

## REVIEW

# Cancer-Related Fatigue: The Approach and Treatment

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As the volume of cancer survivors continues to increase, clinicians are being faced with a growing number of patients with cancer-related fatigue (CRF). Survivors with a variety of malignancies may experience fatigue. Many potential barriers to the identification of this symptom in a cancer survivor may exist, due in part to both the patient and the clinician. Assessment of patients for fatigue is important because it can profoundly affect their daily lives. Many factors contribute to CRF. Hence, the clinician may face a daunting challenge in attempting to alleviate CRF. Treatment modalities for CRF include nonpharmacologic interventions, such as psychosocial interventions, exercise, sleep therapy, and acupuncture. Pharmacologic interventions include stimulants, namely modafinil and methylphenidate. In some patients antidepressants may be beneficial. Clinicians should assess cancer survivors for the presence of fatigue and focus on its treatment in an attempt to ensure that these patients have the best possible symptom control.

**KEY WORDS:** cancer-related fatigue; cancer survivors; exercise; stimulants.

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## INTRODUCTION

Advances in the diagnosis and treatment of malignancies have resulted in the growth of the number of cancer survivors, estimated now in the United States to be more than 10 million<sup>1</sup>. Today, almost two-thirds of patients diagnosed with cancer are expected to survive 5 or more years. Due to these successes, cancer is now being considered a chronic illness similar to diabetes, hypertension, and cardiovascular disease. Today, physicians and other healthcare workers are facing the challenges associated with the long-term sequela of cancer and its treatment. Cancer survivors can have a myriad of comorbid conditions as well as symptoms that can affect not only their overall medical condition but also the quality of their daily lives.

Fatigue is a common symptom experienced by cancer patients and cancer survivors. Fatigue may be defined as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning<sup>2</sup>. Fatigue is also a multidimensional symptom because it encompasses physical, mental, and emotional aspects. Patients can experience fatigue anywhere along the spectrum of cancer care. Fatigue may be the presenting

symptom of their malignancy or a long-term side effect of their treatment. Up to 30% of cancer survivors report a loss of energy for years after they complete treatment<sup>3-5</sup>. Fatigue can have a profound effect on the patient's life. Some are unable to return to work or engage in their usual activities of daily living. Fatigue results in significant stress and anxiety for both the patient and family members. There are several barriers that contribute to inadequate assessment and treatment of this symptom. In a busy outpatient practice, clinicians are faced with time constraints that limit their ability to inquire about this symptom. In addition, clinicians might feel uncomfortable discussing this symptom because of lack of knowledge in this area and the concern of limited treatment options. On the other hand, cancer survivors are at times reluctant to mention they have fatigue because of the fear that it could represent disease recurrence or that they might be considered a complainer. In addition, some patients think that it is an expected outcome of their cancer and its treatment. However, due to the increasing incidence of this symptom and the potential profound effect that it can have on a patient's daily life, healthcare providers should be encouraged to inquire about the presence of this symptom as well as focus on its treatment.

A variety of studies have been performed that illustrate the importance of fatigue. Lutgendorf et al. conducted a longitudinal study of gynecologic patients in the year after diagnosis and found an increase in fatigue in survivors of both early-stage and advanced disease compared to healthy individuals<sup>6</sup>. In another study, performed by Ersek et al., involving ovarian cancer survivors, fatigue was found to be the most severe physical symptom<sup>7</sup>. Fossa found that patients treated for Hodgkin's disease had more chronic fatigue than testicular survivors and both groups had more problems with fatigue compared to the general population<sup>8</sup>. Breast cancer survivors, 20 months after autologous hematopoietic cell transplantation, had higher levels of fatigue than in a matched noncancer cohort of women<sup>9</sup>. Based on ICD-10 diagnoses, fatigue in cancer survivors ranges from 17% to 21%<sup>10</sup>. If other criteria are used, such as a fatigue scale scores, the range is higher, 33% to 53%<sup>11</sup>. Because of the wide variation in study designs to date, current data is limited and further research is needed in this area. The cause of fatigue in long-term cancer survivors that are disease-free may be because of persistent activation of the immune system or to late treatment effects on major organ systems<sup>12,13</sup>. The exact biologic mechanisms for fatigue with respect to cancer treatment, such as chemotherapy and radiation therapy, have not been fully elucidated. Other potential factors to consider are anemia; comorbid conditions, such as coronary artery disease; metabolic abnormalities; endocrine disorders such as hypothyroidism; sleep disorders; emotional distress including anxiety and depression; and medications.

## EVALUATION OF PATIENTS WITH CRF

For patients who are long-term cancer survivors, a fatigue screen should occur as they transition from active treatment and close monitoring by their oncologist to long-term management by their primary care physician. After transition, these patients should be screened at appropriate intervals and as clinically indicated. For example, more frequent screening may be necessary if CRF is identified as an issue in a patient. There are several survey tools that may be used in screening. A simple visual analog scale (VAS) with anchors of 0 and 10 (with 0 as no fatigue and 10 as the worst imaginable fatigue) may be very easy and practical to incorporate into a busy clinical setting. A recommended screening question is “How would you rate your fatigue on a scale of 0 to 10 over the past week?” The National Comprehensive Cancer Network (NCCN) has developed a practice guideline for CRF that may be helpful to practitioners<sup>14</sup>.

### APPROACH TO MILD FATIGUE (0–3)

Patients with mild fatigue who exhibit no interference with daily activities should receive education and general CRF management strategies. General strategies include energy conservation and distraction<sup>15,16</sup>. Energy conservation consists of prioritizing and pacing activities with delegating less critical activities to others. A diary may be helpful for the patient to identify times of high and low energy during a time period, allowing for improved planning of necessary activities at times of peak energy and postponing nonessential activities. Other energy conservation strategies include use of labor-saving devices, limiting naps to 20 to 30 minutes or less, performing 1 activity at a time, and structuring the daily schedule. Activities that may distract the patient may also be beneficial. These may include games, music, reading, or socializing.

### APPROACH TO MODERATE FATIGUE (4–6) AND SEVERE FATIGUE (7–10)

Usually fatigue gradually improves over time, although there is a subset of patients that may experience severe and prolonged fatigue after active treatment. Patients with moderate to severe fatigue, especially those experiencing interference with daily activities, require education and general CRF management strategies along with a detailed medical evaluation encompassing a comprehensive history including fatigue onset, duration, intensity, changes over time, other related symptoms and factors linked to fatigue improvement or decline. Important aspects for the long-term survivor include the type and length of cancer treatment (Table 1). Because medications may interact or cause untoward side effects such as sedation or anxiety, thus increasing fatigue, a careful review of all medications (prescribed and over the counter medications as well as herbal, vitamin, and mineral supplements) used should be performed.

## TREATMENT INTERVENTIONS

Treatment options may be categorized as nonpharmacologic and pharmacologic (Table 2).

Table 1. Contributing Issues in Cancer-Related Fatigue

Symptom burden
Pain
Anxiety
Depression
Sleep dysfunction
Obstructive sleep apnea
Restless leg syndrome
Narcolepsy
Insomnia
Nutritional imbalances
Weight changes
Changes in caloric intake
Fluid and electrolyte imbalances
Motility disorders
Physical function changes
Decreased physical activity
Decreased physical conditioning
Medical issues
Anemia (from various etiologies)
Other comorbidities
Infection
Cardiac dysfunction
Connective tissue diseases
Pulmonary dysfunction
Renal dysfunction
Hepatic dysfunction
Neurologic dysfunction
Endocrine dysfunction
Hypothyroidism
Hypogonadism
Diabetes mellitus
Adrenal insufficiency
Medications
Sedating agents (hypnotics, narcotics, neuropathic agents, etc.)
Beta-blockers
Supplements (homeopathic agents)
Other (drug interactions and other medication side effects)
Cancer treatment effects
Chemotherapy
Radiation therapy
Surgery
Bone marrow transplantation
Biologic response modifiers
Hormonal treatment

## NONPHARMACOLOGIC INTERVENTIONS

Nonpharmacologic interventions include psychosocial interventions, exercise, attention-restoring therapy, dietary management, and sleep therapy.

### Psychosocial Interventions

Patients should receive guidance regarding management of stress, anxiety, and depression. Both anxiety and depression may be linked with subsequent fatigue, but these diagnoses may be complicated because some frequent symptoms are due to the underlying fatigue. Interventions to reduce stress and increase psychosocial support include education<sup>17</sup>, support groups<sup>18</sup>, individual counseling<sup>19</sup>, comprehensive coping strategies<sup>20</sup>, stress management training<sup>21</sup>, and individualized behavioral intervention<sup>22</sup>. Other interventions include listening to a guided-imagery tape daily, prioritizing daily activities, and encouraging discussion of how fatigue has affected lifestyle and emotional well-being. These interventions have been shown to reduce fatigue levels and have the strongest

**Table 2. Cancer-Related Fatigue Treatment Interventions**

Nonpharmacologic interventions	Pharmacologic interventions
Psychosocial (Category 1) <ul style="list-style-type: none"> <li>• Education</li> <li>• Support groups</li> <li>• Individual counseling</li> <li>• Coping strategies</li> </ul>	Stimulants <ul style="list-style-type: none"> <li>• Methylphenidate</li> <li>• Modafanil</li> </ul>
<ul style="list-style-type: none"> <li>• Stress management training</li> <li>• Individualized behavioral intervention</li> </ul>	Antidepressants <ul style="list-style-type: none"> <li>• Selective serotonin re-uptake inhibitors</li> <li>Paroxetine</li> </ul>
Exercise (Category 1) <ul style="list-style-type: none"> <li>• Behavioral Therapy               <ul style="list-style-type: none"> <li>Stimulus Control</li> <li>Sleep Restriction</li> <li>Sleep hygiene</li> </ul> </li> </ul>	Sertraline <ul style="list-style-type: none"> <li>• Other antidepressant</li> <li>Bupropion</li> </ul>
Sleep Therapy <ul style="list-style-type: none"> <li>• Behavioral Therapy               <ul style="list-style-type: none"> <li>Stimulus Control</li> <li>Sleep Restriction</li> <li>Sleep hygiene</li> </ul> </li> </ul>	Steroids
Acupuncture	

evidence support (category 1), although fatigue was a secondary endpoint in many of these studies. A recent meta-analysis of psychological and activity-based interventions for CRF included 30 randomized controlled trials<sup>23</sup>. Fifty percent of psychological trials rated as fair or better in quality yielded significant findings favoring the intervention.

## Exercise

Physical exercise training programs may increase functional capacity, leading to decreased effort in performing usual activities and less fatigue<sup>24-25</sup>. Exercise has the strongest evidence supporting its effectiveness among nonpharmacologic interventions for managing CRF<sup>26-29</sup>. Exercise in patients with CRF consists of a variety of studies including patients that were on active treatment as well as those who had completed treatments. Limitations in these studies included small sample sizes, diverse experimental designs, and many limited to women with breast cancer as well as variations in length of the exercise intervention from 6 weeks to 6 months. The exercise types are diverse and have included bed-cycle ergometer, home-based walking programs, and stationary cycling; some studies allowed participants to choose their preferred form of aerobic exercise. Also, strength and resistance training, flexibility training, routine stretching, yoga, and seated exercise have also been studied.

A 2008 Cochrane analysis on the effects of exercise for the management of CRF reported on 28 randomized controlled trials<sup>30</sup>. The majority of trials included breast cancer patients, and 16 studies used supervised, institutional programs. Programs ranged in duration from 3 to 32 weeks with an average of 12 weeks. Exercise was statistically more effective than the control, both during and after treatment. It is reasonable to encourage all patients to participate in moderate levels of physical activity after treatment.

An exercise program should be customized to meet the requirements of the individual patient, with consideration of the patient's overall medical status, the level of physical conditioning, and the specifics of the cancer treatment as factors in development of the exercise program. Age and sex may play a part in the decision-making but their significance

may vary. Some patients with substantial deconditioning may benefit from referral to a physical medicine and rehabilitation program or physical therapy program. Others with major comorbidities should have a thorough medical evaluation before beginning an exercise program.

## Sleep Therapy

Sleep disturbances are frequently challenging in cancer patients. They often involve aspects of sleep quality rather than sleep quantity. A variety of factors may affect sleep and include daytime napping, anxiety, and depression as well as side effects of medications, dietary aspects, and nocturnal waking (bathroom usage, hot flashes). Behavioral therapies for sleep improvement include stimulus control, sleep restriction, and sleep hygiene. With stimulus control, patients are advised to go to bed when sleepy, have a routine bedtime and rising time, and get out of bed after 20 minutes of wakefulness when first going to bed and with night time awakening. Sleep restriction involves avoidance of long or late day naps and limiting total time in bed. Sleep hygiene recommendations include caffeine and exercise avoidance near bedtime, comfortable sleep surroundings (dark, cool, peaceful, and relaxing), and soothing activities at bedtime (reading, tranquil music). Several studies have demonstrated the benefit of behavioral therapies for sleep improvement and fatigue in long-term cancer survivors<sup>31-33</sup>. In addition, behavioral therapies may often be combined with complimentary therapies to address sleep issues. Techniques such as breathing control, progressive muscle relaxation, and guided-imagery control have been combined with massage therapy, yoga, muscle relaxation, and mindfulness-based stress reduction. Most are preliminary studies but are suggestive of fatigue reductions<sup>34-35</sup>.

## Acupuncture

Acupuncture to treat CRF has not been well studied. There have been 2 small trials that suggest a possible benefit from acupuncture<sup>36-37</sup>. Molassiotis et al. studied 47 cancer patients after chemotherapy in a randomized controlled trial with a 3-group design—acupuncture (n=15), acupressure (n=,16) and sham acupressure (n=16). Improvements in fatigue were 36%, 19%, and 0.6%, respectively. Further study with larger cohorts is necessary to conclude whether there is a benefit with this intervention.

## PHARMACOLOGIC INTERVENTIONS

The classes of pharmacologies that have been studied most in managing CRF include stimulants, antidepressants, steroids, and the cholinesterase inhibitor, donepezil.

### Stimulants

The most frequent stimulants used for management of CRF are methylphenidate and modafanil. Methylphenidate is a central nervous system stimulant similar to amphetamine with a short plasma half-life of 2 hours, a rapid onset of action, and a duration of action of 3 to 6 hours<sup>38</sup>. The baseline dose is usually 5 mg in the morning and at noon with titration

as needed with a maximum dosing of 1 mg/kg/d. The most frequent side effects are tachycardia, nervousness, insomnia, and anorexia, especially at higher doses. Open-label studies suggest an improvement in fatigue<sup>39-40</sup>. In a randomized controlled trial, 112 patients were assigned to 5 mg of methylphenidate or placebo and able to repeat dosing every 2 hours as needed to a maximum of 20 mg daily. At 7 days, significant improvement in fatigue compared to baseline was noted in both groups<sup>41</sup>. The authors suggested that the observed benefits might be due to daily contact with the study nurse or the placebo effect. A large randomized controlled trial is needed to confirm these findings.

Modafinil is a nonamphetamine central nervous system stimulant approved for the treatment of narcolepsy. There has been limited experience in treatment of CRF, but it has been well tolerated. The usual dose of modafinil is 100 to 200 mg in the morning, with a second dose at noon or shortly thereafter, with a maximum dose of 400 mg per day. One pilot study using modafinil in patients with brain tumor noted improvement across cognitive, mood, and fatigue outcome measures, with a maximum benefit at 8 weeks after starting treatment<sup>42</sup>. In a preliminary report, a randomized controlled trial of 642 patients receiving chemotherapy suggested a benefit with modafinil versus placebo; however, this benefit was limited to those with severe fatigue<sup>43</sup>.

### Antidepressants

Fatigue and depression are commonly associated. There have been a few randomized placebo-controlled trials in cancer patients with selective serotonin re-uptake inhibitors (paroxetine, sertraline) that have not shown any improvement in fatigue although depression improved<sup>44-46</sup>. In those with insomnia and depression, antidepressants such as nortriptyline and amitriptyline may be beneficial due to the sedative aspects. There is one small open-label study that suggests bupropion may aid patients with CRF<sup>47</sup>.

## OTHER PHARMACOLOGIC TREATMENTS

### Steroids

Steroids have been the most helpful in patients with end-stage cancer and CRF<sup>48</sup>. The mechanism of action is unknown. The side effects of these drugs limit their routine use. In trials using steroids for CRF, other outcome measures, such as strength, weakness, or activity level, were substituted for fatigue. There is no consensus that these measures accurately reflect measurement of fatigue.

### Donepezil

Donepezil is a selective acetylcholinesterase inhibitor. Pilot studies using this medication for CRF have not shown any benefit compared to placebo<sup>49</sup>.

### Summary

Fatigue is a frequent and difficult to manage symptom in many cancer survivors. Its assessment should begin at cancer diagnosis and should continue through the spectrum of

disease management and transition to long-term survivorship. Initially, conditions that may cause fatigue should be identified and addressed. Frequently, multiple factors may contribute to fatigue. Both nonpharmacologic and pharmacologic interventions are available. The nonpharmacologic therapies of psychosocial interventions and exercise have the strongest evidence supporting use (Category 1). Other nonpharmacologic and pharmacologic interventions have lesser supporting evidence but still may be effective for some patients. An evidence-based clinical guideline is available for practitioners through the NCCN<sup>14</sup>.

### Key Points

- CRF commonly occurs in long-term cancer survivors and is frequently associated with other symptoms (pain, depression, anxiety, and sleep dysfunction).
- Patients should be screened for CRF at transition to long-term survivorship and then screened routinely depending upon the presence and intensity of the symptom.
- Patients with mild fatigue should receive education and general CRF management strategies.
- Patients with moderate to severe fatigue require a detailed medical evaluation including a comprehensive history querying fatigue-specific aspects and a thorough physical examination. They should also receive similar educational and management strategies as those with mild fatigue.
- Nonpharmacologic treatment interventions include psychosocial interventions, exercise, sleep therapy, and acupuncture.
- Psychosocial interventions and exercise have the strongest evidence support (Category 1).
- Pharmacologic treatment interventions include stimulants, antidepressants, and steroids.
- Antidepressants have not been effective for patients with CRF alone but has been in those patients with both CRF and depression.
- Steroids are most often used for patients with CRF at the end of life.
- Continued research to identify pathophysiologic mechanisms and more effective treatment strategies for CRF is necessary.

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