

NCCN

Survivorship: Fatigue, Version 1.2014

Clinical Practice Guidelines in Oncology

Crystal S. Denlinger, MD; Jennifer A. Ligibel, MD;
Madhuri Are, MD; K. Scott Baker, MD, MS;
Wendy Demark-Wahnefried, PhD, RD;
Debra L. Friedman, MD, MS; Mindy Goldman, MD;
Lee Jones, PhD; Allison King, MD; Grace H. Ku, MD;
Elizabeth Kvale, MD; Terry S. Langbaum, MAS;
Kristin Leonardi-Warren, RN, ND; Mary S. McCabe, RN, BS, MS;
Michelle Melisko, MD; Jose G. Montoya, MD;

Kathi Mooney, RN, PhD; Mary Ann Morgan, PhD, FNP-BC;
Javid J. Moslehi, MD; Tracey O'Connor, MD;
Linda Overholser, MD, MPH; Electra D. Paskett, PhD;
Muhammad Raza, MD; Karen L. Syrjala, PhD;
Susan G. Urba, MD; Mark T. Wakabayashi, MD, MPH;
Phyllis Zee, MD; Nicole McMillian, MS; and
Deborah Freedman-Cass, PhD

NCCN defines cancer-related fatigue 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.”¹ Fatigue is a common symptom in patients with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation

Abstract

Many cancer survivors report that fatigue is a disruptive symptom even after treatment ends. Persistent cancer-related fatigue affects quality of life, because individuals become too tired to fully participate in the roles and activities that make life meaningful. Identification and management of fatigue remains an unmet need for many cancer survivors. This section of the NCCN Guidelines for Survivorship provides screening, evaluation, and management recommendations for fatigue in survivors. Management includes education and counseling, physical activity, psychosocial interventions, and pharmacologic treatments. (*J Natl Compr Canc Netw* 2014;12:876–887)

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.

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

Please Note

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Disclosures for the NCCN Survivorship Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Survivorship Panel members can be found on page 887. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

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

therapy, bone marrow transplantation, or treatment with biological response modifiers.²⁻⁴ According to a survey of 1569 patients with cancer, the symptom is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.^{5,6} Cancer survivors report that fatigue continues to be a disruptive symptom after treatment ends,⁷⁻¹⁴ with studies showing that 17% to 29% of cancer survivors experience persistent fatigue for years after the completion of active therapy.^{15,16} Persistent cancer-related fatigue affects quality of life, because individuals become too tired to fully participate in the roles and activities that make life meaningful.^{9,17} Disability-related issues are also relevant for cancer survivors, because obtaining or retaining disability benefits from insurers is often difficult for patients with cancer-related

fatigue. Identification and management of fatigue remains an unmet need for many cancer survivors.

The specific mechanisms involved in the pathophysiology of cancer-related fatigue are unknown. Proposed mechanisms include proinflammatory cytokines, hypothalamic-pituitary-adrenal axis dysregulation, circadian rhythm desynchronization, skeletal muscle wasting, and genetic dysregulation.¹⁸⁻²³ Several studies have focused on the cause of fatigue, especially in cancer survivors with no evidence of active disease, and have suggested that persistent immune system activation and chronic inflammatory processes may be involved.^{7,24-26} Evidence supporting these mechanisms is limited.

Text cont. on page 883.

NCCN Survivorship Panel Members

*^{a,c}Crystal S. Denlinger, MD/Chair†
Fox Chase Cancer Center

*^{c,d}Jennifer A. Ligibel, MD/Vice Chair†
Dana-Farber/Brigham and Women's Cancer Center

^fMadhuri Are, MD‡
Fred & Pamela Buffett Cancer Center at
The Nebraska Medical Center

^{b,e}K. Scott Baker, MD, MSE‡§
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

^cWendy Demark-Wahnefried, PhD, RD‡§
University of Alabama at Birmingham
Comprehensive Cancer Center

^{b,d}Debra L. Friedman, MD, MSE‡§
Vanderbilt-Ingram Cancer Center

*^gMindy Goldman, MD‡
UCSF Helen Diller Family Comprehensive Cancer Center

^{c,d}Lee Jones, PhD‡¶
Memorial Sloan-Kettering Cancer Center

^bAllison King, MD‡¶‡
Siteman Cancer Center at Barnes-Jewish Hospital and
Washington University School of Medicine

Grace H. Ku, MD‡‡
UC San Diego Moores Cancer Center

^{b,h}Elizabeth Kvale, MD‡
University of Alabama at Birmingham
Comprehensive Cancer Center

^aTerry S. Langbaum, MAS‡
The Sidney Kimmel Comprehensive Cancer Center at
Johns Hopkins

^gKristin Leonardi-Warren, RN, ND#
University of Colorado Cancer Center

^bMary S. McCabe, RN, BS, MS#
Memorial Sloan-Kettering Cancer Center

^{b,c,d,g}Michelle Melisko, MD†
UCSF Helen Diller Family Comprehensive Cancer Center

^eJose G. Montoya, MD‡
Stanford Cancer Institute

^{a,d}Kathi Mooney, RN, PhD#
Huntsman Cancer Institute at the University of Utah

^{c,e}Mary Ann Morgan, PhD, FNP-BC#
Moffitt Cancer Center

Javid J. Moslehi, MD‡‡
Dana-Farber/Brigham and Women's Cancer Center

^{d,h}Tracey O'Connor, MD†
Roswell Park Cancer Institute

^cLinda Overholser, MD, MPH‡
University of Colorado Cancer Center

^cElectra D. Paskett, PhD‡
The Ohio State University Comprehensive Cancer Center -
James Cancer Hospital and Solove Research Institute

^{f,h}Muhammad Raza, MD‡
St. Jude Children's Research Hospital/
The University of Tennessee Health Science Center

^kKaren L. Syrjala, PhD‡
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

*^fSusan G. Urba, MD†‡
University of Michigan Comprehensive Cancer Center

^gMark T. Wakabayashi, MD, MPH‡
City of Hope Comprehensive Cancer Center

*^hPhyllis Zee, MD‡‡¶
Robert H. Lurie Comprehensive Cancer Center of
Northwestern University

NCCN Staff: Nicole McMillian, MS, and
Deborah Freedman-Cass, PhD

KEY:

*Writing Committee Member

Subcommittees: ^aAnxiety and Depression; ^bCognitive Function;
^cExercise; ^dFatigue; ^eImmunizations and Infections; ^fPain;
^gSexual Function; ^hSleep Disorders

Specialties: [‡]Bone Marrow Transplantation; ^{‡‡}Cardiology;
^{‡‡‡}Epidemiology; ^{‡‡‡‡}Exercise/Physiology; ^{‡‡‡‡‡}Gynecology/
Gynecologic Oncology; ^{‡‡‡‡‡‡}Hematology/Hematology Oncology;
^{‡‡‡‡‡‡‡}Infectious Diseases; ^{‡‡‡‡‡‡‡‡}Internal Medicine; ^{‡‡‡‡‡‡‡‡‡}Medical Oncology;
^{‡‡‡‡‡‡‡‡‡‡}Neurology/Neuro-Oncology; ^{‡‡‡‡‡‡‡‡‡‡‡}Nursing; ^{‡‡‡‡‡‡‡‡‡‡‡‡}Nutrition Science/
Dietician; ^{‡‡‡‡‡‡‡‡‡‡‡‡‡}Patient Advocacy; ^{‡‡‡‡‡‡‡‡‡‡‡‡‡‡}Pediatric Oncology; ^{‡‡‡‡‡‡‡‡‡‡‡‡‡‡‡}Psychiatry,
Psychology, Including Health Behavior; ^{‡‡‡‡‡‡‡‡‡‡‡‡‡‡‡‡}Supportive Care
Including Palliative, Pain Management, Pastoral Care, and
Oncology Social Work

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.

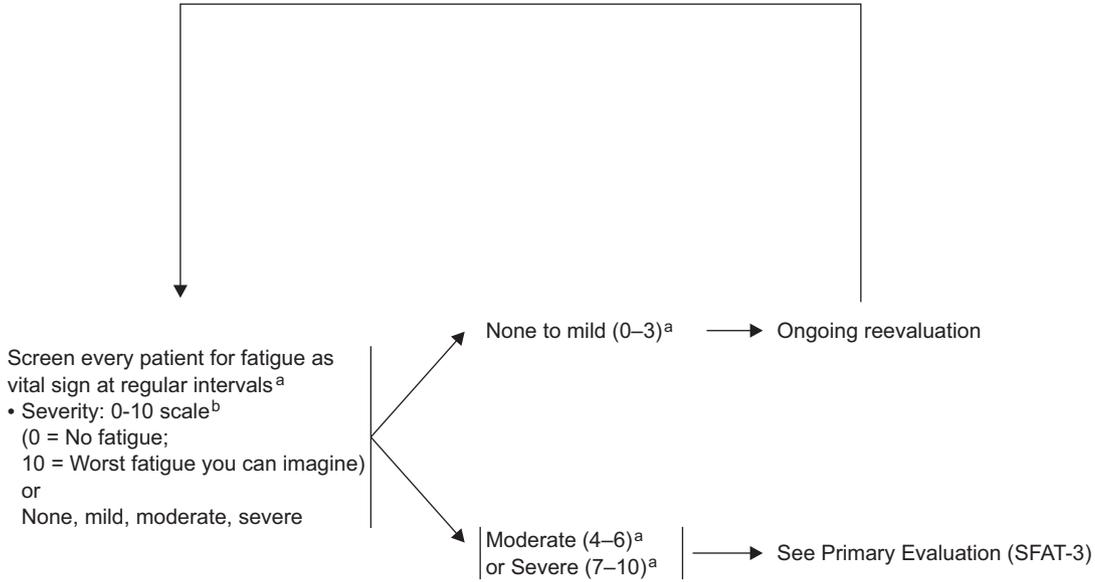
CONSIDERATIONS FOR FATIGUE IN CANCER SURVIVORS

- Fatigue is a common complaint in individuals undergoing cancer therapy and can be a persistent problem for some cancer survivors in the months and years after cancer diagnosis.
 - Receipt of chemotherapy and radiation are both predisposing factors for cancer-related fatigue, but fatigue can be seen in some patients who are treated with surgery alone.
 - The time-course of fatigue is unique to the survivor and their treatment plan, but some general principles apply: mild to moderate fatigue is common in cancer survivors who undergo chemotherapy and/or radiation; mild to moderate fatigue lasting up to 1 year can occur in a proportion of cancer survivors.
 - Fatigue that initially presents months after the completion of adjuvant therapy and fatigue that worsens during this period warrant additional evaluation.

SFAT-1

Survivorship: Fatigue, Version 1.2014

SCREENING



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

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

SFAT-2

PRIMARY EVALUATION FATIGUE SCORE:
MODERATE OR SEVERE (4-10)

EVALUATION

History and Physical (H&P):

- Focused fatigue history
 - ▶ Onset, pattern, duration
 - ▶ Change over time
 - ▶ Associated or alleviating factors
 - ▶ Interference with function
- Evaluate disease status
 - ▶ Evaluate risk of recurrence based on stage, pathologic factors, and treatment history
 - ▶ Perform review of systems to determine if other symptoms substantiate suspicion for recurrence
- Assessment of treatable contributing factors:
 - ▶ Comorbidities
 - ◊ Alcohol/substance abuse
 - ◊ Cardiac dysfunction
 - ◊ Endocrine dysfunction (eg, hypothyroidism, hypogonadism, adrenal insufficiency)
 - ◊ Pulmonary dysfunction
 - ◊ Renal dysfunction
 - ◊ Anemia
 - ◊ Arthritis
 - ▶ Medications (consider persistent use of sleep aids, pain medications, or antiemetics)
 - ▶ Emotional distress, screen for anxiety and depression
 - ▶ Sleep disturbance (eg, insomnia, sleep apnea, vasomotor symptoms, restless leg syndrome) (See SSD-1*)
 - ▶ Pain
 - ▶ Nutritional issues
 - ◊ Weight/caloric intake changes
 - ▶ Deconditioning/loss of muscle mass

Laboratory evaluation:

- Consider performing laboratory evaluation based on presence of other symptoms, onset, and severity of fatigue
 - ▶ CBC with differential
 - ◊ Compare end-of-treatment hemoglobin/hematocrit with current values
 - ◊ Assess other cell lines (WBC and platelets)
 - ▶ Comprehensive metabolic panel
 - ◊ Assess electrolytes
 - ◊ Assess hepatic and renal function
 - ▶ Endocrinologic evaluation
 - ◊ Consider evaluation of TSH in patients who have received prior head/neck, torso, or breast radiation
 - ◊ Consider more comprehensive evaluation or referral to specialist if other symptoms present

Imaging:

- Consider radiologic assessment only if high risk of disease recurrence OR if accompanying signs and symptoms suggest presence of metastatic disease
- Consider ECHO or MUGA for patients treated with an anthracycline, trastuzumab, bevacizumab, or other VEGF- or HER2-targeted therapy
- Consider chest radiograph and oxygen saturation testing for pulmonary complaints

*Available online, in these guidelines, at NCCN.org.

SFAT-3

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

Survivorship: Fatigue, Version 1.2014

TREATMENT OF CONTRIBUTING FACTORS

- Treat contributing factors:
 - ▶ Medications/side effects
 - ▶ Pain (See SPAIN-1*)
 - ▶ Emotional distress
See (SANXDE-1*) and NCCN Guidelines for Distress Management†
 - ▶ Anemia
 - ◊ Treat iron B₁₂, folate deficiency, if present
 - ◊ Consider referral/further evaluation for persistent anemia or cytopenias
 - ▶ Sleep disturbance (See SSD-1*)
 - ▶ Nutritional deficit/imbalance
 - ▶ Comorbidities

→ See Interventions for Cancer Survivors (SFAT-5)

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†To view the most recent version of these guidelines, visit NCCN.org.

SFAT-4

INTERVENTIONS FOR CANCER SURVIVORS

Patient/Family Education and CounselingPhysical ActivityOther Behavioral Interventions^cPharmacologic^f

Information about known pattern of fatigue during and following treatment

- Self-monitoring of fatigue levels
- Energy conservation
 - Set priorities
 - Pace
 - Schedule activities at times of peak energy

- Maintain adequate levels of physical activity (category 1) (See SE-1* and SE-4*)
- Survivors at higher risk of injury (eg, those living with neuropathy, cardiomyopathy, lymphedema, or other long-term effects of therapy or other comorbidities) should be referred to a physical therapist or exercise specialist
- Make use of local resources to help patients increase exercise
 - Exercise classes at cancer centers
 - Community programs focused on cancer survivors
 - Exercise professional certified by the American College of Sports Medicine
 - For patients with severe fatigue interfering with function, consider referral to a physical therapist or physiatrist

- Psychosocial interventions (category 1)
 - Cognitive behavioral therapy^d/behavioral therapy (category 1)
 - Psychoeducational therapies/educational therapies (category 1)
 - Supportive expressive therapies (category 1)^e
- Nutrition consultation
- Cognitive behavioral therapy^d for sleep (category 1)
 - Stimulus control
 - Sleep restriction
 - Sleep hygiene

Consider psychostimulants^g (methylphenidate or modafinil^h) after ruling out other causes of fatigue and failure of other interventions

*Available online, in these guidelines, at NCCN.org.

^cInterventions 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.

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

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

^fPharmacologic interventions remain investigational but have been reported to improve symptoms of fatigue in some patients.

^gPsychostimulants are occasionally used to treat cancer-related fatigue. Several studies have evaluated their efficacy in the setting of active treatment and results have been mixed. There are extremely limited data regarding the use of these agents in the posttreatment setting.

^hMore evidence exists for methylphenidate and less for modafinil. These agents should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in patients with cancer.

SFAT-5

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

Text cont. from page 877.

Screening for Fatigue

All survivors should be screened for fatigue to ensure that those with moderate to severe fatigue are identified and treated promptly and effectively. Because fatigue is a subjective experience, clinicians must rely on patients' descriptions of their fatigue level. The panel recommends the use of a severity scale, with survivors being asked, "How would you rate your fatigue on a scale of 0 to 10 over the past 7 days?" Alternately, screening can be performed with patients asked to rate their fatigue as none, mild, moderate, or severe. Scores of 0 to 3 or none to mild fatigue require no further assessment or interventions; these patients should be rescreened at regular intervals. Patients with scores of 4 or greater or indicating moderate or severe fatigue should be evaluated further. Studies in patients with cancer have revealed a marked decrease in physical functioning at a reported fatigue level of 7 or higher on the 0 to 10 scale.^{27,28}

Evaluation for Moderate to Severe Fatigue

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. A thorough history is warranted, because the recommended workup for fatigue differs according to the timing of fatigue onset in relation to the completion of active therapy and the presence of predisposing factors and other symptoms. Fatigue has a variable natural history, with some patients complaining of only mild levels of fatigue even during active therapy and others experiencing severe fatigue for years after treatment completion.

In general, mild to moderate levels of fatigue that persist for 6 to 12 months after the completion of therapy likely do not warrant an extensive workup, unless other symptoms are present. Conversely, when moderate to severe fatigue begins after or worsens during this period, or when other symptoms are present, such as pain, pulmonary complaints, or unintentional weight loss, a more extensive workup is warranted to screen for the presence of metastatic disease or other comorbidities.

Regardless of fatigue onset, it is always relevant to screen for common contributing factors, such as emotional distress, sleep disturbance, pain, and the use of prescriptions or over-the-counter medications or supplements. Possible medical causes of fatigue, including cardiac disease and hypothyroidism,

should also be assessed. Disease and treatment considerations also affect recommendations for screening, such as the inclusion of echocardiograms for patients who received cardiotoxic treatments, and thyroid screening for patients who received radiation to the neck or thorax.

Management of Fatigue

Several interventions and strategies have been shown to help alleviate fatigue and reduce distress caused by this symptom in patients with cancer and survivors; recommended strategies and interventions are described herein. For additional information about fatigue in survivors and patients with cancer, please see the NCCN Guidelines for Cancer-Related Fatigue (to view the most recent version of these guidelines, visit NCCN.org). The following guidelines may be modified to fit the individual survivor's circumstances.

Treatment of Contributing Factors

Management of fatigue in survivors first includes the treatment of contributing factors, such as pain, distress, anemia, and sleep disturbances (more information on treatment of pain, anxiety/depression, and sleep disorders in survivors can be found throughout the full version of these guidelines, available online at NCCN.org).

Patient and Family Education and Counseling

Education and counseling can be beneficial in helping patients cope with fatigue. Understanding typical patterns of fatigue during and after treatment can help patients set reasonable expectations regarding improvements in energy after the completion of cancer therapy and can help allay concerns that persistent fatigue after the completion of therapy is evidence of disease recurrence. Counseling can help patients develop strategies for self-monitoring of fatigue and techniques, such as energy conservation, that may be helpful in the immediate post-treatment period.²⁹

Physical Activity

Activity enhancement is a category 1 recommendation. Improving strength, energy, and fitness through regular exercise, even a moderate walking exercise program, has been shown to facilitate the transition from patient to survivor, decrease anxiety and depression, improve body image, and increase toler-

ance for physical activity. Therefore, survivors with moderate to severe fatigue should be encouraged to maintain adequate levels of physical activity (category 1). Robust data support the efficacy of increased physical activity for reducing fatigue in patients with cancer and survivors.^{30–36} A recent meta-analysis of randomized controlled trials found that cancer survivors who participated in exercise interventions, either during or after treatment for cancer, experienced significant improvements in fatigue compared with patients randomized to the control group.³⁷ Another meta-analysis of 44 studies, including 3254 cancer survivors, concluded that moderate-intensity resistance exercise among older cancer survivors reduced fatigue.³⁰

Survivors at a higher risk of injury should be referred to a physical therapist or exercise specialist (also see “Physical Activity,” page 882).

Psychosocial Interventions

Psychosocial interventions, such as cognitive behavioral therapy (CBT), psychoeducational therapy, and supportive expressive therapy, including support groups, counseling, and journal writing (all category 1 recommendations), have also been shown to reduce fatigue in cancer survivors, although data are not entirely consistent.^{38–43} Several meta-analyses have evaluated the role of psychosocial interventions in reducing fatigue. For example, Kangas et al⁴² reported a weighted pooled mean effect of -0.31 for psychosocial interventions on fatigue in an analysis of 3620 patients with cancer from 41 studies. Jacobsen et al⁴⁴ analyzed 30 randomized controlled trials and found a significant effect size (dw) for psychological interventions (dw, 0.10; 95% CI, 0.02–0.18), but not for activity-based programs (dw, 0.05; 95% CI, -0.08 –0.19). A meta-analysis by Duijts et al³⁸ 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 (standardized mean difference [SMD], -0.16).

Several published studies support the conclusion that CBT interventions designed to optimize sleep quality in patients with cancer may also improve fatigue.^{45–48} Two randomized clinical trials of patients who reported chronic insomnia in the survivorship phase demonstrated improvements in both sleep and fatigue after 4 to 5 weekly behavioral therapy

sessions.^{39,40,49} Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.^{45,47} Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.^{48,50} The American Academy of Sleep Medicine has recommended 3 specific therapies for chronic insomnia in healthy individuals: relaxation training, cognitive behavior therapy, and stimulus control therapy.⁵¹

Pharmacologic Interventions

Psychostimulants, such as methylphenidate and modafinil, are also used to treat fatigue, although data regarding their use to treat fatigue in cancer survivors are limited. A 54% response rate to methylphenidate was reported in a phase II trial of 37 breast cancer survivors.⁵² A randomized trial in 154 patients postchemotherapy also found an improvement in fatigue symptoms in the dexamethylphenidate arm.⁵³ A recent meta-analysis of 5 randomized controlled trials of patients with cancer found limited evidence for the efficacy of 4 or more weeks of methylphenidate treatment for cancer-related fatigue (mean difference, -3.70 ; 95% CI, -7.03 to -0.37 ; $P=.03$).⁵⁴

Modafinil also shows some promise for management of posttreatment fatigue in small trials. Morrow et al⁵⁵ conducted an open-label study of modafinil for 51 breast cancer survivors with persistent fatigue. The dose was 200 mg/d for 1 month. A reduction in fatigue was reported among 86% of these survivors. In a pilot study of 30 adults with previously treated brain tumors, modafinil was associated with improvement in fatigue by 8 weeks.⁵⁶ Currently, the panel agrees that methylphenidate or modafinil may be considered after ruling out other causes of fatigue, although they acknowledge the limited data supporting the use of these agents in this setting.

Small pilot studies and one recent randomized controlled trial have evaluated the impact of supplements, including ginseng and vitamin D, for cancer-related fatigue.⁵⁷ The evidence to date is inconsistent, and the panel currently does not recommend the use of supplements for the treatment of fatigue.

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Survivorship: Fatigue, Version 1.2014

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Survivorship: Fatigue, Version 1.2014

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Survivorship: Fatigue, Version 1.2014

Individual Disclosures for the NCCN Survivorship Panel					
Panel Member	Clinical Research Support/Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Madhuri Are, MD	None	None	None	None	5/15/13
K. Scott Baker, MD, MS	None	None	None	None	11/22/13
Wendy Demark-Wahnefried, PhD, RD	National Cancer Institute; Harvest for Health Gardening Project for Breast Cancer Survivors; and Nutrigenomic Link between Alpha-Linolenic Acid and Aggressive Prostate Cancer	American Society of Clinical Oncology	None	American Society of Preventive Oncology	11/13/13
Crystal S. Denlinger, MD	Bayer HealthCare; ImClone Systems Incorporated; MedImmune Inc.; OncoMed Pharmaceuticals; Astex Pharmaceuticals; Merrimack Pharmaceuticals; and Pfizer Inc.	Eli Lilly and Company	None	None	1/9/14
Debra L. Friedman, MD, MS	None	None	None	None	5/26/13
Mindy Goldman, MD	None	None	None	None	Pending
Lee W. Jones, PhD	None	None	None	None	2/2/12
Allison King, MD	None	None	None	None	8/12/13
Grace H. Ku, MD	None	None	None	None	8/13/13
Elizabeth Kvale, MD	None	None	None	None	10/7/13
Terry S. Langbaum, MAS	None	None	None	None	8/13/13
Kristin Leonardi-Warren, RN, ND	None	None	None	None	1/6/14
Jennifer A. Ligibel, MD	None	None	None	None	10/3/13
Mary S. McCabe, RN, BS, MS	None	None	None	None	8/12/13
Michelle Melisko, MD	Celldex Therapeutics; and Galena Biopharma	Agendia BV; Genentech, Inc.; and Novartis Pharmaceuticals Corporation	None	None	10/11/13
Jose G. Montoya, MD	None	None	None	None	12/6/13
Kathi Mooney, RN, PhD	University of Utah	None	None	None	9/30/13
Mary Ann Morgan, PhD, FNP-BC	None	None	None	None	8/19/13
Javid J. Moslehi, MD	None	ARIAD Pharmaceuticals, Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	None	1/27/14
Tracey O'Connor, MD	None	None	None	None	6/13/13
Linda Overholser, MD, MPH	None	Antigenics Inc.; and Colorado Central Cancer Registry Care Plan Project	None	None	10/10/13
Electra D. Paskett, PhD	Merck & Co., Inc.	None	None	None	6/13/13
Muhammad Raza, MD	None	None	None	None	8/23/12
Karen L. Syrjala, PhD	None	None	None	None	10/3/13
Susan G. Urba, MD	None	Eisai Inc.; and Helsinn Therapeutics (U.S.), Inc.	None	None	10/9/13
Mark T. Wakabayashi, MD, MPH	None	None	None	None	6/19/13
Phyllis Zee, MD	Philips/Respironics	Merck & Co., Inc.; Jazz Pharmaceuticals; Vanda Pharmaceuticals; and Purdue Pharma LP	None	None	3/26/14

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