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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer-Related Fatigue

Version 2.2018 — February 20, 2018

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ϐ Internal medicine	τ Orthopedics
Ϙ Urology	ξ Bone marrow transplantation
‡ Hematology/Hematology oncology	£ Supportive care including palliative, pain management, pastoral care, and oncology social work
θ Psychiatry, psychology, including health behavior	* Discussion Section Writing Committee



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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 indicated.

See [NCCN Categories of Evidence and Consensus](#).

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NCCN Guidelines Version 2.2018 Updates

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Updates in Version 2.2018 of the NCCN Guidelines for Cancer-Related Fatigue from Version 1.2018 include:

MS-1

- The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2018 of the NCCN Guidelines for Cancer-Related Fatigue from Version 2.2017 include:

FT-2

Standards of Care for Cancer-Related Fatigue in Children/Adolescents and Adults

- 7th bullet has been deleted: "Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner."
- 8th bullet has been modified: "Implementation of guidelines for fatigue *evaluation* and management is best accomplished by interdisciplinary teams who are able to tailor interventions to the needs of the individual patient. Consider referral to an appropriate specialist or supportive care provider (eg, survivorship, palliative care, integrative oncology, psychology, psychiatry, ~~and~~ physical therapy)."

FT-3

Screening

- Top pathway has been modified: "Education, counseling, and general strategies for management of fatigue *with an emphasis on continued surveillance*"

Footnotes

- "e" has been modified: See "General Strategies for Management of Fatigue" and "Patient/Family Education and Counseling" on FT-5.

FT-4

Assessment of Treatable Contributing Factors:

- "*Vitamin status*" was added to "Nutritional deficits/imbalance"
- The column titled, "Patient Clinical Status" has been deleted. The reader is now directed to "General Strategies for Management of Fatigue."

FT-5

General Strategies for Management of Fatigue and Patient/Family Education and Counseling

- This page now contains content from the former FT-6, FT-7 and FT-8.

Post-Treatment

- Post-Treatment, 2nd bullet has been deleted: "Monitor fatigue levels"

FT-6

Nonpharmacologic

- 3rd sub-bullet has been modified: "Consider initiation and/or *encourage maintenance of* an exercise program, as appropriate per health care provider, *consisting of* both endurance (walking, jogging, or swimming) and resistance (~~light weights~~) *training exercises*" (Also for *FT-7*).



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.

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



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Cancer-Related Fatigue

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

- **Fatigue is rarely an isolated symptom and most commonly occurs with other symptoms, such as pain, emotional 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 using age-appropriate measures 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 and that fatigue can persist following treatment.**
- **Implementation of guidelines for fatigue evaluation and management is best accomplished by interdisciplinary teams who are able to tailor interventions to the needs of the individual patient. Consider referral to an appropriate specialist or supportive care provider (eg, survivorship, palliative care, integrative oncology, psychology, psychiatry, physical therapy).**
- **Educational and training programs should be implemented to ensure that health care professionals have knowledge and skills in the assessment and management of fatigue.**
- **Cancer-related fatigue should be included in clinical health outcome studies as an independent variable and potential moderator of outcome.**
- **Quality of fatigue management should be included in institutional continuous quality improvement projects.**
- **Medical care contracts should include reimbursement for the management of fatigue.**
- **Disability insurance should include coverage for the continuing effects of fatigue.**
- **Consider referral to rehabilitation as indicated: physical therapy, occupational therapy, and physical medicine from diagnosis to end of life.**

Note: All recommendations are category 2A unless otherwise indicated.

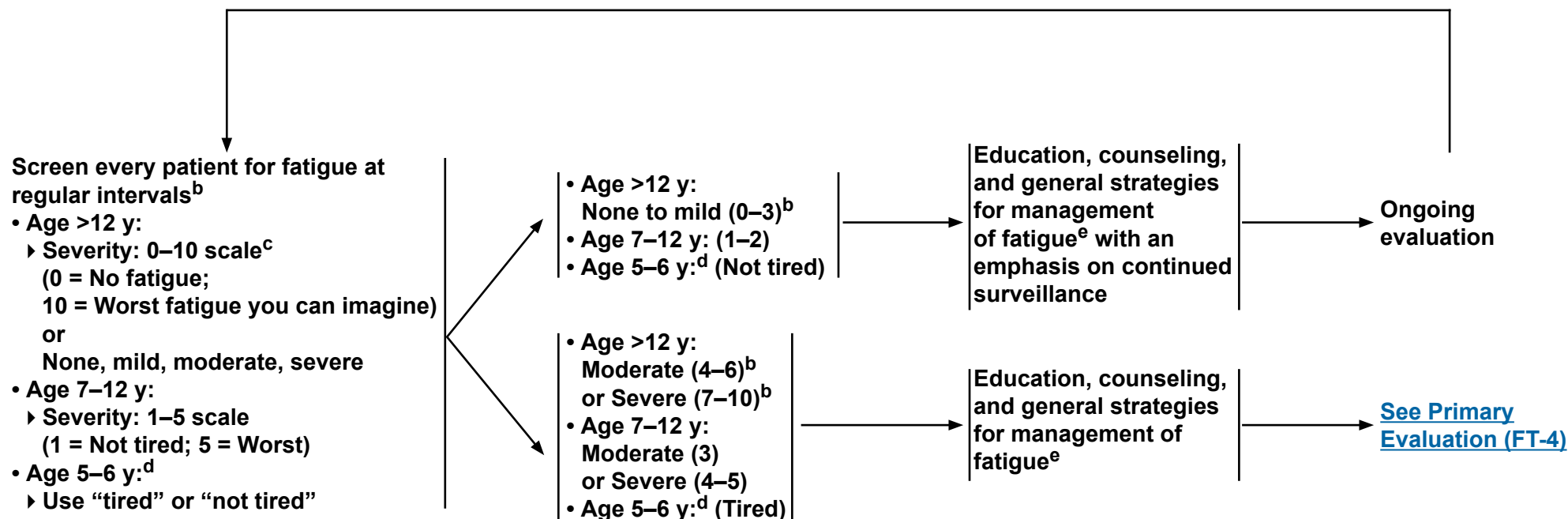
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Cancer-Related Fatigue

SCREENING^a



^aSee Discussion Appendix for screening resources ([MS-24](#)).

^bRecommended screen and re-evaluation: “How would you rate your fatigue on a scale of 0–10 over the past 7 days?”

^cButt Z, Wagner LI, Beaumont JL, et al. Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. J Pain Symptom Manage 2008;35(1):20-30.

^dFatigue scale for children is simplified: Use “tired” or “not tired” as screen for young children (age <6 or 7 y).

^eSee “General Strategies for Management of Fatigue” and “Patient/Family Education and Counseling” on [FT-5](#).

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Cancer-Related Fatigue

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

Focused History

- Disease status and treatment
 - Consider recurrence and/or progression
 - Prescription medications/OTCs and supplements
- Medications/side effects/drug interactions
 - [See NCCN Guidelines for Older Adult Oncology \(OAO-H\)](#)
- 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
- Economic status and resources for obtaining tangible support

Assessment of Treatable Contributing Factors

- Pain
- Emotional distress
 - Depression
 - Anxiety
- Anemia
- Sleep disturbance/poor sleep hygiene (eg, insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome)
- Nutritional deficits/imbalance
 - Vitamin status
 - Weight/caloric intake changes
 - Fluid electrolyte imbalance: sodium, potassium, calcium, magnesium
- Decreased functional status
 - Physical activity level
 - Deconditioning
- Comorbidities/Cancer treatment sequelae
 - Alcohol/substance abuse
 - Cardiac dysfunction
 - Endocrine dysfunction (eg, hot flashes, hypothyroidism, hypogonadism, adrenal insufficiency)
 - Gastrointestinal dysfunction
 - Hepatic dysfunction
 - Infection
 - Neurologic dysfunction
 - Pulmonary dysfunction
 - Renal dysfunction

Management
of concurrent
symptoms
and treatable
contributing
factors

Medications/side effects/
drug interactions

Pain
[See NCCN Guidelines
for Adult Cancer Pain](#)

Emotional distress
[See NCCN Guidelines for
Distress Management](#)

Anemia
[See NCCN Guidelines
for Cancer- and
Chemotherapy-Induced
Anemia](#)

Sleep disturbance/
poor sleep hygiene
[See NCCN Guidelines
for Survivorship](#)

Nutritional deficit/
imbalance

Decreased functional
status

Comorbidities

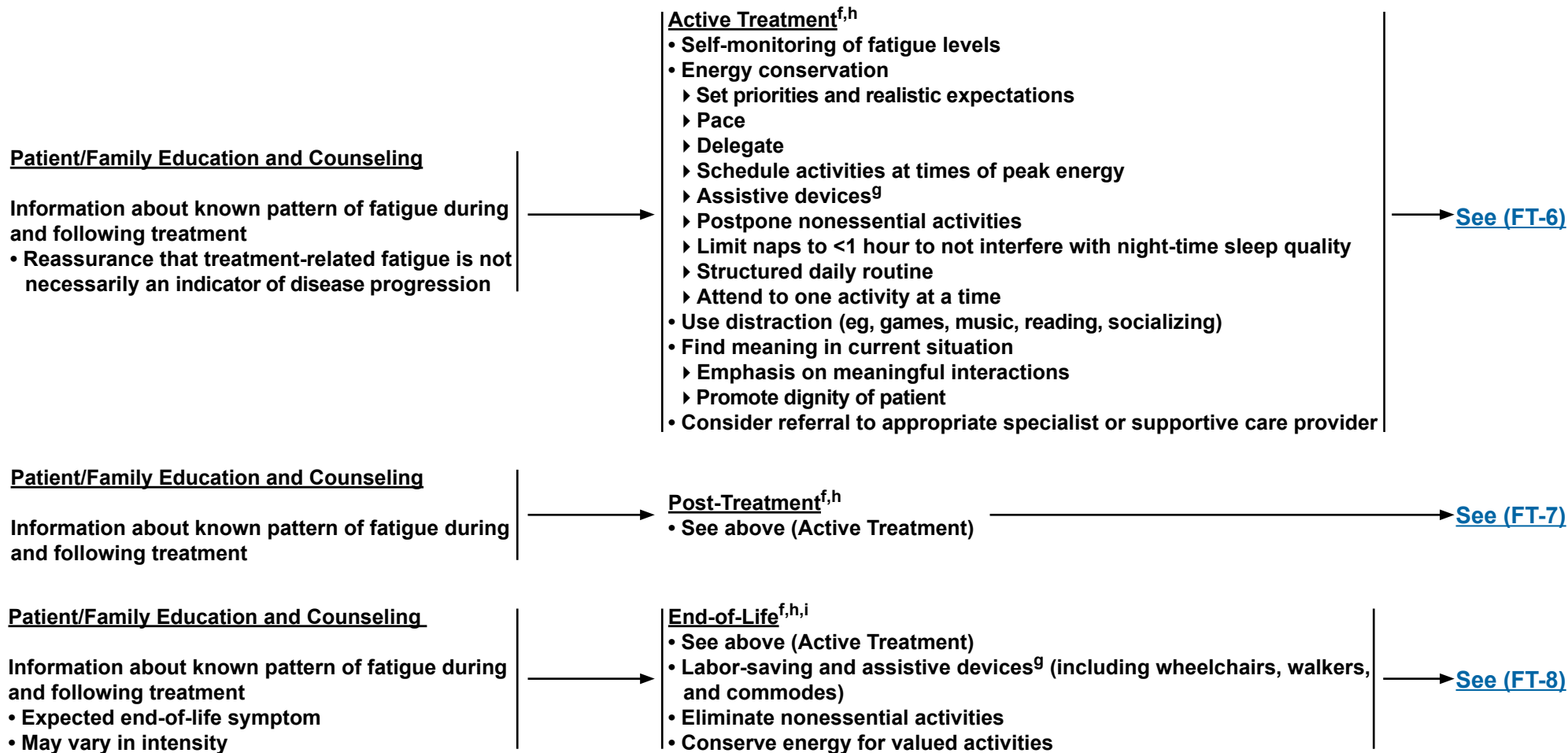
[See \(FT-5\) for General
Strategies for Management
of Fatigue](#)

Note: All recommendations are category 2A unless otherwise indicated.

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



GENERAL STRATEGIES FOR MANAGEMENT OF FATIGUE



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

^gExamples 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).

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

ⁱAlso [see NCCN Guidelines for Palliative Care](#).

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Cancer-Related Fatigue

INTERVENTIONS FOR PATIENTS ON ACTIVE TREATMENT^{f,h}

Nonpharmacologic

- **Physical activity (category 1)**
 - ▶ **Maintain optimal level of activity**
 - ▶ **Cautions in determining level of activity:**
 - ◊ Bone metastases
 - ◊ Thrombocytopenia
 - ◊ Anemia
 - ◊ Fever or active infection
 - ◊ Limitations secondary to metastases or other comorbid illnesses
 - ◊ Safety issues (ie, assessment of risk of falls)
 - ▶ **Consider initiation and/or encourage maintenance of an exercise program, as appropriate per health care provider, consisting of both endurance (walking, jogging, or swimming) and resistance (weights) training.^j**
 - ▶ **Yoga (category 1)**
 - ▶ **Consider referral to rehabilitation: physical therapy, occupational therapy, and physical medicine**
- **Physically based therapies**
 - ▶ **Massage therapy (category 1)**
- **Psychosocial interventions**
 - ▶ **Cognitive behavioral therapy (CBT)^k/Behavioral therapy (BT) (category 1)^l**
 - ▶ **Psycho-educational therapies/Educational therapies (category 1)**
 - ▶ **Supportive expressive therapies^m**
- **Nutrition consultation**
- **CBT^k for sleep**
 - ▶ **Stimulus control/Sleep restriction/Sleep hygiene**
- **Bright white light therapyⁿ**

Repeat screening and evaluation
[See \(FT-3\) and \(FT-4\)](#)
[See \(FT-5\) for General Strategies for Management of Fatigue](#)

Pharmacologic

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

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

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

^j[See NCCN Guidelines for Survivorship \(SE-3\).](#)

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

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

^mSupportive expressive therapies (eg, support groups, counseling, journal writing) facilitate expression

of emotion and foster support from one or more people.

ⁿBright white light therapy of 10,000 lux is most frequently self-administered in the early morning for 30–90 minutes. Timing needs to be adjusted for those who sleep during the day.

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

Note: All recommendations are category 2A unless otherwise indicated.

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



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Cancer-Related Fatigue

INTERVENTIONS FOR PATIENTS POST-TREATMENT^{f,h}

Nonpharmacologic

- **Physical activity (category 1)**
 - Maintain optimal level of activity
 - Consider initiation and/or encourage maintenance of an exercise program, as appropriate per health care provider, consisting of both endurance (walking, jogging, or swimming) and resistance (weights) training^j
 - Cautions in determining level of activity:
 - ◊ Late effects of treatment (eg, cardiomyopathy)
 - ◊ Safety issues (ie, assessment of risk of falls)
 - Yoga (category 1)
- **Psychosocial interventions (category 1)**
 - CBT^j/BT (category 1)^l
 - Mindfulness-based stress reduction (category 1)
 - Psycho-educational therapies/Educational therapies (category 1)
 - Supportive expressive therapies (category 1)^m
- **Nutrition consultation**
- **CBT^k for sleep (category 1)**
 - Stimulus control
 - Sleep restriction
 - Sleep hygiene

Pharmacologic^p

- **Consider psychostimulants^o (methylphenidate) after ruling out other causes of fatigue**
- **Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines ([See NCCN Guidelines for Adult Cancer Pain, Distress Management, and Cancer- and Chemotherapy-Induced Anemia](#))**
- **Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities**

Repeat screening and evaluation
[See \(FT-3\) and \(FT-4\)](#)
[See \(FT-5\) for General Strategies for Management of Fatigue](#)

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

^hInterventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources. Consider referral to appropriate specialist or supportive care provider.

^j[See NCCN Guidelines for Survivorship \(SE-3\).](#)

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

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

^mSupportive expressive therapies (eg, support groups, counseling, journal writing) facilitate expression of emotion and foster support from one or more people.

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

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

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INTERVENTIONS FOR PATIENTS AT THE END OF LIFE^{f,h,i}

Nonpharmacologic

- **Physical activity**
 - **Optimize level of activity with careful consideration of the following constraints:**
 - ◊ **Bone metastases**
 - ◊ **Thrombocytopenia**
 - ◊ **Anemia**
 - ◊ **Fever or active infection**
 - ◊ **Limitations secondary to metastases or other comorbid illnesses**
 - ◊ **Safety issues (ie, assessment of risk of falls)**
- **Psychosocial interventions**

Pharmacologic

- **Consider psychostimulants^o (methylphenidate) after ruling out other causes of fatigue**
 - **Consider corticosteroids^q (prednisone or dexamethasone)**
- **Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines ([See NCCN Guidelines for Adult Cancer Pain, Distress Management, and Cancer- and Chemotherapy-Induced Anemia](#))**
- **Optimize treatment for sleep dysfunction and comorbidities**

Repeat screening and evaluation
[See \(FT-3\) and \(FT-4\)](#)
[See \(FT-5\) for General Strategies for Management of Fatigue](#)

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

^hInterventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources. Consider referral to appropriate specialist or supportive care provider.

ⁱAlso [see NCCN Guidelines for Palliative Care](#).

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

^qYennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol* 2013;31:3076-3082. Paulsen O, Klepstad P, Rosland JH, et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *J Clin Oncol* 2014;32:3221-8.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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Cancer-Related Fatigue

Overview

Fatigue in patients with cancer has been under-reported, under-diagnosed, and under-treated. 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.¹⁻⁹ The specific mechanisms involved in the pathophysiology of cancer-related fatigue (CRF) are unknown. Proposed mechanisms include pro-inflammatory cytokines,⁹⁻¹³ hypothalamic-pituitary-adrenal (HPA) axis dysregulation,¹⁰ circadian rhythm desynchronization,¹⁴ skeletal muscle wasting,¹⁵ and genetic dysregulation;¹⁶ however, limited evidence supports these proposed mechanisms.

CRF is very common. According to a survey of 1569 patients with cancer, the symptom is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.^{17,18} In patients with metastatic disease, the prevalence of CRF exceeds 75%.¹⁹⁻²² Moderate or severe fatigue was reported by 983 of 2177 patients (45%) who were undergoing active outpatient treatment and 150 of 515 survivors (29%) with complete remission from breast, prostate, colorectal, or lung cancer.²³ Results from a 1-year longitudinal study comparing 68 patients with non-metastatic breast cancer undergoing chemotherapy treatment to 60 cancer-free control participants showed that fatigue increased during chemotherapy treatment ($P = .003$) and was significantly greater for patients, relative to controls ($P < .01$ for all time points).²⁴ A meta-analysis including 27 studies of 12,237 survivors of breast cancer showed that predictors of severe fatigue include higher disease stage (II or III vs. 0 or I; RR, 1.18; 95% CI, 1.08–1.28) and chemotherapy treatment (RR, 1.12; 95% CI, 1.06–1.19).²⁵ A study including 1869 patients treated with hematopoietic cell transplantation

showed that female sex and chronic pain are associated with greater fatigue.⁵

Cancer survivors report that fatigue is a disruptive symptom months or even years after treatment ends.^{6,25-34} Persistent CRF affects quality of life (QOL), as patients become too tired to fully participate in the roles and activities that make life meaningful.^{28,35,36} CRF may also influence the time it takes to return to work following treatment.³⁷ Patients perceive fatigue to be the most distressing symptom associated with cancer and its treatment, more distressing even than pain or nausea and vomiting, which can generally be managed by medications.³⁸

Health care professionals have been challenged in their efforts to help patients manage CRF and to remain as fully engaged in life as possible. Because of the successes in cancer treatment, health care professionals are now likely to see patients with prolonged states of fatigue related to the late effects of treatment. Disability-related issues are relevant and often challenging, especially for patients with cancer who are cured of their malignancy but have continued fatigue.³⁹ It is often difficult for patients with CRF to obtain or retain disability benefits from insurers. Health care professionals should advocate for patients who require disability benefits and educate insurers about this issue.

To address the important problem of CRF, NCCN convened a panel of experts. The NCCN Guidelines for Cancer-Related Fatigue, first published in 2000⁴⁰ and updated annually, synthesize the available research and clinical experience in this field and provide recommendations for patient care. The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).



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Cancer-Related Fatigue

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Cancer-Related Fatigue, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: cancer fatigue. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.⁴¹

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Defining Cancer-Related Fatigue

The distinction between tiredness, fatigue, and exhaustion is generally not made in practice, despite conceptual differences.^{42,43} The Guidelines Panel defines CRF as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Compared with the fatigue experienced by healthy individuals, CRF is more severe, more distressing, and less likely to be relieved by rest. In terms of the

defining characteristics, it is important to note the subjective sense of tiredness reported by the patient. As with pain, the clinician must rely on the description of fatigue and accompanying distress provided by the patient. Fatigue that interferes with usual functioning is another substantial component of the definition for CRF and the source of much distress for patients.⁴⁴

Standards of Care for Assessment and Management

The panel developed the Standards of Care for CRF using the NCCN Guidelines for Adult Cancer Pain and the NCCN Guidelines for Distress Management (both available at www.NCCN.org) as exemplar models (see *Standards of Care for Cancer-Related Fatigue in Children/Adolescents and Adults* in the algorithm). These fatigue standards represent the best level of care for the assessment and management of fatigue in patients with cancer, including children, adolescents, and adults, and should provide guidance for health care professionals as they implement these guidelines in their respective institutions and clinical settings. The overall goal of the standards and guidelines is to ensure that all patients with cancer experiencing fatigue are identified and given prompt, effective treatment. The NCCN Guidelines provide “best care” information based on current evidence to support treatment.⁴⁵

Fatigue should be screened, assessed, and managed for most patients according to the clinical practice guidelines. It is a subjective experience that should be systematically assessed using patient self-reports and other sources of data. However, because it is a symptom that is perceived by the patient, fatigue can be described most accurately by self-report. Patients should be screened for the presence and severity of fatigue at their initial clinical visit, at regular intervals during and/or following cancer treatment, and as clinically



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indicated.⁴⁶ The history and physical examination, laboratory data, and descriptions of patient behavior by family members, especially regarding children, are important sources of additional information.

Patients and families should be informed that managing fatigue is an integral part of total health care, and all patients should receive symptom management. If patients cannot tolerate their cancer treatment or if they must choose between treatment and QOL, control of their disease may be diminished.⁴⁷ Rehabilitation may include physical therapy, occupational therapy, and physical medicine, and should be considered as indicated from diagnosis to end of life.

The guidelines for fatigue evaluation and management are best implemented by an interdisciplinary institutional committee, including experts in medicine, nursing, social work, physical therapy, and nutrition.⁴⁸ However, current practices in assessing and treating fatigue are inadequate and inconsistent at many institutions.⁴⁹ The panel recognizes that education and training programs are needed to prepare oncology experts in fatigue management. These are now being offered, but much more attention to these programs within the institutional setting is necessary if professionals are to become skilled in managing fatigue.⁵⁰ There is variation among institutions regarding which professional disciplines and staff can provide appropriate specialized consultation for fatigue. Therefore, in addition to implementation of fatigue treatment guidelines, health care providers should familiarize themselves with the type of supportive care staff available at their institution. Supportive care staff may include experts in survivorship, palliative care, integrative oncology, psychology, psychiatry, and physical therapy, among others.

The NCCN Panel recommends that assessment of CRF levels be included in outcomes research. Quality of fatigue management should

be included in institutional continuous quality improvement projects. Institutions can make faster progress in implementing these guidelines if they monitor adherence and progress with the guidelines.⁵⁰ 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.

Guidelines for Evaluation and Treatment

The general schema of the fatigue algorithm defines 4 phases: screening, primary evaluation, intervention, and re-evaluation. During the first phase, the health care professional must screen for fatigue and, if present, assess 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 includes an evaluation of concurrent symptoms and contributing factors frequently associated with fatigue, and can be treated as an initial step in managing fatigue. If, however, a patient either does not have one of these treatable contributing factors or continues to have moderate-to-severe fatigue after treatment of the factors, the health care professional should recommend additional treatment based on the NCCN Guidelines for Cancer-Related Fatigue.

After the evaluation phase, the guidelines delineate a set of interventions for the amelioration of fatigue based on clinical status (ie, active cancer treatment, post-treatment, end of life). Education and counseling are believed to be central to the effective management of fatigue. Additional interventions that are both nonpharmacologic and pharmacologic may be introduced; in many instances a combination of approaches must be used. The treatment of fatigue is continuous and,



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as indicated by the re-evaluation of patients, leads to an iterative loop in fatigue screening and management. Regardless of whether or not a patient demonstrates moderate-to-severe fatigue, health care professionals should continue to monitor for fatigue both throughout and after treatment, as fatigue symptoms have been shown to persist for years. While there are no studies that have evaluated the long-term treatment of fatigue, it should be assessed, and measures should be taken to reduce its impact on QOL.

Screening

The first phase of the algorithm emphasizes the screening of every patient for the presence or absence of fatigue using age-appropriate measures. Valid and reliable instruments are available to measure fatigue in children, adolescents, and adults (see *Appendix*); however, the effectiveness of these methods is limited without adequate implementation. 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. The evaluation of fatigue in children may be simplified to a scale of 1 to 5 and modified even further in young children (age 5–6 years) who may be asked more simply if they are “tired” or “not tired.” 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. 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.^{6,25}

Currently, screening is not systematic or effective in many practice settings for various reasons, which often include patient or family barriers and clinician barriers. For example, patients may not want to bother their health care professional in the clinic or office or when they are hospitalized. Patients are also concerned that if they report high levels of fatigue, they might have their treatment altered. Patients do not want to be perceived as complaining and, therefore, may not mention fatigue. Patients may also assume that they must live with fatigue, because they believe there is no treatment for it. Health care professionals may not initiate a discussion about fatigue for many of the same reasons. First, clinicians may not recognize that fatigue is a problem for the patient. As a symptom, fatigue has been unrecognized and untreated, whereas medical advances have led to better control over the more noticeable or less subtle acute symptoms of nausea, vomiting, and pain. Second, health care professionals may not be aware that there are effective treatments for fatigue, despite the lack of understanding about the underlying pathophysiology and mechanisms responsible for CRF.

Given these barriers, screening for CRF must be emphasized.⁵¹ Clinical experience with fatigue assessment has shown that some patients cannot put a numeric value on their fatigue. Consequently, some patients may need to rate fatigue as mild, moderate, or severe. In some circumstances, other sources of data must be used. For example, the patient may not be aware that fatigue has negatively affected his or her life; however, the spouse, parents, or other family members may be more cognizant of these changes and the effect of fatigue. An appendix to this discussion provides additional information and resources to assist in the selection of instruments to measure CRF.

Using the numeric rating scale (ie, 0–10 scale), fatigue studies in patients with cancer have revealed a marked decrease in physical

functioning at the level of 7 or higher.⁵² In another study, ratings of symptom interference guided the selection of numeric rating cutpoints for the levels of mild, moderate, and severe fatigue. Interference levels on the MD Anderson Symptom Inventory (MDASI) scale were found to be well differentiated with the cutpoints for mild, moderate, or severe fatigue.²³ Based on these validated levels of fatigue intensity, the panel believes that the numeric rating scale can be used as a guide in practice settings and decision-making.

Primary Evaluation Phase

Focused History

When fatigue is rated as moderate to severe, with a score of 4 to 10, a more focused history and physical examination should be conducted as part of the primary evaluation phase outlined in the algorithms. One component of this evaluation is an assessment of the patient's current disease status, which encompasses the type and length of treatment, its capacity to induce fatigue, and the patient's response to treatment (see *Primary Evaluation* in the algorithm). If possible, it should be determined whether the fatigue is related to a recurrence of the malignancy for those patients assumed to be disease-free or whether it is related to a progression of the malignancy for patients with underlying disease. Disease recurrence or progression 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 or progression, informing patients and family members may substantially reduce their anxiety levels.

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. Polypharmacy (ie, use of ≥ 4 medications) and potentially inappropriate medication use is common among older adults with cancer.⁵³ It may be appropriate to delete or adjust the dose of medications to treat fatigue. In some cases, altering either the dosage or dosing interval of a medication may be sufficient to improve the condition.

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

The panel also recognizes the important role of social support throughout the course of cancer treatment and survivorship.⁵⁴ Fatigue is a major cause of functional dependence for patients with cancer, especially among the elderly.⁵⁵ Besides assisting with daily living, caregivers provide cancer-specific support such as monitoring treatment side effects, aiding in fatigue and pain management, and administering medicine, among others.⁵⁶ The availability of dependable caregivers can significantly impact the functional, emotional, and financial capacity of a patient coping with cancer and the pursuit



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

Assessment of Treatable Contributing Factors

The panel identified factors that are often causative elements in the fatigue experience and, therefore, should be specifically assessed during the focused evaluation. These factors include pain, emotional distress, sleep disturbance, poor sleep hygiene, anemia, nutrition, activity level, medication side effect profiles, alcohol/substance abuse, and comorbidities/cancer treatment sequelae. In a randomized controlled trial (RCT) of 152 patients with advanced cancer, protocol patient-tailored treatment of the accompanying physical symptoms was coordinated by a nurse and resulted in a higher impact on fatigue than standard oncologic care.⁵⁷

Descriptive studies have shown that, in both adults and children, fatigue seldom occurs by itself and more commonly clusters with sleep disturbance, poor sleep hygiene, emotional distress (eg, depression, anxiety), or pain.⁵⁸⁻⁶¹ Assessment of pain along with emotional distress and institution of effective treatment are essential. Fatigue and depression have also been documented as concurrent symptoms in patients with cancer.^{5,62,63}

Sleep disturbances are a neglected problem in oncology⁶⁴ and may range from hypersomnia to insomnia.^{65,66} Sleep disturbances are prevalent in 30% to 75% of patients with cancer.⁶⁷ Several studies have shown that patients with cancer experiencing fatigue during active treatment spend increased time resting and sleeping but their pattern of sleep is often severely disrupted. Patients may benefit from evaluation and education to improve sleep quality. In addition, sleep apnea can develop as a consequence of cancer treatment in the settings of surgery affecting the upper airway, changes in body composition, and

alterations in hormone status (eg, thyroid, estrogen, testosterone); therefore, obstructive sleep apnea should also be evaluated.

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

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



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CRF is associated with decreased functional status. A survey conducted by Mustian and colleagues including 753 patients receiving systemic chemotherapy showed that CRF interfered with physical functioning in the majority of patients.⁶⁸ Interference was moderate, and was noted to be higher in women, non-whites, and patients with metastatic disease. Patients with moderate-to-severe fatigue should be queried about their functional status, including changes in exercise or activity patterns and the influence of deconditioning. Can patients accomplish normal daily or enjoyable activities? Can they participate in formal or informal exercise programs? What is the amount and frequency of exercise? Has the patient modified exercise or other activity patterns since the development of fatigue? This assessment is important when formulating a treatment plan that may include exercise. Exercise has been beneficial in lowering fatigue levels in certain populations of patients with cancer.^{69,70} However, before recommending an exercise program, the health care provider or exercise expert (eg, physiatrist, physical therapist) should assess the conditioning level of the patient. It is often difficult to convince fatigued patients that exercise will improve their symptoms. It may be best to begin with discussions and low-level activities, which gradually increase over a period of time. This is especially important if the patient is significantly deconditioned.

Cancer treatment sequelae and non-cancer-related comorbidities may contribute substantially to symptoms of fatigue in the patient with cancer. Therefore, the status of comorbidities must be reviewed in conjunction with the present treatment management strategies. If the comorbidity is not optimally managed, it may be necessary to further evaluate and improve management. For example, if a patient has underlying congestive heart failure secondary to anthracycline cardiomyopathy and is experiencing symptoms of dyspnea and angina, fatigue may often be improved by stabilizing the condition and

decreasing the frequency of episodes of congestive heart failure. This may entail introduction of new medications, titration of current medications, or both. It may also involve an invasive interventional assessment of the patient's cardiac status.

Comorbidities that need review and assessment include cardiac, pulmonary, renal, gastrointestinal, hepatic, neurologic, and endocrine dysfunction (including hot flashes, hypothyroidism, hypogonadism, or adrenal insufficiency), as well as infection. There is a high incidence of thyroid dysfunction in normal individuals and in patients receiving thyroid medications.⁷¹ Attention should be given to thyroid problems in patients with cancer. 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. 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 cross-section pilot study including men with advanced cancer showed that abnormally low levels of testosterone may be associated with fatigue.⁷² However, additional research in a larger patient population is needed to clarify the incidence of hypogonadism and its association with specific malignancies and neurotoxic chemotherapy. Finally, health care providers should also be alert for signs of alcohol or substance abuse. These detrimental habits can often lead to or aggravate other health problems such as sleep disturbance and result in fatigue.

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 due to its

influence on CRF management and treatment strategies. However, some general treatment guidelines apply across all clinical categories.⁷³

If any treatable contributing factor discussed above is identified during the primary evaluation phase, it should be treated as an initial approach to fatigue management. Other NCCN Clinical Practice Guidelines are also available to guide supportive care including the NCCN Guidelines for Adult Cancer Pain, Distress Management, Cancer- and Chemotherapy-Induced Anemia, Antiemesis, Survivorship, Palliative Care, and Prevention and Treatment of Cancer-Related Infections (available at www.NCCN.org).

General Strategies for Management of Fatigue

Education about fatigue and its natural history should be offered to all patients with cancer,⁵¹ especially for patients beginning potential fatigue-inducing treatments (such as radiation, chemotherapy, or biotherapy) before the onset of fatigue. A Cochrane systematic review including 14 RCTs with 2213 patients with cancer showed that educational interventions may impact CRF (standardized mean difference [SMD], -0.27; 95% CI, -0.51 to -0.04), CRF intensity (SMD, -0.28; 95% CI, -0.52 to -0.04), and interference of CRF on daily life (SMD, -0.35; 95% CI, -0.54 to -0.16), though the quality of the evidence was sometimes low.⁷⁴ Patients should be informed that if fatigue does occur, it may be a consequence of the treatment and is not necessarily an indication that the treatment is not working or that the disease is progressing. This reassurance is important, as fear of progression is a main reason for the under-reporting of fatigue.

Patients who are completing treatment and their families should be educated about the pattern and level of fatigue that can be expected during this period. Although a significant subset of patients continue to experience distressing levels of fatigue that interfere with function, most

patients experience a gradual decrease in fatigue and return of energy to normal levels.^{27,75} Regular monitoring of fatigue levels can document the decrease in fatigue that normally occurs after treatment. Health care providers should continue to screen regularly for fatigue during follow-up visits.

In addition to education, the panel recommends counseling for patients about general strategies (energy conservation and distraction) useful in coping with fatigue.^{51,76} Energy conservation is defined as the deliberately planned management of one's personal energy resources to prevent their depletion. It encompasses a common sense approach that helps patients set realistic expectations, prioritize and pace activities, and delegate less essential activities.⁷⁷ A multisite clinical trial of energy conservation in 296 patients receiving cancer treatment reported significantly lower fatigue in patients receiving the experimental intervention.⁷⁸ Patients should be counseled that it is permissible to postpone all nonessential activities if they are experiencing moderate-to-severe fatigue. 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. Daytime naps can replenish energy, but it is advisable to limit these to less than an hour to avoid disturbing nighttime sleep. Patients may also use labor-saving techniques such as wearing a bath robe instead of drying off with a towel or assistive devices such as a walker, grabbing tools, and a bedside commode.

One useful plan is to maintain a daily and weekly diary that allows the patient to ascertain peak energy periods and then plan activities accordingly within a structured routine. Daily self-monitoring of fatigue levels in a treatment log or diary can also be helpful. Activities designed to distract (eg, games, music, reading, socializing) may be helpful in decreasing fatigue, although the mechanism is unknown. An emphasis



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

Education and counseling could potentially be delivered via telehealth and/or the internet, especially for patients in the palliative care setting and for patients who are not under active treatment.^{79,80}

Interventions for Patients on Active Treatment

Nonpharmacologic Interventions

Nonpharmacologic treatment of fatigue is beneficial in patients with cancer.^{81,82} A meta-analysis including 113 studies and 11,525 patients showed that nonpharmacologic interventions, specifically exercise [weighted effect size (WES), 0.30; 95% CI, 0.25–0.36; $P < .001$] and psychological interventions (WES, 0.27; 95% CI, 0.21–0.33; $P < .001$), improve CRF, while pharmacologic interventions do not significantly improve CRF (WES, 0.09; 95% CI, 0.00–0.19; $P = .05$).⁸³ Of the specific nonpharmacologic interventions during active cancer treatment, the panel recommends physical activity (category 1), physically based therapies, and psychosocial interventions. Nutritional consultation, cognitive behavioral therapy (CBT) for sleep, and bright white light therapy (BWLTL) also have some supporting evidence for treating CRF in patients on active cancer treatment.⁸⁴ These interventions align with recommendations from the Oncology Nursing Society (ONS).^{85–87} Both ASCO⁸⁸ and the pan-Canadian practice guidelines⁸⁹ used the ADAPTE method to take advantage of these existing guidelines (ie, NCCN, ONS) to enhance efficient production, reduce duplication, and promote the local update of quality guideline recommendations by their organizations.

Physical Activity

Although there are a number of factors that contribute to the decline in functionality, fatigue is one of the major contributors. A meta-analysis

including 8 studies with 478 breast cancer survivors showed that exercise might improve CRF by counteracting low-grade inflammatory mediators (eg, interleukin 6).⁹⁰ A large number of small- to moderate-sized studies have been performed to evaluate the feasibility of interventions designed to increase physical activity during therapy, and to explore the impact of increased activity upon CRF, QOL, treatment-related side effects, and other endpoints. Systematic reviews have correlated exercise with improvement in fatigue for patients with prostate cancer,⁹¹ lymphoma,⁹² and hematologic malignancies;⁹³ in patients who are undergoing adjuvant radiation therapy;⁹⁴ and in patients who have undergone hematopoietic cell transplant.⁹⁵

A thorough review of the impact of physical activity on CRF (measured using various outcomes) is beyond the scope of this discussion. However, several meta-analyses have been conducted to provide a comprehensive evaluation of the impact of increased activity upon CRF. One meta-analysis included 70 studies and 4881 patients with cancer during or following treatment.⁹⁶ Exercise reduced CRF by a mean effect of 0.32 (95% CI, 0.21–0.43) and 0.38 (95% CI, 0.21–0.54) during and after cancer therapy, respectively. Another meta-analysis including 72 studies and 5367 patients in active treatment or follow-up showed a moderate effect of exercise in reducing CRF, when compared to a control group (SMD, -0.45; 95% CI, -0.57 to -0.32, $P < .001$).⁹⁷ Impact on fatigue levels did not significantly differ by type of exercise, though stronger effects were seen for solid tumors vs. hematologic and mixed malignancies. A 2012 Cochrane analysis included 56 randomized trials ($n = 4826$), 36 of which were conducted among participants undergoing active cancer treatment.⁹⁸ Exercise resulted in a decrease in fatigue from baseline to 12 weeks' follow-up (SMD, -0.38; 95% CI, -0.57 to -0.18) or when comparing differences in follow-up scores at 12 weeks (SMD -0.73; 95% CI, -1.14 to -0.31). A



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meta-analysis focusing exclusively on aerobic exercise (26 RCTs and 2830 participants) showed that this type of exercise may reduce fatigue, especially in patients who received adjuvant therapy.⁹⁹ Other smaller analyses confirmed a significant effect of exercise intervention on fatigue.¹⁰⁰⁻¹¹²

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. The U.S. Surgeon General recommends 30 minutes of moderate activity most days of the week for all populations.¹¹³ Some observational and interventional studies have suggested that patients with cancer who engage in at least 3 to 5 hours of moderate activity per week may experience better outcomes and have fewer side effects of therapy, including fatigue.^{69,114-118}

Patients may be referred to exercise specialists (eg, physical therapist, physical medicine, rehabilitation specialist) as indicated for assessment and an exercise prescription. The American College of Sports Medicine has developed a certification program for cancer rehabilitation that is available for exercise professionals who specialize in the care of patients with cancer. They also convened a roundtable discussion and published specific guidelines for physical activity testing and exercise programs for patients with cancer.¹¹⁹

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 comorbid illnesses
- Safety issues (ie, risk of falls)

The exercise program itself should be individualized based on the patient's age, gender, type of cancer, and physical fitness level. Both endurance (eg, walking, swimming) and resistance exercise (ie, weight training) may be encouraged. Consider cancer-specific exercise programs if available. The program should begin at a low level of intensity and duration, progress slowly, and be modified as the patient's condition changes.

Yoga

A recent Cochrane review including 24 studies with 2166 patients with breast cancer showed that there is moderate-quality evidence that yoga reduces CRF, compared to no therapy (pooled SMD, -0.48; 95% CI, -0.75 to -0.20) and psychoeducation (pooled SMD, -0.90; 95% CI, -1.31 to -0.50).¹²⁰ When compared to exercise, however, this review showed that yoga did not significantly reduce CRF, though the quality of evidence was low. Several RCTs have demonstrated that yoga intervention impacts CRF during treatment.¹²¹⁻¹²⁷ Three of these studies targeted patients undergoing radiation therapy.^{121,122,127} In an RCT including 352 women with nonmetastatic breast cancer undergoing chemotherapy, a Tibetan yoga program did not significantly impact CRF, compared to a stretching program and usual care.¹²⁸ However, exploratory analyses ($n = 74$) showed that practicing yoga at least twice per week was associated with better sleep-related outcomes 6 months after intervention completion (ie, fewer daily disturbances and better sleep quality and efficiency), when compared to participants who practiced yoga less than twice per week. Another RCT targeted 60 patients with breast cancer who were undergoing adjuvant chemotherapy.¹²⁹ Fatigue was improved in patients randomized to receive 8 weeks of Anusara yoga sessions, twice per week ($P < .001$).

Two small randomized trials for patients with non-Hodgkin's lymphoma showed that qigong, a practice involving movement, posture, and breathing, may help reduce fatigue.^{130,131} A randomized trial including 96 patients with lung cancer who were undergoing chemotherapy treatment showed that tai chi reduced CRF, compared to low-impact exercise ($P < .05$).¹³²

The panel recommends yoga for treatment of CRF in patients on active cancer treatment (category 1). More data are needed to establish the effectiveness of yoga in reducing fatigue in males and in other cancers besides breast cancer.¹³³ An RCT including 54 patients with non-metastatic colorectal cancer were randomized to either weekly yoga (for 10 weeks) or to a waitlist control group.¹²⁵ Modest group differences were found for sleep disturbances 3 months after intervention completion ($P = .04$). Study results may have been affected by attrition and poor intervention adherence rates.

Physically Based Therapies

Physically based therapies are those performed on a patient by a therapist or lay person, such as massage therapy or acupuncture. Massage therapy may be effective in reducing CRF,¹³⁴⁻¹³⁶ with one meta-analysis including five RCTs with 667 patients showing favorable effects on CRF (SMD, -0.61; 95% CI, -1.09 to -0.13, $P = .01$).¹³⁷ The panel recommends massage therapy as a category 1 recommendation for treatment of CRF in patients on active treatment.

Four systematic reviews suggest that acupuncture and acupressure may have beneficial properties, though the studies acknowledge that a paucity of data makes it difficult to definitively evaluate the benefits.¹³⁸⁻

¹⁴¹ Positive effects of acupuncture on fatigue have been reported in small samples but need to be confirmed in larger RCTs.¹⁴² These small trials were conducted during active non-palliative radiation therapy^{143,144}

and both during and after chemotherapy treatment.¹⁴⁵⁻¹⁴⁷ A small RCT showed that patients with CRF ($N = 78$) who received infrared laser moxibustion, a type of acupuncture in which the herb moxa (*Artemisia vulgaris*) is burned on or near the skin at acupoints, had less fatigue, compared to patients who received sham laser moxibustion ($P = .002$).¹⁴⁸ Significant group differences persisted up to 4 weeks after intervention completion ($P = .006$). Another RCT examining the effects of transcutaneous electrical acupoint stimulation (TEAS) on CRF in patients with non-small cell lung cancer receiving chemotherapy showed that patients randomized to receive TEAS reported less fatigue than patients randomized to receive sham TEAS ($P = .005$) or routine nursing care ($P < .01$).¹⁴⁹

Psychosocial Interventions

Although a strong correlation exists between emotional distress and fatigue, the precise relationship is not clearly understood. Current psychosocial interventional studies may target one or more biologic mechanisms (eg, 5-HT3 neurotransmitter deregulation, vagal afferent activation, alteration in muscle and adenosine triphosphate metabolism, HPA axis dysfunction, circadian rhythm dysfunction, cytokine deregulation); however, most studies to date fail to identify the underlying targeted mechanism. The exception includes interventions aimed at increasing relaxation, thereby diminishing stress and activation of the HPA axis. Because of the inherent difficulty of conducting mechanistically based interventions, 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. Patients should be counseled regarding coping with fatigue and educated about anxiety and depression, which are commonly associated with fatigue during cancer treatment.¹⁵⁰



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Several meta-analyses evaluated the impact of psychosocial interventions on CRF. Analyzing 41 studies on 3620 patients with cancer, Kangas et al¹⁰² reported a weighted pooled mean effect of -0.31 for psychosocial interventions on fatigue. Goedendorp et al¹⁵¹ reported that, out of 27 RCTs included in their analysis, 7 showed significantly reduced fatigue. Of interest, 80% of fatigue-specific interventions were effective, compared to 14% of non-specific strategies. Jacobsen et al¹⁵² analyzed 30 RCTs and found a significant effect for psychological interventions but not for activity-based programs.

Studies testing interventions to decrease fatigue can be grouped as cognitive behavioral therapy (CBT)/behavioral therapy (BT), psycho-educational therapies/educational therapies, and supportive expressive therapies, based on review of 3 meta-analyses.^{102,151,152} Of note, the categories in which interventions have been grouped are different in each of the meta-analyses and have been compared to the work reported by the ONS Putting Evidence into Practice (PEP).^{86,87,153} These studies can be categorized based on their primary outcome parameter: fatigue or other. In many studies, fatigue was a secondary endpoint measured by a single item or a subscale of an instrument designed to measure emotional distress, QOL, or general symptom burden. Furthermore, fatigue was not an eligibility requirement. In studies specifically designed to measure fatigue, no severity 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.

A meta-analysis by Duijts and colleagues¹⁰¹ reported that, like exercise programs, behavioral techniques including cognitive therapy, relaxation techniques, counseling, social support, hypnosis, and biofeedback are beneficial in improving fatigue among patients with breast cancer during and after treatment. Substantial data in literature provide high-level

evidence during active treatment for CBT/BT¹⁵⁴⁻¹⁶⁰ and psycho-educational therapies/educational therapies,^{84,161-172} and these psychosocial interventions are recommended by the panel for treatment of CRF (category 1). However, one RCT in which patients with cancer were randomized to receive either a fatigue management education program or standard of care failed to demonstrate an effect on CRF.¹⁷³ Potential explanations by the study investigators for the negative results include the program failing to capture the complexity of CRF, contamination bias, measurement response shift, and patient reluctance regarding patient education. Supportive expressive therapies (eg, in-person or online support groups, counseling, journal writing) may serve as an emotional outlet and as a support network. There is less robust evidence for supportive expressive therapies during active treatment and it is therefore a category 2A recommendation.

Complementary therapies such as muscle relaxation, music therapy, hypnosis, and stress reduction based on mindfulness have been evaluated in combination with CBT approaches, though some of these therapies have also been evaluated on their own.^{154,174-179} The data suggest that these therapies may be effective in reducing fatigue in patients with cancer. For example, education regarding stress management may help improve sleep quality. Secondary analyses from a 10-week cognitive behavioral stress management program for women undergoing adjuvant treatment for breast cancer ($N = 240$) showed that those randomized to receive the stress management intervention reported a reduction in fatigue-related daytime interference, relative to participants randomized to a psychoeducational control group ($P < .05$).¹⁸⁰ Mediation analyses showed that these results were accounted for by self-reported improvements in sleep quality. Another RCT including 155 patients with breast cancer did not find a statistically



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significant difference in fatigue between those randomized to a stress management group and those in a control group.¹⁸¹ However, larger studies are needed.

Nutrition Consultation

Many patients with cancer have changes in nutritional status. Because cancer and treatment can interfere with dietary intake, nutrition consultation may be helpful in managing the nutritional deficiencies that result from anorexia, diarrhea, nausea, and vomiting.¹⁸² Adequate hydration and electrolyte balance are also essential in preventing and treating fatigue.

Sleep Therapy

There are numerous types of CBT for sleep; the most frequently used include stimulus control, sleep restriction, and sleep hygiene. Stimulus control includes going to bed when sleepy, going to bed at approximately the same time each night, and maintaining a regular rising time each day. Getting out of bed after 20 minutes if unable to fall asleep, both when first going to bed and when awakening during the night, are key aspects of stimulus control. Sleep restriction requires avoiding long or late afternoon naps and limiting total time in bed.¹⁸³ Techniques to promote a good night's sleep and optimal functioning the next day, such as avoiding caffeine after noon and establishing an environment that is conducive to sleep (eg, dark, quiet, comfortable) are components of sleep hygiene. These strategies were 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.¹⁸⁴ For children with cancer, a consistent bedtime and routine, an environment conducive to sleeping, and the presence of security objects (such as blankets and toys) are effective measures (see *Assessment of Treatable Contributing Factors*).

Bright White Light Therapy

Bright light treatment involves exposure to very high fluorescent light (typically 10,000 lux), emitted from a "light box" that is usually purchased for at-home use. This type of therapy has been used for the treatment of mood disorders and sleep disturbances in the general population and in older adults.¹⁸⁵⁻¹⁸⁸ Bright light therapy stimulates the suprachiasmatic nucleus of the hypothalamus, which regulates circadian rhythms.

BWLT has been associated with positive changes in fatigue in women with breast cancer during chemotherapy^{189,190} and over the course of 7 weeks in cancer survivors who were up to 3 years post completion of chemotherapy and radiation therapy.¹⁹¹ Thus far, samples have been small, and the risks associated with BWLT need to be balanced with the benefits. Further, the optimal timing and length of treatment require further study, though BWLT is most commonly administered in the early morning for 30 to 90 minutes, and timing may be adjusted for those who sleep during the day. Studies are currently in process to investigate the optimal use of BWLT for patients with CRF (eg, the LITE study¹⁹²). The panel recommends that home-based BWLT be included as a nonpharmacologic strategy for treating CRF in patients on active treatment.

Pharmacologic Interventions

There is some evidence for pharmacologic therapy as treatment for fatigue, although a significant placebo response has been observed in a randomized trial.¹⁹³ 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 the potential risks of sedative-hypnotic drugs, which include severe allergic reactions and complex



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sleep-related behaviors, including sleep-driving. A table summarizing the medications commonly used to promote sleep is provided at the National Cancer Institute Physician Data Query website.¹⁹⁴ Prescribing considerations for these classes of agents include increased likelihood of problems with daytime sleepiness, fatigue, withdrawal symptoms, dependency, rebound insomnia, problems with sleep maintenance, memory problems, anticholinergic symptoms, orthostasis, and the potential for drug-drug interactions involving the cytochrome p450 isoenzyme system.

The psychostimulant methylphenidate has been evaluated for its effect on CRF with mixed results in patients undergoing cancer therapy.¹⁹⁵⁻¹⁹⁸ A meta-analysis including 7 studies showed that methylphenidate reduces CRF, compared to a placebo (SMD, -0.28; 95% CI, -0.44 to -0.12).¹⁹⁹ Analyzing five RCTs, Minton et al²⁰⁰ attributed a significant benefit to psychostimulants in alleviating fatigue compared to placebo (Z-score [Z] = 2.83; $P = .005$). Patients have reported minor side effects with methylphenidate, including headache and nausea.

The wakefulness-promoting non-amphetamine psychostimulant, modafinil, has been approved for use in narcolepsy. In a large RCT, Jean-Pierre et al²⁰¹ randomized 867 patients undergoing chemotherapy to 200 mg of modafinil per day or placebo. Of the 631 evaluable patients, 315 received modafinil and 316 received placebo. Improvement in fatigue was observed in patients with severe fatigue ($P = .017$), but not in patients with mild or moderate fatigue. Toxicity was similar between the two arms. Secondary analyses from this study showed that, among patients with severe fatigue, depression improved in those randomized to receive modafinil [$t(54) = 4.79$; $P < .001$], compared to those randomized to receive a placebo [$t(73) = 3.56$; $P < .01$], potentially due to impact on positive affect ($P = .007$).²⁰² A phase III randomized, placebo-controlled trial assessing the effect of modafinil

measured the improvement in fatigue in patients with metastatic prostate or breast cancer undergoing docetaxel chemotherapy.²⁰³ Fatigue was measured using the MDASI and no statistically significant difference was seen between treatment arms (35.9 vs. 39.6; 95% CI, -8.9–1.4; $P = .15$). There was an increase in toxicity, with patients experiencing grade 2 or higher nausea and vomiting in the modafinil arm (45.4% vs. 25%). A phase II RCT conducted with 54 patients receiving RT for primary brain tumors showed that armodafinil was well-tolerated and improved fatigue after RT completion in those who reported greater fatigue at baseline assessment, though overall between-group differences did not reach statistical significance.²⁰⁴ A recent meta-analysis including 3 studies showed that modafinil did not significantly reduce CRF, compared to placebo treatment.¹⁹⁹ Due to the limited number of studies and the marginal improvement in CRF in response to modafinil and armodafinil, it is not a recommended treatment.

The use of dietary supplements to alleviate the symptoms of fatigue has yielded mixed results. While coenzyme Q10 and guarana were evaluated and showed no benefit,^{179,205} there may be some data to support the use of American ginseng.¹⁷⁹ In a phase III RCT of 364 patients experiencing CRF, symptom improvement as measured by the Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF) following treatment with 2000 mg Wisconsin ginseng was observed.²⁰⁶ In the overall population, improvement at 4 weeks was not statistically significant (ginseng, 14.4 points; standard deviation [SD], 27.1 vs. placebo, 8.2 points; SD, 24.8; $P = .07$). However, at 8 weeks, a statistically significant improvement ($P = .003$) in patients receiving ginseng (20 points; SD, 27) versus patients given the placebo (10.3 points; SD, 26.1) was observed. Furthermore, improvement was greatest in patients undergoing active cancer treatment compared to



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patients who had completed treatment. A phase II randomized study examining the effect of ginger extract (6-gingerol) in 88 patients receiving moderately to highly emetogenic adjuvant chemotherapy showed that patients who received the ginger extract reported significantly less grade 3 fatigue, compared to patients who received a placebo (2% vs. 20%, respectively; $P = .02$).²⁰⁷ Though an RCT showed that L-carnitine may be associated with improved fatigue in patients with hypothyroidism who underwent surgery for thyroid cancer ($n = 27$; $P < .05$),²⁰⁸ other studies have shown no significant benefit of this dietary supplement on CRF.^{179,209,210}

Based on currently available data, the panel included consideration of the psychostimulant methylphenidate as a recommendation for patients undergoing active cancer treatment when other causes of fatigue have been excluded. However, use of psychostimulants in older adults should be treated with caution, as older adults may need a lower dosage than younger adults.²¹¹ The data were not sufficient to support the recommendation for modafinil. Studies on the selective serotonin reuptake inhibitor paroxetine showed no influence by this antidepressant on fatigue in patients receiving chemotherapy.^{212,213} Antidepressants are not recommended to reduce fatigue. See the relevant NCCN Guidelines for Supportive Care (available at www.NCCN.org) for details on the management of pain, distress, emesis, and anemia. Treatment for nutritional deficit or imbalance and comorbidities may be optimized as indicated. Increased public and professional education regarding sleep, sleep hygiene, sleep disturbances, and daytime consequences of sleep loss are recommended.

Interventions for Patients Post-Treatment

Improvements in cancer survival rates have led to efforts to enhance symptom management, QOL, and overall functioning of individuals post-treatment. As previously mentioned, fatigue can be an acute effect of cancer or treatment, but it can also be a long-term or late effect.²¹⁴ Patients may continue to report unusual fatigue for months or years after treatment cessation.^{26,27,29-33} The cause of fatigue during post-treatment is unclear and probably multifactorial.²¹⁵ Researchers have suggested that such fatigue may be due to persistent activation of the immune system^{26,216} or to other factors, including the late effects of treatment on major organ systems.²¹⁶ One cross-sectional comparative study investigated fatigue and physiologic biomarkers of immune system activation in 20 breast cancer survivors who were fatigued (mean, 5 years since diagnosis) and in 20 non-fatigued survivors.²¹⁶ Fatigued survivors had significantly higher serum markers (interleukin-1 receptor antagonist [IL-1ra], soluble tumor necrosis factor type II, and neopterin) and lower cortisol levels when compared with non-fatigued survivors. Significantly higher numbers of circulating T lymphocytes that correlated with elevated serum IL-1ra levels also suggest that persistent fatigue in survivors may be caused by a chronic inflammatory process involving the T-cell compartment.²⁶ Longitudinal studies examining fatigue in long-term disease-free survivors are needed.

To date, most research reports of incidence and prevalence rates of fatigue during post-treatment are limited by their cross-sectional designs,^{214,217-220} lack of comparison groups,²¹⁸ heterogeneous samples,²¹⁷ differing fatigue scales, lack of consistency in applying diagnostic criteria,²²¹ small sample sizes,²¹⁶ varying baseline survivorship definitions (ie, time since diagnosis vs. time since treatment cessation), and different mean survivorship durations. Additionally, most fatigue studies of patients who are post-treatment



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and disease-free have been conducted in Caucasian, English-speaking patients with breast cancer,^{26,216,219} and peripheral stem cell or bone marrow transplant patients^{222,223} with few exceptions.^{29,31,33} These design issues make it difficult to reach conclusions about the prevalence, incidence, and duration of fatigue; the associated risk factors; and QOL. Incidence and prevalence rates for fatigue in this population range from 17% to 21% when strict ICD-10 diagnostic criteria are applied,²¹⁷ and range from 33% to 53% when other criteria (such as a score of 4 or more on the 0–10 fatigue scale) are used.²²⁴ 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.⁷⁵ As a consequence, what constitutes valid incidence and prevalence rates in disease-free patients requires more study.

Risk factors associated with fatigue during post-treatment of patients who are disease-free include pretreatment fatigue, anxiety and depression levels,²²⁵ physical activity levels,^{226,227} coping methods and cancer-related stressors, comorbidities, type of malignancy, prior treatment patterns, and treatment late effects. In a Norwegian study of Hodgkin's disease survivors in remission for more than 5 years, higher fatigue levels were documented in those who had pulmonary dysfunction; the prevalence of chronic fatigue was 2 to 3 times higher than in survivors without pulmonary dysfunction.²²⁴ No significant correlations in this study were found between fatigue and cardiac sequelae as measured by echocardiography, exercise testing, and chest radiography.²²⁴

Nonpharmacologic Interventions

Specific interventions recommended to manage fatigue during active cancer treatment are also recommended for the post-treatment of patients who are disease-free;⁷³ however, there are fewer studies of

physically based therapies post-treatment, compared to studies of patients actively undergoing treatment.

Physical Activity

Physical activity is a category 1 recommendation for patients who have completed treatment. Improving strength, energy, and fitness through regular exercise has been shown to facilitate the transition from patient to survivor, decrease anxiety and depression, improve body image, and increase tolerance for physical activity even in patients who implement a moderate walking exercise program. However, if the patient is significantly deconditioned, weak, or has relevant late effects of treatment (such as cardiopulmonary limitations), referral to a physiatrist or a supervised rehabilitation program may be indicated. Exercise should be recommended with caution in patients who have fever or remain anemic, neutropenic, or thrombocytopenic after treatment. Both endurance (eg, walking, swimming) and resistance exercise (ie, weight training) may be encouraged.

Of the nonpharmacologic approaches for managing CRF, exercise has the best evidence to support its effectiveness.^{73,228-242} A meta-analysis of 44 studies including 3254 cancer survivors concluded that exercise reduced fatigue, especially in programs that involved moderate-intensity, resistance exercise among older cancer survivors.²⁴³ A meta-analysis including 9 RCTs with 1156 breast cancer survivors showed that supervised exercise may improve CRF (SMD, -0.51; 95% CI, -0.81 to -0.21).²⁴⁴ 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 survivor's abilities to prevent exacerbation of cancer treatment toxicities.^{226,227} Tailored exercise programs delivered using the internet may also help reduce fatigue, based on results of a randomized trial

including 81 survivors of breast cancer who were treated with adjuvant therapy ($P < .001$).²³⁷

Yoga may also reduce fatigue in cancer survivors, and it is recommended for these patients by the Society of Integrative Oncology.¹⁷⁹ A systematic review including 14 trials with 828 patients showed that yoga may successfully reduce CRF following completion of cancer treatment (SMD, -0.68; 95% CI, -0.93 to -0.43).⁸² An RCT including 200 survivors of breast cancer showed that those assigned to hatha yoga sessions twice per week for 12 weeks reported less fatigue at 3-month follow-up, relative to a wait-list control group ($P = .002$).¹²³ Frequency of yoga practice was strongly associated with less fatigue at 3-month follow-up ($P < .001$). In another RCT including 97 older cancer survivors, the effects of a 4-week yoga intervention on CRF were assessed.¹²⁴ After 4 weeks, participants receiving the yoga intervention reported less fatigue, relative to a standard care group ($P = .03$). In a small randomized trial including 34 breast cancer survivors, a yoga intervention delivered via DVD improved CRF, though effects were not significantly different from participants who received a strength training intervention.²⁴⁵ The panel recommends yoga for patients who have completed treatment (category 1).

For further guidance on physical activity, see the NCCN Guidelines for Survivorship (available at www.NCCN.org).

Psychosocial Interventions

Psychosocial interventions, including CBT/BT, mindfulness-based stress reduction, psycho-educational therapies/educational therapies, and supportive expressive therapies are category 1 recommendations.^{101,161,174,175,215,246-253} The panel also supports mindfulness-based stress reduction as a category 1 recommendation for cancer survivors. An RCT including 322 breast cancer survivors

showed that a mindfulness-based stress reduction program improved self-reported fatigue interference and severity, compared to that reported by a usual care group ($P < .01$).²⁵⁴ Another intervention including 252 distressed (ie, score of 4 or higher on the NCCN Distress Thermometer) breast cancer survivors showed that women randomized to receive a mindfulness-based intervention reported a significantly greater reduction in fatigue, compared to women who were randomized to receive a supportive expressive group therapy intervention, with between-group effects being large ($d = 0.45$).²⁵⁵ Additional small RCTs also support the use of mindfulness-based interventions for CRF in cancer survivors.^{256,257}

Additional details on these interventions are provided in the preceding pages in the section on psychosocial interventions for patients on active treatment.

Additional Nonpharmacologic Approaches

CBT for sleep (category 1) and nutrition consultation may be helpful for fatigue management during post-treatment.^{153,258} A number of published studies support the conclusion that CBT interventions designed to optimize sleep quality in patients who completed cancer treatment may improve fatigue.²⁵⁹⁻²⁶³ Positive effects on both sleep and fatigue after 4 to 5 weekly BT sessions have been reported in RCTs of patients in the survivorship phase who reported chronic insomnia.²⁶⁴⁻²⁶⁶ Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.^{259,260} Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.^{184,261} The American Academy of Sleep Medicine (AASM) has recommended 3 specific therapies for chronic insomnia in healthy individuals: relaxation training, CBT, and stimulus control therapy.²⁶⁷ AASM has also published clinical guidelines for the management of chronic insomnia in adults.²⁶⁸

Regarding physically based therapies, a randomized phase III trial including 288 breast cancer survivors showed that self-administered acupressure significantly reduced fatigue ($P < .001$).²⁶⁹ The Society of Integrative Oncology recommends acupuncture for patients who have completed cancer treatment, though the benefit of this intervention is potentially small.¹⁷⁹ The panel currently does not recommend any physically based therapies (eg, massage therapy, acupuncture) for cancer survivors.

Pharmacologic Interventions

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 patients with breast cancer in remission.²⁷⁰ An RCT of 154 patients post-chemotherapy also found an improvement in fatigue symptoms in the active arm.²⁷¹ Similarly to patients receiving active treatment, modafinil has limited study data in patients post treatment. Though pilot studies suggested that modafinil may be associated with reduced fatigue,^{272,273} the improved outcome did not hold in larger trials^{203,274} (see *Interventions for Patients on Active Treatment*). The panel agrees that methylphenidate may be considered after ruling out other causes of fatigue but does not recommend the use of modafinil.

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

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.²⁷⁵ 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.^{276,277} At the end of life, most research has demonstrated that patients with cancer experience fatigue in the context of multiple symptoms. In a study of 278 Swedish adults admitted to a palliative care unit, 100% reported fatigue; other symptoms included pain (83%), dyspnea (77%), and appetite loss (75%).²⁷⁸ In a large sample of adults receiving palliative care ($N = 1000$), Walsh and colleagues²⁷⁹ noted that individuals with advanced cancer had multiple symptoms. Pain was the most prevalent (84%), followed by fatigue (69%), weakness (66%), and lack of energy (61%). Walsh and Rybicki²⁸⁰ cluster-analyzed 25 symptoms in 1000 consecutive admissions to a palliative care program and found 7 symptom clusters. The fatigue cluster included easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, and taste changes. Pain and fatigue could have a synergistic effect that worsens the overall symptom experience in elderly patients with cancer.^{44,281} In a case study of 15 adults with advanced disease, fatigue resulted in substantial regret, sadness, and sense of loss due to the deterioration of one's health.²⁷⁷ Mystakidou and colleagues²⁸² reported that a patient's desire for hastened death was predicted by feelings of sadness, a lack of appetite, pain, and fatigue.

Children with advanced cancer also experienced multiple symptoms at the end of life, most commonly fatigue, pain, and dyspnea.²⁸³ According

to parents who cared for a child at the end of life, more than 90% of the children experienced fatigue and almost 60% experienced significant suffering from it.²⁸³

Individuals with advanced cancer and their caregivers need information about the management of symptoms, including fatigue.²⁸⁴ This includes information about the causes, patterns, and consequences of fatigue during treatment for advanced cancer and end-of-life care. Several major consequences of fatigue have been described, including its effect on functional status, emotional distress, and suffering. As fatigue escalates, it is likely to increasingly interfere with usual activities.²⁷⁷ Families need to be apprised of this issue so they can plan accordingly. Fatigue is likely to have a significant effect on emotional well-being.^{277,283}

Given the high prevalence of fatigue and other symptoms at the end of life, symptom management needs to be a major focus of care. Active commitment by the health care team to palliative care is critical when aggressive cancer therapy is given to patients with a low likelihood of long-term survival.²⁸³ Interventions for fatigue should be initiated to relieve or diminish suffering, though it is recognized that some causes of fatigue cannot be assuaged.⁷³ See the NCCN Guidelines for Palliative Care for more information on intervention for patients receiving end-of-life care (available at www.NCCN.org).

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 physical activity or psychosocial intervention as indicated. Though a recent Cochrane systematic review including 14 studies with 3077 participants showed that there is little evidence to support psychosocial interventions for CRF in patients with incurable

cancer receiving palliative care,²⁸⁵ psychosocial interventions for these patients may focus on meaning and dignity, and gaining acceptance of the limitations imposed by fatigue. It may include a re-emphasis on meaningful family interactions that do not require high-level physical activity.²⁸⁶ Sustaining a sense of meaning has been demonstrated to allow patients with cancer to endorse a high QOL despite significant symptoms.²⁸⁷ Studies suggest that interventions aimed at sustaining or enhancing meaning and/or dignity can significantly reduce distress related to symptoms and improve overall QOL.²⁸⁸⁻²⁹⁰

Although fatigue may increase at the end of life, 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, though it is important to consider patients' physical constraints (see section regarding Physical Activity under *Interventions for Patients on Active Treatment*). Based on a systematic review of 20 exercise studies relevant to fatigue and muscle wasting in multiple myeloma, Strong²⁹¹ summarized weight-bearing precautions for bone metastases and exercise guidelines for adults with solid tumors and hematologic cancers, older cancer survivors, and individuals with CRF. An exercise protocol for multiple myeloma that incorporated aerobic, resistance, and flexibility exercises was also recommended.

Smaller studies assessing the impact of physical activity in patients with cancer at the end of life have been conducted. A group exercise program was evaluated in a pilot study of 63 Norwegian outpatients receiving palliative care.²⁹² The program consisted of two 50-minute sessions twice a week for 6 weeks that combined strength building, standing balance, and aerobic exercise. The exercise participants had less physical fatigue and increased walking distance. There were no adverse effects of exercise, although 29 of the 63 participants did not complete the program due to sudden death, or medical and social



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reasons. A small RCT including 60 patients with advanced cancer receiving palliative care showed that a physiotherapy program including exercise, myofascial release, and proprioceptive neuromuscular facilitation techniques reduced fatigue.²⁹³ A small pilot study was conducted to evaluate an exercise program for 9 individuals with advanced cancer enrolled in a home hospice program.²⁹⁴ A physical therapist guided participants in the selection of several activities (eg, walking, arm exercises with resistance, marching in place, dancing), 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 a trend toward increased QOL and decreased anxiety. Although more research is needed, physical activity, which may include both endurance and resistance exercise as deemed appropriate by the health care provider, shows promise as a fatigue management strategy at the end of life; psychosocial interventions, sleep therapy, family interaction, and nutritional therapy are also helpful.

Pharmacologic Interventions

There continues to be interest in psychostimulant drugs for patients with cancer at the end of life, although studies have had mixed results. Methylphenidate has been shown to yield improvement in fatigue in patients with advanced cancer in two pilot studies.^{295,296} However, two RCTs reported an improvement in fatigue in both the methylphenidate and placebo arms.^{297,298} An RCT in patients with advanced non-small cell lung cancer (n = 160) showed no significant improvement between patients treated with modafinil (n = 75) versus placebo (n = 85). Although well-tolerated, the mean score change between groups as measured by the FACT-F scale was not significant (0.20; 95% CI, -3.56–3.97).²⁷⁴ Overall, methylphenidate may be considered with caution for select terminal patients. Another psychostimulant, dexamphetamine,

was evaluated for fatigue in patients with advanced cancer.²⁹⁹ The results of an RCT 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.

There is evidence supporting the effectiveness of corticosteroids (ie, prednisone and its derivative; dexamethasone) in providing short-term relief for fatigue and improving QOL.³⁰⁰⁻³⁰³ An RCT in patients with advanced cancer demonstrated significant improvement of fatigue in patients receiving dexamethasone (n = 43) compared to patients receiving placebo (n = 41) for 14 days ($P = .008$).³⁰⁴ Improved outcomes were determined from the FACT-F subscale as the primary endpoint. An assessment of overall QOL showed improvement at day 15 ($P = .03$) and in physical well-being measured at day 8 ($P = .007$) and day 15 ($P = .002$) by the Edmonton Symptom Assessment System for physical distress. This study was effective as a short-term therapy, but the long-term effects were not evaluated.³⁰⁴ In an RCT investigating the effects of methylprednisone in patients with advanced cancer receiving opioids, fatigue was measured in patients given methylprednisone twice a day (n = 26) versus patients in the placebo group (n = 24).³⁰⁵ Patients receiving methylprednisone experienced a 17-point improvement on the EORTC-QOL Questionnaire C30 compared to the 3-point decline recorded by the placebo group (-17 vs. 3 points; $P = .003$).³⁰⁵ A prospective observational study from Japan including 179 patients with advanced cancer who received corticosteroids showed that treatment response to corticosteroids was associated with greater baseline fatigue, fair general condition, and absence of fluid retention symptoms.³⁰⁶

Given the toxicity associated with long-term use, consideration of steroids is restricted to the terminally ill, patients with fatigue and concomitant anorexia, and patients with pain related to brain or bone



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metastases. Effects of the progestational agent megestrol acetate has been investigated in these patients. A systematic review paper demonstrated the safety and efficacy of megestrol acetate in treating cachexia for patients with cancer.³⁰⁷ However, a second systematic review and meta-analysis of 4 studies revealed no benefit of progestational steroids compared with placebo for treatment of CRF ($Z = 0.78$; $P = 0.44$).^{200,308} Double-blind RCTs have shown that melatonin³⁰⁹ and Panax ginseng extract³¹⁰ do not significantly improve fatigue in patients with advanced cancer receiving palliative care.

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

Re-Evaluation Phase

Because fatigue may arise at many points during 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 Guidelines for Cancer-Related Fatigue recommend that patients be evaluated regularly for fatigue using a brief screening instrument and be treated as indicated by their fatigue level. Fatigue should be minimally evaluated with the scale outlined in the algorithm; however, there are additional tools for the measurement of fatigue that may be employed to identify fatigue as appropriate (see Appendix).

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

Nonpharmacologic interventions may include a physical activity program to improve functional capacity and activity tolerance; psychosocial programs to manage stress and increase support; implementation of energy conservation strategies; and nutritional, sleep, and other physically based interventions as appropriate. Pharmacologic therapy may include drugs used to treat comorbidities. A 2014 update on the use of the psychostimulant methylphenidate suggests that it may provide some benefit.³¹¹ A second agent that may be helpful for short-term use in advanced cancer is the corticosteroid methylprednisolone.^{46,304,305} However, potential treatment modalities in managing fatigue require further research.



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Effective management of CRF involves an informed and supportive oncology care team that assesses fatigue levels regularly, counsels and educates patients regarding strategies for coping with fatigue, and uses institutional experts for referral of patients with unresolved fatigue.⁴⁸ The oncology care team must recognize the many patient-, provider-, and system-related behaviors that can impede effective fatigue management.⁵⁰ Reducing barriers by use of available resources and evidence-based guidelines increases benefits to patients experiencing fatigue.^{312,313}

Appendix

Fatigue Measurement for the Health Care Professional

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. Lancet 2003;362:640-650. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12944066>.

- *Provides a detailed description of six scales [PFS, FACT-F, SCFS, MFI-20, BFI, CLAS] frequently used in patients with cancer to measure fatigue.*

Jacobsen PB. Assessment of fatigue in cancer patients. J Natl Cancer Inst Monogr 2004:93-97. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15263047>.

- *Includes factors to consider when 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10929689>.

- *Study evaluates psychometric properties of several commonly used fatigue measures (POMS-F, MAF, LFS, MFI).*

National Cancer Institute. Fatigue (PDQ) Health Professional Version. 2014. Available at: <http://www.cancer.gov/cancertopics/pdq/supportivecare/fatigue/HealthProfessional>. Accessed May 1, 2015.

- *Gives citation links to nine commonly used scales to measure fatigue (BFI, FACT-A, FACT-F, PFS, SCFS, FSI, POMS-F, CFS, VAS-F, and MFSI).*

Reeve BB, Stover AM, Alfano CM, et al. The Piper Fatigue Scale-12 (PFS-12): psychometric findings and item reduction in a cohort of breast cancer survivors. Breast Cancer Res Treat 2012;136:9-20. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22933027>.

- *Provides psychometric properties for a shortened version of a commonly used fatigue measure.*

Stover AM, Reeve BB, Piper BF, et al. Deriving clinically meaningful cut-scores for fatigue in a cohort of breast cancer survivors: a Health, Eating, Activity, and Lifestyle (HEAL) Study. Qual Life Res 2013;22:2279-2292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23420495>.

- *This resource provides information about clinically meaningful cut-scores for fatigue using the PFS-R.*

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Commonly Used Tools to Assess Cancer-Related Fatigue^P

Screening Tool/ Assessment	Number/Type of Dimensions	Type of Scale	No. of Items	Length/ Ease of Use	Validated in Patients with Cancer	A/P/E ^S	Reliability/ Internal Consistency	Other
Brief Fatigue Inventory ⁵²	1 (severity)	11-point Likert	9	Short, easy to use	Yes, mixed cancers ^{52,314}	A,P,E	$\alpha=0.82-0.97$	Questions about general activity, mood, walking ability, normal work, relationships, overall QOL; hard to distinguish between mild and moderate; validated in other languages
Daily Fatigue Cancer Scale ³¹⁵	1 (severity)	10-point Likert	3	Short, easy to use	Yes, mixed cancers ³¹⁵	A	na	Items measure tired, lacking energy, and feeling weary
EORTC QLQ-C30 ^{‡, 302}	1 (severity)	4-point Likert	3	Easy to use	Yes, mixed cancers ^{316,317}	A,P,E	$\alpha=0.80-0.85$	Measures physical fatigue; not recommended as the only scale for end-of-life fatigue ³¹⁸
EORTC QLQ-FA12 ^{*, 319}	3 (physical, emotional, cognitive)	4-point Likert	12	Easy to use	Yes, mixed cancers ³¹⁹	A,P,E	$\alpha=0.79-0.90$	To be used in conjunction with EORTC QLQ-C30
Fatigue Questionnaire ³²⁰	1 (severity)	4-point Likert	11	Easy to use	Yes, cancer vs. normal population, ³²⁰ Hodgkin lymphoma ³²¹	A,P,E	$\alpha=0.88-0.90$	Measures physical and mental fatigue
Visual Analogue Fatigue Scale ³²²	1 (severity)	Analogue	18	Short, easy to use	Yes, patients with cancer compared to healthy controls ³²²	A,P,E	$\alpha=0.91-0.96$	Measures physical and mental fatigue; may help measure fatigue in 24-hour period but less effective over longer time periods



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Screening Tool/ Assessment	Number/Type of Dimensions	Type of Scale	No. of Items	Length/ Ease of Use	Validated in Patients with Cancer	A/P/E [§]	Reliability/ Internal Consistency	Other
Fatigue Symptom Inventory ³²³	4 (severity, frequency, diurnal variation, interference)	11-point Likert	14	Reasonable	Yes, breast, ³²³⁻³²⁶ metastatic, ³²⁷ and mixed cancers ³²⁸	A,P	r=0.35–0.75 α=0.92–0.95	Two additional quantifiable fatigue questions; able to distinguish change over time; weak test-retest reliability
Functional Assessment of Cancer Therapy, Fatigue ³²⁹	5 (physical, social/family, emotional, functional, fatigue)	5-point Likert	41/13	Long but subscale is reasonable and simple	Yes, breast, ³³⁰ mixed cancers ^{220,331-333}	A,P,E	r=0.90 α=0.93–0.95	Items consist of general health-related QOL (28 items) plus fatigue subscale of 13 items; lacks construct validity; measures change over time
Multi-Dimensional Fatigue Inventory-20 ³³⁴	5 (general, physical, mental, reduced activity, reduced motivation)	5-point Likert	20	Reasonable	Yes, breast ^{335,336} , uterine, ^{337,338} mixed cancers ^{334,339-341}	A,P,E	α=0.65–0.80	Likert scale incorporates VAS
Multi-Dimensional Fatigue Symptom Inventory ³⁴²	5 (general, physical, mental, emotional, vigor)	5-point Likert	83/30	Variable length, can be complicated	Yes, mixed ^{342,343} and breast cancer ³⁴⁴	A,P	r>0.50 α=0.87–0.96	Full version is long (83 items) but short form is a reasonable alternative ³⁴⁵
Piper Fatigue Score-12 ³⁴⁶	4 (sensory, behavioral/severity, affective meaning, cognitive/mood)	11-point Likert	12	Easy to use	Yes, breast cancer ^{346,347}	P	r=0.87–0.89	Shortened from revised Piper Fatigue Score that has been tested more extensively ^{162,346-354} ; reliability is based on subscales in single study



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Screening Tool/ Assessment	Number/Type of Dimensions	Type of Scale	No. of Items	Length/ Ease of Use	Validated in Patients with Cancer	A/P/E [§]	Reliability/ Internal Consistency	Other
NCCN Problem List	1 (general)	Dichotomous (yes/no)	1	Easy to use	Yes, breast cancer and colorectal cancer ³⁵⁵	A	na	Taken from NCCN Distress Thermometer and Problem List
PROMIS CAT ³⁵⁶	3 (fatigue, sleep disturbance, sleep impairment)	1 (never) to 5 (always)	Up to 20	Not burdensome	Yes, mixed cancers ³⁵⁶	A	$\alpha=0.92-0.94$	Scores correlate significantly with FACIT-Fatigue and the Insomnia Severity Index ($r = -0.57-0.83$, $P < .001$) ³⁵⁶
Schwartz Cancer Fatigue Scale, Revised ³⁵⁷	2 (physical and perceptual)	5-point Likert	6	Reasonable and clear	Yes, mixed cancers ^{357,358}	A	$\alpha=0.90$	Shortened from the original 28-item Schwartz Cancer Fatigue Scale ³⁵⁹

[¶] Tools are grouped as unidimensional tools followed by multidimensional tools and listed in alphabetical order within each subset.

[§] A/P/E, active treatment/post-treatment/end-of-life.

[‡] EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30

* EORTC QLQ-FA12, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Cancer-Related Fatigue module



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