, in one Norwegian study, a small proportion of long-term disease-free cancer patients who had preexisting coronary artery disease had 30% higher fatigue levels than controls. In another Norwegian study investigating fatigue in Hodgkin disease survivors experiencing remission for more than 5 years, higher fatigue levels were documented in those who had pulmonary dysfunction.¹⁵⁵ In these survivors, the prevalence of chronic fatigue was 2 to 3 times higher than in survivors who did not have this impairment. No significant correlations in this study were found between fatigue and cardiac sequelae as measured with echocardiography, exercise testing, and chest radiography.¹⁵⁵ Prior treatment patterns may affect the survivor's fatigue. For example, in a study of 322 posttreatment disease-free patients with breast cancer, women who had undergone previous combination therapy versus other forms of treatment had the highest fatigue scores,¹⁵⁹ whereas those who had undergone radiation therapy had the lowest 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 exercise must be individualized to the survivors' abilities to prevent exacerbation of cancer treatment toxicities.^{164,165}

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,^{12,15} most patients experience a gradual decrease in fatigue and return of energy to normal levels.^{14,156} Regular self-monitoring of fatigue levels is helpful to document the decrease of fatigue that normally occurs after treatment. Health care providers should continue to screen regularly for fatigue during follow-up visits.

Nonpharmacologic Interventions: Specific interventions recommended to manage fatigue during active cancer treatment are also recommended for disease-free patients posttreatment,⁷⁸ although physically based therapies have less support.

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.¹⁶⁷ However, if the patient is significantly deconditioned or weak, or experiences relevant late effects of treatment (e.g., 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.^{18,168–175}

Psychosocial Interventions: Psychosocial interventions, including CBT/BT, psychoeducational/educational therapies, and supportive expressive therapies are category 1 recommendations.^{112,115,162,176–181} Additional details on these interventions are provided in the preceding pages in the section on psychosocial interventions for patients on active treatment.

Additional Nonpharmacologic Approaches: Nutritional consultation and CBT for sleep (category 1)^{104,125} may be helpful for posttreatment management of fatigue.

Pharmacologic Interventions: Cause-specific pharmacologic therapy may include hypnotics as a short-term treatment for insomnia. If indicated, anemia

should also be treated (see NCCN Guidelines on Cancer- and Chemotherapy-Induced Anemia; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Whether psychostimulants are useful for posttreatment management of fatigue in disease-free patients 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

Although the assessment and management of fatigue at the end of life parallels the general principles of these guidelines, 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.

Although fatigue will likely increase substantially as the disease progresses, patterns of fatigue are variable. For some adults, fatigue may be characterized as constant and unrelenting, whereas for others it is unpredictable and may occur suddenly.^{53,183} Most research has shown that at the end of life, 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%).¹⁸⁴

In a large sample of adults (N = 1000) receiving palliative care, Walsh et al.¹⁸⁵ noted that individuals with advanced cancer had multiple symptoms, with pain was the most prevalent (84% of patients), followed by fatigue (69%), weakness (66%), and lack of energy (61%). Walsh and Rybicki¹⁸⁶ 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.^{39,187} also suggested the possibility 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.¹⁸⁸

Education and Counseling of Patient and Family:

Individuals with advanced cancer and their care-

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givers need information about the management of symptoms, including fatigue,¹⁸⁹ with specific information related to the disease trajectory.^{190,191} 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.¹⁸³ Families must 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.^{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 a great deal of suffering from it.¹⁸⁸ In a case study of 15 adults with advanced disease, Krishnasamy¹⁸³ found that fatigue resulted in substantial regret, sadness, and sense of loss regarding the deterioration of health. Mystakidou et al.¹⁹² reported that patient desire for a hastened death was predicted by feelings of sadness, lack of appetite, pain, and fatigue.

Given the high prevalence of fatigue and other symptoms at the end of life, symptom management must be a major focus of care. The health care team's active commitment to palliative care is critical when aggressive cancer therapy is administered to those with a low likelihood of long-term survival.¹⁸⁸ Although no effective therapy exists for some causes of fatigue and other symptoms, treatment of those more amenable to therapy could help to relieve suffering.⁷⁸

General Strategies for Management of Fatigue:

Energy conservation is a self-care strategy for individuals with advanced cancer and their caregivers.⁸¹ 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 a 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 and strategies (e.g., bedside commode, walker, raised toilet seat, energy-saving appliances, tools for grabbing). In a situation of escalating fatigue at the end of life, family members

may wish to designate people to assume activities relinquished by the person with cancer.

Nonpharmacologic Interventions: Although no category 1 evidence exists for nonpharmacologic interventions at the end of life, clinicians are encouraged to consider matching the patient with an activity enhancement, psychosocial, nutritional, or sleep intervention as indicated. Nutritional consultation is recommended when weight changes occur. Fatigue may increase at the end of life, and some individuals may choose to be active despite their failing health. Some evidence indicates that exercise is beneficial for individuals with incurable cancer and short life expectancy. A group exercise program was pilot-tested in 63 Norwegian palliative care outpatients,¹⁹³ and consisted of two 50-minute sessions twice a week for 6 weeks. A combination of strength building, standing balance, and aerobic exercise was used. The exercise participants had less physical fatigue and increased walking distance. No adverse effects of exercise were noted, although 46% of the 63 participants did not complete the program.

A small pilot study was conducted to evaluate an exercise program for 9 individuals with advanced cancer enrolled in a home hospice program.¹⁹⁴ A physical therapist guided participants in the selection of several activities (e.g., walking, performing 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 also 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 in this population.

A 12-week exercise program tested on 82 men with locally advanced or metastatic prostate cancer was compared with a waitlist control group (N = 73). The men in the exercise group reported less interference of fatigue with daily activities and better QOL. They also showed 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.¹⁹⁵ summarized weight-bearing

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precautions for bone metastases and exercise guidelines for adults with solid tumors and hematologic cancers, older cancer survivors, and people with cancer-related fatigue. They also recommended an exercise protocol for multiple myeloma that incorporated aerobic, resistance, and flexibility exercises.

Pharmacologic Interventions: Interest continues to be shown in using psychostimulant drugs for patients with cancer at the end of life, although studies have had mixed results. In a meta-analysis of 2 studies (n = 264) comparing methylphenidate to placebo, the active drug was found to be effective in reducing fatigue.¹⁴⁷ However, neither study had a large effect size, and one study showed that 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. In a more recent clinical trial, d-threo-methylphenidate did not show efficacy in preventing fatigue during radiotherapy for brain tumors.¹⁹⁶ However, other studies have shown this drug to have positive results in preventing fatigue in breast cancer survivors,¹⁹⁷ patients with advanced cancer,¹⁹⁸ and people with HIV.¹⁹⁹

Another psychostimulant, dexamphetamine (10 mg twice daily for 8 days), was evaluated for fatigue in patients with advanced cancer.²⁰⁰ 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 psychostimulants show that additional randomized controlled trials are needed before a definitive recommendation can be made.

Although the wakefulness promoting agent, modafinil, has been approved by the FDA for use in narcolepsy, it does not have an indication for fatigue in cancer patients. However, recent small studies have shown it to have some promise for managing cancer-related fatigue. Morrow et al.²⁰¹ conducted an open-label study of modafinil, 200 mg daily for 1 month, in 82 breast cancer survivors with persistent fatigue. Among these patients, 83% reported reduced fatigue, 10% experienced no improvement, and 7% dropped out of the study. In a randomized pilot study of 16 adults with brain tumors, Kaleita et al.²⁰² titrated the modafinil dose from 100 to 600 mg (optimal dose) for 13 to 17 days and concluded that modafinil was safe and effective for treating fatigue.

A case report of modafinil showed improvements in daytime wakefulness and normalization of the sleepwake cycle in 2 adult patients with advanced cancer.²⁰³ 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 sufficient evidence currently exists to recommend wakefulness-enhancing drugs for cancer patients who have moderate or severe fatigue, and recommends that more research be performed in this area.

In addition to psychostimulants, interest has been shown in the progestational agent, megestrol acetate (MA), for improving fatigue, appetite, and well-being.²⁰⁴ One study showed that MA had fewer side effects than dexamethasone.²⁰⁵ A systematic review paper showed the safety and efficacy of MA for cancer patients.²⁰⁶ However, a systematic review and meta-analysis of 4 studies^{207–210} showed no benefit of progestational steroids compared with placebo for treating cancer-related fatigue.¹⁴⁷

Experts have proposed that micronutrient deficiency could be responsible for increased fatigue in patients with advanced cancer. Some chemotherapy agents, such as ifosfamide and cisplatin, cause a urinary loss of carnitine.²¹¹ Carnitine is a micronutrient involved in the production of energy at the cellular level²¹² that has been shown to be deficient in people who are chronically ill. Patients with advanced cancer are at risk for carnitine deficiency because of decreased intake and increased renal loss. L-carnitine supplementation has been examined in 3 small open-label studies examining safety and dose-finding.²¹³ 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.^{214,215} The planned intent-to-treat analysis showed no significant improvement in serum L-carnitine levels or fatigue. However, an exploratory analysis of adherent patients 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.

Reevaluation Phase

Because fatigue may arise at many points in the course of a patient's disease and treatment, ongoing reevalua-

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tion of the patient's status (with appropriate modifications and institution of new treatments) is an integral part of effective, overall fatigue management.

Summary

These 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 and undergoes 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 reevaluated regularly. If none of the factors are present or if the fatigue is unresolved, appropriate fatigue management and treatment strategies are selected based on the patient's clinical status (e.g., undergoing active cancer treatment, posttreatment, 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, the fatigue can still be treated with nonpharmacologic and pharmacologic interventions.

Nonpharmacologic interventions may include a moderate exercise program to improve functional capacity and activity tolerance, psychosocial programs to manage stress and increase support, 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 suggest the need for further research on the use of psychostimulants as potential treatment modalities for 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,²¹⁶ and refers patients with unresolved fatigue to institutional experts.⁴⁵ The oncology care team must recognize the many patient-, provider-, and system-related behaviors that can impede effective fatigue management. Using available resources and evidence-based guidelines to reduce barriers increases benefits to patients experiencing fatigue.^{217,218}

References

1. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet* 2003;362:640–650.
2. Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol* 1997;34:13–19.
3. Collins JJ, Devine TD, Dick GS, et al. The measurement of symptoms in young children with cancer: the validation of the Memorial Symptom Assessment Scale in children aged 7–12. *J Pain Symptom Manage* 2002;23:10–16.
4. Dean GE, Spears L, Ferrell BR, et al. Fatigue in patients with cancer receiving interferon alpha. *Cancer Pract* 1995;3:164–172.
5. Hann DM, Garovoy N, Finkelstein B, et al. Fatigue and quality of life in breast cancer patients undergoing autologous stem cell transplantation: a longitudinal comparative study. *J Pain Symptom Manage* 1999;17:311–319.
6. Irvine D, Vincent L, Graydon JE, et al. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. A comparison with the fatigue experienced by healthy individuals. *Cancer Nurs* 1994;17:367–378.
7. Jacobsen PB, Hann DM, Azzarello LM, et al. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. *J Pain Symptom Manage* 1999;18:233–242.
8. Longman AJ, Braden CJ, Mishel MH. Side-effects burden, psychological adjustment, and life quality in women with breast cancer: pattern of association over time. *Oncol Nurs Forum* 1999;26:909–915.
9. Sitzia J, Huggins L. Side effects of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy for breast cancer. *Cancer Pract* 1998;6:13–21.
10. Wagner LI, Cella D. Fatigue and cancer: causes, prevalence and treatment approaches. *Br J Cancer* 2004;91:822–828.
11. Hofman M, Ryan JL, Figueroa-Moseley CD, et al. Cancer-related fatigue: the scale of the problem. *Oncologist* 2007;12(Suppl 1):4–10.
12. Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. *J Behav Med* 1998;21:1–18.
13. Bower JE, Ganz PA, Aziz N, et al. T-cell homeostasis in breast cancer survivors with persistent fatigue. *J Natl Cancer Inst* 2003;95:1165–1168.
14. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol* 2000;18:743–753.

Cancer-Related Fatigue

15. Broeckel JA, Jacobsen PB, Horton J, et al. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1998;16:1689–1696.
16. Crom DB, Hinds PS, Gattuso JS, et al. Creating the basis for a breast health program for female survivors of Hodgkin disease using a participatory research approach. *Oncol Nurs Forum* 2005;32:1131–1141.
17. Fossa SD, Dahl AA, Loge JH. Fatigue, anxiety, and depression in long-term survivors of testicular cancer. *J Clin Oncol* 2003;21:1249–1254.
18. Haghighat S, Akbari ME, Holakouei K, et al. Factors predicting fatigue in breast cancer patients. *Support Care Cancer* 2003;11:533–538.
19. Ruffer JU, Flechtner H, Tralls P, et al. Fatigue in long-term survivors of Hodgkin's lymphoma; a report from the German Hodgkin Lymphoma Study Group (GHSG). *Eur J Cancer* 2003;39:2179–2186.
20. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. *Ann Oncol* 2002;13:589–598.
21. Servaes P, Verhagen S, Schreuder HW, et al. Fatigue after treatment for malignant and benign bone and soft tissue tumors. *J Pain Symptom Manage* 2003;26:1113–1122.
22. Olson K. A new way of thinking about fatigue: a reconceptualization. *Oncol Nurs Forum* 2007;34:93–99.
23. Olson K, Krawchuk A, Quddusi T. Fatigue in individuals with advanced cancer in active treatment and palliative settings. *Cancer Nurs* 2007;30:E1–10.
24. Hinds PS, Quargnenti A, Bush AJ, et al. An evaluation of the impact of a self-care coping intervention on psychological and clinical outcomes in adolescents with newly diagnosed cancer. *Eur J Oncol Nurs* 2000;4:6–17; discussion 18–19.
25. Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. *Semin Hematol* 1997;34:4–12.
26. Ferrell BR, Grant M, Dean GE. Bone tired: the experience of fatigue and its impact on quality of life. *Oncol Nurs Forum* 1996;23:1539–1547.
27. Janda M, Gerstner N, Obermair A, et al. Quality of life changes during conformal radiation therapy for prostate carcinoma. *Cancer* 2000;89:1322–1328.
28. Nail L, Jones L. Fatigue as a side effect of cancer treatment: impact on quality of life. *Quality of life: a nursing challenge*. 1995;4:8–13.
29. Morrow GR, Andrews PL, Hickok JT, et al. Fatigue associated with cancer and its treatment. *Support Care Cancer* 2002;10:389–398.
30. Bower JE. Cancer-related fatigue: links with inflammation in cancer patients and survivors. *Brain Behav Immun* 2007;21:863–871.
31. Schubert C, Hong S, Natarajan L, et al. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun* 2007;21:413–427.
32. Miller AH, Ancoli-Israel S, Bower JE, et al. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol* 2008;26:971–982.
33. Berger AM, Wielgus K, Hertzog M, et al. Patterns of circadian activity rhythms and their relationships with fatigue and anxiety/depression in women treated with breast cancer adjuvant chemotherapy. *Support Care Cancer* 2009;18:105–114.
34. al-Majid S, McCarthy DO. Cancer-induced fatigue and skeletal muscle wasting: the role of exercise. *Biol Res Nurs* 2001;2:186–197.
35. Rich TA. Symptom clusters in cancer patients and their relation to EGFR ligand modulation of the circadian axis. *J Support Oncol* 2007;5:167–174; discussion 176–167.
36. Mock V, Atkinson A, Barsevick A, et al. NCCN practice guidelines for cancer-related fatigue. *Oncology (Williston Park)* 2000;14:151–161.
37. Stone P, Hardy J, Broadley K, et al. Fatigue in advanced cancer: a prospective controlled cross-sectional study. *Br J Cancer* 1999;79:1479–1486.
38. Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. *Eur J Cancer Care (Engl)* 1996;5:8–23.
39. Given CW, Given B, Azzouz F, et al. Comparison of changes in physical functioning of elderly patients with new diagnoses of cancer. *Med Care* 2000;38:482–493.
40. Hinds PS, Hockenberry-Eaton M, Gilger E, et al. Comparing patient, parent, and staff descriptions of fatigue in pediatric oncology patients. *Cancer Nurs* 1999;22:277–288; quiz 288–279.
41. Given B, Given CW, McCorkle R, et al. Pain and fatigue management: results of a nursing randomized clinical trial. *Oncol Nurs Forum* 2002;29:949–956.
42. Mock V, McCorkle R, Ropka ME. Fatigue and physical functioning during breast cancer treatment. *Oncol Nurs Forum* 2002;29:338.
43. Nail LM. Fatigue in patients with cancer. *Oncol Nurs Forum* 2002;29:537.
44. Malik UR, Makower DF, Wadler S. Interferon-mediated fatigue. *Cancer* 2001;92:1664–1668.
45. Escalante CP, Grover T, Johnson BA, et al. A fatigue clinic in a comprehensive cancer center: design and experiences. *Cancer* 2001;92:1708–1713.
46. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer* 1999;85:1186–1196.
47. Piper BF, Dodd MJ, Ream E. Improving the clinical measurement of cancer treatment-related fatigue. *Better health through nursing research: international state of the science*, Vol. 99. Washington, DC: American Nurses Association; 1999.
48. Hinds PS, Hockenberry M, Tong X, et al. Validity and reliability of a new instrument to measure cancer-related fatigue in adolescents. *J Pain Symptom Manage* 2007;34:607–618.
49. Hockenberry MJ, Hinds PS, Barrera P, et al. Three instruments to assess fatigue in children with cancer: the child, parent and staff perspectives. *J Pain Symptom Manage* 2003;25:319–328.
50. Varni JW, Burwinkle TM, Katz ER, et al. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer* 2002;94:2090–2106.
51. Grant M. Fatigue and quality of life with cancer. In: Winningham ML, Barton-Burke M, eds. *Fatigue in Cancer: A Multidimensional Approach*. Sudbury: Jones & Bartlett; 2000:353–364.
52. Cella D, Peterman A, Passik S, et al. Progress toward guidelines for the management of fatigue. *Oncology (Williston Park)* 1998;12:369–377.
53. Barsevick AM, Whitmer K, Walker L. In their own words: using the common sense model to analyze patient descriptions of cancer-related fatigue. *Oncol Nurs Forum* 2001;28:1363–1369.
54. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue

Cancer-Related Fatigue

- Coalition. *Oncologist* 2000;5:353–360.
55. Holley S. Cancer-related fatigue. Suffering a different fatigue. *Cancer Pract* 2000;8:87–95.
 56. Cleeland C, Wang XS. Measuring and understanding fatigue. *Oncology* 1999;13:91–97.
 57. Portenoy RK, Itri LM. Cancer-related fatigue: guidelines for evaluation and management. *Oncologist* 1999;4:1–10.
 58. Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer patients: a review. *Eur J Cancer Care (Engl)* 2001;10:245–255.
 59. Berger AM, Walker SN. An explanatory model of fatigue in women receiving adjuvant breast cancer chemotherapy. *Nurs Res* 2001;50:42–52.
 60. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. *Oncol Nurs Forum* 2001;28:465–470.
 61. Hinds PS, Hockenberry M, Rai SN, et al. Nocturnal awakenings, sleep environment interruptions, and fatigue in hospitalized children with cancer. *Oncol Nurs Forum* 2007;34:393–402.
 62. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. *J Clin Oncol* 2000;18:893–903.
 63. Newell S, Sanson-Fisher RW, Girgis A, Ackland S. The physical and psycho-social experiences of patients attending an outpatient medical oncology department: a cross-sectional study. *Eur J Cancer Care (Engl)* 1999;8:73–82.
 64. Loge JH, Abrahamsen AF, Ekeberg, Kaasa S. Fatigue and psychiatric morbidity among Hodgkin's disease survivors. *J Pain Symptom Manage* 2000;19:91–99.
 65. Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? *Support Care Cancer* 1998;6:101–108.
 66. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 2001;19:895–908.
 67. Berger AM, Mitchell SA. Modifying cancer-related fatigue by optimizing sleep quality. *J Natl Compr Canc Netw* 2008;6:3–13.
 68. Roscoe JA, Kaufman ME, Matteson-Rusby SE, et al. Cancer-related fatigue and sleep disorders. *Oncologist* 2007;12(Suppl 1):35–42.
 69. Berger AM, Parker KP, Young-McCaughan S, et al. Sleep wake disturbances in people with cancer and their caregivers: state of the science. *Oncol Nurs Forum* 2005;32:E98–126.
 70. Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. *Oncol Nurs Forum* 1998;25:51–62.
 71. Berger AM, Farr L. The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. *Oncol Nurs Forum* 1999;26:1663–1671.
 72. Palesh OG, Collie K, Batiuchok D, et al. A longitudinal study of depression, pain, and stress as predictors of sleep disturbance among women with metastatic breast cancer. *Biol Psychol* 2007;75:37–44.
 73. Dimeo FC, Stieglitz RD, Novelli-Fischer U, et al. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. *Cancer* 1999;85:2273–2277.
 74. Mock V, Frangakis C, Davidson NE, et al. Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. *Psychooncology* 2005;14:464–477.
 75. Schwartz AL. Daily fatigue patterns and effect of exercise in women with breast cancer. *Cancer Pract* 2000;8:16–24.
 76. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000;160:526–534.
 77. Strasser F, Palmer JL, Schover LR, et al. The impact of hypogonadism and autonomic dysfunction on fatigue, emotional function, and sexual desire in male patients with advanced cancer: a pilot study. *Cancer* 2006;107:2949–2957.
 78. Mitchell SA, Beck SL, Hood LE, et al. Putting evidence into practice: evidence-based interventions for fatigue during and following cancer and its treatment. *Clin J Oncol Nurs* 2007;11:99–113.
 79. Barsevick AM, Whitmer K, Sweeney C, Nail LM. A pilot study examining energy conservation for cancer treatment-related fatigue. *Cancer Nurs* 2002;25:333–341.
 80. Richardson A, Ream E, Wilson-Barnett J. Fatigue in patients receiving chemotherapy: patterns of change. *Cancer Nurs* 1998;21:17–30.
 81. Barsevick AM, Dudley W, Beck S, et al. A randomized clinical trial of energy conservation for patients with cancer-related fatigue. *Cancer* 2004;100:1302–1310.
 82. Graydon JE, Bubela N, Irvine D, Vincent L. Fatigue-reducing strategies used by patients receiving treatment for cancer. *Cancer Nurs* 1995;18:23–28.
 83. Richardson A, Ream EK. Self-care behaviours initiated by chemotherapy patients in response to fatigue. *Int J Nurs Stud* 1997;34:35–43.
 84. Mustian KM, Morrow GR, Carroll JK, et al. Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue. *Oncologist* 2007;12(Suppl 1):52–67.
 85. Mustian K, Palesh OG, Heckler CE, et al. Cancer-related fatigue interferes with activities of daily living among 753 patients receiving chemotherapy: a URCC CCOP study [abstract]. *J Clin Oncol* 2008;26(Suppl 1):Abstract 9500.
 86. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull* 2008;134:700–741.
 87. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev* 2008;CD006145.
 88. U.S. Department of Health & Human Services. HHS Announces Physical Activity Guidelines for Americans [news release]. Available at: <http://www.hhs.gov/news/press/2008pres/10/20081007a.html>. Accessed January 6, 2010.
 89. Courneya KS, Friedenreich CM, Sela RA, et al. The group psychotherapy and home-based physical exercise (group-hope) trial in cancer survivors: physical fitness and quality of life outcomes. *Psychooncology* 2003;12:357–374.
 90. Courneya KS, Mackey JR, Bell GJ, et al. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *J Clin Oncol* 2003;21:1660–1668.
 91. Drouin JS, Armstrong H, Krause S. Effects of aerobic exercise training on peak aerobic capacity, fatigue, and psychological factors during radiation for breast cancer. *Rehab Oncol* 2005;23:11–17.
 92. Schwartz AL, Mori M, Gao R, et al. Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. *Med Sci Sports Exerc* 2001;33:718–723.
 93. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2003;21:1653–1659.
 94. Sood A, Barton DL, Bauer BA, Loprinzi CL. A critical review of

Cancer-Related Fatigue

- complementary therapies for cancer-related fatigue. *Integr Cancer Ther* 2007;6:8–13.
95. Balk J, Day R, Rosenzweig M, Beriwal S. Pilot, randomized, modified, double-blind, placebo-controlled trial of acupuncture for cancer-related fatigue. *J Soc Integr Oncol* 2009;7:4–11.
 96. Mao JJ, Styles T, Cheville A, et al. Acupuncture for nonpalliative radiation therapy-related fatigue: feasibility study. *J Soc Integr Oncol* 2009;7:52–58.
 97. Molassiotis A, Sylt P, Diggins H. The management of cancer-related fatigue after chemotherapy with acupuncture and acupressure: a randomised controlled trial. *Complement Ther Med* 2007;15:228–237.
 98. Vickers AJ, Straus DJ, Fearon B, Cassileth BR. Acupuncture for postchemotherapy fatigue: a phase II study. *J Clin Oncol* 2004;22:1731–1735.
 99. Post-White J, Kinney ME, Savik K, et al. Therapeutic massage and healing touch improve symptoms in cancer. *Integr Cancer Ther* 2003;2:332–344.
 100. Cassileth BR, Vickers AJ. Massage therapy for symptom control: outcome study at a major cancer center. *J Pain Symptom Manage* 2004;28:244–249.
 101. Stark D, Kiely M, Smith A, et al. Anxiety disorders in cancer patients: their nature, associations, and relation to quality of life. *J Clin Oncol* 2002;20:3137–3148.
 102. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *Cochrane Database Syst Rev* 2009;CD006953.
 103. Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. *Health Psychol* 2007;26:660–667.
 104. Eaton LH, Tipton JM, eds. *Oncology Nursing Society Putting Evidence into Practice: Improving Oncology Patient Outcomes*. Pittsburgh: Oncology Nursing Society; 2009.
 105. Carlson LE, Garland SN. Impact of mindfulness-based stress reduction (MBSR) on sleep, mood, stress and fatigue symptoms in cancer outpatients. *Int J Behav Med* 2005;12:278–285.
 106. Cohen M, Fried G. Comparing relaxation training and cognitive-behavioral group therapy for women with breast cancer. *Res Soc Work Pract* 2007;17:313–323.
 107. Decker TW, Cline-Elsen J, Gallagher M. Relaxation therapy as an adjunct in radiation oncology. *J Clin Psychol* 1992;48:388–393.
 108. Jacobsen PB, Meade CD, Stein KD, et al. Efficacy and costs of two forms of stress management training for cancer patients undergoing chemotherapy. *J Clin Oncol* 2002;20:2851–2862.
 109. Armes J, Chalder T, Addington-Hall J, et al. A randomized controlled trial to evaluate the effectiveness of a brief, behaviorally oriented intervention for cancer-related fatigue. *Cancer* 2007;110:1385–1395.
 110. Luebbert K, Dahme B, Hasenbring M. The effectiveness of relaxation training in reducing treatment-related symptoms and improving emotional adjustment in acute non-surgical cancer treatment: a meta-analytical review. *Psychooncology* 2001;10:490–502.
 111. Montgomery GH, Kangas M, David D, et al. Fatigue during breast cancer radiotherapy: an initial randomized study of cognitive-behavioral therapy plus hypnosis. *Health Psychol* 2009;28:317–322.
 112. Boesen EH, Ross L, Frederiksen K, et al. Psychoeducational intervention for patients with cutaneous malignant melanoma: a replication study. *J Clin Oncol* 2005;23:1270–1277.
 113. Gaston-Johansson F, Fall-Dickson JM, Nanda J, et al. The effectiveness of the comprehensive coping strategy program on clinical outcomes in breast cancer autologous bone marrow transplantation. *Cancer Nurs* 2000;23:277–285.
 114. Kim Y, Roscoe JA, Morrow GR. The effects of information and negative affect on severity of side effects from radiation therapy for prostate cancer. *Support Care Cancer* 2002;10:416–421.
 115. Lindemalm C, Strang P, Lekander M. Support group for cancer patients. Does it improve their physical and psychological wellbeing? A pilot study. *Support Care Cancer* 2005;13:652–657.
 116. Ream E, Richardson A, Alexander-Dann C. Supportive intervention for fatigue in patients undergoing chemotherapy: a randomized controlled trial. *J Pain Symptom Manage* 2006;31:148–161.
 117. Yates P, Aranda S, Hargraves M, et al. Randomized controlled trial of an educational intervention for managing fatigue in women receiving adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 2005;23:6027–6036.
 118. Allison PJ, Edgar L, Nicolau B, et al. Results of a feasibility study for a psycho-educational intervention in head and neck cancer. *Psychooncology* 2004;13:482–485.
 119. Godino C, Jodar L, Duran A, et al. Nursing education as an intervention to decrease fatigue perception in oncology patients. *Eur J Oncol Nurs* 2006;10:150–155.
 120. Williams SA, Schreier AM. The role of education in managing fatigue, anxiety, and sleep disorders in women undergoing chemotherapy for breast cancer. *Appl Nurs Res* 2005;18:138–147.
 121. Yesilbalkan OU, Karadakovan A, Goker E. The effectiveness of nursing education as an intervention to decrease fatigue in Turkish patients receiving chemotherapy. *Oncol Nurs Forum* 2009;36:E215–222.
 122. Forester B, Kornfeld DS, Fleiss JL. Psychotherapy during radiotherapy: effects on emotional and physical distress. *Am J Psychiatry* 1985;142:22–27.
 123. Brown JK. A systematic review of the evidence on symptom management of cancer-related anorexia and cachexia. *Oncol Nurs Forum* 2002;29:517–532.
 124. Owen DC, Parker KP, McGuire DB. Comparison of subjective sleep quality in patients with cancer and healthy subjects. *Oncol Nurs Forum* 1999;26:1649–1651.
 125. Page MS, Berger AM, Johnson LB. Putting evidence into practice: evidence-based interventions for sleep-wake disturbances. *Clin J Oncol Nurs* 2006;10:753–767.
 126. Bootzin RR, Epstein D, Wood J. Stimulus control instructions. In: Hauri P, ed. *Case Studies in Insomnia*. New York: Plenum Press; 1991:19–28.
 127. Morin C, Espie C. *Insomnia: A Clinical Guide to Assessment and Treatment*. New York: Kluwer Academic; 2003.
 128. Berger AM, VonEssen S, Khun BR, et al. Feasibility of a sleep intervention during adjuvant breast cancer chemotherapy. *Oncol Nurs Forum* 2002;29:1431–1441.
 129. Davidson JR, Waisberg JL, Brundage MD, MacLean AW. Nonpharmacologic group treatment of insomnia: a preliminary study with cancer survivors. *Psychooncology* 2001;10:389–397.
 130. Quesnel C, Savard J, Simard S, et al. Efficacy of cognitive-behavioral therapy for insomnia in women treated for nonmetastatic breast cancer. *J Consult Clin Psychol* 2003;71:189–200.
 131. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the

Cancer-Related Fatigue

- efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: sleep and psychological effects. *J Clin Oncol* 2005;23:6083–6096.
132. Dirksen SR, Epstein DR. Efficacy of an insomnia intervention on fatigue, mood and quality of life in breast cancer survivors. *J Adv Nurs* 2008;61:664–675.
 133. Epstein DR, Dirksen SR. Randomized trial of a cognitive-behavioral intervention for insomnia in breast cancer survivors. *Oncol Nurs Forum* 2007;34:E51–59.
 134. Espie CA, Fleming L, Cassidy J, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomnia in patients with cancer. *J Clin Oncol* 2008;26:4651–4658.
 135. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An american academy of sleep medicine report. *Sleep* 2006;29:1415–1419.
 136. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008;4:487–504.
 137. Ahles TA, Tope DM, Pinkson B, et al. Massage therapy for patients undergoing autologous bone marrow transplantation. *J Pain Symptom Manage* 1999;18:157–163.
 138. Cohen L, Warneke C, Fouladi RT, et al. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. *Cancer* 2004;100:2253–2260.
 139. Kim SD, Kim HS. Effects of a relaxation breathing exercise on fatigue in haemopoietic stem cell transplantation patients. *J Clin Nurs* 2005;14:51–55.
 140. Kim SD, Kim HS. Effects of a relaxation breathing exercise on anxiety, depression, and leukocyte in hemopoietic stem cell transplantation patients. *Cancer Nurs* 2005;28:79–83.
 141. Cannici J, Malcolm R, Peek LA. Treatment of insomnia in cancer patients using muscle relaxation training. *J Behav Ther Exp Psychiatry* 1983;14:251–256.
 142. Carlson LE, Specia M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. *Psychosom Med* 2003;65:571–581.
 143. Carlson LE, Specia M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients. *Psychoneuroendocrinology* 2004;29:448–474.
 144. Shapiro SL, Bootzin RR, Figueredo AJ, et al. The efficacy of mindfulness-based stress reduction in the treatment of sleep disturbance in women with breast cancer: an exploratory study. *J Psychosom Res* 2003;54:85–91.
 145. U.S. Food and Drug Administration. FDA Requests Label Change for All Sleep Disorder Drug Products. FDA News. March 14, 2007. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108868.htm>. Accessed August 12, 2007.
 146. National Cancer Institute. Sleep Disturbance in Cancer Patients. Available at: <http://www.nci.nih.gov/cancertopics/pdq/supportivecare/sleepdisorders/HealthProfessional/>. Accessed January 6, 2010.
 147. Minton O, Richardson A, Sharpe M, et al. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. *J Natl Cancer Inst* 2008;100:1155–1166.
 148. Morrow GR, Hickok JT, Roscoe JA, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *J Clin Oncol* 2003;21:4635–4641.
 149. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res Treat* 2005;89:243–249.
 150. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–249.
 151. Jacobsen PB, Stein K. Is fatigue a long-term side effect of breast cancer treatment? *Cancer Control* 1999;6:256–263.
 152. Knobel H, Loge JH, Nordoy T, et al. High level of fatigue in lymphoma patients treated with high dose therapy. *J Pain Symptom Manage* 2000;19:446–456.
 153. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med* 2002;64:604–611.
 154. Cella D, Davis K, Breitbart W, Curt G. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol* 2001;19:3385–3391.
 155. Knobel H, Havard Loge J, Brit Lund M, et al. Late medical complications and fatigue in Hodgkin's disease survivors. *J Clin Oncol* 2001;19:3226–3233.
 156. Stewart DE, Wong F, Duff S, et al. "What doesn't kill you makes you stronger": an ovarian cancer survivor survey. *Gynecol Oncol* 2001;83:537–542.
 157. Servaes P, Prins J, Verhagen S, Bleijenberg G. Fatigue after breast cancer and in chronic fatigue syndrome: similarities and differences. *J Psychosom Res* 2002;52:453–459.
 158. Stone P, Richardson A, Ream E, et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Cancer Fatigue Forum. Ann Oncol* 2000;11:971–975.
 159. Woo B, Dibble SL, Piper BF, et al. Differences in fatigue by treatment methods in women with breast cancer. *Oncol Nurs Forum* 1998;25:915–920.
 160. Hann DM, Jacobsen PB, Martin SC, et al. Fatigue in women treated with bone marrow transplantation for breast cancer: a comparison with women with no history of cancer. *Support Care Cancer* 1997;5:44–52.
 161. Mock V, Cameron L, Tompkins C. Every step counts: a walking exercise program for persons living with cancer. Baltimore: Johns Hopkins University; 1997.
 162. Gielissen MF, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol* 2006;24:4882–4887.
 163. Geinitz H, Zimmermann FB, Thamm R, et al. Fatigue in patients with adjuvant radiation therapy for breast cancer: long-term follow-up. *J Cancer Res Clin Oncol* 2004;130:327–333.
 164. Schneider CM, Hsieh CC, Sprod LK, et al. Effects of supervised exercise training on cardiopulmonary function and fatigue in breast cancer survivors during and after treatment. *Cancer* 2007;110:918–925.
 165. Vallance JK, Courneya KS, Plotnikoff RC, et al. Randomized controlled trial of the effects of print materials and step pedometers on physical activity and quality of life in breast cancer survivors. *J Clin Oncol* 2007;25:2352–2359.

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166. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. *J Psychosom Res* 1998;45:53–65.
167. Dimeo FC, Tilmann MH, Bertz H, et al. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. *Cancer* 1997;79:1717–1722.
168. Conn VS, Hafdahl AR, Porock DC, et al. A meta-analysis of exercise interventions among people treated for cancer. *Support Care Cancer* 2006;14:699–712.
169. Douglas E. Exercise in cancer patients. *Physical Therapy Reviews* 2005;10:71–88.
170. Galvao DA, Newton RU. Review of exercise intervention studies in cancer patients. *J Clin Oncol* 2005;23:899–909.
171. Knols R, Aaronson NK, Uebelhart D, et al. Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials. *J Clin Oncol* 2005;23:3830–3842.
172. McNeely ML, Campbell KL, Rowe BH, et al. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *CMAJ* 2006;175:34–41.
173. Oldervoll LM, Kaasa S, Knobel H, Loge JH. Exercise reduces fatigue in chronic fatigued Hodgkins disease survivors--results from a pilot study. *Eur J Cancer* 2003;39:57–63.
174. Stricker CT, Drake D, Hoyer KA, Mock V. Evidence-based practice for fatigue management in adults with cancer: exercise as an intervention. *Oncol Nurs Forum* 2004;31:963–976.
175. Visovsky C, Dvorak C. Exercise and cancer recovery. *Online J Issues Nurs* 2005;10:7.
176. Fawzy FI, Cousins N, Fawzy NW, et al. A structured psychiatric intervention for cancer patients. I. Changes over time in methods of coping and affective disturbance. *Arch Gen Psychiatry* 1990;47:720–725.
177. Fawzy NW. A psychoeducational nursing intervention to enhance coping and affective state in newly diagnosed malignant melanoma patients. *Cancer Nurs* 1995;18:427–438.
178. Spiegel D, Bloom JR, Yalom I. Group support for patients with metastatic cancer. A randomized outcome study. *Arch Gen Psychiatry* 1981;38:527–533.
179. Telch CF, Telch MJ. Group coping skills instruction and supportive group therapy for cancer patients: a comparison of strategies. *J Consult Clin Psychol* 1986;54:802–808.
180. Dolbeault S, Cayrou S, Bredart A, et al. The effectiveness of a psycho-educational group after early-stage breast cancer treatment: results of a randomized French study. *Psychooncology* 2009;18:647–656.
181. Fillion L, Gagnon P, Leblond F, et al. A brief intervention for fatigue management in breast cancer survivors. *Cancer Nurs* 2008;31:145–159.
182. Yennurajalingam S, Bruera E. Palliative management of fatigue at the close of life: “it feels like my body is just worn out”. *JAMA* 2007;297:295–304.
183. Krishnasamy M. Fatigue in advanced cancer—meaning before measurement? *Int J Nurs Stud* 2000;37:401–414.
184. Lundh Hagelin C, Seiger A, Furst CJ. Quality of life in terminal care—with special reference to age, gender and marital status. *Support Care Cancer* 2006;14:320–328.
185. Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Support Care Cancer* 2000;8:175–179.
186. Walsh D, Rybicki L. Symptom clustering in advanced cancer. *Support Care Cancer* 2006;14:831–836.
187. Given B, Given C, Azzouz F, Stommel M. Physical functioning of elderly cancer patients prior to diagnosis and following initial treatment. *Nurs Res* 2001;50:222–232.
188. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. *N Engl J Med* 2000;342:326–333.
189. Wong RK, Franssen E, Szumacher E, et al. What do patients living with advanced cancer and their carers want to know? - a needs assessment. *Support Care Cancer* 2002;10:408–415.
190. Harris KA. The informational needs of patients with cancer and their families. *Cancer Pract* 1998;6:39–46.
191. Rose KE. A qualitative analysis of the information needs of informal carers of terminally ill cancer patients. *J Clin Nurs* 1999;8:81–88.
192. Mystakidou K, Parpa E, Katsouda E, et al. The role of physical and psychological symptoms in desire for death: a study of terminally ill cancer patients. *Psychooncology* 2006;15:355–360.
193. Oldervoll LM, Loge JH, Paltiel H, et al. The effect of a physical exercise program in palliative care: a phase II study. *J Pain Symptom Manage* 2006;31:421–430.
194. Porock D, Kristjanson LJ, Tinnelly K, et al. An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. *J Palliat Care* 2000;16:30–36.
195. Strong A, Karavatas G, Reicherter EA. Recommended exercise protocol to decrease cancer-related fatigue and muscle wasting in patients with multiple myeloma. *Topics in Geriatric Rehabilitation* 2006;22:172–186.
196. Butler JM Jr, Case LD, Atkins J, et al. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. *Int J Radiat Oncol Biol Phys* 2007;69:1496–1501.
197. Hanna A, Sledge G, Mayer ML, et al. A phase II study of methylphenidate for the treatment of fatigue. *Support Care Cancer* 2006;14:210–215.
198. Sarhill N, Walsh D, Nelson KA, et al. Methylphenidate for fatigue in advanced cancer: a prospective open-label pilot study. *Am J Hosp Palliat Care* 2001;18:187–192.
199. Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. *Arch Intern Med* 2001;161:411–420.
200. Auret KA, Schug SA, Bremner AP, Bulsara M. A randomized, double-blind, placebo-controlled trial assessing the impact of dexamphetamine on fatigue in patients with advanced cancer. *J Pain Symptom Manage* 2009;37:613–621.
201. Morrow GR, Ryan JL, Kohli S. Modafinil (Provigil®) for persistent post-treatment fatigue: an open label study of 82 women with breast cancer [abstract]. *MASCC International Symposia*; June 22–24, 2006; Toronto, Canada. Abstract 11-070.
202. Kaleita T, Cloughesy J, Ford W. A pilot study of modafinil (Provigil®) for treatment of fatigue and neurobehavioral dysfunction in adult brain tumor patients [abstract]. *Ninth Annual Meeting of the Society for Neuro-Oncology*; November 18–21, 2004; Toronto, Canada. Abstract QL-06.
203. Caraceni A, Simonetti F. Psychostimulants: new concepts for palliative care from the modafinil experience? *J Pain Symptom*

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- Manage 2004;28:97–99.
204. Loprinzi CL, Michalak JC, Schaid DJ, et al. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *J Clin Oncol* 1993;11:762–767.
 205. Loprinzi CL, Kugler JW, Sloan JA, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol* 1999;17:3299–3306.
 206. Pascual Lopez A, Roque i Figuls M, Urrutia Cuchi G, et al. Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. *J Pain Symptom Manage* 2004;27:360–369.
 207. Bruera E, Ernst S, Hagen N, et al. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. *Cancer Prev Control* 1998;2:74–78.
 208. De Conno F, Martini C, Zecca E, et al. Megestrol acetate for anorexia in patients with far-advanced cancer: a double-blind controlled clinical trial. *Eur J Cancer* 1998;34:1705–1709.
 209. Simons JP, Aaronson NK, Vansteenkiste JF, et al. Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. *J Clin Oncol* 1996;14:1077–1084.
 210. Westman G, Bergman B, Albertsson M, et al. Megestrol acetate in advanced, progressive, hormone-insensitive cancer. Effects on the quality of life: a placebo-controlled, randomised, multicentre trial. *Eur J Cancer* 1999;35:586–595.
 211. Graziano F, Bisonni R, Catalano V, et al. Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. *Br J Cancer* 2002;86:1854–1857.
 212. Cruciani RA, Dvorkin E, Homel P, et al. L-carnitine supplementation for the treatment of fatigue and depressed mood in cancer patients with carnitine deficiency: a preliminary analysis. *Ann N Y Acad Sci* 2004;1033:168–176.
 213. Cruciani RA, Dvorkin E, Homel P, et al. Safety, tolerability and symptom outcomes associated with L-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: a phase I/II study. *J Pain Symptom Manage* 2006;32:551–559.
 214. Cruciani RA, Dvorkin E, Homel P, et al. L-carnitine supplementation in patients with advanced cancer and carnitine deficiency: a double-blind, placebo-controlled study. *J Pain Symptom Manage* 2009;37:622–631.
 215. Cruciani RA, Dvorkin E, Homel P, et al. L-carnitine supplementation in patients with advanced cancer and carnitine deficiency: a double-blind, placebo-controlled study. *J Pain Symptom Manage* 2009;37:622–631.
 216. Johnson JE. Self-regulation theory and coping with physical illness. *Res Nurs Health* 1999;22:435–448.
 217. Borneman T, Piper BF, Sun VC, et al. Implementing the Fatigue Guidelines at one NCCN member institution: process and outcomes. *J Natl Compr Canc Netw* 2007;5:1092–1101.
 218. Piper BF, Borneman T, Sun VC, et al. Cancer-related fatigue: role of oncology nurses in translating national comprehensive cancer network assessment guidelines into practice. *Clin J Oncol Nurs* 2008;12:37–47.

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Individual Disclosures for the NCCN Cancer-Related Fatigue Panel

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