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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Cancer-Related Fatigue

Version 1.2011

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Cancer-Related Fatigue

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

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

See NCCN Categories of Evidence and Consensus

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NCCN Guidelines™ Version 1.2011 Updates Cancer-Related Fatigue

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Updates in Version 1.2011 of the NCCN Cancer-Related Fatigue Guidelines from Version 1.2010 include:

FT-3

- **Third column, Bottom pathway: "Education plus general strategies to manage fatigue" changed to "Education plus primary evaluation of fatigue".**

FT-4

- **Under Primary Evaluation Fatigue Score:**
  - **Focused history:**
    - **Under Disease status and treatment: "Current medications/medication changes" was removed. Second arrow changed to "Prescription medications/OTCs and supplements".**
    - **"Social support status/availability of caregivers" was added.**
  - **Assessment of treatable contributing factors:**
    - **"Nutrition Assessment" changed to "Nutritional deficits/Imbalance"**
    - **"Activity level" changed to "Decreased functional status"**
      -First arrow changed to "Decreased activity level"
      -"Decreased physical fitness" changed to "Deconditioning"
  - **Comorbidities**
    - **"Gastrointestinal (GI) dysfunction" was added. "Alcohol/substance abuse" was moved under comorbidities.**
- **Third column, after Treatable contributing factors: Medications/Side effects was added.**
- **Last column: "Follow-up, no active treatment (except hormone therapy)" changed to "Follow-up, post-treatment (no active treatment except hormone therapy)".**

FT-5, FT-6, FT-7

- **General strategies for management of fatigue: "Limit naps to 20-30 minutes or less so as to not interfere with night-time sleep quality" changed to "Limit naps to < 1 hour to not interfere..."**
- **Nonpharmacologic; Under Caution: "Immunosuppression/neutropenia" and accompanying footnote were removed.**
- **Pharmacologic:**
  - **"Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities" was added.**
  - **"Treat for anemia as indicated..." changed to "Treat for pain, emotional distress, and anemia..."**
  - **"Consider sleep medication" was removed.**
- **Footnote "f" that states, "Examples include use of reachers for grasping items beyond arm's length, sock-aids for pulling on socks, rolling carts for transporting items, escalators and elevators for traveling between building floors, and electrical appliances for performing common household tasks (eg, opening cans)" is new to the page.**
- **Footnote "j": Support groups, counseling and journal writing were added as examples of supportive expressive therapies.**

FT-7

- **General strategies for management of fatigue:**
  - **Wheelchairs, walkers, and commodes were added as examples of "Labor-saving and assistive devices".**
  - **"Limit naps to 20-30 minutes or less so as to not interfere with night-time sleep quality" was removed.**

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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.

Note: All recommendations are category 2A unless otherwise indicated.
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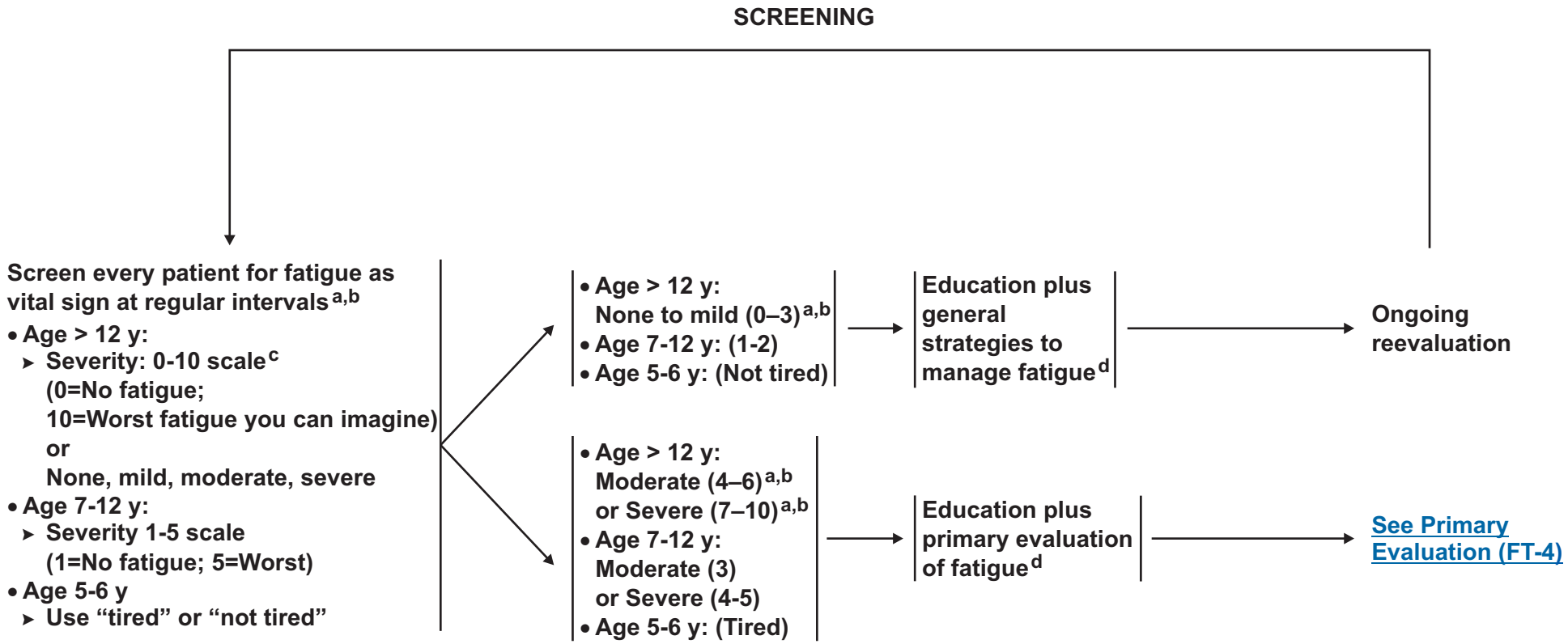
STANDARDS OF CARE IN CHILDREN/ADOLESCENTS AND ADULT CANCER-RELATED FATIGUE MANAGEMENT

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

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[a]Recommended screen: "How would you rate your fatigue on a scale of 0-10 over the past 7 days?"
[b]Fatigue scale for children is simplified: Use "tired" or "not tired" as screen for young children (age < 6 or 7 y).
[c]Butt Z, Wagner LI, Beaumont JL, et al. Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. Journal of Pain and Symptom Management 2008; 35(1): 20-30.
[d]See "Patient/Family Education and Counseling" and "General Strategies for Management of Fatigue" based on clinical status: Active Treatment (FT-5), Post-Treatment (FT-6), End of Life (FT-7).

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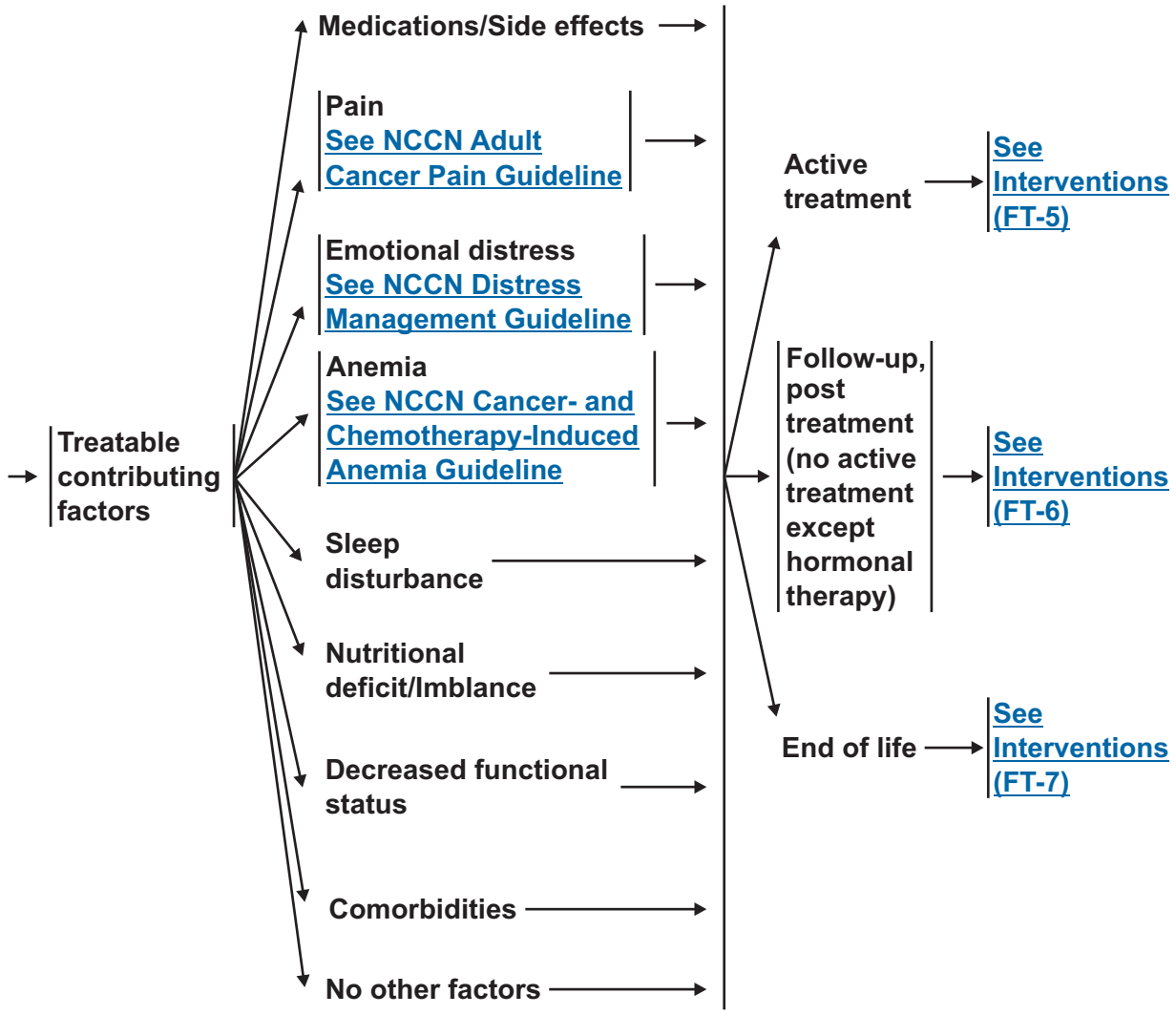
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PRIMARY EVALUATION FATIGUE SCORE: MODERATE OR SEVERE
Age > 12 y (4-10), Age 7-12 y (3-5), or Age 5-6 y (Tired)

PATIENT CLINICAL STATUS

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

Assessment of treatable contributing factors:
- Medications/Side effects (eg, sedation)
- Pain
- Emotional distress
  - Depression
  - Anxiety
- Anemia
- Sleep disturbance (eg, insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome)
- Nutritional deficits/Imbalance
  - Weight/caloric intake changes
  - Fluid electrolyte imbalance: sodium, potassium, calcium, magnesium
- Decreased functional status
  - Decreased activity level
  - Deconditioning
- Comorbidities
  - Alcohol/substance abuse
  - Cardiac dysfunction
  - Endocrine dysfunction (eg, hot flashes, hypothyroidism, hypogonadism, adrenal insufficiency)
  - Gastrointestinal (GI) dysfunction
  - Hepatic dysfunction
  - Infection
  - Neurologic dysfunction
  - Pulmonary dysfunction
  - Renal dysfunction



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INTERVENTIONS FOR PATIENTS ON ACTIVE TREATMENT[e]

Patient/Family Education and Counseling

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

→

General Strategies for Management of Fatigue
- Self-monitoring of fatigue levels
- Energy conservation
  - Set priorities
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Labor-saving devices[f]
  - Postpone nonessential activities
  - Limit naps to < 1 hour to not interfere with night-time sleep quality
  - Structured daily routine
  - Attend to one activity at a time
- Use distraction (eg, games, music, reading, socializing)

→

SPECIFIC INTERVENTIONS

Nonpharmacologic[g]
- Activity enhancement (category 1)
  - Maintain optimal level of activity
  - Consider initiation of exercise program of both endurance and resistance exercise
  - Consider referral to rehabilitation: physical therapy, occupational therapy & physical medicine
  - Caution:
    - Bone metastases
    - Thrombocytopenia
    - Anemia
    - Fever or active infection
    - Limitations secondary to metastases or other illnesses
- Physically-based therapies
  - Massage therapy (category 1)
- Psychosocial interventions
  - Cognitive behavioral therapy (CBT)[h]/ Behavioral therapy (BT) (category 1)[i]
  - Psycho-educational therapies/Educational therapies (category 1)
  - Supportive expressive therapies[j]
- Nutrition consultation
- CBT[h] for sleep
  - Stimulus control
  - Sleep restriction
  - Sleep hygiene

Pharmacologic
- Consider psychostimulants[k] (methylphenidate or modafanil) after ruling out other causes of fatigue
- Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines™ (See appropriate NCCN Supportive Care Guidelines)
- Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities

→ Repeat evaluation See (FT-4)

[e] See Discussion for information on differences between Active treatment, Post-Treatment, and End-of-Life treatment. (See MS-1)

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

[g] Interventions should be culturally specific and tailored to the patients and families because not all patients may be able to integrate these options due to variances in individual circumstances and resources.

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

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

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

[k] Pharmacological interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. There is more evidence for methylphenidate and less for modafinil. These agents should be used cautiously and should not be used until treatment and disease specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in cancer patients.

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INTERVENTIONS FOR PATIENTS POST-TREATMENT[e]

Patient/Family Education and Counseling

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

→

General Strategies for Management of Fatigue

- Self monitoring of fatigue levels
- Energy conservation
  - Set priorities
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Labor-saving devices[f]
  - Postpone nonessential activities
  - Limit naps to < 1 hour to not interfere with night-time sleep quality
  - Structured daily routine
  - Attend to one activity at a time
- Use distraction (eg, games, music, reading, socializing)

→

SPECIFIC INTERVENTIONS

Nonpharmacologic[g]

- Activity enhancement (category 1)
  - Maintain optimal level of activity
  - Consider initiation of exercise program of both endurance and resistance exercise
  - Consider referral to rehabilitation: physical therapy, occupational therapy, physical medicine
  - Caution:
    - Late effects of treatment (eg, cardiomyopathy)
- Psychosocial interventions (category 1)
  - CBT[h]/BT (category 1)[i]
  - Psycho-educational therapies/ Educational therapies (category 1)
  - Supportive expressive therapies (category 1)[j]
- Nutrition consultation
- CBT[h] for sleep (category 1)
  - Stimulus control
  - Sleep restriction
  - Sleep hygiene

→

Pharmacologic[l]

- Consider psychostimulants[k] (methylphenidate or modafanil) after ruling out other causes of fatigue
- Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines™ (See appropriate NCCN Supportive Care Guidelines)
- Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities

→

Repeat evaluation
See (FT-4)

[e] See Discussion for information on differences between Active treatment, Post-Treatment, and End-of-Life treatment. (See MS-1)

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

[g] Interventions should be culturally specific and tailored to the patients and families because not all patients may be able to integrate these options due to variances in individual circumstances and resources.

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

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

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

[k] Pharmacological interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. There is more evidence for methylphenidate and less for modafinil. These agents should be used cautiously and should not be used until treatment and disease specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in cancer patients.

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

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

Patient/Family Education and Counseling

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

→

General Strategies for Management of Fatigue

- Energy conservation
  - Set priorities
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Labor-saving and assistive devices[f] (including wheelchairs, walkers and commodes)
  - Eliminate nonessential activities
  - Structured daily routine
  - Attend to one activity at a time
  - Conserve energy for valued activities
- Use distraction (eg, games, music, reading, socializing)

→

SPECIFIC INTERVENTIONS

Nonpharmacologic[g]

- Activity enhancement
  - Optimize level of activity with careful consideration of the following constraints:
    - Bone metastases
    - Thrombocytopenia
    - Anemia
    - Fever or active infection
    - Assessment of safety issues (ie, risk of falls, stability)
- Psychosocial interventions
- Nutrition consultation

→

Pharmacologic

- Consider psychostimulants[k] (methylphenidate or modafanil) after ruling out other causes of fatigue
  - Consider corticosteroids (prednisone or dexamethasone)
- Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines™ (See appropriate NCCN Supportive Care Guidelines)
- Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities

→ Repeat evaluation See (FT-4)

[e] See Discussion for information on differences between Active treatment, Post-Treatment, and End-of-Life treatment. (See MS-1)

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

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

[k] Pharmacological interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. There is more evidence for methylphenidate and less for modafinil. These agents should be used cautiously and should not be used until treatment and disease specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in cancer patients.

[m] Also See NCCN Palliative Care Guidelines.

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

Fatigue is a common symptom in patients with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biological response modifiers.[1-10] According to a survey of 1,569 cancer patients, the symptom is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.[11, 12] 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.[13-22] The distinction between tiredness, fatigue, and exhaustion has not been made, despite conceptual differences.[23, 24] Patients perceive fatigue to be the most distressing symptom associated with cancer and its treatment, more distressing even than pain or nausea and vomiting, which, for most patients, can generally be managed by medications.[25, 26]

Fatigue in cancer patients has been under-reported, under-diagnosed, and under-treated. Persistent cancer-related fatigue affects quality of life (QOL), as cancer patients become too tired to fully participate in the roles and activities that make life meaningful.[17, 27, 28] Health care professionals have been challenged in their efforts to help patients manage this distressful symptom and to remain as fully engaged in life as possible. Because of the successes in cancer treatment, health care professionals are now likely to see patients with prolonged states of fatigue related to the late effects of treatment. Disability-related issues are relevant and often challenging, especially for cancer patients who are cured of their malignancy but have continued fatigue.[29] Despite biomedical literature documenting this entity, it is often difficult for patients with cancer-related fatigue to obtain or retain disability benefits from insurers. Health care professionals should advocate for patients who require disability benefits and educate insurers about this issue.

Despite the prevalence of cancer-related fatigue, the specific mechanisms involved in its pathophysiology are unknown. Proposed mechanisms include pro-inflammatory cytokines,[30-32] 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 experts. The NCCN Cancer-Related Fatigue Guideline, first published in 2000[36] and updated annually, synthesizes the available research and clinical experience in this field as well as provides recommendations for patient care.

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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. Compared with the fatigue experienced by healthy individuals, cancer-related fatigue is more severe, more distressing,[13, 37] and less likely to be relieved by rest.[38] In terms of the defining characteristics, it is important to note the subjective sense of tiredness reported by the patient. As with pain, the clinician must rely on patients' descriptions of their fatigue and accompanying distress. Fatigue that interferes with usual functioning is another substantial component of the definition for cancer-related fatigue and the source of much distress for patients.[7, 39, 40] Investigations have documented a significant effect of fatigue on physical functioning during cancer treatment and it is uncertain whether patients regain full functioning when treatment is over.[41, 42]

Standards of Care for Assessment and Management

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

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

Fatigue should be screened, assessed, and managed for most patients according to the clinical practice guideline. This guideline provides "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 following cancer treatment, and as clinically indicated. Screening should identify fatigue. Patients and families should be informed that managing fatigue is an integral part of total health care. All patients should receive symptom management. Furthermore, if patients cannot tolerate their cancer treatment or if they must choose between treatment and QOL, control of their disease may be diminished.[44]

Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner. The guideline for fatigue is best Implemented by an interdisciplinary institutional committee, including 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 within institutional settings is necessary if professionals are to become skilled in managing fatigue.

The NCCN Panel recommends that assessment of cancer-related fatigue levels be included in outcomes research. Quality of fatigue management should be included in institutional continuous quality improvement (CQI) projects. Institutions can make faster progress in

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implementing the guidelines if they monitor adherence and progress with the guidelines. Medical care contracts should reimburse for managing fatigue, including referrals to a physical therapist, dietitian, or the institution's symptom management service. Disability insurance should include coverage for the continuing effects of fatigue that lead to persistent disability. Rehabilitation should begin with a cancer diagnosis and should continue even after cancer treatment ends.

Guidelines for Evaluation and Treatment

The general schema of the fatigue algorithm incorporates the following phases: screening, primary evaluation, intervention, and re-evaluation. 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 during the primary evaluation phase of the algorithm to conduct a more focused history and physical examination. This phase also includes an in-depth fatigue assessment and an evaluation of contributing factors frequently associated with fatigue, and can be treated as an initial step in managing fatigue. If, however, a patient either does not have one of these treatable contributing factors or continues to have moderate-to-severe fatigue after treatment of the factors, the health care professional should recommend additional treatment based on the NCCN Cancer-Related Fatigue Guidelines.

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

Screening

The first phase of the algorithm emphasizes screening of every patient for the presence or absence of fatigue. If fatigue is present, a quantitative or semiquantitative assessment should be performed and documented. For example, on a 0 to 10 numeric rating scale (zero = no fatigue and 10 = worst fatigue imaginable), mild fatigue is indicated as a score of 1 to 3, moderate fatigue as 4 to 6, and severe fatigue as 7 to 10.[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 and common management strategies for fatigue. Periodic re-screening and re-evaluation are recommended. Inpatients should be screened daily and outpatients screened at subsequent routine and follow-up visits. It should be emphasized that survivors or patients who have completed treatment must still be monitored for fatigue, because fatigue may exist beyond the period of active treatment.[13, 16, 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. Patients do not want to be perceived as complaining and, therefore, may not mention fatigue. Or, they may assume that they just have to live with fatigue because they believe there is no treatment for it. Health care professionals may not initiate a discussion about fatigue for many of the

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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 there are effective treatments for fatigue. In addition, the underlying pathophysiology and mechanisms of fatigue have not been elucidated.

Given these barriers, screening for cancer-related fatigue must be emphasized. Clinical experience with fatigue assessment has shown that some patients cannot put a numeric value on their fatigue. Consequently, some patients may need to rate fatigue as mild, moderate, or severe. In addition, in some circumstances, other sources of data must be used. For example, the patient may not be aware that fatigue has negatively affected his or her life; however, the spouse, parents, or other family members may be more cognizant of these changes and the effect of fatigue. An appendix to this manuscript provides additional information and resources to assist in the selection of instruments to measure cancer-related fatigue.

Using the numeric rating scale (i.e., 0 to 10 scale), fatigue studies in cancer patients have revealed a marked decrease in physical functioning at the level of 7 or higher.[46] The authors of an international study on fatigue in breast and prostate cancer patients evaluated and compared fatigue intensity levels with scores from the MOS-SF-36 Physical Functioning Subscale.[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 [Fatigue Score: moderate-to-severe (4-10)]

Focused History and Physical Examination

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

A review of systems should be completed. This review may be helpful in determining the various organ systems affected and in directing the physical evaluation and diagnostic workup. Another component of the focused history is an in-depth fatigue assessment[56] 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. The health care professional must evaluate fatigue's effect on normal functioning and its effect on the patient's daily living or enjoyable activities. Because fatigue is a subjective condition involving

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a combination of symptoms and is experienced and reported differently by each person, it is important that the in-depth assessment includes the patient's self-assessment of the causes of fatigue.

The panel also recognized the important role of social support throughout the course of cancer treatment and survivorship (reviewed by Given, Given, and Kozchik[57]). Fatigue is a major cause of functional dependence for cancer patients, especially among the elderly.[58] Besides assisting with daily living, caregivers provided multiple cancer-specific support such as monitoring treatment side effects, aiding in fatigue and pain management, administering medicine, among others.[59] The availability of dependable caregivers impacts the functional, emotional, as well as financial capacity of a cancer patient in coping with the disease and can be a significant contributing factor for fatigue.

Assessment of Treatable Contributing Factors

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

Descriptive studies have shown that, in adults as well as in children, fatigue seldom occurs by itself and that it more commonly clusters with sleep disturbance, emotional distress (e.g., depression, anxiety), or pain.[7, 60-63] 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 Stephens[64] documented depression in 33% of 987 lung cancer patients and found that fatigue was an independent predictor of depression in this group. Newell and colleagues[65] found fatigue was the most commonly experienced and debilitating physical symptom for 201 oncology patients; about 25% of these patients also experienced depression. In 457 patients with Hodgkin's disease, Loge and colleagues[66] 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 Smets[67] 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[68] and may range from hypersomnia to insomnia.[69, 70] Sleep disturbances are prevalent in 30% to75% of patients with cancer.[71] Several studies have shown that fatigued cancer patients in active treatment spend increased time resting and sleeping but that their pattern of sleep is often severely disrupted.[72, 73] When sleep disturbances are present, the patient should be assessed for depression because this is a common manifestation.[74] Patients may benefit from evaluation and education to improve sleep quality. In addition, sleep apnea can develop as a consequence of cancer treatment in the settings of surgery affecting the upper airway, changes in body composition, and alterations in hormone status (i.e., thyroid, estrogen, testosterone); therefore, obstructive sleep apnea should also be evaluated.

Studies have shown fatigue's association with anemia in cancer patients and its amelioration with erythropoietin. Patients should undergo a nutritional assessment to evaluate weight gain and loss,

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

Patients with moderate-to-severe fatigue should be queried about their functional status, 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.[75-77] However, before recommending an exercise program, the health care provider or exercise expert (e.g., physiatrist, physical therapist) should assess the conditioning level of the patient. It is often difficult to convince fatigued patients that exercise will improve their symptoms. It may be best to begin with discussions and low levels of activities, which gradually increase over a period of time. This is especially important if the patient is significantly deconditioned.

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

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

Non-cancer comorbidities may contribute substantially to symptoms of fatigue in the cancer patient. The status of comorbidities must be reviewed in conjunction with the present treatment management strategies. If the comorbidity is not optimally managed, it may be necessary to further evaluate and improve that management. For example, if a patient has underlying congestive heart failure secondary to anthracycline cardiomyopathy and is experiencing symptoms of dyspnea and angina, fatigue may often be improved by stabilizing the condition and decreasing the frequency of episodes of congestive heart failure. This may entail introduction of new medications, titration of current medications, or both. It may also involve an invasive interventional assessment of the patient's cardiac status. Comorbidities that need review and assessment include cardiac, pulmonary, renal, gastrointestinal, hepatic, neurologic, and endocrine dysfunction (including hot flashes, hypothyroidism, hypogonadism or adrenal insufficiency), as well as infection. Canaris and colleagues[78] noted the high incidence of thyroid dysfunction in normal individuals and in

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patients receiving thyroid medications; they suggested that more attention must be given to thyroid problems in both the general and cancer-patient populations. Development of hypothyroidism occurs after radiation therapy for Hodgkin's disease and other non-Hodgkin's lymphomas, head and neck cancers, and breast cancer, as well as after total body irradiation in bone marrow transplantation. Also, hypothyroidism has been noted in patients who have received interferon alfa-2b, aldesleukin (interleukin-2), L-asparaginase, and a multitude of combination chemotherapies. Hypogonadism is commonly seen in patients with advanced cancer. A recent cross-sectional pilot study by Strasser and colleagues[79] explored whether hypogonadism contributes to fatigue in men with advanced cancer. The results of the study indicate that abnormally low levels of testosterone are associated with fatigue. However, additional research with larger samples is needed to clarify the incidence of hypogonadism and its association with specific malignancies and neurotoxic chemotherapy.

Patient Clinical Status

After the primary fatigue evaluation is completed, the patient's clinical status (active cancer treatment, post-treatment 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.[80]

If any of the treatable contributing factors discussed above is identified during the primary evaluation phase, it should be treated as an initial approach to fatigue management. NCCN clinical practice guidelines are also available to guide the treatment of pain (see NCCN Adult Cancer Pain Guidelines), distress (see NCCN Distress Management Guidelines), and anemia (see NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines). Treatment of sleep disturbances, nutritional alterations, and physical deconditioning are discussed under "Nonpharmacologic Interventions" for patients on active treatment, post-treatment, or at 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 patients[52] but is particularly essential for patients beginning potentially fatigue-inducing treatments (such as radiation, chemotherapy, or biotherapy), before the onset of fatigue. 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.

General Strategies for Management of Fatigue

In addition to education, the panel recommends counseling for patients about general strategies (energy conservation and distraction) useful in coping with fatigue. Energy conservation is defined as the deliberately planned management of one's personal energy resources to prevent their depletion. It encompasses a common sense approach that helps patients to prioritize and pace activities, and to delegate less essential activities.[81] Patients should be counseled that it is permissible to postpone all nonessential activities if they are experiencing moderate-to-severe fatigue. One useful plan is to maintain a daily and weekly diary that allows the patient to ascertain peak energy periods.[82] The fatigued patient can then plan activities accordingly within a structured routine. A multisite clinical trial of energy conservation in 296 patients receiving cancer treatment by Barsevick and colleagues[83] 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,

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socializing) are helpful in decreasing fatigue, although the mechanism is unknown.[84, 85] Although day-time naps are often helpful in replenishing energy, it is advisable to limit these to under an hour so as to avoid disturbing night-time sleep. Patients may also use labor-saving techniques such as wearing a bath robe instead of drying off with a towel or devices such as a walker, grabbing tools, and a bedside commode.

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.[86]

Activity Enhancement

In cancer patients, the adverse effects of therapy results in decreased activity and physical performance. Although there are a number of factors that contribute to the decline in functionality, fatigue is one of the major contributors. Mustian and colleagues[87] conducted a study in patients receiving systemic chemotherapy to determine the impact of fatigue on physical function as measured by the Activities of Daily Living Index (ADLs). 753 patients were enrolled (64% female). 85.4% and 79.3 % of patients reported fatigue after the first and second cycles of chemotherapy respectively. The mean severity of fatigue was 5.0 for the first cycle and 4.7 for the second cycle (scale 0-10, 10 = severe fatigue). Cancer-related fatigue interfered with all ADLs in the majority of patients. Interference was moderate, and was noted to be higher in women, non-whites and patients with metastatic disease.

A large number of small- to moderate-sized studies have been performed to both evaluate the feasibility of interventions to increase physical activity during and after therapy, and to explore the impact of increased activity upon cancer-related fatigue, quality of life, treatment-related side effects, and other end points. A thorough review of the impact of physical activity on these varied outcomes is beyond the scope of this manuscript. However, many of these studies have specifically evaluated the effect of increased activity upon cancer-related fatigue, and several meta-analyses have been conducted over the past five years to provide a comprehensive evaluation of the impact of increased activity upon cancer-related fatigue.

The two most recent analyses provide a clear picture of the current status of this area of investigation. Kangas and colleagues[88] reported the results of 19 articles that reported the effectiveness of physical exercise on fatigue-related outcomes. 17 studies were randomized controlled trials (RCT) of which 17 trials reported fatigue outcome and 10 reported vigor/vitality outcomes. None of the trials required that patients have a specified a level of fatigue at the time of study entry. 35% of studies demonstrated an improvement in fatigue and 30% demonstrated an improvement in vigor/vitality. For fatigue, the weighted pooled mean effect size was -0.42 (95% CI, -0.599 to -0.231) and for vigor/vitality -0.69 (95% CI, 0.43 to 0.949). Thus, the effect size for fatigue was felt to be “on the edge of moderate” and clinically significant, while the effect size for vigor/vitality was moderate to large. Of interest, no significant difference in effect size was noted between studies using different fatigue outcome measures. Exercise interventions had a stronger effect when administered during therapy as opposed to after therapy was completed. Overall, patients with breast cancer derived greater benefit than those with other malignancies. A 2008 Cochrane analysis[89] reported the results of 28

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RCTs that investigated the effect of exercise on cancer-related fatigue;. 19 studies included patients with a specific cancer diagnosis while 9 included various cancers. The majority of cancer specific trials investigated breast cancer patients (n=16); 13 studies investigated home-based or unsupervised exercise programs and 16 investigated supervised, institutional programs. Interventions ranged from three to 32 weeks with an average of 12 weeks. 18 studies reported outcome measures beyond the endpoint of the intervention. Overall, exercise was more effective in relieving fatigue than the control intervention (SMD -0.23; 95% CI, -0.33 to -0.13). The exercise intervention was statistically more effective than the control arm both during (SMD -0.18, 95%CI-0.32 to -0.05) and after therapy (SMD -0.37; 95% CI, -0.49 to -0.23). An improvement in fatigue was noted in patients with breast cancer and prostate cancer. No improvement was noted in the single study for colorectal cancer or multiple myeloma.

It is reasonable to encourage all patients to engage in a moderate level of physical activity during and after cancer treatment. Currently there is not sufficient evidence to recommend a specific amount of physical activity for cancer populations. The US Surgeon General recommends 30 minutes of moderate activity most days of the week for all populations.[90] Some observational and interventional studies have suggested that cancer patients who engage in at least 3-5 hours of moderate activity per week may experience better outcomes and have fewer side effects of therapy, including fatigue.[75, 76, 91-95]

Some patients may require referrals to exercise specialists such as physical therapy, physical medicine or rehabilitation for assessment and an exercise prescription. The American College of Sports Medicine has recently developed a certification program for cancer rehabilitation that is available for exercise professionals who specialize in care of cancer populations. They also convened a roundtable and published specific guidelines for physical activity testing and prescription in cancer patients in the resulting report.[96]

Specific issues that should trigger a referral for physical therapy:

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

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

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

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

Physically-based Therapies

Therapies performed on the patient by a therapist or a lay person includes acupuncture and massage therapy. Positive effects of acupuncture on fatigue have been reported in small samples and need to be confirmed by conducting randomized controlled trials (RCT).[97] These small trials were conducted during active non-palliative radiation

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therapy [98, 99] and post-chemotherapy treatment;[100, 101] one RCT (n=230)[102] and one retrospective review (n=1290)[103] 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.[104] 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), Psycho-educational Therapies/Educational Therapies, and Supportive Expressive therapies. These groups were titled after reviewing three recent meta-analyses of the effects of these interventions on CRF.[88, 105, 106] Of note, the categories in which interventions have been grouped are different in each of the meta-analyses and compared to the work reported by the Oncology Nursing Society (ONS) Putting Evidence into Practice (PEP).[107] These studies can be categorized based on their primary outcome parameter: fatigue or other. In many of these studies, fatigue was a secondary endpoint measured by a single item or a subscale of an instrument designed to measure emotional distress, quality of life or general symptom burden. Furthermore in many of these studies, fatigue was not an eligibility requirement and in those studies that were directed specifically of fatigue, no severity cut off score was used. Thus, patients enrolled in these studies may or may not have had significant levels of fatigue, thereby limiting the potential impact of the intervention.

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

In addition to the issues noted above, outcome parameters used by investigators are highly variable. All currently published studies use patient's self-report measurement exclusively as the outcome measure. Most studies do not reflect the impact of fatigue on function, report fatigue-related behaviors, or utilize objective measures of functionality (example: the six-minute walk).

Substantial data in literature provide high level evidence during active treatment for CBT/BT [108-113] and for Psycho-educational Therapies/Educational Therapies [41, 86, 105, 106, 114-123]. Supportive expressive therapies, including face or online support groups, counselling, and journal writing, may serve as an emotional outlet as well as an avenue to receive support and encouragement. There is less robust evidence for supportive expressive therapies during active treatment and therefore it was rated as a category 2A recommendation.[124]

Nutrition Consultation

Many cancer patients have changes in nutritional status. Because cancer and treatment can interfere with dietary intake, nutrition

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consultation may be helpful in managing the nutritional deficiencies that result from anorexia, diarrhea, nausea, and vomiting.[125] Adequate hydration and electrolyte balance are also essential in preventing and treating fatigue.

Sleep Therapy

Cancer patients report significant disturbances in sleep patterns that could cause or exacerbate fatigue. Both insomnia and hypersomnia are common, with disrupted sleep as a common denominator.[126] Non-pharmacological interventions to improve sleep quality have been organized into four general types of therapies that include cognitive-behavioral, complementary, psycho-education/information and exercise therapies.[127] These interventions are designed to optimize sleep quality and some have also been shown to decrease fatigue.[107]

There are numerous types of CBT; the most frequently used include stimulus control, sleep restriction, and sleep hygiene. Stimulus control includes going to bed when sleepy, going to bed at approximately 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.[128] Sleep restriction includes avoiding long or late afternoon naps and limiting total time in bed.[129] Sleep hygiene includes techniques to promote a good night's sleep and optimal functioning the next day, such as avoiding caffeine after noon and establishing an environment that is conducive to sleep (e.g., dark, quiet, and comfortable). These strategies were employed in a pilot study with women during adjuvant breast cancer chemotherapy. Sleep/wake patterns remained consistent with normal values except for increased number and length of nighttime awakenings.[130] 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.

A number of published studies[131-133] support the conclusion that cognitive-behavioral therapy interventions designed to optimize sleep quality in cancer patients may also improve fatigue. Two randomized clinical trials of patients in the survivorship phase after cancer treatment who reported chronic insomnia resulted in positive effects on both sleep and fatigue after 4-5 weekly behavioral therapy sessions.[134-136] Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.[131, 132] Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.[130, 133] The American Academy of Sleep Medicine (AASM) has recommended three specific therapies for chronic insomnia in healthy individuals: relaxation training, cognitive behavior therapy, and stimulus control therapy.[137] AASM has also published clinical guidelines for the management of chronic insomnia in adults.[138]

CBT therapies are often combined with complimentary therapies, such as breathing control, progressive muscle relaxation, and guided imagery techniques, to relax the individual. Complementary therapies such as massage therapy,[102, 103, 139] yoga,[140-142] muscle relaxation,[109, 143] and stress reduction based on mindfulness[108, 144-146] have been evaluated in pilot studies; the preliminary data suggest that they may be effective in reducing fatigue in cancer patients. Cohen and Fried[147] compared a cognitive behavioral and a relaxation and guided imagery interventions to 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.

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Pharmacologic Interventions

Though a wide variety of prescription pharmacologic options are available to improve sleep quality, there is little empirical evidence for the use of these agents in patients with cancer and their use may be associated with adverse side effect profiles. Clinicians need to be aware of a recent Food and Drug Administration (FDA) warning regarding potential risks of sedative-hypnotics drugs that include severe allergic reactions and complex sleep-related behaviors, including sleep-driving.[148] A table summarizing the medications commonly used to promote sleep is provided at the National Cancer Institute PDQ web-site.[149] Prescribing considerations with these classes of agents include increased likelihood of problems with daytime sleepiness, fatigue, withdrawal symptoms, dependency, rebound insomnia, problems with sleep maintenance, memory problems, anticholinergic symptoms, orthostasis, and the potential for drug-drug interactions involving cytochrome p450 isoenzyme system. Increased public and professional education regarding sleep, sleep disturbances, and daytime consequences of sleep loss are recommended.

There is some evidence for pharmacologic therapy as a fatigue treatment, although a significant placebo response has been observed in randomized trials.[150] A recent meta-analysis of ten studies concluded that the treatment of anemia during chemotherapy with erythropoietin resulted in a reduction of fatigue (see the NCCN Cancer- and Chemotherapy- Induced Anemia Guidelines).[151] Studies on a selective serotonin reuptake inhibitor paroxetine showed no influence by this antidepressant on fatigue in patients receiving chemotherapy.[152, 153] Antidepressants are not recommended to lower fatigue. See the relevant NCCN Supportive Care Guidelines for details on the management of pain, emotional distress, and anemia. Treatment for nutritional deficit or imbalance and comorbidities may be optimized as indicated.

The psychostimulant methylphenidate has been evaluated for its effect on cancer-related fatigue with mixed results in patients undergoing cancer therapy. A pilot study found a benefit in fatigue scores in 12 patients with melanoma undergoing interferon compared to historical controls.[154] But a randomized, placebo-controlled trial of d-threo-methylphenidate to prevent fatigue during radiotherapy for brain tumors did not demonstrate efficacy for the drug in preventing fatigue.[155] Similarly, a randomized study on 57 women receiving adjuvant chemotherapy for breast cancer failed to show a difference between the active arm and placebo.[156] Most recently, Moraska et al[157] reported results of a phase III, double-blinded trial. One hundred and forty-eight patients, most of which were receiving chemotherapy, were randomized to methylphenidate (54 mg/d) or placebo for four weeks. No difference in fatigue score was observed between the groups; however, a subset analysis found a benefit with the psychostimulant in patients with severe fatigue and/or advanced disease (P=0.02). Analyzing five randomized trials of cancer patients on or off anti-neoplastic treatment, Minton and colleagues[158] attributed a significant benefit to psychostimulants in alleviating fatigue compared to placebo (Z= 2.83; P=0.005). Methylphenidate has side effects including headache and nausea that have been reported as minor.

The wakefulness-promoting non-amphetamine psychostimulant, modafinil, has been approved for use in narcolepsy. Data on cancer-related fatigue from a large randomized controlled trial are now available. Jean-Pierre and colleagues[159] randomized 867 patients undergoing chemotherapy to 200 mg of modafinil per day or placebo. Improvement in fatigue was observed in patients with severe fatigue, but not in those with mild or moderate fatigue. Toxicity was similar in the two arms.

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On reviewing the current literature, the NCCN panel included consideration of psychostimulants as a recommendation for patients undergoing active cancer treatment when other causes of fatigue have been excluded.

Interventions for Patients Post-Treatment

More than 11 million U.S. people now living have a history of cancer. Of the approximately 1,479,350 persons in the United States who will be diagnosed with cancer in 2009, 66% are expected to survive at least 5 years.[160] These improvements in survival have led to efforts to enhance symptom management, QOL, and overall functioning of individuals post-treatment. As previously mentioned, fatigue is an acute effect of cancer or treatment, but it can also be a long-term or late effect.[161, 162] Patients may continue to report unusual fatigue for months or years after treatment cessation.[13-16, 18-22] Researchers have suggested that such fatigue may be due to persistent activation of the immune system[14, 163] or to other factors, such as late effects of treatment on major organ systems.[163] However, there are few longitudinal studies examining fatigue in long-term disease-free survivors.

Incidence and prevalence rates for fatigue in this population range from 17% to 21% when strict ICD-10 diagnostic criteria are applied[164] and range from 33% to 53% when other criteria (such as a score of 4 or more on the 0 to 10 fatigue scale) are used.[165] In contrast to these findings, Canadian and U.S. ovarian cancer survivors (n = 100), who were diagnosed a mean of 7.2 years before the survey, reported equivalent energy levels when compared with the general population.[166] As a consequence, what constitutes valid incidence and prevalence rates in disease-free patients requires more study.

In general, most research reports to date are limited by their cross sectional designs,[26, 54, 162, 164, 167-169] lack of comparison groups,[26, 54, 169] heterogeneous samples,[164, 170] use of differing fatigue scales, small sample sizes,[163] varying baseline survivorship definitions (i.e., time since diagnosis versus time since treatment cessation), and different mean survivorship durations. These design issues make it difficult to reach conclusions about the effect of fatigue's prevalence, incidence, duration, associated risk factors, and QOL. Additionally, most fatigue studies of post-treatment disease-free patients have been conducted in Caucasian, English-speaking breast cancer,[14, 163, 167] and peripheral stem cell or bone marrow transplant patients[170, 171] with few exceptions.[18, 20, 22]

The cause of fatigue in post-treatment disease-free patients is unclear and probably multifactorial.[172] One cross-sectional comparative study investigated fatigue and physiologic biomarkers of immune system activation in 20 breast cancer survivors who were fatigued (a mean of 5 years since diagnosis) and in 20 non-fatigued survivors.[163] Fatigued survivors had significantly higher serum markers (interleukin-1 receptor antagonist [IL-1ra], soluble tumor necrosis factor type II [sTNF-RII], and neopterin) and lower cortisol levels when compared with non-fatigued survivors. Significantly higher numbers of circulating T lymphocytes that also correlated with elevated serum IL-1ra levels suggesting that persistent fatigue in survivors may be caused by a chronic inflammatory process involving the T-cell compartment.[14]

Other risk factors associated with fatigue in post-treatment disease-free patients include pretreatment fatigue, anxiety and depression levels,[173] physical level activities,[174, 175] coping methods and cancer-related stressors, comorbidities,[176] type of malignancy, prior treatment patterns, and treatment late effects. For example, in one Norwegian study, a small proportion of long-term disease-free cancer patients who had pre-existing coronary artery disease had 30% higher fatigue levels compared with controls. In another Norwegian study that investigated

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fatigue in Hodgkin's disease survivors in remission for more than 5 years, higher fatigue levels were documented in those who had pulmonary dysfunction.[165] In these survivors, the prevalence of chronic fatigue was 2 to 3 times higher than in survivors who did not have such impairment. No significant correlations in this study were found between fatigue and cardiac sequelae as measured by echocardiography, exercise testing, and chest radiography.[165] Prior treatment patterns may affect the survivor's fatigue. For example, in a study of 322 post-treatment disease-free breast cancer patients, the highest fatigue scores occurred in women who had received previous combination therapy versus other forms of treatment.[169] Women who had received radiation therapy had the lowest fatigue scores. Two studies testing the effects of physical activity interventions on fatigue in breast cancer survivors found that individualized, prescriptive exercise reduced fatigue. However, researchers emphasize it is critical that exercise be individualized to the survivors abilities to prevent exacerbation of cancer treatment toxicities.[174, 175]

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,[13, 16] most patients experience a gradual decrease in fatigue and return of energy to normal levels.[15, 166] 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. As in the case of active treatment, patients can benefit from general fatigue management strategies including energy conservation and distraction.

Nonpharmacologic Interventions

Specific interventions recommended to manage fatigue during active cancer treatment are also recommended for disease-free patients post-treatment,.[80] except 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.[177] However, if the patient is significantly deconditioned, weak, or have relevant late effects of treatment (such as cardiopulmonary limitations), referral to a physiatrist or a supervised rehabilitation program may be indicated. Exercise should be recommended with caution in patients who have fever or remain anemic, neutropenic, or thrombocytopenic after treatment. Of the nonpharmacologic approaches for managing cancer-related fatigue, exercise has the best evidence to support its effectiveness.[80, 178-185]

Psychosocial interventions

Psychosocial interventions, including CBT/BT, psycho-educational therapies/educational therapies, and supportive expressive therapies are category 1 recommendations.[114, 117, 172, 186-191] Additional details on these interventions are provided in the preceding pages in the section on psychosocial interventions for patients on active treatment.

Additional Nonpharmacological Approaches.

Nutritional consultation and CBT for sleep (category 1)[107, 127] may be helpful for fatigue management in patients post-treatment.

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Pharmacologic Interventions

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

Some evidence exists to support the use of psychostimulants following cancer therapy. A 54% response rate to methylphenidate has been reported in a phase II trial of 37 breast cancer patients in remission.[192] A randomized trial in 154 patients post-chemotherapy also found an improvement in fatigue symptoms in the active arm.[193] Modafinil also shows some promise for management of post-treatment fatigue in small trials. Morrow et al[194] conducted an open label study of modafinil for 51 breast cancer survivors with persistent fatigue. The dose was 200 mg per day for one month. Eighty-six percent reported reduction in fatigue. In a pilot study of 30 adults with previously treated brain tumors, modafinil was associated with improvement in fatigue by eight weeks.[195] Currently, the panel agrees that methylphenidate or modafinil may 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 this guideline, there are a few issues that are specific to this population. Factors that have a greater likelihood of association with fatigue at the end of life include anemia, medication adverse effects and polypharmacy, cognitive impairment, adverse effects of recent treatment, and malnutrition.[196] Evaluating and correcting these contributing factors could reduce fatigue severity.

It is likely that fatigue will increase substantially as the disease progresses; however, patterns of fatigue are variable. For some adults, fatigue may be characterized as constant and unrelenting; for others, it is unpredictable and may come on suddenly.[53, 197] At the end of life, most research has demonstrated that cancer patients experience fatigue in the context of multiple symptoms. In a study of 278 Swedish adults admitted to a palliative care unit, 100% reported fatigue; other symptoms included pain (83%), dyspnea (77%), and appetite loss (75%).[198] In a large sample of adults (N = 1000) receiving palliative care, Walsh and colleagues[199] noted that individuals with advanced cancer had multiple symptoms. Pain was the most prevalent (84% of patients), followed by fatigue (69%), weakness (66%), and lack of energy (61%). Walsh and Rybicki[200] cluster-analyzed 25 symptoms in 1000 consecutive admissions to a palliative care program and found seven symptom clusters. The fatigue cluster included easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, and taste changes. There is also the possibility, suggested by Given and colleagues,[39, 201] 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.[202]

Education and Counseling of Patient and Family

Individuals with advanced cancer and their caregivers need information about the management of symptoms, including fatigue,[203] with specific information related to the disease trajectory.[204, 205] 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.[197] Families need to be apprised of this problem so they can begin planning for it. In addition, fatigue is likely to have increasing

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effect on emotional well-being.[197, 202] 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.[202] In a case study of 15 adults with advanced disease, Krishnasamy found that fatigue resulted in substantial regret, sadness, and sense of loss due to the deterioration of one's health.[197] Mystakidou and colleagues[206] reported that patient desire for a hastened death was predicted by feeling sad, lack of appetite, pain, and fatigue.

Given the high prevalence of fatigue and other symptoms at the end of life, symptom management needs to be a major focus of care. Active commitment by the health care team to palliative care is critical when aggressive cancer therapy is given to those with a low likelihood of long-term survival.[202] Although there is no effective therapy for some causes of fatigue and other symptoms, treatment of those more amenable to therapy could help to relieve suffering.[80]

General Strategies for Management of Fatigue

Energy conservation is a self-care strategy for individuals with advanced cancer and their caregivers.[83] 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, eliminating non-essential activities, pacing oneself, taking extra rest periods, and planning high-energy activities at times of peak energy. It may also include the use of assistive devices and labor-saving techniques. Use of distraction may also be helpful. Patients receiving palliative care should be allowed to take day-time naps as long as they do not disturb night-time sleep. In a situation of escalating fatigue at the end of life, family members may wish to designate individuals to assume activities relinquished by the individual with cancer.

Nonpharmacologic Interventions

Although there is no category 1 evidence for 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 end of life and some individuals may choose to be active despite failing health. There is some evidence that exercise is beneficial to individuals with incurable cancer and short life expectancy. A group exercise program was pilot-tested in 63 Norwegian palliative care outpatients.[207] The program consisted of two 50-minute sessions twice a week for six weeks. A combination of strength building, standing balance, and aerobic exercise was used. The exercise participants had less physical fatigue and increased walking distance. There were no adverse effects of exercise although 46% of the 63 participants did not complete the program.

A small pilot study was conducted to evaluate an exercise program for nine individuals with advanced cancer enrolled in a home hospice program.[208] A physical therapist guided participants in the selection of several activities (such as walking, performing arm exercises with resistance, marching in place, and dancing). These were performed at different times throughout the day on a schedule devised jointly by the therapist and participant. All participants were able to increase their activity level over a 2-week period without increased fatigue. There was also a trend toward increased QOL and decreased anxiety. Although more research is needed, enhanced activity shows promise as a fatigue management strategy at the end of life. Psychosocial interventions, sleep therapy, family interaction, and nutritional therapy are also helpful to this population.

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

Based on a systematic review of 20 exercise studies relevant to fatigue and muscle wasting in multiple myeloma, Strong[209] summarized weight-bearing precautions for bone metastases as well as exercise guidelines for adults with solid tumors and hematological cancers; older cancer survivors; and individuals with cancer-related fatigue. They also recommended an exercise protocol for multiple myeloma that incorporated aerobic, resistance, and flexibility exercises.

Pharmacologic Interventions

There continues to be interest in using psychostimulant drugs for cancer patients at the end of life although studies have had mixed results. Methylphenidate has been shown to yield improvement in fatigue in advanced cancer patients in two pilot studies.[210, 211] However, a randomized trial of 112 patients reported an improvement in both the active and placebo arms; methylphenidate was not superior over placebo after one week of treatment.[212] Another psychostimulant, dexamphetamine (10 mg twice daily for 8 days), was evaluated for fatigue in patients with advanced cancer.[213] 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. A small case report of modafinil showed improvements in daytime wakefulness and normalization of the sleep-wake cycle in 2 adult patients under palliative care.[214] Overall, methylphenidate or modafinil may be considered with caution for selected terminal patients.

There is some evidence in literature that supported the effectiveness of corticosteroids (prednisone and its derivative, and dexamethasone) in providing short-term relief for fatigue and improving quality of life.[215-217] Given the toxicity associated with long-term use, consideration of steroids are restricted to the terminally ill. In addition, there has been interest in the progestational agent megestrol acetate to improve fatigue. [218, 219]A systematic review paper demonstrated the safety and efficacy of megestrol acetate in treating cachexia for cancer patients.[220] However, a systematic review and meta-analysis of four studies revealed no benefit of progestational steroids compared with placebo for treatment of cancer-related fatigue (Z=0.78; P=0.44).[151, 158]

Again, treatment for sleep dysfunction, nutritional deficit, or comorbidities may be optimized as required, and clinicians are advised to refer to the appropriate NCCN Supportive Care Guidelines for management of pain, distress, and anemia for end-of-life patients. It has been proposed that micronutrient deficiency could be responsible for increased fatigue in advanced cancer patients. Some chemotherapy agents such as ifosfamide and cisplatin cause a urinary loss of carnitine.[221] Carnitine is a micronutrient involved in the production of energy at the cellular level[222] that has been shown to be deficient in people who are chronically ill. Advanced cancer patients are at risk for carnitine deficiency because of decreased intake and increased renal loss. L-carnitine supplementation has been examined in three small open label studies examining safety and dose-finding.[223] 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.[224] The planned intent-to-treat analysis showed no significant improvement in serum l-carnitine levels or fatigue. However, an exploratory analysis with adherent patients only using data from both the double blind and open label

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phases of the study reversed the primary result. Based on the positive findings of the exploratory analysis, the investigators recommended a larger randomized clinical trial to examine efficacy of this agent.

Re-Evaluation Phase

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

Summary

The NCCN Cancer-Related Fatigue Guidelines propose a treatment algorithm in which patients are evaluated regularly for fatigue using a brief screening instrument and are treated as indicated by their fatigue level.

Management of fatigue begins with primary oncology team members who perform the initial screening and either provide basic education and counseling or expand the initial screening to a more focused evaluation for moderate or higher levels of fatigue. At this point, the patient is assessed for current disease and treatment status, a review of body systems, and an in-depth fatigue evaluation. In addition, the patient is assessed for the presence of treatable factors known to contribute to fatigue. If any of these conditions are present, they should be treated according to practice guidelines, with referral to other care professionals as appropriate, and the patient's fatigue should be re-evaluated regularly. If none of the factors are present or if the fatigue is unresolved, selection of appropriate fatigue management and treatment strategies is done within the context of the patient's clinical status: (i.e., receiving active cancer treatment, post-treatment, or at the end of life). Management of fatigue is cause-specific when conditions known to cause fatigue can be identified and treated. When specific causes of fatigue cannot be identified and corrected, nonpharmacologic and pharmacologic treatment of the fatigue should still be done.

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

Effective management of cancer-related fatigue involves an informed and supportive oncology care team that assesses patients' fatigue levels regularly, counsels and educates patients regarding strategies for coping with fatigue,[225] and uses institutional experts for referral of patients with unresolved fatigue.[45] The oncology care team must recognize the many patient-, provider-, and system-related behaviors that can impede effective fatigue management. Reducing barriers by use of available resources and evidence-based guidelines increases benefits to patients experiencing fatigue.[226, 227]

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Appendix

Fatigue Measurement

A resource to facilitate selection of instruments to measure fatigue

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

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

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

National Cancer Institute. Fatigue (PDQ) Health Professional Version (Accessed November 4, 2010). Available at: http://www.cancer.gov/cancertopics/pdq/supportivecare/fatigue/HealthProfessional
(Gives citation links to nine commonly used scales to measure fatigue.)

Oncology Nursing Society. Measuring oncology nursing-sensitive patient outcomes: Fatigue evidence-based summary (Accessed November 4, 2010). Available at: http://www.ons.org/Research/PEP/Topics/Fatigue
(Provides two detailed tables summarizing scale descriptions and psychometric properties for 13 scales.)

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

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

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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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12944066.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9253779.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11779663.

4. Dean GE, Spears L, Ferrell BR, et al. Fatigue in patients with cancer receiving interferon alpha. Cancer Pract 1995;3:164-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7599673.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10355210.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7954384.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10534963.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10382190.

9. Sitzia J, Huggins L. Side effects of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy for breast cancer. Cancer Pract 1998;6:13-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9460322.

10. Wagner LI, Cella D. Fatigue and cancer: causes, prevalence and treatment approaches. Br J Cancer 2004;91:822-828. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15238987.

11. Henry DH, Viswanathan HN, Elkin EP, et al. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. Support Care Cancer 2008;16:791-801. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18204940.

12. Hofman M, Ryan JL, Figueroa-Moseley CD, et al. Cancer-related fatigue: the scale of the problem. Oncologist 2007;12 Suppl 1:4-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17573451.

13. Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. J Behav Med 1998;21:1-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9547419.

14. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12902446.

15. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10673515.

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16. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9586880.

17. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16270109.

18. Fossa SD, Dahl AA, Loge JH. Fatigue, anxiety, and depression in long-term survivors of testicular cancer. J Clin Oncol 2003;21:1249-1254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12663711.

19. Haghighat S, Akbari ME, Holakouei K, et al. Factors predicting fatigue in breast cancer patients. Support Care Cancer 2003;11:533-538. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12730728.

20. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14522376.

21. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12056710.

22. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14654263.

23. Olson K. A new way of thinking about fatigue: a reconceptualization. Oncol Nurs Forum 2007;34:93-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17562637.

24. Olson K, Krawchuk A, Quddusi T. Fatigue in individuals with advanced cancer in active treatment and palliative settings. Cancer Nurs 2007;30:E1-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17666968.

25. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12849624.

26. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9253778.

27. 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. Available at: http://www.ons.org/Publications/ONF.

28. Janda M, Gerstner N, Obermair A, et al. Quality of life changes during conformal radiation therapy for prostate carcinoma. Cancer 2000;89:1322-1328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11002229.

29. Morrow GR, Andrews PL, Hickok JT, et al. Fatigue associated with cancer and its treatment. Support Care Cancer 2002;10:389-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12136222.

30. Bower JE. Cancer-related fatigue: links with inflammation in cancer patients and survivors. Brain Behav Immun 2007;21:863-871. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17543499.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17178209.

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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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18281672.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19381692.

34. al-Majid S, McCarthy DO. Cancer-induced fatigue and skeletal muscle wasting: the role of exercise. Biol Res Nurs 2001;2:186-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11547540.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17500504.

36. Mock V, Atkinson A, Barsevick A, et al. NCCN Practice Guidelines for Cancer-Related Fatigue. Oncology (Williston Park) 2000;14:151-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11195408.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10188894.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9117043.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10800975.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10452204.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12096292.

42. Mock V, McCorkle R, Ropka ME. Fatigue and physical functioning during breast cancer treatment. Oncol Nurs Forum 2002;29:338. Available at: http://www.ons.org/Publications/ONF.

43. Nail LM. Fatigue in patients with cancer. Oncol Nurs Forum 2002;29:537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11979285.

44. Malik UR, Makower DF, Wadler S. Interferon-mediated fatigue. Cancer 2001;92:1664-1668. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11598884.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11598891.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10091805.

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.

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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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17629669.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12691683.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11932914.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10028520.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11683307.

54. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000;5:353-360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11040270.

55. Holley S. Cancer-related fatigue. Suffering a different fatigue. Cancer Pract 2000;8:87-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11898182.

56. Portenoy RK, Itri LM. Cancer-related fatigue: guidelines for evaluation and management. Oncologist 1999;4:1-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10337366.

57. Given BA, Given CW, Kozachik S. Family support in advanced cancer. CA Cancer J Clin 2001;51:213-231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11577488.

58. Luciani A, Jacobsen PB, Extermann M, et al. Fatigue and functional dependence in older cancer patients. Am J Clin Oncol 2008;31:424-430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18838877.

59. van Ryn M, Sanders S, Kahn K, et al. Objective burden, resources, and other stressors among informal cancer caregivers: a hidden quality issue? Psychooncology 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20201115.

60. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11806675.

61. Berger AM, Walker SN. An explanatory model of fatigue in women receiving adjuvant breast cancer chemotherapy. Nurs Res 2001;50:42-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19785244.

62. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11338755.

63. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17573303.

64. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin

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Oncol 2000;18:893-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10673533.

65. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10476109.

66. Loge JH, Abrahamsen AF, Ekeberg, Kaasa S. Fatigue and psychiatric morbidity among Hodgkin's disease survivors. J Pain Symptom Manage 2000;19:91-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10699536.

67. Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? Support Care Cancer 1998;6:101-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9540167.

68. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol 2001;19:895-908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11157043.

69. Berger AM, Mitchell SA. Modifying cancer-related fatigue by optimizing sleep quality. J Natl Compr Canc Netw 2008;6:3-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18267055.

70. Roscoe JA, Kaufman ME, Matteson-Rusby SE, et al. Cancer-related fatigue and sleep disorders. Oncologist 2007;12 Suppl 1:35-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17573454.

71. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16270104.

72. Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. Oncol Nurs Forum 1998;25:51-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9460773.

73. Berger AM, Farr L. The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. Oncol Nurs Forum 1999;26:1663-1671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10573683.

74. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17166646.

75. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10326708.

76. Mock V, Frangakis C, Davidson NE, et al. Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. Psychooncology 2005;14:464-477. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15484202.

77. Schwartz AL. Daily fatigue patterns and effect of exercise in women with breast cancer. Cancer Pract 2000;8:16-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10732535.

78. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10695693.

79. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17103445.

Printed by Jorge Garc?a on 12/30/2010 8:50:59 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

80. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17441401.

81. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12394560.

82. Richardson A, Ream E, Wilson-Barnett J. Fatigue in patients receiving chemotherapy: patterns of change. Cancer Nurs 1998;21:17-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9494227.

83. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15022300.

84. Graydon JE, Bubela N, Irvine D, Vincent L. Fatigue-reducing strategies used by patients receiving treatment for cancer. Cancer Nurs 1995;18:23-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7866973.

85. Richardson A, Ream EK. Self-care behaviours initiated by chemotherapy patients in response to fatigue. Int J Nurs Stud 1997;34:35-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9055119.

86. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17573456.

87. 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]. Presented at the American Society of Clinical Oncology Annual Meeting. Abstract 9500.

88. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18729569.

89. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev 2008:CD006145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18425939.

90. U.S. Department of Health & Human Services. News Release October 7, 2008. Available at: http://www.hhs.gov/news/press/2008pres/10/20081007a.html. Accessed October 11, 2010.

91. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12748973.

92. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12721239.

93. 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. Available at: http://onlinelibrary.wiley.com/doi/10.1002/cncr.22267/pdf.

94. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11323538.

95. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin

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Oncol 2003;21:1653-1659. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12721238.

96. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409-1426. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20559064.

97. Sood A, Barton DL, Bauer BA, Loprinzi CL. A critical review of complementary therapies for cancer-related fatigue. Integr Cancer Ther 2007;6:8-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17351022.

98. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19476729.

99. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19476739.

100. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18054724.

101. Vickers AJ, Straus DJ, Fearon B, Cassileth BR. Acupuncture for postchemotherapy fatigue: a phase II study. J Clin Oncol 2004;22:1731-1735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15117996.

102. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14713325.

103. Cassileth BR, Vickers AJ. Massage therapy for symptom control: outcome study at a major cancer center. J Pain Symptom Manage 2004;28:244-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15336336.

104. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12118028.

105. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. Cochrane Database Syst Rev 2009:CD006953. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19160308.

106. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18020836.

107. Eaton LH, Tipton JM, eds. Oncology Nursing Society Putting Evidence into Practice: Improving oncology patient outcomes. Pittsburgh, PA: Oncology Nursing Society; 2009.

108. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16262547.

109. Decker TW, Cline-Elsen J, Gallagher M. Relaxation therapy as an adjunct in radiation oncology. J Clin Psychol 1992;48:388-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1602030.

110. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12065562.

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111. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17661342.

112. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11747061.

113. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19450037.

114. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15718325.

115. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10939175.

116. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12136225.

117. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16041464.

118. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16488348.

119. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16135471.

120. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15227717.

121. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16618589.

122. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16106331.

123. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19581225.

124. Forester B, Kornfeld DS, Fleiss JL. Psychotherapy during radiotherapy: effects on emotional and physical distress. Am J Psychiatry 1985;142:22-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3966583.

125. Brown JK. A systematic review of the evidence on symptom management of cancer-related anorexia and cachexia. Oncol Nurs

Printed by Jorge Garc?a on 12/30/2010 8:50:59 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Forum 2002;29:517-532. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11979284.

126. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10573681.

127. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17193942.

128. Bootzin RR, Epstein D, Wood J. Stimulus control instructions. In: Hauri P, ed. Case studies in insomnia. New York, NY: Plenum Press; 1991:19-28.

129. Morin C, Espie C. Insomnia: A clinical guide to assessment and treatment. New York: Kluwer Academic; 2003.

130. Berger AM, VonEssen S, Khun BR, et al. Feasibilty of a sleep intervention during adjuvant breast cancer chemotherapy. Oncol Nurs Forum 2002;29:1431-1441. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12432414.

131. Davidson JR, Waisberg JL, Brundage MD, MacLean AW. Nonpharmacologic group treatment of insomnia: a preliminary study with cancer survivors. Psychooncology 2001;10:389-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11536417.

132. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12602439.

133. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: Sleep and psychological effects. J Clin Oncol 2005;23:6083-6096. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16135475.

134. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18302607.

135. Epstein DR, Dirksen SR. Randomized trial of a cognitive-behavioral intervention for insomnia in breast cancer survivors. Oncol Nurs Forum 2007;34:E51-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17878117.

136. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18591549.

137. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17162987.

138. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18853708.

139. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10517036.

140. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15139072.

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141. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15656848.

142. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15681986.

143. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6358270.

144. Carlson LE, Speca 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12883107.

145. Carlson LE, Speca 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14749092.

146. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12505559.

147. Cohen M, Fried G. Comparing Relaxation Training and Cognitive-Behavioral Group Therapy for Women With Breast Cancer. Research on Social Work Practice 2007;17:313-323. Available at: http://rsw.sagepub.com/content/17/3/313.abstract.

148. Food and Drug Administration. FDA News (March 14, 2007). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108868.htm. Accessed October 11, 2010.

149. National Cancer Institute. Sleep Disorders PDQ (Health Professional Version). 2010. Available at: http://www.nci.nih.gov/cancertopics/pdq/supportivecare/sleepdisorders/HealthProfessional. Accessed October 11, 2010.

150. de la Cruz M, Hui D, Parsons HA, Bruera E. Placebo and nocebo effects in randomized double-blind clinical trials of agents for the therapy for fatigue in patients with advanced cancer. Cancer 2010;116:766-774. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19918921.

151. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18695134.

152. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14673053.

153. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15754122.

154. Schwartz AL, Thompson JA, Masood N. Interferon-induced fatigue in patients with melanoma: a pilot study of exercise and methylphenidate. Oncol Nurs Forum 2002;29:E85-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12183762.

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155. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17869448.

156. Mar Fan HG, Clemons M, Xu W, et al. A randomised, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. Support Care Cancer 2008;16:577-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17972110.

157. Moraska AR, Sood A, Dakhil SR, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05C7 trial. J Clin Oncol 2010;28:3673-3679. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20625123.

158. Minton O, Richardson A, Sharpe M, et al. Drug therapy for the management of cancer-related fatigue. Cochrane Database Syst Rev 2010;7:CD006704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20614448.

159. Jean-Pierre P, Morrow GR, Roscoe JA, et al. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program Research base study. Cancer 2010;116:3513-3520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564068.

160. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474385.

161. Jacobsen PB, Stein K. Is Fatigue a Long-term Side Effect of Breast Cancer Treatment? Cancer Control 1999;6:256-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10758555.

162. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10908825.

163. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002;64:604-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12140350.

164. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11454886.

165. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11432890.

166. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11733968.

167. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12069869.

168. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11038033.

169. Woo B, Dibble SL, Piper BF, et al. Differences in fatigue by treatment methods in women with breast cancer. Oncol Nurs Forum