National Comprehensive Cancer Network®

## NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Cancer-Related Fatigue

Version 2.2023 — January 30, 2023

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# NCCN Guidelines Version 2.2023
# Cancer-Related Fatigue

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# NCCN Guidelines Version 2.2023
# Cancer-Related Fatigue

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

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

# NCCN Guidelines Version 2.2023
# Cancer-Related Fatigue



**Updates in Version 2.2023 of the NCCN Guidelines for Cancer-Related Fatigue from Version 1.2023 include:**

MS-1
• The Discussion was updated to reflect the changes in the algorithm.

**Updates in Version 1.2023 of the NCCN Guidelines for Cancer-Related Fatigue from Version 2.2022 include:**

FT-4
• Primary Evaluation for Fatigue Score: Moderate or Severe Age >12 y (4–10), Age 7–12 y (3–5), or Age 5–6 y (Tired)
  ▸ Assessment of Treatable Contributing Factors
    ◊ Comorbidities/Cancer treatment sequelae
      – Bullet 1 revised: Alcohol~~/~~ *and drug misuse and illicit* substance ~~ab~~use

FT-5
• Title revised: General Strategies for the Management of Fatigue*/Patient and Family/Caregiver Education and Counseling*
• "Patient and Family/Caregiver(s) Education and Counseling with" was removed from the left column.

FT-6
• Interventions for Patients on Active Treatment
  ▸ Nonpharmacologic
    ◊ Bullet removed: Physically based therapies
  ▸ Pharmacologic
    ◊ Bullet 1 revised: Consider psychostimulants (methylphenidate) *in consideration of other modifiable causes* ~~after ruling out other causes of fatigue~~ (Also for FT-7 and FT-8)
    ◊ Bullet removed: Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines (See appropriate NCCN Guidelines for Supportive Care)
    ◊ Bullet removed: Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities (Also for FT-7 and FT-8)
  ▸ Footnotes
    ◊ Footnote k added: Morishita S, et al. Hematology 2020;25:95-100.
    ◊ Footnote m revised: A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and behaviors and to facilitate psychological adjustment. *Trial evidence shows CBT-I can improve fatigue among participants with insomnia symptoms.* (Also for FT-7)
    ◊ Footnote p revised: Bright white light therapy of 1250–10,000 lux is most frequently self-administered in the early morning for 30–*40* ~~90~~ minutes. Timing needs to be adjusted for those who sleep during the day *(Xiao P, et al. J Pain and Symptom Manage 2022;63:e188-e202)*.

FT-7
• Interventions for Patients Post-Treatment
  ▸ Pharmacologic
    ◊ Bullet removed: Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines (See NCCN Guidelines for Adult Cancer Pain, Distress Management, and Hematopoietic Growth Factors) (Also for FT-8)

ABBR-1
• New section added: Abbreviations

# NCCN Guidelines Version 2.2023
# Cancer-Related Fatigue

## DEFINITION OF CANCER-RELATED FATIGUE

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

**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.**

## 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 and signs, such as pain, emotional distress, anemia, and sleep disturbances, in symptom clusters. Therefore, patients should be screened for multiple symptoms and signs 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 family/caregiver(s) 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, occupational therapy, physical medicine).**
- **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.**

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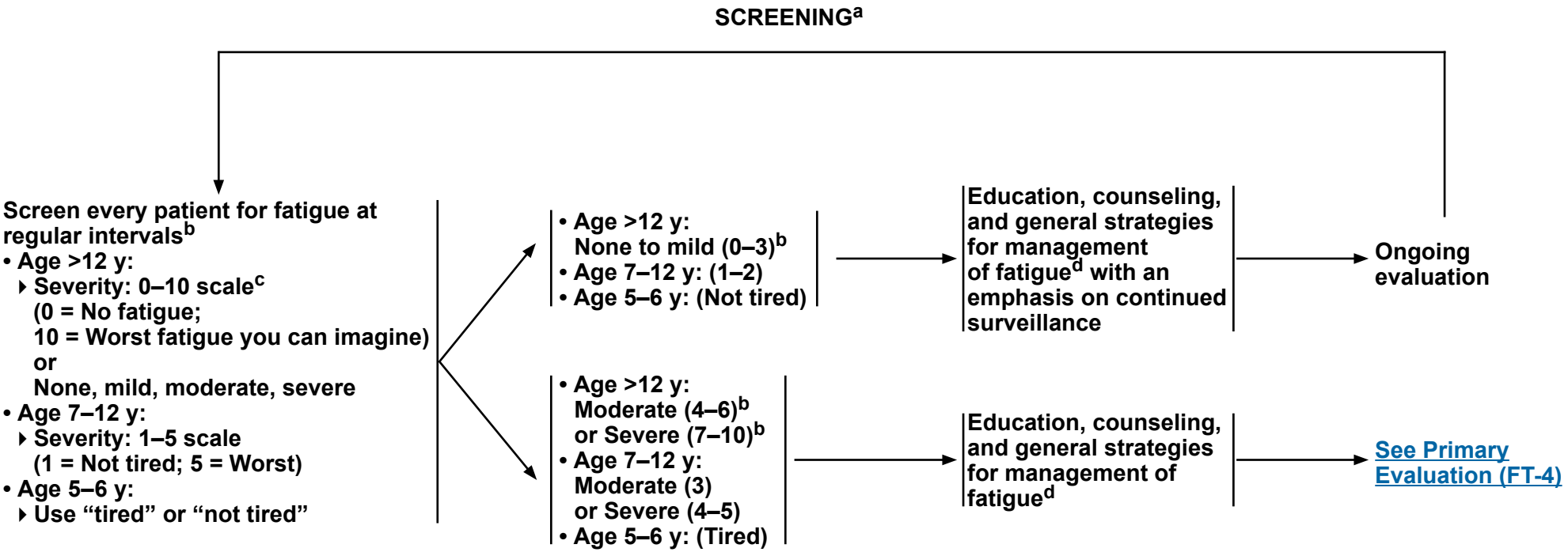


[a] See Discussion Appendix for screening resources.
[b] Recommended screen and re-evaluation: "How would you rate your fatigue on a scale of 0–10 over the past 7 days?"
[c] Butt Z, Wagner LI, Beaumont JL, et al. Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. J Pain Symptom Manage 2008;35:20-30.
[d] See General Strategies for the Management of Fatigue/Patient and Family/Caregiver Education and Counseling (FT-5).

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**PRIMARY EVALUATION FOR 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, treatments, and recent hospitalizations
  - Cancer treatment (eg, radiation therapy, systemic therapy)
  - Consider recurrence and/or progression
- Medications/side effects/drug interactions/misuse
  - See NCCN Guidelines for Older Adult Oncology (OAO-H)
- Review of systems
- In-depth fatigue history
  - Onset, pattern, and 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 (eg, insomnia, hypersomnia/narcolepsy, obstructive sleep apnea, restless legs syndrome, circadian rhythm sleep-wake disorders)
- Nutritional deficits/imbalance
  - Vitamin imbalance
  - Weight/caloric intake changes
  - Fluid electrolyte imbalance: sodium, potassium, calcium, and magnesium
- Decreased functional status
  - Physical activity level
  - Deconditioning
- Comorbidities/Cancer treatment sequelae
  - Alcohol and drug misuse and illicit substance use
  - Cardiac dysfunction
  - Endocrine dysfunction (eg, hot flashes, hypothyroidism, hypogonadism, adrenal insufficiency), with special concern for people receiving immunotherapy
  - 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 Management of Cancer- and Chemotherapy-Induced Anemia in the NCCN Guidelines for Hematopoietic Growth Factors →
- Sleep disturbance/poor sleep hygiene → See NCCN Guidelines for Survivorship →
- Nutritional deficit/imbalance →
- Decreased functional status →
- Comorbidities → See NCCN Guidelines for Management of Immunotherapy-Related Toxicities →

→ See (FT-5) for General Strategies for the Management of Fatigue/Patient and Family/Caregiver Education and Counseling

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## GENERAL STRATEGIES FOR THE MANAGEMENT OF FATIGUE/ PATIENT AND FAMILY/CAREGIVER EDUCATION AND COUNSELING

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

→ **Active Treatment**[e,f,g]

- Consider initiation and/or encourage maintenance of a physical activity/exercise program
- Self-monitor fatigue levels
- Energy conservation[h]
  - Set priorities and realistic expectations
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Use labor-saving and assistive devices[i]
  - Postpone nonessential activities
  - Limit naps to not interfere with night-time sleep quality
  - Have a structured daily routine
  - Attend to one activity at a time
- Consider referral to appropriate specialist or supportive care provider
- Review list of medications to identify agents that may be contributing to fatigue and adjust accordingly

→ See (FT-6)

- Information about known pattern of fatigue during and following treatment

→ **Post-Treatment**[e,f,g]

- See above (Active Treatment)

→ See (FT-7)

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

→ **End of Life**[e,f,g,j]

- See above (Active Treatment)
- Eliminate nonessential activities
- Conserve energy for valued activities

→ See (FT-8)

[e] See Discussion for information on differences between active treatment, post-treatment, and end-of-life treatment.
[f] Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources.
[g] There is limited scientific evidence for children.
[h] There is a lack of scientific evidence in this area.
[i] Examples include use of reachers for grasping items beyond arm's length, sock aids for pulling on socks, rolling carts for transporting items, wheelchairs, walkers, commodes, escalators and elevators for traveling between building floors, and electrical appliances for performing common household tasks (eg, opening cans).
[j] Also see NCCN Guidelines for Palliative Care.

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## INTERVENTIONS FOR PATIENTS ON ACTIVE TREATMENT[e,f,g]

**Nonpharmacologic**

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

**Pharmacologic**

- Consider psychostimulants[q] (methylphenidate) in consideration of other modifiable causes

→ Repeat screening and evaluation
See (FT-3) and (FT-4)
See (FT-5) for General Strategies for the Management of Fatigue/Patient and Family/Caregiver Education and Counseling

[e] See Discussion for information on differences between active treatment, post-treatment, and end-of-life treatment.
[f] Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources.
[g] There is limited scientific evidence for children.
[k] Morishita S, et al. Hematology 2020;25:95-100.
[l] See NCCN Guidelines for Survivorship: Physical Activity.
[m] A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and behaviors and to facilitate psychological adjustment. Trial evidence shows CBT-I can improve fatigue among participants with insomnia symptoms.
[n] CBT/BT influences thoughts and promotes changes in behavior; it includes a variety of strategies (eg, cognitive restructuring, relaxation, mindfulness).
[o] Supportive expressive therapies (eg, support groups, counseling, journal writing) facilitate expression of emotion and foster support from one or more people.
[p] Bright white light therapy of 1250–10,000 lux is most frequently self-administered in the early morning for 30–40 minutes. Timing needs to be adjusted for those who sleep during the day (Xiao P, et al. J Pain and Symptom Manage 2022;63:e188-e202).
[q] Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in older adults and patients with cancer.

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## INTERVENTIONS FOR PATIENTS POST-TREATMENT[e,f,g]

**Nonpharmacologic**

- **Physical activity (category 1)**
  - **Maintain optimal level of activity**
  - **Consider initiation and/or encourage maintenance of a physical activity/exercise program, as appropriate per health care provider, consisting of cardiovascular endurance (walking, jogging, or swimming) and resistance (weights) training[l]**
  - **Cautions in determining level of activity:**
    - ◊ **Late effects of treatment (eg, cardiomyopathy)**
    - ◊ **Safety issues (ie, assessment of risk of falls)**
  - **Consider referral to rehabilitation: physical therapy, occupational therapy, and physical medicine**
  - **Yoga (category 1)**
- **Psychosocial interventions (category 1)**
  - **CBT[l]/BT (category 1)[n]**
  - **Mindfulness-based stress reduction (category 1)**
  - **Psycho-educational therapies/Educational therapies (category 1)**
  - **Supportive expressive therapies (category 1)[o]**
- **CBT-I[m] (category 1)**
  - **Stimulus control/Sleep restriction/Sleep hygiene**
- **Bright white light therapy**
- **Acupuncture**
- **Nutrition consultation**

**Pharmacologic[r]**

- **Consider psychostimulants[q] (methylphenidate) in consideration of other modifiable causes**

→ **Repeat screening and evaluation**
**See (FT-3) and (FT-4)**
**See (FT-5) for General Strategies for the Management of Fatigue/Patient and Family/Caregiver Education and Counseling**

[e] See Discussion for information on differences between active treatment, post-treatment, and end-of-life treatment.
[f] Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources. Consider referral to appropriate specialist or supportive care provider.
[g] There is limited scientific evidence for children.
[l] See NCCN Guidelines for Survivorship: Physical Activity.
[m] A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and behaviors and to facilitate psychological adjustment. Trial evidence shows CBT-I can improve fatigue among participants with insomnia symptoms.
[n] CBT/BT influences thoughts and promotes changes in behavior; it includes a variety of strategies (eg, cognitive restructuring, relaxation, mindfulness).
[o] Supportive expressive therapies (eg, support groups, counseling, journal writing) facilitate expression of emotion and foster support from one or more people.
[q] Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in older adults and patients with cancer.
[r] Adjust 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[e,f,g,j]

**Nonpharmacologic**

- **Physical activity[s]**
  - **Optimize level of activity with careful consideration of the following:**
    - ◊ **Patient goals**
    - ◊ **Bone metastases**
    - ◊ **Thrombocytopenia**
    - ◊ **Anemia**
    - ◊ **Fever or active infection**
    - ◊ **Limitations secondary to metastases or other comorbid illnesses**
    - ◊ **Recommendations for physical and occupational therapy**
    - ◊ **Safety issues (ie, assessment of risk of falls)**

**Pharmacologic**

- **Consider psychostimulants[q] (methylphenidate) in consideration of other modifiable causes**
- **Consider short-term use of corticosteroids[t] (prednisone or dexamethasone [adults only]) for patients with advanced cancer**

→ **Repeat screening and evaluation**
**See (FT-3) and (FT-4)**
**See (FT-5) for General Strategies for the Management of Fatigue/ Patient and Family/Caregiver Education and Counseling**

[e] See Discussion for information on differences between active treatment, post-treatment, and end-of-life treatment.
[f] Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources. Consider referral to appropriate specialist or supportive care provider.
[g] There is limited scientific evidence for children.
[j] Also see NCCN Guidelines for Palliative Care.
[q] Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in older adults and patients with cancer.
[s] A structured exercise protocol depending on the patient's tolerance level can be used to improve fatigue experienced by patients with advanced cancer in hospice care (Vira P, et al. Am J Hosp Palliat Care 2021;38:503-511).
[t] Yennurajalingam S, et al. J Clin Oncol 2013;31:3076-3082. Paulsen O, et al. J Clin Oncol 2014;32:3221-3228.

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## ABBREVIATIONS

| | |
|---|---|
| **BT** | **behavioral therapy** |
| **CBT** | **cognitive behavioral therapy** |
| **CBT-I** | **cognitive behavioral therapy for insomnia** |

| 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.

National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2023
# Cancer-Related Fatigue

## Discussion

This discussion corresponds to the NCCN Guidelines for Cancer-Related Fatigue. Last updated: January 30th, 2023.

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## Overview

Fatigue in patients with cancer has been underreported, underdiagnosed, and undertreated. 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,[9-12] hypothalamic-pituitary-adrenal (HPA) axis dysregulation,[12] circadian rhythm desynchronization,[13] skeletal muscle wasting,[14] and genetic dysregulation.[15] These mechanisms may be interdependent.[16] Ultimately, there is limited evidence to support a firm conclusion regarding underlying causes of CRF, and longitudinal studies that evaluate fatigue before, during, and after cancer treatment are needed.[16]

CRF is very common. A systematic review and meta-analysis of 129 studies with 71,568 patients reported a 49% prevalence of fatigue but noted a significant degree of heterogeneity among studies.[17] The prevalence of fatigue decreased from 65% in 1996 to 44% in 2020. A contributing factor could be the publication and implementation of multiple guidelines on CRF.[17] According to a survey of 1569 patients with cancer, the symptom is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.[18,19] In patients with metastatic disease, the prevalence of CRF exceeds 75%.[20-23] 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.[24] 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).[25] 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; relative risk [RR], 1.18; 95% CI, 1.08–1.28) and chemotherapy treatment (RR, 1.12; 95% CI, 1.06–1.19).[26] A study including 1869 patients treated with hematopoietic cell transplantation (HCT) 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.[6,26-35] Persistent CRF affects quality of life (QOL), as patients become too tired to fully participate in the roles and activities that make life meaningful.[28,36-38] CRF may also influence the time it takes to return to work following treatment.[39] 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.[40]

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 lasting 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.[41] 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 Clinical Practice Guidelines (NCCN Guidelines®) Cancer-Related Fatigue, first published in 2000[42] 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 at www.NCCN.org.

## 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 peer-reviewed biomedical literature.[43]

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 during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. When citing published studies and recommendations from other organizations, the terms used (eg, *male*, *female*) reflect the cited sources.

The complete details of the development and update of the NCCN Guidelines are available at www.NCCN.org.

## Defining Cancer-Related Fatigue

The distinction between tiredness, fatigue, and exhaustion is generally not made in practice, despite conceptual differences.[44,45] The Cancer-Related Fatigue 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.[46]

## 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.[47]

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 indicated.[48] The history and physical examination, laboratory data, and descriptions of patient behavior by family members/caregivers, 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.[49] 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.[50] However, current practices in assessing and treating fatigue are inadequate and inconsistent at many institutions.[51] 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.[52] 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. Referral to an appropriate specialist or supportive care provider should be considered. Supportive care staff may include experts in survivorship, palliative care, integrative oncology, psychology, psychiatry, physical therapy, occupational therapy, and physical medicine 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.[52] 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 four 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, 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 semi-quantitative assessment should be performed and documented. For example, on a 0 to 10 numeric rating scale (0 = 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 (aged 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/caregiver 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.[6,26]

Currently, screening is not systematic nor effective in many practice settings for various reasons, which often include patient or family/caregiver 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 may also be 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.[53] 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/caregivers 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. Amarsheda et al[54] described multiple instruments used to assess CRF in breast cancer.

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.[55] 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.[24] 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, the patient's response to treatment (see *Primary Evaluation* in the algorithm), and recent hospitalizations. 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/caregivers may substantially reduce their anxiety levels.

Review and adjustment 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 and/or misuse 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 increased fatigue. Polypharmacy (ie, use of ≥4 medications) and potentially inappropriate medication use is common among older adults with cancer.[56] It may be appropriate to 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.[57] Fatigue is a major cause of functional dependence for patients with cancer, especially among the elderly.[58] 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 other forms of support.[59] The availability of dependable caregivers can significantly impact the functional, emotional, and financial capacity of a

patient coping with cancer and the pursuant fatigue. A support network can also 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, anemia, sleep disturbance, nutritional deficits/imbalance, decreased functional status, and comorbidities/cancer treatment sequelae. In a randomized controlled trial (RCT) of 152 patients with advanced cancer, protocolized 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.[60]

Descriptive studies have shown that, in both adults and children, fatigue seldom occurs by itself and more commonly clusters with sleep disturbance, emotional distress (eg, depression, anxiety), or pain.[61-64] 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.[5,65,66]

Sleep disturbances are a neglected problem in oncology[67] and may range from hypersomnia to insomnia.[68,69] Sleep disturbances are prevalent in 30% to 75% of patients with cancer.[70] 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 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, television 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 imbalance/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.

CRF is associated with decreased functional status. A survey conducted by Mustian and colleagues that included 753 patients receiving systemic chemotherapy showed that CRF interfered with physical functioning in the majority of patients.[71] Interference was moderate, and was noted to be

higher in females, 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.[72,73] However, before recommending an exercise program, the health care provider or exercise expert (eg, physiatrist, physical therapist) should assess the conditioning level of the patient. It is often difficult to convince patients with fatigue that exercise will improve their symptoms. It may be best to begin with discussions and low-level activities, which can gradually be increased 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, and neurologic dysfunction, as well as infection. In patients receiving immunotherapy treatment, fatigue may be a presenting symptom of an endocrine disorder secondary to immunotherapy, such as a thyroid or pituitary disorder.[74] There is also a high incidence of thyroid dysfunction in normal individuals and in patients receiving thyroid medications.[75] Development of hypothyroidism occurs after radiation therapy for Hodgkin disease and other non-Hodgkin lymphomas, head and neck cancers, and breast cancer, as well as after total body irradiation in bone marrow transplantation. Hypogonadism is commonly seen in patients with advanced cancer. A cross-sectional pilot study including males with advanced cancer showed that abnormally low levels of testosterone may be associated with fatigue. [76] 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. Therefore, attention should be given to thyroid and endocrine problems (including hot flashes, hypothyroidism, hypogonadism, or adrenal insufficiency) in patients with cancer. Finally, health care providers should also be alert for signs of alcohol and drug misuse and illicit substance use. 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.[77]

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, Hematopoietic Growth Factors (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/Patient and Family/Caregiver Education and Counseling

Education about fatigue and its natural history should be offered to all patients with cancer,[53] especially 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), although the quality of the evidence was sometimes low.[78] Patients should be informed that if fatigue occurs, 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 underreporting 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.[79,80] 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 (physical activity and energy conservation) useful for coping with fatigue.[53,81] A meta-analysis including eight studies with 478 breast cancer survivors showed that exercise might improve CRF by counteracting low-grade inflammatory mediators (eg, interleukin 6).[82] 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.[83] A multisite clinical trial of energy conservation in 296 patients receiving cancer treatment reported significantly lower fatigue in patients receiving the experimental intervention.[84] However, evidence supporting energy conservation in patients with CRF is generally lacking. 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/caregivers 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 not interfere with night-time sleep quality. Patients may also use labor-saving techniques such as wearing a bathrobe 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 log or diary that allows the patient to self-monitor fatigue levels and ascertain peak energy periods and then plan activities accordingly within a structured routine.

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. It also convened a roundtable discussion and published specific guidelines for physical activity testing and exercise programs for patients with cancer.[85] 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.[86-90]

## Interventions for Patients on Active Treatment

### *Nonpharmacologic Interventions*

Nonpharmacologic treatment of fatigue is beneficial in patients with cancer.[91-93] 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; $P = .05$).[94] Of the specific nonpharmacologic interventions during active cancer treatment, the panel recommends physical activity (category 1), massage therapy (category 1), and psychosocial interventions. There is also supporting evidence for nutrition consultation, cognitive behavioral therapy (CBT) for insomnia, and bright white light therapy (BWLT) for CRF treatment in patients on active cancer treatment.[95] These interventions align with recommendations from the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines[96] and the Oncology Nursing Society (ONS).[97-99] Both American Society of Clinical Oncology (ASCO)[100] and the pan-Canadian practice guidelines[101] 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*

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 associated exercise with improvement in fatigue for patients with breast cancer,[102,103] prostate cancer,[104,105] colorectal cancer,[106] lymphoma,[107] and hematologic malignancies[108,109]; in patients who are undergoing adjuvant radiation therapy[110]; and in patients who have undergone HCT.[111]

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.[112-117] Other smaller analyses confirmed a significant effect of exercise intervention on fatigue.[118-130] A systematic review of 16 meta-analyses showed a general benefit of exercise for CRF, but the ability to draw definitive conclusions about this benefit is limited by the variety of participant characteristics, fatigue measurement tools, and intervention characteristics evaluated in these meta-analyses.[131] A systematic review of systematic reviews and meta-analysis of 10 studies reported that physical training had a beneficial effect on fatigue in all cancer populations (SMD, -0.33; 95% CI, -0.43 to -0.23).[132] Wolvers and colleagues identified three main physical behavior profiles, suggesting that treatment options should be better tailored to suit specific needs.[133]

It is reasonable to encourage all patients to engage in a moderate level of physical activity during and after cancer treatment. Currently there is no 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.[134] 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.[72,135-139]

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

- Bone metastases
- Thrombocytopenia[140] (low platelets)
- Anemia (low red blood cells)
- Fever, active infection, or post-surgery
- 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 cardiovascular endurance (eg, walking,[141,142] 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 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).[143] When compared to exercise, however, this review showed that yoga did not significantly reduce CRF, although the quality of evidence was low. Several RCTs have demonstrated that yoga intervention impacts CRF during treatment.[144-151] Three of these studies targeted patients undergoing radiation therapy.[144,145,150] In an RCT including 352 females with non-metastatic breast cancer undergoing chemotherapy, a Tibetan yoga program did not significantly impact CRF compared to a stretching program and usual care.[152] 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.[153] Fatigue was improved in patients randomized to receive 8 weeks of Anusara yoga sessions, twice per week ($P$ < .001).

Some randomized trials have shown some benefit of tai chi and qigong, a practice involving movement, posture, and breathing, to CRF.[154-158] These benefits have also been observed in two systematic reviews.[159,160] However, one of these reviews showed that tai chi has a significant short-term benefit on CRF but that the long-term benefit is less clear.[159] A systematic review and meta-analysis of 1268 patients with breast cancer suggest that at the 3-month follow-up, tai chi did not alleviate fatigue when compared to conventional supportive care interventions, such as CBT.[161] However, tai chi along with conventional supportive care interventions significantly reduced symptoms of fatigue.

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.[162] 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.[148] 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.

*Massage Therapy*

Physically based therapies are those performed on a patient by a therapist or lay person, and include massage therapy or acupuncture. Massage therapy may be effective in reducing CRF,[163-166] 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).[167] The panel recommends massage therapy as a category 1 recommendation for treatment of CRF in patients on active treatment.

*Acupuncture/Acupressure*

Six systematic reviews suggest that acupuncture and acupressure may have beneficial properties, although the studies acknowledge that a paucity of data makes it difficult to definitively evaluate the benefits.[168-173] Positive effects of acupuncture on fatigue have been reported in small samples but need to be confirmed in larger RCTs.[174,175] These small trials were conducted during active non-palliative radiation therapy,[176,177] and during and after chemotherapy treatment.[178-180] 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).[181] 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 (NSCLC) 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).[182]

*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.[183]

Several meta-analyses evaluated the impact of psychosocial interventions on CRF. Analyzing 41 studies on 3620 patients with cancer, Kangas et al[120] reported a weighted pooled mean effect of -0.31 for psychosocial interventions on fatigue. Goedendorp et al[184] reported that, of 27 RCTs included in their analysis, seven showed significantly reduced fatigue. Of interest, 80% of fatigue-specific interventions were effective, compared to 14% of non-specific strategies. Jacobsen et al[185] 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 CBT/behavioral therapy (BT), psycho-educational therapies/educational therapies, and supportive expressive therapies, based on review of three meta-analyses.[120,184,185] 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).[98,99,186] 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 colleagues[119] reported that, like exercise programs, behavioral techniques including CBT, 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/BT[187-194] and psycho-educational therapies/educational therapies,[95,195-206] 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.[207] 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, arts therapy, and stress reduction based on mindfulness have been evaluated in combination with CBT approaches, although some of these therapies have also been evaluated on their own.[194,208-219] 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 females 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 ($P < .05$).[220] Mediation analyses showed that these results were accounted for by self-reported improvements in sleep quality. Another RCT including 155 patients with breast cancer found no statistically significant difference in fatigue between those randomized to a stress management group and those in a control group.[221] A systematic review and analysis of 29 studies with 3476 participants or survivors diagnosed with different cancers found that mindfulness-based stress reduction, especially for breast cancer, improved multiple physiological parameters such as fatigue and stress.[222] However, the benefits might not be long-lasting.[223] The results of a Bayesian network meta-analysis that examined multiple interventions irrespective of the cancer stage determined that mindfulness-based stress reduction therapy, psychoeducational therapy, and CBT improved CRF.[224] Stress management and meditation interventions did not significantly improve CRF, nor did multimodal interventions. One RCT determined that music therapy during radiation treatment for 116 patients with breast or gynecological cancer could alleviate CRF and depression.[225] However, larger studies are needed.

An e-health-based self-management system can help alleviate fatigue but does not improve overall QOL.[226]

*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.[227] Adequate hydration and electrolyte balance are also essential in preventing and treating fatigue.[105] Large RCTs are needed to determine the impact of nutrition therapy on CRF.

*Sleep Therapy*

There are numerous types of CBTs for insomnia; 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.[228] Techniques to promote a good night's sleep and optimal functioning the next day, such as avoiding caffeine after noon and establishing an environment that is conducive to sleep (eg, dark, quiet, comfortable), are components of sleep hygiene. These strategies were used in a pilot study with females during adjuvant breast cancer treatment with chemotherapy. Sleep/wake patterns remained consistent with normal values except for increased number and length of nighttime awakenings.[229] For children with cancer, a consistent bedtime and routine, an environment conducive to sleep, and the presence of security objects (such as blankets and toys) are effective measures (see *Assessment of Treatable Contributing Factors*).

*Bright White Light Therapy*

BWLT involves exposure to very high fluorescent light (typically 1250–10,000 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.[230-233] BWLT stimulates the suprachiasmatic nucleus of the hypothalamus, which regulates circadian rhythms.

BWLT has been associated with positive changes in fatigue in females with breast cancer during treatment with chemotherapy.[234,235] 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, although BWLT is most commonly administered in the early morning for 30 to 40 minutes, and timing may be adjusted for those who sleep during the day.[236] A systematic review and meta-analysis of 13 RCTs reported that light therapy, at an intensity of 417.9 to 12,000 lux, alleviated CRF (SMD = 0.45; $P$ = .007).[236] In a meta-analysis of nine studies, Hung et al[237] reported that compared to dim red light, daily BWLT for 30 minutes in the morning was associated with an amelioration in CRF severity ($k$ = 5; Hedges' $g$ = -0.414; 95% CI, -0.740 to -0.087; $P$ = .013). 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.[238] A systematic review and meta-analysis demonstrated that 26% of patients treated with a placebo reported an improvement in CRF compared to 36% in patients treated by other means.[239] Another study found that the placebo response is non-trivial and statistically significant.[240] As such, studies need to have sufficient power to account for the placebo effect. This should be taken into consideration when designing a clinical trial.

Although 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 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 (http://www.cancer.gov/cancertopics/pdq/supportivecare/sleepdisorders/HealthProfessional). Prescribing considerations for these classes of agents include increased likelihood of problems with daytime sleepiness, fatigue, withdrawal symptoms, dependency, rebound insomnia, sleep maintenance, memory, anticholinergic symptoms, orthostasis, and the potential for drug-drug interactions involving the cytochrome p450 isoenzyme system.

A systematic review of systematic reviews and pooled meta-analysis of six studies comprising patients undergoing cancer treatment and/or after treatment determined that psychostimulants may be moderately effective in reducing CRF (SMD, -0.20; 95% CI, -0.32 to 0.08; $P < .0001$).[241] The psychostimulant methylphenidate significantly reduced fatigue (SMD, -0.69; 95% CI, -1.29 to -0.09; $P < .0001$). Other studies that evaluated methylphenidate for its effect on CRF yielded mixed results in patients undergoing cancer therapy.[242-245] A meta-analysis including seven studies showed that methylphenidate reduces CRF compared to a placebo (SMD, -0.28; 95% CI, -0.44 to -0.12).[246] Analyzing five RCTs, Minton et al[247] 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 al[248] 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 ($P = .007$).[249] 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 chemotherapy.[250] 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 to 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, although overall between-group differences did not reach statistical significance.[251] A meta-analysis including three studies showed that modafinil did not significantly reduce CRF, compared to placebo treatment.[246] 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. Although one review showed no benefit of coenzyme Q10 and guarana,[211] another systematic review showed that guarana extract combined with a fatigue reduction diet may successfully

treat CRF.[252] There may also be some data to support the use of American ginseng.[211] 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 of Wisconsin ginseng was observed.[253] 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 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; $P = .02$).[254] A systematic review of seven clinical trials and one retrospective study concluded that although there is some evidence that ginseng is effective at combating CRF, there are insufficient high-quality trials to fully support the inclusion of ginseng as a standard treatment option for CRF.[255] Although an RCT showed that L-carnitine may be associated with improved fatigue in patients with hypothyroidism who underwent surgery for thyroid cancer ($n = 27$; $P < .05$),[256] other studies have shown no significant benefit of this dietary supplement on CRF.[211,257,258]

Based on currently available data, the panel included consideration of the psychostimulant methylphenidate in consideration of other modifiable causes of fatigue for patients undergoing active cancer treatment. Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Use of psychostimulants in older adults should be treated with caution, as older adults may need a lower dosage than younger adults.[259] 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.[260,261] One small study ($N = 40$) showed improved CRF after 4 weeks of treatment with 150 mg of the bupropion sustained-release antidepressant.[262] Antidepressants are not recommended to reduce fatigue.

### 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.[263] Patients may continue to report unusual fatigue for months or years after treatment cessation.[27,29-32,79,264] The cause of fatigue during post-treatment is unclear and probably multifactorial.[265] Researchers have suggested that such fatigue may be due to persistent activation of the immune system[27,266] or to other factors, including the late effects of treatment on major organ systems.[266] 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.[266] 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.[27] 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,[263,267-270] lack of comparison groups,[268] heterogeneous samples,[267] differing fatigue scales, lack of consistency in applying diagnostic criteria,[271] small sample sizes,[266] 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 and disease-free have been conducted in White, English-speaking patients with breast cancer,[27,266,269] and in patients treated with peripheral stem cell or bone marrow transplant[272,273] with few exceptions.[29,31,32] 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 *International Classification of Diseases, Tenth Revision* (ICD-10) diagnostic criteria are applied,[267] 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.[274] 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.[80] As a consequence, what constitutes valid incidence and prevalence rates in patients who are disease-free requires more study.

Risk factors associated with fatigue during post-treatment of patients who are disease-free include pretreatment fatigue, anxiety and depression levels,[275] physical activity levels,[276,277] coping methods and cancer-related stressors, comorbidities, type of malignancy, prior treatment patterns, and treatment late effects. In a Norwegian study of Hodgkin disease survivors in remission for more than 5 years, higher fatigue levels were documented in those who had pulmonary dysfunction; the prevalence of chronic fatigue was two to three times higher than in survivors without pulmonary dysfunction.[274] No significant correlations in this study were found between fatigue and cardiac sequelae as measured by echocardiography, exercise testing, and chest radiography.[274]

### *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[77]; 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 cardiovascular 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.[77,85,278-288] 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.[289] A systematic review of 140 independent meta-analyses by Fuller et al found a significant beneficial effect of aerobic and resistance exercises in 75% of the studies.[290] The results from a systematic review and meta-analysis of RCTs that included

individuals with colorectal cancer pre-treatment, during treatment, or following treatment determined that compared to usual care, exercise improved health outcomes such as fatigue (SMD, 0.23; 95% CI, 0.01–0.45; *P* = .04) and QOL (SMD, 0.21; 95% CI, 0.05–0.37; *P* < .01).[106] A Cochrane systematic review including 26 studies of physical activity interventions for females with breast cancer who completed adjuvant therapy showed small improvements in CRF upon intervention completion (SMD, -0.32; 95% CI, -0.47 to -0.18), with results from four trials showing that improvements are sustained for at least 3 months post-intervention (SMD, -0.47; 95% CI, -0.84 to -0.11).[291] However, the beneficial effects of CBT diminish over long periods of time. Van Gessel et al followed up with patients from two RCTs and found that only about half of the participants still reported comparable fatigue levels as they did immediately post-CBT.[292] A meta-analysis including nine RCTs with 1156 breast cancer survivors showed that supervised exercise may improve CRF (SMD, -0.51; 95% CI, -0.81 to -0.21).[293] 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.[276,277] 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).[282]

Yoga may also reduce fatigue in cancer survivors, and it is recommended for these patients by the Society for Integrative Oncology.[211] 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).[92] 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).[146] 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.[147] 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, although effects were not significantly different from participants who received a strength training intervention.[294] The panel recommends yoga for patients who have completed treatment (category 1).

A systematic review and meta-analysis of 22 RCTs found that that there was low-level evidence that tai chi can improve QOL and sleep and moderate-level evidence that tai chi can reduce fatigue.[295] Another systematic review also reported improved fatigue and sleep quality in cancer survivors who underwent tai chi training but indicated that the evidence level was low.[296] Qigong was found to ameliorate sleep and fatigue post-intervention in a systematic review and meta-analysis.[297] However, the beneficial effects were not significant after a period of 3 months. Chinese traditional wushu was evaluated in a systematic review and meta-analysis of 18 studies.[298] While no benefit was noted in terms of cancer-related fatigue in patients who are breast cancer survivors, the researchers found an improvement in sleep quality.

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.[119,195,265,299-308] 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).[309] Another intervention including 252 distressed (ie, score of 4 or higher on the NCCN Distress Thermometer) breast cancer survivors showed that females randomized to receive a mindfulness-based intervention reported a significantly greater reduction in fatigue, compared to females who were randomized to receive a supportive expressive group therapy intervention, with between-group effects being large ($d$ = 0.45).[310] Additional small RCTs also support the use of mindfulness-based interventions for CRF in cancer survivors.[311,312] One RCT with 89 breast cancer survivors assessed the benefits of *Reimagine*, an online symptom self-management curriculum, and determined that *Reimagine* has a strong impact on fatigue and depression.[313] Further studies are needed to further evaluate the impact of psychoeducation therapies.

Additional details on these interventions are provided in the preceding pages in the section on *Psychosocial Interventions* under *Interventions for Patients on Active Treatment*.

*Additional Nonpharmacologic Approaches*

CBT for insomnia (category 1) and nutrition consultation may be helpful for fatigue management during post-treatment.[186,314] 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.[315-319] Positive effects on both sleep and fatigue after four to five weekly BT sessions have been reported in RCTs of patients in the survivorship phase who reported chronic insomnia.[320-322] Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.[315,316] Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.[229,317] The American Academy of Sleep Medicine (AASM) has recommended three specific therapies for chronic insomnia in healthy individuals: relaxation training, CBT, and stimulus control therapy.[323] AASM has also published clinical guidelines for the management of chronic insomnia in adults.[324]

A meta-analysis including 10 RCTs (about half included patients with breast cancer only) with 1327 patients with various malignancies showed that acupuncture reduced CRF (SMD, -1.26; 95% CI, -1.80 to -0.71; $P$ < .01).[325] This finding persisted when including only patients who are no longer undergoing treatment ($n$ = 4; 285 patients; SMD, -1.38; 95% CI, -2.16 to -0.61; $P$ < .01). ASCO and the Society for Integrative Oncology recommend acupuncture for patients who have completed cancer treatment, although the benefit of this intervention is potentially small.[211,326] The panel recommends acupuncture for cancer survivors.

The panel currently does not recommend BWLT for cancer survivors. However, emerging data from RCTs show that BWLT may reduce CRF in this population.[327-329] Large randomized trials are needed in this area.

***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.[330] An RCT of 154 patients post-chemotherapy also found an improvement in fatigue symptoms in the active arm.[331] Similarly to patients receiving active treatment, modafinil has limited study data in patients post-treatment. Although pilot studies suggested that modafinil may be associated with reduced fatigue,[332,333] the improved outcome was not maintained in larger trials[250,334] (see *Interventions for Patients on Active Treatment*). The panel agrees that methylphenidate may be considered in consideration of other modifiable causes of fatigue but does not recommend the use of modafinil. Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded.

In one small RCT whereby cancer survivors (*N* = 40) were given open-label placebo drugs or no treatment, the results showed that placebos improved CRF.[335] A phase II study investigating the efficacy of American ginseng in head and neck cancer survivors concluded that the evidence was insufficient for ginseng to be recommended as a treatment modality.[336]

### 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.[337] Evaluating and correcting these contributing factors could reduce fatigue severity.

It is likely that fatigue will increase substantially as 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.[338,339] 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%).[340] In a large sample of adults receiving palliative care (N = 1000), Walsh and colleagues[341] noted that individuals with advanced cancer had multiple symptoms. Pain was the most prevalent (84%), followed by fatigue (69%), weakness (66%), and lack of energy (61%). Walsh and Rybicki[342] cluster-analyzed 25 symptoms in 1000 consecutive admissions to a palliative care program and found seven symptom clusters. The fatigue cluster included easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, and taste changes. Pain and fatigue could have a synergistic effect that worsens the overall symptom experience in older patients with cancer.[46,343] 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.[339] Mystakidou and colleagues[344] 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.[345] 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.[345]

Individuals with advanced cancer and their caregivers need information about the management of symptoms, including fatigue.[346] 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.[339] 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.[339,345]

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.[345] Interventions for fatigue should be initiated to relieve or diminish suffering, although it is recognized that some causes of fatigue cannot be assuaged.[77] 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*

There is currently no category 1 evidence for nonpharmacologic interventions at the end of life. Psychosocial interventions for these patients may focus on meaning and dignity, and gaining acceptance of the limitations imposed by fatigue. This may include a re-emphasis on meaningful family interactions that do not require high-level physical activity.[347] However, a 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.[348] Therefore, psychosocial interventions were removed from the list of recommended nonpharmacologic strategies for treatment of CRF in patients receiving end-of-life care for the 2019 update.

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 expectancies, although it is important to consider patients' goals (see section regarding *Physical Activity* under *Interventions for Patients on Active Treatment*). A structured exercise protocol depending on the patient's tolerance level can be used to improve fatigue experienced by patients with advanced cancer in hospice care.[349] Based on a systematic review of 20 exercise studies relevant to fatigue and muscle wasting in multiple myeloma, Strong[350] 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. Three systematic reviews including patients with advanced cancer showed that exercise interventions improved CRF.[351-353] However, these results were not always consistent.[354] Smaller studies assessing the impact of physical activity in patients with cancer at the end of life have been conducted.[355-357] 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.[358,359] Two RCTs reported an improvement in fatigue in both the methylphenidate and placebo arms.[360,361] However, another RCT found no significant difference between methylphenidate and placebo in patients with advanced cancer.[362] An RCT in patients with advanced NSCLC (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 Functional Assessment for Chronic Illness Therapy – Fatigue (FACIT)-F scale was not significant (0.20; 95% CI, -3.56 to 3.97).[334] Overall, methylphenidate may be considered with caution for select patients with terminal cancer. Another psychostimulant, dexamphetamine, was evaluated for fatigue in patients with advanced cancer.[363] 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 adults in providing short-term relief for fatigue and improving QOL.[364-367] 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).[368] Improved outcomes were determined from the FACIT-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.[368] In an RCT investigating the effects of methylprednisolone in patients with advanced cancer receiving opioids, fatigue was measured in patients given methylprednisolone twice a day (n = 26) versus patients in the placebo group (n = 24).[369] Patients receiving methylprednisolone 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).[369] 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.[370]

Given the toxicity associated with long-term use, consideration of steroids is restricted to the terminally ill, patients with fatigue and concomitant anorexia, and patients with pain related to brain or bone metastases. Effects of the progestational agent megestrol acetate have been investigated in these patients. A systematic review demonstrated the safety and efficacy of megestrol acetate in treating cachexia for patients with cancer.[371] However, a second systematic review and meta-analysis of four studies revealed no benefit of progestational steroids compared with placebo for treatment of CRF (Z = 0.78; $P$ = .44).[247,372] Double-blind RCTs have shown that melatonin[373] and Panax ginseng extract[374] do not significantly improve fatigue in patients with advanced cancer receiving palliative care.

### 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 used 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 nutrition consultation, sleep, massage, and acupuncture 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.[375] A second agent that may be helpful for short-term use in advanced cancer is the corticosteroid methylprednisolone.[48,368,369] However, potential treatment modalities in managing fatigue require further research.

Effective management of CRF involves an informed and supportive oncology care team that assesses fatigue levels regularly, counsels and educates patients regarding strategies for coping with fatigue, and uses institutional experts for referral of patients with unresolved fatigue.[50] The oncology care team must recognize the many patient-, provider-, and system-related behaviors that can impede effective fatigue management.[52] Reducing barriers by use of available resources and evidence-based guidelines increases benefits to patients experiencing fatigue. [376,377]

## 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.

- *This resource provides a detailed description of six scales [PFS, FACT-F, SCFS, MFI-20, BFI, and 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.

- *This resource 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.

- *This study evaluates psychometric properties of several commonly used fatigue measures (POMS-F, MAF, LFS, and 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.

- *This resource gives citation links to 10 commonly used scales to measure fatigue (BFI, FACT-A, FACIT-F, PFS, SCFS, FSI, POMS-F, CFS, VAS-F, and MFSI).*

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- *This resource provides psychometric properties for a shortened version of a commonly used fatigue measure.*

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

***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[§] | Reliability/ Internal Consistency | Other |
|---|---|---|---|---|---|---|---|---|
| Brief Fatigue Inventory[55] | 1 (severity) | 11-point Likert | 9 | Short, easy to use | Yes, mixed cancers[55,378] | A,P,E | α=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[379] | 1 (severity) | 10-point Likert | 3 | Short, easy to use | Yes, mixed cancers[379] | A | N/A | Items measure tiredness, lacking energy, and feeling weary |
| EORTC QLQ-C30[‡],[366] | 1 (severity) | 4-point Likert | 3 | Easy to use | Yes, mixed cancers[380,381] | A,P,E | α=0.80–0.85 | Measures physical fatigue; not recommended as the only scale for end-of-life fatigue[382] |
| EORTC QLQ-FA12[*] ,[383,384] | 3 (physical, emotional, cognitive) | 4-point Likert | 12 | Easy to use | Yes, mixed cancers[383,384] | A,P,E | α=0.79–0.90 | To be used in conjunction with EORTC QLQ-C30 |
| Fatigue Questionnaire[385] | 1 (severity) | 4-point Likert | 11 | Easy to use | Yes, cancer vs. normal population,[385] Hodgkin lymphoma[386] | A,P,E | α=0.88–0.90 | Measures physical and mental fatigue |
| Visual Analogue Fatigue Scale[387] | 1 (severity) | Analogue | 18 | Short, easy to use | Yes, patients with cancer compared to healthy controls[387] | A,P,E | α=0.91–0.96 | Measures physical and mental fatigue; may help measure fatigue in 24-hour period but less effective over longer time periods |

| 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[388] | 4 (severity, frequency, diurnal variation, interference) | 11-point Likert | 14 | Reasonable | Yes, breast,[388-391] metastatic,[392] and mixed cancers[393] | A,P | r=0.35–0.75<br>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[394] | 5 (physical, social/family, emotional, functional, fatigue) | 5-point Likert | 41/13 | Long but subscale is reasonable and simple | Yes, breast[395] and mixed cancers[270,396-398] | A,P,E | r=0.90<br>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[399] | 5 (general, physical, mental, reduced activity, reduced motivation) | 5-point Likert | 20 | Reasonable | Yes, breast,[400,401] uterine,[402,403] and mixed cancers[399,404-406] | A,P,E | α=0.65–0.80 | Likert scale incorporates VAS |
| Multi-Dimensional Fatigue Symptom Inventory[407] | 5 (general, physical, mental emotional, vigor) | 5-point Likert | 83/30 | Variable length, can be complicated | Yes, mixed[407,408] and breast cancer[409] | A,P | r>0.50<br>α=0.87–0.96 | Full version is long (83 items) but short form is a reasonable alternative[410] |
| Piper Fatigue Score-12[411] | 4 (sensory, behavioral/ severity, affective meaning, cognitive/mood) | 11-point Likert | 12 | Easy to use | Yes, breast cancer[411,412] | P | r=0.87–0.89 | Shortened from revised Piper Fatigue Score that has been tested more extensively[196,411-419]; reliability is based on subscales in single study |
| NCCN Problem List | 1 (general) | Dichotomous (yes/no) | 1 | Easy to use | Yes, breast cancer and colorectal cancer[420] | A | N/A | Taken from NCCN Distress Thermometer and Problem List |

| 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 |
|---|---|---|---|---|---|---|---|---|
| PROMIS CAT[421] | 3 (fatigue, sleep disturbance, sleep impairment) | 1 (never) to 5 (always) | Up to 20 | Not burdensome | Yes, mixed cancers[421] | A | α=0.92–0.94 | Scores correlate significantly with FACIT-Fatigue and the Insomnia Severity Index ($r$ = -0.57 to 0.83; $P$ < .001)[421] |
| Schwartz Cancer Fatigue Scale, Revised[422] | 2 (physical and perceptual) | 5-point Likert | 6 | Reasonable and clear | Yes, mixed cancers[422,423] | A | α=0.90 | Shortened from the original 28-item Schwartz Cancer Fatigue Scale[424] |

[₽] 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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