National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer-Related Fatigue

Version 1.2016

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NCCN Guidelines Version 1.2016 Panel Members
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‡ Hematology/Hematology oncology
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Ω Gynecologic oncology
€ Pediatric oncology
τ Orthopedics
ξ Bone marrow transplantation
£ Supportive care including palliative, pain management, pastoral care, and oncology social work
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Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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

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

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 1.2016 Updates Cancer-Related Fatigue

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Discussion

Updates in Version 1.2016 of the NCCN Guidelines for Cancer-Related Fatigue from Version 2.2015 include:

MS-1

- **The Discussion section was updated to reflect the changes in the algorithm.**

FT-2

- **4th bullet has been modified: "All patients should be screened for fatigue at their initial visit, at regular intervals ~~as a vital sign~~ during and following cancer treatment, and as clinically indicated."**
  - **"as a vital sign" was removed from FT-3 as well.**
- **Last bullet modified: ~~Rehabilitation should begin with the cancer diagnosis~~"Consider referral to rehabilitation as indicated: physical therapy, occupational therapy, and physical medicine from diagnosis to end of life."**

FT-4

- **Under Assessment of Treatable Contributing Factors:**
  - **7th bullet: removed "(eg, sedation)" and added *drug interactions* linking to the NCCN Guidelines for Older Adult Oncology**

FT-5

- **Under Nonpharmacologic the following additions are new to the page:**
  - **Caution has been modified: "Cautions in determining level of activity" and has moved under "Maintain optimal level of activity" (Also for FT-6).**
  - **Yoga (category 1) (Also for FT-6).**
  - **Safety issues (ie, assessment of risk of falls, ~~stability~~) (Also for FT-6 and FT-7).**
  - **Bright white light therapy**
    - **"Bright white light therapy of 10,000 lux is most frequently self-administered in the early morning for 30–90 minutes. Timing needs to be adjusted for those who sleep during the day." is the corresponding footnote.**
- **Footnote "m": the last sentence has been modified, "Optimal dosing and schedule have not been established for use of psychostimulants in older adults and patients with cancer." (Also for FT-6 and FT-7).**

FT-7

- **Under Nonpharmacologic the following addition is new to the page: "Limitations secondary to metastases or other comorbid illnesses."**

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 cancer patient 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, such as pain, distress, anemia, and sleep disturbances, in symptom clusters. Therefore, patients should be screened for multiple symptoms that may vary according to diagnosis, treatment, and stage of disease.**
- **Fatigue is a subjective experience that should be systematically assessed using patient self-reports and other sources of data.**
- **Fatigue should be screened, assessed, and managed according to clinical practice guidelines.**
- **All patients should be screened for fatigue at their initial visit, at regular intervals during and following cancer treatment, and as clinically indicated.**
- **Fatigue should be recognized, evaluated, monitored, documented, and treated promptly for all age groups, at all stages of disease, prior to, during, and following treatment.**
- **Patients and families should be informed that management of fatigue is an integral part of total health care and that fatigue can persist following treatment.**
- **Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner.**
- **Implementation of guidelines for fatigue management is best accomplished by interdisciplinary teams who are able to tailor interventions to the needs of the individual patient. Consider referral to an appropriate specialist or supportive care provider.**
- **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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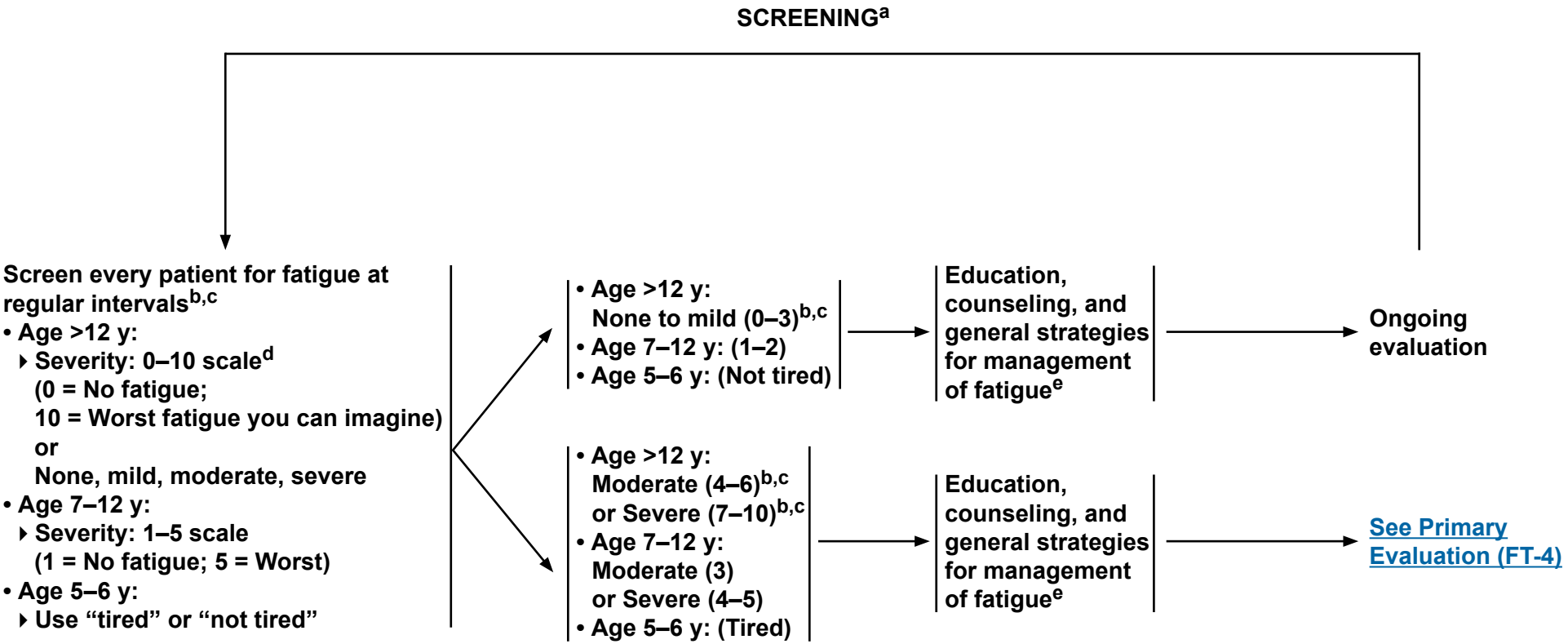
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[a]See Discussion Appendix for screening resources (MS-23).
[b]Recommended screen and re-evaluation: "How would you rate your fatigue on a scale of 0–10 over the past 7 days?"
[c]Fatigue scale for children is simplified: Use "tired" or "not tired" as screen for young children (age <6 or 7 y).
[d]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(1):20-30.
[e]See "Patient/Family Education and Counseling" and "General Strategies for Management of Fatigue" based on clinical status: Active Treatment (FT-5), Post-Treatment (FT-6), and End of Life (FT-7).

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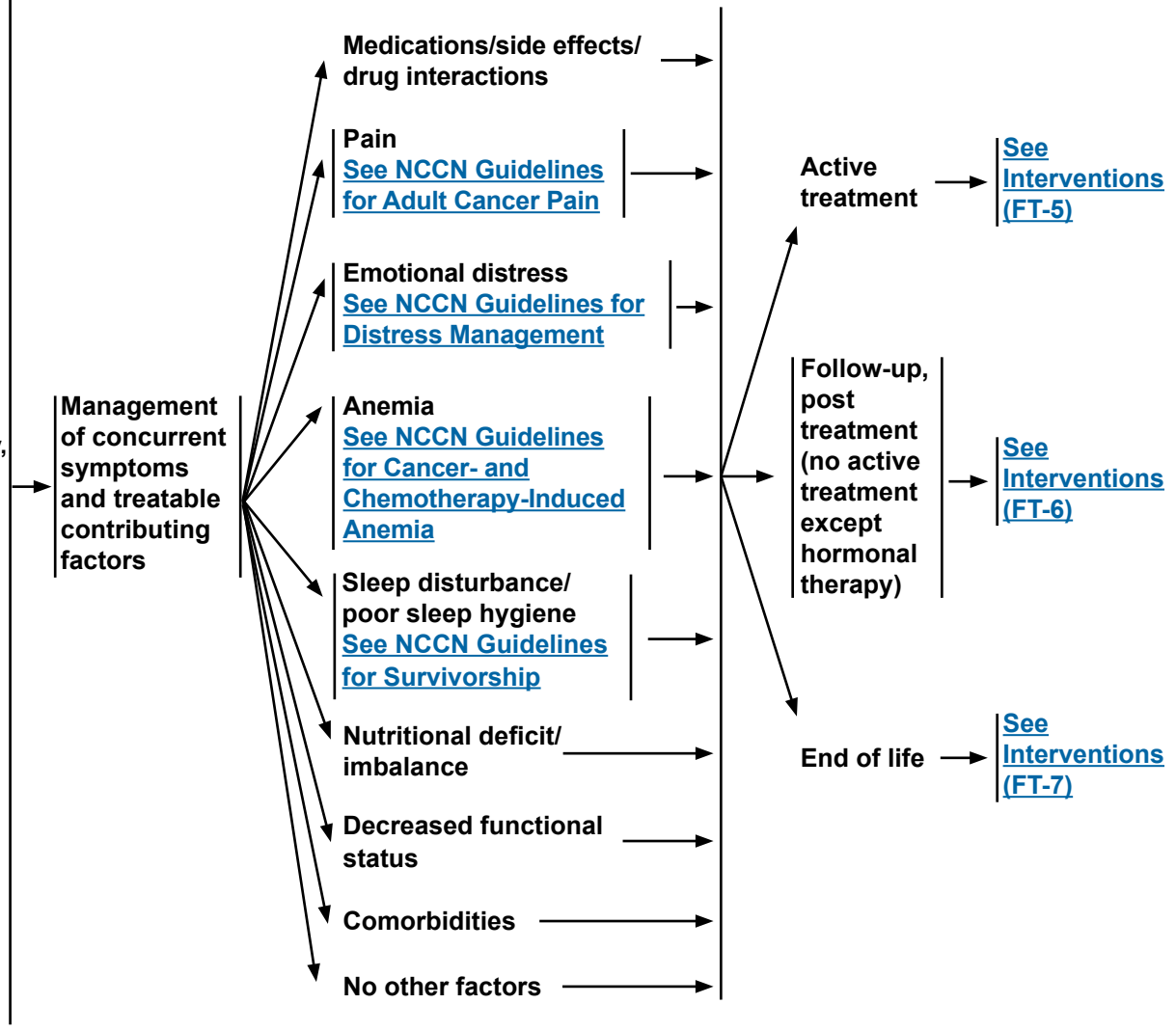
PRIMARY EVALUATION FATIGUE SCORE: MODERATE OR SEVERE
Age >12 y (4–10), Age 7–12 y (3–5), or Age 5–6 y (Tired)

Focused History

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

Assessment of Treatable Contributing Factors

- Pain
- Emotional distress
  - Depression
  - Anxiety
- Anemia
- Sleep disturbance/poor sleep hygiene (eg, insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome)
- Nutritional deficits/imbalance
  - Weight/caloric intake changes
  - Fluid electrolyte imbalance: sodium, potassium, calcium, magnesium
- Decreased functional status
  - Physical activity level
  - Deconditioning
- Medications/side effects/drug interactions
  - See NCCN Guidelines for Older Adult Oncology (OAO-H)
- Comorbidities
  - Alcohol/substance abuse
  - Cardiac dysfunction
  - Endocrine dysfunction (eg, hot flashes, hypothyroidism, hypogonadism, adrenal insufficiency)
  - Gastrointestinal dysfunction
  - Hepatic dysfunction
  - Infection
  - Neurologic dysfunction
  - Pulmonary dysfunction
  - Renal dysfunction



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INTERVENTIONS FOR PATIENTS ON ACTIVE TREATMENT[f]

Patient/Family Education and Counseling

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

General Strategies for Management of Fatigue

- Self-monitoring of fatigue levels
- Energy conservation
  - Set priorities and realistic expectations
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Labor-saving devices[g]
  - Postpone nonessential activities
  - Limit naps to <1 hour to not interfere with night-time sleep quality
  - Structured daily routine
  - Attend to one activity at a time
- Use distraction (eg, games, music, reading, socializing)
- Find meaning in current situation
  - Emphasis on meaningful interactions
  - Promote dignity of patient
- Consider referral to appropriate specialist or supportive care provider

SPECIFIC INTERVENTIONS

Nonpharmacologic[h]

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

Pharmacologic

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

→ Repeat screening and evaluation See (FT-3) and (FT-4)

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

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

[h] 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.

[i] See NCCN Guidelines for Survivorship (SE-3).

[j] 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.

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

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

[m] 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.

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

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INTERVENTIONS FOR PATIENTS POST-TREATMENT[f]

Patient/Family Education and Counseling

General Strategies for Management of Fatigue

SPECIFIC INTERVENTIONS

Nonpharmacologic[h]

Pharmacologic[o]

Information about known pattern of fatigue during and following treatment

- Monitor fatigue levels
- Energy conservation
  - Set priorities and realistic expectations
  - Pace
  - Schedule activities at times of peak energy
  - Limit naps to <1 hour to not interfere with night-time sleep quality
  - Structured daily routine
  - Attend to one activity at a time
- Use distraction (eg, games, music, reading, socializing)
- Find meaning in current situation
  - Emphasis on meaningful interactions
  - Promote dignity of patient

- Physical activity (category 1)
  - Maintain optimal level of activity
  - Cautions in determining level of activity:
    - ◊ Late effects of treatment (eg, cardiomyopathy)
    - ◊ Safety issues (ie, assessment of risk of falls)
    - ◊ Consider initiation of exercise program of both endurance and resistance exercise[i]
  - Yoga (category 1)
  - Consider referral to rehabilitation: physical therapy, occupational therapy, physical medicine
- Psychosocial interventions (category 1)
  - CBT[j]/BT (category 1)[k]
  - Mindfulness-based stress reduction (category 1)
  - Psycho-educational therapies/Educational therapies (category 1)
  - Supportive expressive therapies (category 1)[l]
- Nutrition consultation
- CBT[j] for sleep (category 1)
  - Stimulus control
  - Sleep restriction
  - Sleep hygiene

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

Repeat screening and evaluation See (FT-3) and (FT-4)

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

[h] 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.

[i] See NCCN Guidelines for Survivorship (SE-3).

[j] 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.

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

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

[m] 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.

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

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INTERVENTIONS FOR PATIENTS AT THE END OF LIFE[f,h,p]

Patient/Family Education and Counseling

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

→

General Strategies for Management of Fatigue

- Energy conservation
  - Set priorities and realistic expectations
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Labor-saving and assistive devices[g] (including wheelchairs, walkers, and commodes)
  - Eliminate nonessential activities
  - Structured daily routine
  - Attend to one activity at a time
  - Conserve energy for valued activities
- Use distraction (eg, games, music, reading, socializing)
- Find meaning in current situation
  - Emphasis on meaningful interactions
  - Promote dignity of patient

→

SPECIFIC INTERVENTIONS

Nonpharmacologic[h]

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

→

Pharmacologic

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

→

Repeat screening and evaluation See (FT-3) and (FT-4)

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

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

[h]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.

[m]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.

[p]Also see NCCN Guidelines for Palliative Care.

[q]Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol 2013;31:3076-3082. Paulsen O, Klepstad P, Rosland JH, et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. J Clin Oncol July 7 2014 (online ahead of print).

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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Overview

Fatigue is a common symptom in patients with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biological response modifiers.[1-4] The specific mechanisms involved in the pathophysiology of cancer-related fatigue (CRF) are unknown. Proposed mechanisms include pro-inflammatory cytokines,[5-7] hypothalamic-pituitary-adrenal (HPA) axis dysregulation,[5] circadian rhythm desynchronization,[8] skeletal muscle wasting,[9] and genetic dysregulation;[10] however, limited evidence supports these proposed mechanisms.

CRF is very common. According to a survey of 1569 patients with cancer, the symptom is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.[11,12] In patients with metastatic disease, the prevalence of CRF exceeds 75%.[13-16] Using a cutpoint of ≥4 for moderate fatigue and ≥7 for severe fatigue on a 0 to 10 point scale, moderate/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.[17] 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).[18] Cancer survivors report that fatigue is a disruptive symptom months or even years after treatment ends.[19-26] 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.[27]

Fatigue in patients with cancer has been under-reported, under-diagnosed, and under-treated. Persistent CRF affects quality of life (QOL), as patients become too tired to fully participate in the roles and activities that make life meaningful.[21,28] CRF may also influence the time it takes to return to work following treatment.[29] Health care professionals have been challenged in their efforts to help patients manage this distressful symptom and to remain as fully engaged in life as possible. Because of the successes in cancer treatment, health care professionals are now likely to see patients with prolonged states of fatigue related to the late effects of treatment. Disability-related issues are relevant and often challenging, especially for patients with cancer who are cured of their malignancy but have continued fatigue.[30] Despite biomedical literature documenting this entity, it is often difficult for patients with CRF to obtain or retain disability benefits from insurers. Health care professionals should advocate for patients who require disability benefits and educate insurers about this issue.

To address the important problem of CRF, NCCN convened a panel of experts. The NCCN Guidelines for Cancer-Related Fatigue, first published in 2000[31] and updated annually, synthesize the available research and clinical experience in this field and provide recommendations for patient care.

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 published between 07/24/2014 and 08/10/2015**,** using the following search terms: cancer related fatigue or cancer fatigue or cancer induced fatigue. The PubMed database was

chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[32]

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 PubMed search resulted in 202 citations, and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org). The guidelines update for 2015 is described in *JNCCN -- Journal of the National Comprehensive Cancer Network*.[33]

Defining Cancer-Related Fatigue

The distinction between tiredness, fatigue, and exhaustion has not been made in practice, despite conceptual differences.[34,35] The Guidelines Panel defines CRF as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Compared with the fatigue experienced by healthy individuals, CRF is more severe, more distressing, and less likely to be relieved by rest. In terms of the defining characteristics, it is important to note the subjective sense of tiredness reported by the patient. As with pain, the clinician must rely on the description of fatigue and accompanying distress provided by the patient. Fatigue that interferes with usual functioning is another substantial component of the definition for CRF and the source of much distress for patients.[36] Investigations have documented a significant effect of fatigue on physical functioning during cancer treatment, and it is uncertain whether patients regain full functioning when treatment is over.[37,38]

Standards of Care for Assessment and Management

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

Fatigue should be screened, assessed, and managed for most patients according to the clinical practice guidelines. The NCCN Guidelines provide “best care” information based on current evidence to support treatment.[39] 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.[40] Screening should identify fatigue. Patients and families should be informed that managing fatigue is an integral part of total health care. All patients should receive symptom management. Furthermore, if patients cannot tolerate their cancer treatment or if they must choose between treatment and QOL, control of their disease may be diminished.[41]

Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner. The guidelines for fatigue are best implemented by an interdisciplinary institutional committee, including experts in medicine, nursing, social work, physical therapy, and nutrition.[42] 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. 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.

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. Medical care contracts should reimburse for managing fatigue, including referrals to a physical therapist, dietitian, or the institution’s symptom management service. Disability insurance should include coverage for the continuing effects of fatigue that lead to persistent disability. Rehabilitation may include physical therapy, occupational therapy, and physical medicine, and should be considered as indicated from diagnosis to end of life.

Guidelines for Evaluation and Treatment

The general schema of the fatigue algorithm defines 4 phases: screening, primary evaluation, intervention, and re-evaluation. During the first phase, the health care professional must screen for fatigue and, if present, assess intensity level. If the intensity level is moderate to severe, the health care professional is directed during the primary evaluation phase of the algorithm to conduct a more focused history and physical examination. This phase also includes an in-depth fatigue assessment and 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. Valid and reliable instruments are available to measure fatigue in children, adolescents, and adults (see *Appendix*); however, the effectiveness of these methods is limited without adequate implementation. If fatigue is present, a quantitative or semiquantitative assessment should be performed and documented. For example, on a 0 to 10 numeric rating scale (zero = no fatigue and 10 = worst fatigue imaginable), mild fatigue is indicated as a score of 1 to 3, moderate fatigue as 4 to 6, and severe fatigue as 7 to 10. The evaluation of fatigue in children may be simplified to a scale of 1 to 5 and modified even further in young children (age 5–6 years) who may be asked more simply if they are “tired” or “not tired.” If the screening process determines that if fatigue is absent or at a mild level, the patient and family should receive education and common management strategies for fatigue. Periodic re-screening and re-evaluation are recommended. Inpatients should be screened daily and outpatients should be screened at subsequent routine and follow-up visits. It should be emphasized that survivors or patients who have completed treatment must still be monitored for fatigue, because fatigue may exist beyond the period of active treatment.[43]

Currently, screening is not systematic or effective in many practice settings for various reasons, which often include patient or family barriers and clinician barriers. For example, patients may not want to bother their health care professional in the clinic or office or when they are hospitalized. Patients are also concerned that if they report high levels of fatigue, they might have their treatment altered. Patients do not want to be perceived as complaining and, therefore, may not mention fatigue. Or, they may 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. Researchers have begun to document the prevalence and incidence of fatigue, correlating these data with the degree of disruption to QOL.[44-46] Second, health care professionals may not be aware that there are effective treatments for fatigue despite a lack of knowledge about the underlying pathophysiology and mechanisms.

Given these barriers, screening for CRF must be emphasized.[47] Clinical experience with fatigue assessment has shown that some patients cannot put a numeric value on their fatigue. Consequently, some patients may need to rate fatigue as mild, moderate, or severe. In some circumstances, other sources of data must be used. For example, the patient may not be aware that fatigue has negatively affected his or her life; however, the spouse, parents, or other family members may be more cognizant of these changes and the effect of fatigue. An appendix to this discussion provides additional information and resources to assist in the selection of instruments to measure CRF.

Using the numeric rating scale (ie, 0–10 scale), fatigue studies in patients with cancer have revealed a marked decrease in physical functioning at the level of 7 or higher.[48] 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.[17] 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 and Physical Examination

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

As part of a focused history, a review of systems should be completed. This review may be helpful in determining the various organ systems affected and in directing the physical evaluation and diagnostic workup. Another component of the focused history is an in-depth fatigue assessment 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. The health care professional must evaluate the effect of fatigue on normal functioning, including effects on daily living or enjoyable activities. Because fatigue is a subjective condition involving a combination of symptoms and is experienced and reported differently by each person, it is important that the in-depth assessment includes the patient's self-assessment of the causes of fatigue.

The panel also recognized the important role of social support throughout the course of cancer treatment and survivorship (reviewed by Given, Given, and Kozachik[49]). Fatigue is a major cause of functional dependence for patients with cancer, especially among the elderly.[50] Besides assisting with daily living, caregivers provide cancer-specific support such as monitoring treatment side effects, aiding in fatigue and pain management, and administering medicine, among others.[51] 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 also can be provided when the patient lacks the economic and supportive resources to obtain tangible support.

Assessment of Concurrent Symptoms & Treatable Contributing Factors

As part of this focused evaluation, the panel identified factors that are often causative elements in the fatigue experience and, therefore, should be specifically assessed. These factors include pain, emotional distress, sleep disturbance, poor sleep hygiene, anemia, nutrition,

activity level, medication side effect profiles, alcohol/substance abuse, and comorbidities.

Descriptive studies have shown that, in adults as well as in children, fatigue seldom occurs by itself and more commonly clusters with sleep disturbance, poor sleep hygiene, emotional distress (eg, depression, anxiety), or pain.[52-55] Assessment of pain along with emotional distress and institution of effective treatment are essential. In a randomized controlled trial (RCT) of 152 patients with advanced cancer, protocol patient-tailored treatment of the accompanying physical symptoms was coordinated by a nurse and resulted in a higher impact on fatigue than standard oncologic care.[56]

Fatigue and depression have been documented as concurrent symptoms in patients with cancer. Hopwood and Stephens[57] documented depression in 33% of 987 patients with lung cancer and found that fatigue was an independent predictor of depression in this group. In 457 patients with Hodgkin's disease, Loge and colleagues[58] found that 26% of patients had fatigue for 6 months or longer (defined as fatigue "cases") and that fatigue correlated moderately with depression (r = .41).

Sleep disturbances are a neglected problem in oncology[59] and may range from hypersomnia to insomnia.[60,61] Sleep disturbances are prevalent in 30% to 75% of patients with cancer.[62] 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. When sleep disturbances are present, the patient should be assessed for depression, because this is a common manifestation.[63] Patients may benefit from evaluation and education to improve sleep quality. In addition, sleep apnea can develop as a consequence of cancer treatment in the settings of surgery affecting the upper airway, changes in body composition, and alterations in hormone status (eg, thyroid, estrogen, testosterone); therefore, obstructive sleep apnea should also be evaluated.

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

Patients should undergo a nutritional assessment to evaluate weight gain and loss, caloric intake changes, impediments to nutritional intake, anemia, 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.

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 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.[64,65] However, before recommending an exercise program, the health care provider or exercise expert (eg, physiatrist, physical therapist) should assess the conditioning level of the patient. It is often difficult to convince fatigued patients that exercise will improve their symptoms. It may be best to begin with discussions and low-level activities, which gradually increase over a period of time. This is especially important if the patient is significantly deconditioned.

Review of current medications (including over-the-counter, herbal, vitamins, and other supplements) is essential. In addition, recent medication changes should be noted. Medications and medication interactions may contribute to the worsening of fatigue. For example, certain cardiac medications (such as beta-blockers) may elicit bradycardia and subsequent fatigue. Combinations of different classes of medications (such as narcotics, antidepressants, antiemetics, and antihistamines) may contribute to excessive drowsiness and increasing fatigue. Polypharmacy (ie, use of ≥4 medications) and potentially inappropriate medication use is common among older adults with cancer.[66] It may be appropriate to delete or adjust the dose of medications to treat fatigue. In some cases, altering either the dosage or dosing interval of a medication may be sufficient to improve the condition.

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

Non-cancer comorbidities may contribute substantially to symptoms of fatigue in the patient with cancer. Therefore, the status of comorbidities must be reviewed in conjunction with the present treatment management strategies. If the comorbidity is not optimally managed, it may be necessary to further evaluate and improve management. For example, if a patient has underlying congestive heart failure secondary to anthracycline cardiomyopathy and is experiencing symptoms of dyspnea and angina, fatigue may often be improved by stabilizing the condition and decreasing the frequency of episodes of congestive heart failure. This may entail introduction of new medications, titration of current medications, or both. It may also involve an invasive interventional assessment of the patient's cardiac status. Comorbidities that need review and assessment include cardiac, pulmonary, renal, gastrointestinal, hepatic, neurologic, and endocrine dysfunction (including hot flashes, hypothyroidism, hypogonadism, or adrenal insufficiency), as well as infection. Canaris et al[67] noted the high incidence of thyroid dysfunction in normal individuals and in patients receiving thyroid medications; it was suggested that more attention be given to thyroid problems in both the general population and in patients with cancer. Development of hypothyroidism occurs after radiation therapy for Hodgkin's disease and other non-Hodgkin's lymphomas, head and neck cancers, and breast cancer, as well as after total body irradiation in bone marrow transplantation. Hypothyroidism has been noted in patients who have received interferon alfa-2b, aldesleukin

(interleukin-2), L-asparaginase, and a multitude of combination chemotherapies. Hypogonadism is commonly seen in patients with advanced cancer. Strasser et al[68] explored whether hypogonadism contributes to fatigue in men with advanced cancer in a cross-sectional pilot study. Data indicated that abnormally low levels of testosterone are associated with fatigue. 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.

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.[69]

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

Interventions for Patients on Active Treatment

Education and Counseling of Patient and Family

Education about fatigue and its natural history should be offered to all patients with cancer,[47] but it is particularly essential for patients beginning potential fatigue-inducing treatments (such as radiation, chemotherapy, or biotherapy) before the onset of fatigue. Patients should be informed that if fatigue does occur, it may be a consequence of the treatment and is not necessarily an indication that the treatment is not working or that the disease is progressing. This reassurance is important, as fear of progression is a main reason for the under-reporting of fatigue. Daily self-monitoring of fatigue levels in a treatment log or diary can be helpful.

General Strategies for Management of Fatigue

In addition to education, the panel recommends counseling for patients about general strategies (energy conservation and distraction) useful in coping with fatigue.[47] 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.[70] Patients should be counseled that it is permissible to postpone all nonessential activities if they are experiencing moderate-to-severe fatigue. One useful plan is to maintain a daily and weekly diary that allows the patient to ascertain peak energy periods and then plan activities accordingly within a structured routine. A multisite clinical trial of energy conservation in 296 patients receiving cancer treatment reported significantly lower fatigue in patients receiving the experimental intervention.[71] Some participants in the descriptive studies suggested that activities designed to distract (eg, games, music, reading, socializing) are helpful in decreasing fatigue, although the mechanism is unknown. Daytime naps can replenish energy, but it is advisable to limit these to under an hour to avoid disturbing nighttime sleep. Patients may also use labor-saving techniques such as wearing a bath robe instead of drying off with a towel or devices such as a walker, grabbing tools, and a bedside commode.

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

Nonpharmacologic Interventions

Of the specific nonpharmacologic interventions during active cancer treatment, physical activity (category 1), physically based therapies (category 1), and some psychosocial interventions (category 1) have the strongest evidence base for treating fatigue; however, nutritional consultation, cognitive behavioral therapy (CBT) for sleep, and bright white light therapy have some supporting evidence.[72] These interventions align with recommendations from the Oncology Nursing Society (ONS).[73-75] Both ASCO[76] and the pan-Canadian practice guidelines[77] 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

In patients with cancer, the adverse effects of therapy result in decreased activity and physical performance. Although there are a number of factors that contribute to the decline in functionality, fatigue is one of the major contributors. Mustian and colleagues[78] conducted a study in patients receiving systemic chemotherapy to determine the impact of fatigue on physical function as measured by the Activities of Daily Living (ADLs) Index. Of the 753 patients enrolled, 64% were female. In the first and second cycles of chemotherapy, 85.4% and 79.3% of patients reported fatigue, respectively. The mean severity of fatigue was 5.0 for the first cycle and 4.7 for the second cycle (scale 0–10, 10 = severe fatigue). CRF interfered with all ADLs in the majority of patients. Interference was moderate, and was noted to be higher in women, non-whites, and patients with metastatic disease.

A large number of small- to moderate-sized studies have been performed to 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. A thorough review of the impact of physical activity on these varied outcomes is beyond the scope of this discussion. However, several meta-analyses have been conducted to provide a comprehensive evaluation of the impact of increased activity upon CRF. One meta-analysis included 70 studies and 4881 patients with cancer during or following treatment.[79] Exercise reduced CRF by a mean effect of 0.32 (95% CI, 0.21–0.43) and 0.38 (95% CI, 0.21–0.54) during and after cancer therapy, respectively.[79] A more recent meta-analysis including 72 studies and 5367 patients in active treatment or follow-up showed a moderate effect of exercise in reducing CRF, when compared to a control group (SMD, -0.45, 95% CI, -0.57 to -0.32, $P <$ .001).[80] Impact on fatigue levels did not significantly differ by type of exercise, though stronger effects were seen for solid tumors vs. hematologic and mixed malignancies. A 2012 Cochrane analysis included 56 randomized trials (n = 4826), 36 of which were conducted among participants undergoing active cancer treatment.[81] Exercise resulted in a decrease in fatigue from baseline to 12 weeks' follow-up (standardized mean difference [SMD], -0.38; 95% CI, -0.57 to -0.18) or when comparing differences in follow-up scores at 12 weeks (SMD -0.73; 95% CI, -1.14 to -0.31).

Systematic reviews have correlated exercise with improvement in fatigue for patients with prostate cancer,[82] lymphoma[83], hematologic malignancies, [84] and in patients who have undergone hematopoietic cell transplant.[85] Other smaller analyses confirmed a significant effect of exercise intervention on fatigue.[86-92]

It is reasonable to encourage all patients to engage in a moderate level of physical activity during and after cancer treatment. Currently there is not sufficient evidence to recommend a specific amount of physical activity. The U.S. Surgeon General recommends 30 minutes of moderate activity most days of the week for all populations.[93] 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.[64,94-98]

Patients may be referred to exercise specialists (eg, physical therapist, physical medicine or rehabilitation specialist) as indicated for assessment and an exercise prescription. The American College of Sports Medicine has developed a certification program for cancer rehabilitation that is available for exercise professionals who specialize in the care of patients with cancer. They also convened a roundtable discussion and published specific guidelines for physical activity testing and exercise programs for patients with cancer.[99]

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

- Patients with comorbidities (such as cardiovascular disease or chronic obstructive pulmonary disease)
- Recent major surgery
- Specific functional or anatomical deficits (such as decreased range of motion due to neck dissection in patients with head and neck cancer)
- Substantial deconditioning

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

- Bone metastases
- Thrombocytopenia (low platelets)
- Anemia (low red blood cells)
- Fever or active infection
- Limitations secondary to metastasis or other comorbid illnesses
- Safety issues (ie, assessment of risk of falls)

The exercise program itself should be individualized based on the patient's age, gender, type of cancer, and physical fitness level. 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

Several recent RCTs have demonstrated that yoga intervention impacts CRF during treatment.[100-105] Two of these studies targeted patients with breast cancer who were undergoing radiation therapy.[100,101] Another RCT targeted 60 patients with breast cancer who were undergoing adjuvant chemotherapy.[106] Fatigue was improved in patients randomized to receive 8 weeks of Anusara yoga sessions, twice per week ($P < .001$).

More data are needed to establish the effectiveness of yoga in reducing fatigue in males and in other cancers.[107] 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.[104] Modest group differences were found for sleep disturbances three months after intervention completion ($P = .04$). Study results may have been affected by attrition and poor intervention adherence rates.

Physically Based Therapies

Therapies performed on the patient by a therapist or lay person include acupuncture and massage therapy. Three systematic reviews suggest that acupuncture and acupressure may have beneficial properties, though the studies acknowledge that a paucity of data makes it difficult to definitively evaluate the benefits.[108-110] Positive effects of acupuncture on fatigue have been reported in small samples but need to be confirmed in RCTs.[111] These small trials were conducted during active non-palliative radiation therapy[112,113] and post-chemotherapy treatment.[114,115]

Massage therapy may also be effective in reducing CRF,[116-118] with one recent 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).[119] However, the data remain limited.

Psychosocial Interventions

Patients should be counseled regarding coping with fatigue and educated about anxiety and depression, which are commonly associated with fatigue during cancer treatment.[120] Although a strong correlation exists between emotional distress and fatigue, the precise relationship is not clearly understood.

Studies testing interventions to decrease fatigue can be grouped as Cognitive Behavioral Therapy (CBT)/Behavioral Therapy (BT), Psycho-educational Therapies/Educational Therapies, and Supportive Expressive Therapies based on review of three meta-analyses.[88,121,122] 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).[74,75,123] 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.

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

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

Several meta-analyses evaluated the impact of psychosocial interventions on CRF. Analyzing 41 studies on 3620 patients with cancer, Kangas et al[88] reported a weighted pooled mean effect of -0.31

for psychosocial interventions on fatigue. Goedendorp et al[121] reported that, out of 27 RCTs included in their analysis, 7 showed significantly reduced fatigue. Of interest, 80% of fatigue-specific interventions were effective compared to 14% of non-specific strategies. Jacobsen et al[122] analyzed 30 RCTs and found a significant effect for psychological interventions but not for activity-based programs.

A meta-analysis by Duijts and colleagues[87] reported that, like exercise programs, behavioral techniques including cognitive therapy, relaxation techniques, counseling, social support, hypnosis, and biofeedback are beneficial in improving fatigue among patients with breast cancer during and after treatment. Substantial data in literature provide high-level evidence during active treatment for CBT/BT[124-128] and Psycho-educational Therapies/Educational Therapies.[37,72,129-139] 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 and stress reduction based on mindfulness have been evaluated in combination with CBT approaches, though some of these therapies have also been evaluated on their own.[124,140-142] The data suggest that these therapies may be effective in reducing fatigue in patients with cancer. Secondary analyses from a 10-week cognitive behavioral stress management program for women undergoing adjuvant treatment for breast cancer (N = 240) showed that those randomized to receive the stress management intervention reported a reduction in fatigue-related daytime interference, relative to participants randomized to a psychoeducational control group ($P < .05$).[143] Mediation analyses showed that these results were accounted for by self-reported improvements in sleep quality. Further, sleep latency (ie, amount of time it takes to fall asleep) was improved for those receiving the stress management intervention, relative to those in the control group ($P < .03$). Another RCT including 155 patients with breast cancer did not find a statistically significant difference in fatigue between those randomized to a stress management group and those in a control group.[144] However, larger studies are needed.

Nutrition Consultation

Many patients with cancer have changes in nutritional status. Because cancer and treatment can interfere with dietary intake, nutrition consultation may be helpful in managing the nutritional deficiencies that result from anorexia, diarrhea, nausea, and vomiting.[145] Adequate hydration and electrolyte balance are also essential in preventing and treating fatigue.

Sleep Therapy

Patients with cancer report significant disturbances in sleep patterns that could cause or exacerbate fatigue. Both insomnia and hypersomnia are common, with disrupted sleep as a common denominator. Non-pharmacologic interventions designed to improve sleep quality have been organized into four general types of therapies that include cognitive-behavioral, complementary, psycho-education/information, and exercise therapies;[146] some have also been shown to decrease fatigue.[123]

There are numerous types of CBT; the most frequently used include stimulus control, sleep restriction, and sleep hygiene. Stimulus control includes going to bed when sleepy, going to bed at approximately 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.[147] Techniques to promote a good night's sleep and optimal functioning the next day, such as avoiding caffeine after noon and establishing an environment that is conducive to sleep (eg, dark, quiet, comfortable) are components of sleep hygiene. These strategies were employed in a pilot study with women during adjuvant breast cancer chemotherapy. Sleep/wake patterns remained consistent with normal values except for increased number and length of nighttime awakenings.[148] For children with cancer, a consistent bedtime and routine, an environment conducive to sleeping, and the presence of security objects (such as blankets and toys) are effective measures (see *Assessment of Concurrent Symptoms & Treatable Contributing Factors*).

Bright White Light Therapy

Bright light treatment involves exposure to very high fluorescent light (typically 10,000 lux), emitted from a "light box" that is usually purchased for at-home use. This type of therapy has been used for the treatment of mood disorders and sleep disturbances in the general population and in older adults.[149-152] Bright light therapy stimulates the suprachiasmatic nucleus of the hypothalamus, which regulates circadian rhythms.

Bright white light therapy (BWLT) has been associated with positive changes in fatigue in women with breast cancer during chemotherapy[153,154] and over 7 weeks in cancer survivors who were up to 3 years post completion of chemotherapy and radiation therapy.[155] Thus far, samples have been small, and the risks associated with BWLT need to be balanced with the benefits. Further, the optimal timing and length of treatment require further study, though BWLT is most commonly administered in the early morning for 30 to 90 minutes, and timing may be adjusted for those who sleep during the day. The NCCN Panel recommends that home-based BWLT be included as a nonpharmacologic strategy for treating CRF in patients on active treatment.

Pharmacologic Interventions

Though a wide variety of prescription pharmacologic options are available to improve sleep quality, there is little empirical evidence for the use of these agents in patients with cancer, and their use may be associated with adverse side effect profiles. Clinicians need to be aware of the U.S. Food and Drug Administration warning regarding potential risks of sedative-hypnotic drugs that include severe allergic reactions and complex sleep-related behaviors, including sleep-driving.[156] A table summarizing the medications commonly used to promote sleep is provided at the National Cancer Institute Physician Data Query website.[157] Prescribing considerations for these classes of agents include increased likelihood of problems with daytime sleepiness, fatigue, withdrawal symptoms, dependency, rebound insomnia, problems with sleep maintenance, memory problems, anticholinergic symptoms, orthostasis, and the potential for drug-drug interactions involving the cytochrome p450 isoenzyme system. Increased public and professional education regarding sleep, sleep hygiene, sleep disturbances, and daytime consequences of sleep loss are recommended.

There is some evidence for pharmacologic therapy as a fatigue treatment, although a significant placebo response has been observed in a randomized trial.[158] Studies on the selective serotonin reuptake inhibitor paroxetine showed no influence by this antidepressant on fatigue in patients receiving chemotherapy.[159,160] Antidepressants are not recommended to reduce fatigue. See the relevant NCCN Guidelines for Supportive Care (available at www.NCCN.org) for details on the management of pain, emotional distress, emesis, and anemia.

Treatment for nutritional deficit or imbalance and comorbidities may be optimized as indicated.

The psychostimulant methylphenidate has been evaluated for its effect on CRF with mixed results in patients undergoing cancer therapy. A pilot study found a benefit in fatigue scores in 12 patients with melanoma undergoing interferon-based treatment compared to historical controls.[161] However, a randomized, placebo-controlled trial of d-threo-methylphenidate to prevent fatigue during radiotherapy for brain tumors did not demonstrate efficacy for the drug in preventing fatigue.[162] Similarly, an RCT of 57 women receiving adjuvant chemotherapy for breast cancer failed to show a difference between the active arm and placebo.[163] Moraska et al[164] reported results of a phase III, double-blinded trial. One hundred forty-eight patients, most of whom were receiving chemotherapy, were randomized to methylphenidate (54 mg/d) or placebo for four weeks. No difference in fatigue score was observed between the groups; however, a subset analysis found a benefit with the psychostimulant in patients with severe fatigue and/or advanced disease (P = .02). Analyzing five RCTs, Minton et al[165] attributed a significant benefit to psychostimulants in alleviating fatigue compared to placebo (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[166] 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. More recently, a phase III randomized, placebo-controlled trial measured the improvement in fatigue in patients with metastatic prostate or breast cancer undergoing docetaxel chemotherapy.[167] Fatigue was measured using the MDASI and no statistically significant difference was seen between treatment arms (35.9 vs. 39.6; 95% CI, -8.9–1.4; P = .15). There was an increase in toxicity, with patients experiencing grade 2 or higher nausea and vomiting in the modafinil arm (45.4% vs. 25%). Due to the limited number of studies and the marginal improvement in CRF in response to modafinil, it is not a recommended treatment.

The use of dietary supplements to alleviate the symptoms of fatigue has yielded mixed results. While coenzyme Q10 and L-Carnitine were evaluated and showed no benefit,[168,169] there may be some data to support the use of ginseng. In a phase III RCT of 364 patients experiencing CRF, improvement of symptoms as measured by the Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF) following treatment with 2000 mg Wisconsin ginseng was observed.[170] In the overall population, improvement at four 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. Statistical significance was observed at four weeks in the active treatment patients (P = .02) compared to the after treatment group (P = .86), with an even greater improvement over placebo at 8 weeks (active treatment, P = .01 vs. post-treatment, P = .07). These values were based on the percent change from baseline measured by the MFSI-SF.

Following review of the current literature, the NCCN Panel included consideration of the psychostimulant methylphenidate as a

recommendation for patients undergoing active cancer treatment when other causes of fatigue have been excluded. However, use of psychostimulants in older adults should be treated with caution, as older adults may need a lower dosage than younger adults.[171] The data were not sufficient to support the recommendation for modafinil.

Interventions for Patients Post-Treatment

More than 11 million U.S. residents have a history of cancer. Of the approximately 1,658,370 persons in the United States who will be diagnosed with cancer in 2015, 68% are expected to survive at least 5 years.[172] These improvements in survival 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.[173] Patients may continue to report unusual fatigue for months or years after treatment cessation.[19,20,22-26] Researchers have suggested that such fatigue may be due to persistent activation of the immune system[19,174] or to other factors, including the late effects of treatment on major organ systems.[174] However, there are few longitudinal studies examining fatigue in long-term disease-free survivors.

Incidence and prevalence rates for fatigue in this population range from 17% to 21% when strict ICD-10 diagnostic criteria are applied,[175] 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.[176] 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.[177] As a consequence, what constitutes valid incidence and prevalence rates in disease-free patients requires more study. Variation of prevalence rates in the literature likely reflects a lack of consistency in applying diagnostic criteria.[178]

Most research reports to date are limited by their cross-sectional designs,[45,173,175,179,180] lack of comparison groups,[45] heterogeneous samples,[175] differing fatigue scales, small sample sizes,[174] varying baseline survivorship definitions (ie, time since diagnosis vs. time since treatment cessation), and different mean survivorship durations. These design issues make it difficult to reach conclusions about the prevalence, incidence, and duration of fatigue; the associated risk factors; and QOL. Additionally, most fatigue studies of patients who are post-treatment and disease-free have been conducted in Caucasian, English-speaking patients with breast cancer,[19,174,179] and peripheral stem cell or bone marrow transplant patients[181,182] with few exceptions.[22,24,26]

The cause of fatigue during post-treatment is unclear and probably multifactorial.[183] 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.[174] 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.[19]

Other risk factors associated with fatigue during post-treatment of patients who are disease-free include pretreatment fatigue, anxiety and depression levels,[184] physical activity levels,[185,186] coping methods and

cancer-related stressors, comorbidities, type of malignancy, prior treatment patterns, and treatment late effects. In a Norwegian study of Hodgkin's disease survivors in remission for more than 5 years, higher fatigue levels were documented in those who had pulmonary dysfunction; the prevalence of chronic fatigue was 2 to 3 times higher than in survivors without pulmonary dysfunction.[176] No significant correlations in this study were found between fatigue and cardiac sequelae as measured by echocardiography, exercise testing, and chest radiography.[176]

Prior treatment patterns may affect fatigue. Women who had received radiation therapy had the lowest fatigue scores. Two studies testing the effects of physical activity interventions on fatigue in breast cancer survivors found that individualized, prescriptive exercise reduced fatigue. However, researchers emphasize it is critical that exercise be individualized to the survivor's abilities to prevent exacerbation of cancer treatment toxicities.[185,186]

Education and Counseling of Patient and Family

Patients who are completing treatment and their families should be educated about the pattern and level of fatigue that can be expected during this period. Although a significant subset of patients continue to experience distressing levels of fatigue that interfere with function, most patients experience a gradual decrease in fatigue and return of energy to normal levels.[20,177] 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. Patients can benefit from general fatigue management strategies including energy conservation and distraction. A focus on finding meaning in life should be an ongoing effort.

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;[69] however, there are fewer studies of physically based therapies post-treatment.

Physical Activity

Physical activity is a category 1 recommendation. Improving strength, energy, and fitness through regular exercise have 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. Of the nonpharmacologic approaches for managing CRF, exercise has the best evidence to support its effectiveness.[69,187-196] 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.[197] 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).[198]

Yoga may also reduce fatigue in cancer survivors. 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 three-month follow-up, relative to a wait-list control group (P = .002).[102] Frequency of yoga practice was strongly associated with less fatigue at three-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.[103] After four weeks, participants receiving the yoga intervention reported less fatigue, relative to a standard care group (P = .03).

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.[87,129,132,140,141,183,199-204] The Guidelines Panel supports mindfulness-based stress reduction as a category 1 recommendation for cancer survivors. In a small RCT including 71 premenopausal women who completed treatment for breast cancer, a mindfulness-based intervention reduced CRF and sleep disturbance (P < .05).[205] In another small pilot RCT including 35 cancer survivors, a 7-week mindfulness-based stress reduction program improved fatigue interference and severity (P < .001), with effects maintained six months after the intervention.[206]

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

Additional Nonpharmacologic Approaches

Nutritional consultation and CBT for sleep (category 1)[123,146] may be helpful for fatigue management during post-treatment. A number of published studies[207-209] support the conclusion that CBT interventions designed to optimize sleep quality in patients with cancer may also improve fatigue. Positive effects on both sleep and fatigue after 4 to 5 weekly BT sessions have been reported in RCTs of patients in the survivorship phase who reported chronic insomnia.[210-212] Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.[207,208] Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.[148,209] 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.[213] AASM has also published clinical guidelines for the management of chronic insomnia in adults.[214]

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.[215] An RCT of 154 patients post-chemotherapy also found an improvement in fatigue symptoms in the active arm.[216] Similarly to patients receiving active treatment, modafinil has limited study data in patients post treatment. Though pilot studies suggested that modafinil may be associated with reduced fatigue,[217,218] the improved outcome did not hold in larger trials[167,219] (see *Interventions for Patients on Active Treatment*). The panel agrees that methylphenidate may be considered after ruling out other causes of fatigue but does not recommend the use of modafinil.

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

Interventions for Patients at the End of Life

Although the assessment and management of fatigue at the end of life parallels the general principles of this guideline, there are a few issues that are specific to this population. Factors that have a greater likelihood of association with fatigue at the end of life include anemia, medication adverse effects and polypharmacy, cognitive impairment, adverse effects of recent treatment, and malnutrition.[220] Evaluating and correcting these contributing factors could reduce fatigue severity.

It is likely that fatigue will increase substantially as the disease progresses; however, patterns of fatigue are variable. For some adults, fatigue may be characterized as constant and unrelenting; for others, it is unpredictable and may come on suddenly.[44,221] 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%).[222] In a large sample of adults receiving palliative care (N = 1000), Walsh and colleagues[223] 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[224] 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. Given et al postulate[36,225] that pain and fatigue could have a synergistic effect that worsens the overall symptom experience in elderly patients with cancer. Children with advanced cancer also experienced multiple symptoms at the end of life, most commonly fatigue, pain, and dyspnea.[226]

Education and Counseling of Patient and Family

Individuals with advanced cancer and their caregivers need information about the management of symptoms, including fatigue.[227] 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.[221] 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.[221,226] 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.[226] 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.[221] Mystakidou and colleagues[228] reported that a patient's desire for hastened death was predicted by feelings of sadness, a lack of appetite, pain, and fatigue.

Given the high prevalence of fatigue and other symptoms at the end of life, symptom management needs to be a major focus of care. Active commitment by the health care team to palliative care is critical when aggressive cancer therapy is given to patients with a low likelihood of long-term survival.[226] Interventions for fatigue should be initiated to relieve or diminish suffering, though it is recognized that some causes of fatigue cannot be assuaged.[69]

General Strategies for Management of Fatigue

Energy conservation is a self-care strategy for individuals with advanced cancer and their caregivers.[71] The goal of energy conservation is to maintain a balance between rest and activity during

times of high fatigue so that valued activities can be maintained. Energy conservation strategies include setting priorities and realistic expectations, delegating activities of lesser importance, eliminating non-essential activities, pacing oneself, taking extra rest periods, and planning high-energy activities at times of peak energy. It may also include the use of assistive devices and labor-saving techniques. Distraction may also be helpful. Patients receiving palliative care should be allowed daytime naps as long as they do not disturb nighttime sleep. In a situation of escalating fatigue at the end of life, family members may wish to designate individuals to assume activities relinquished by the individual with cancer.

Nonpharmacologic Interventions

Although there is no category 1 evidence for nonpharmacologic interventions at the end of life, clinicians are encouraged to consider matching the patient with physical activity or psychosocial intervention as indicated. Psychosocial intervention at this stage may focus on meaning and dignity, and gaining acceptance of the limitations imposed by fatigue. It may include a re-emphasis on meaningful family interactions that do not require high-level physical activity.[229] Sustaining a sense of meaning has been demonstrated to allow patients with cancer to endorse a high QOL despite significant symptoms.[230] Studies suggest that interventions aimed at sustaining or enhancing meaning and/or dignity can significantly reduce distress related to symptoms and improve overall QOL.[231-233]

Although fatigue may increase at end of life, some individuals may choose to be active despite failing health. There is some evidence that exercise is beneficial to individuals with incurable cancer and short life expectancy, though it is important to consider patients' physical constraints (see section regarding Physical Activity under *Interventions for Patients on Active Treatment*). A group exercise program was evaluated in a pilot study of 63 Norwegian outpatients receiving palliative care.[234] The program consisted of two 50-minute sessions twice a week for six weeks that combined strength building, standing balance, and aerobic exercise. The exercise participants had less physical fatigue and increased walking distance. There were no adverse effects of exercise, although 29 of the 63 participants did not complete the program due to sudden death, or medical and social reasons.

A small pilot study was conducted to evaluate an exercise program for nine individuals with advanced cancer enrolled in a home hospice program.[235] A physical therapist guided participants in the selection of several activities (eg, walking, arm exercises with resistance, marching in place, dancing). These were performed at different times throughout the day on a schedule devised jointly by the therapist and participant. All participants were able to increase their activity level over a 2-week period without increased fatigue. There was a trend toward increased QOL and decreased anxiety. Although more research is needed, enhanced activity shows promise as a fatigue management strategy at the end of life; psychosocial interventions, sleep therapy, family interaction, and nutritional therapy are also helpful.

Based on a systematic review of 20 exercise studies relevant to fatigue and muscle wasting in multiple myeloma, Strong[236] 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.

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.[237,238] However, two RCTs reported an improvement in fatigue in both the methylphenidate and placebo arms.[239,240] Another psychostimulant, dexamphetamine (10 mg twice daily for 8 days), was evaluated for fatigue in patients with advanced cancer.[241] 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. A recent RCT in patients with advanced non-small cell lung cancer (n = 160) showed no significant improvement between patients treated with modafinil (n = 75) versus placebo (n = 85). Although well-tolerated, the mean score change between groups as measured by the FACT-F scale was not significant (0.20; 95% CI, -3.56–3.97).[219] Overall, methylphenidate may be considered with caution for selected terminal patients.

There is evidence supporting the effectiveness of corticosteroids (prednisone and its derivative, and dexamethasone) in providing short-term relief for fatigue and improving QOL.[242-245] 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).[246] Improved outcomes were determined from the FACT-F subscale as the primary endpoint. An assessment of overall QOL showed improvement at day 15 (P = .03) and in physical well-being measured at day 8 (P = .007) and day 15 (P = .002) as measured by the Edmonton Symptom Assessment Scale for physical distress. This study was effective as a short-term therapy but the long-term effects were not evaluated.[246] Recently, in a second RCT investigating the effects of methylprednisone in patients with advanced cancer receiving opium, fatigue was measured in patients given 16 mg twice a day of methylprednisone (n = 26) versus patients in the placebo group (n = 24).[247] Patients receiving methylprednisone experienced a 17-point improvement on the EORTC-QOL Questionnaire C30[248] compared to the 3-point decline recorded by the placebo group (-17 vs. 3 points; P = .003).[247]

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. In addition, there has been interest in the progestational agent megestrol acetate to improve fatigue. A systematic review paper demonstrated the safety and efficacy of megestrol acetate in treating cachexia for patients with cancer.[249] 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-score = 0.78; P = 0.44).[165,250]

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

Re-Evaluation Phase

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

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

Summary

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

Management of fatigue begins with primary oncology team members who perform the initial screening and either provide basic education and counseling or expand the initial screening to a more focused evaluation for moderate or higher levels of fatigue. The focused evaluation includes assessment of current disease and treatment status, a review of body systems, and an in-depth fatigue evaluation. In addition, the patient is assessed for the presence of treatable factors known to contribute to fatigue. If present, factors should be treated according to practice guidelines, with referral to other care professionals as appropriate, and the patient's fatigue should be re-evaluated regularly. If none of the factors is present or if the fatigue is unresolved, appropriate fatigue management and treatment strategies are selected within the context of the patient's clinical status (active treatment, post-treatment, or at 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 moderate exercise program to improve functional capacity and activity tolerance; psychosocial programs to manage stress and increase support; implementation of energy conservation strategies; and nutritional and sleep interventions as appropriate. Pharmacologic therapy may include drugs used to treat comorbidities. A recent update on the use of the psychostimulant methylphenidate suggests that it may provide some benefit.[251] A second agent that may be helpful for short-term use in advanced cancer is the corticosteroid methylprednisolone.[40,246,247] 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.[42] The oncology care team must recognize the many patient-, provider-, and system-related behaviors that can impede effective fatigue management. Reducing barriers by use of available resources and evidence-based guidelines increases benefits to patients experiencing fatigue.[252,253]

Appendix

Fatigue Measurement for the Health Care Professional

A resource to facilitate selection of instruments to measure fatigue

Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. Lancet 2003;362:640-650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12944066.

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

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

- *Includes factors to consider when selecting a fatigue measure.*

Meek PM, Nail LM, Barsevick A, et al. Psychometric testing of fatigue instruments for use with cancer patients. Nurs Res 2000;49:181-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10929689.

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

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

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

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

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

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

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

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[48]	1 (severity)	11-point Likert	9	Short, easy to use	Yes, mixed cancers[48,254]	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
EORTC QLQ-C30‡,[245]	1 (severity)	4-point Likert	3	easy to use	Yes, mixed cancers[248,255]	A,P,E	α=0.80–0.85	Measures physical fatigue; not recommended as the only scale for end-of-life fatigue[256]
Fatigue Questionnaire[257]	1 (severity)	4-point Likert	11	easy to use	Yes, cancer vs. normal population,[257] Hodgkin lymphoma[258]	A,P,E	α=0.88–0.90	Measures physical and mental fatigue
Visual Analogue Fatigue Scale[259]	1 (severity)	Analogue	18	Short, easy to use	Yes, patients with cancer compared to healthy controls[259]	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
Fatigue Symptom Inventory[260]	4 (severity, frequency, diurnal variation, interference)	11-point Likert	14	Reasonable	Yes, breast,[260-263] metastatic,[264] and mixed cancers[265]	A,P	r=0.35–0.75 α=0.92–0.95	Two additional quantifiable fatigue questions; able to distinguish change over time; weak test-retest reliability

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
Functional Assessment of Cancer Therapy, Fatigue[266]	5 (physical, social/family, emotional, functional, fatigue)	5-point Likert	41/13	Long but subscale is reasonable and simple	Yes, breast,[267,268] mixed cancers[180,269-271]	A,P,E	r=0.90 α=0.93–0.95	Items consist of general health-related QOL (28 items) plus fatigue subscale of 13 items; lacks construct validity; measures change over time
Multi-Dimensional Fatigue Inventory-20[272]	5 (general, physical, mental, reduced activity, reduced motivation)	5-point Likert	20	Reasonable	Yes, breast[273,274], uterine,[275,276] mixed cancers[272,277-279]	A,P,E	α=0.65–0.80	Likert scale incorporates VAS
Multi-Dimensional Fatigue Symptom Inventory[280]	5 (general, physical, mental emotional, vigor)	5-point Likert	83/30	Variable length, can be complicated	Yes, mixed[280,281] and breast cancer[282]	A,P	r>0.50 α=0.87–0.96	Full version is long (83 items) but short form is a reasonable alternative[283]
Piper Fatigue Score-12[284]	4 (sensory, behavioral/ severity, affective meaning, cognitive/mood)	11-point Likert	12	Easy to use	Yes, breast cancer[284,285]	P	r=0.87–0.89	Shortened from revised Piper Fatigue Score that has been tested more extensively[130,284-292]; reliability is based on subscales in single study
Schwartz Cancer Fatigue Scale, Revised[293]	2 (physical and perceptual)	5-point Likert	6	Reasonable and clear	Yes, mixed cancers[293,294]	A	α=0.90	Shortened from the original 28-item Schwartz Cancer Fatigue Scale[295]

℗ 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

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