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Survivorship: Fatigue, Version 1.2014:

Clinical Practice Guidelines in Oncology

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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.

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 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

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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.

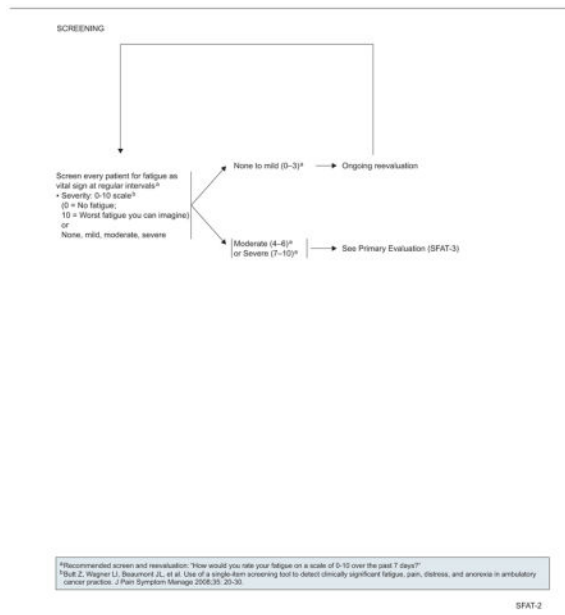
DEFINITION OF CANCER-RELATED FATIGUE

• 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.

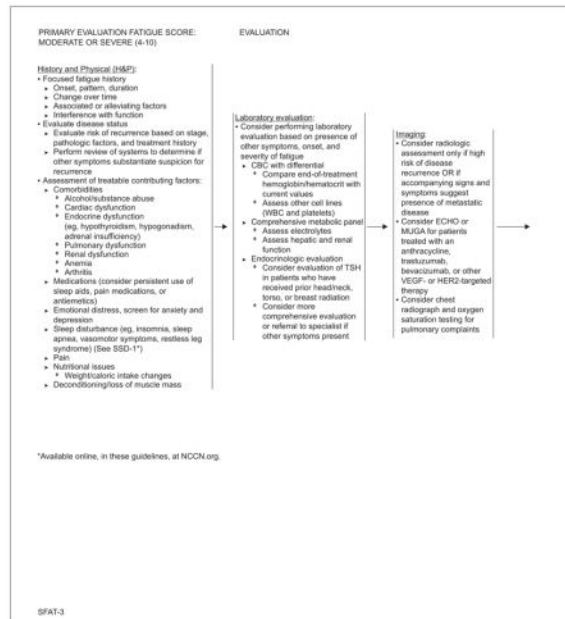
CONSIDERATIONS FOR FATIGUE IN CANCER SURVIVORS

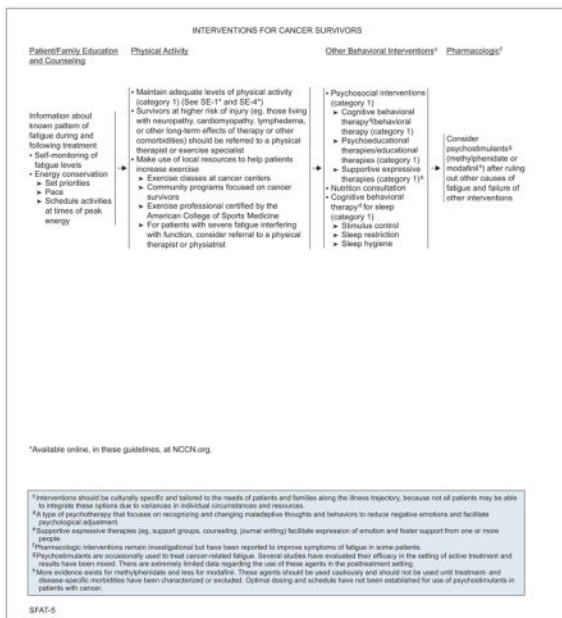
- Fatigue is a common complaint in individuals undergoing cancer therapy and can be a persistent problem for some cancer survivors in the months and years after cancer diagnosis.
- Receipt of chemotherapy and radiation are both predisposing factors for cancer-related fatigue, but fatigue can be seen 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



*Recommended screen and reevaluation: "How would you rate your fatigue on a scale of 0-10 over the past 7 days?"
 *Bull Z, Nguyen L, Rosenfeld J, 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.





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 work-up, 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 tolerance 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 (d_w) for psychological interventions (d_w , 0.10; 95% CI, 0.02–0.18), but not for activity-based programs (d_w , 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.^{45–49} 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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