Management of Cancer-Related Fatigue

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Guidelines for the management of cancer-related fatigue (CRF) emphasize evidence-based strategies for reducing this common symptom in patients with cancer. Exercise has the largest body of data supporting its benefits in reducing CRF. Patient education and counseling also are considered integral to effective CRF management. Additional interventions can be pharmacologic or nonpharmacologic, although a combination of approaches may be employed. Several factors known to be associated with CRF may be particularly amenable to treatment.

Guidelines for the management of cancer-related fatigue (CRF) are available from both the National Comprehensive Cancer Network (NCCN) (Mock et al., 2007) and Oncology Nursing Society (ONS) (Mitchell & Friese, 2007). Current NCCN recommendations describe four categories of consensus regarding evidence for CRF management, whereas ONS guidelines use five categories of evidence for approaches to symptom management (Mock et al.; Mitchell & Friese) (see Table 1). This article will focus primarily on ONS guidelines for CRF management, although NCCN guidelines may be referred to when appropriate.

The clinical status of a patient with cancer (i.e., receiving active treatment, participating in long-term follow-up, or nearing end of life) will influence CRF management strategies. As described by Piper et al. (2008) in an article beginning on page 37 in this supplement, the initial fatigue evaluation is used to identify whether pain, emotional distress, anemia, insomnia, deconditioning, nutritional issues, or comorbidities are present. These factors, if present, will guide the management of moderate or severe CRF (Mock et al., 2007). The current ONS fatigue guidelines rate screening for and managing etiologic factors as strategies likely to be effective in fatigue management (Mitchell, Beck, Hood, Moore, & Tanner, 2007). Additional interventions can be pharmacologic or nonpharmacologic; in many cases, a combination of approaches is employed.

Nonpharmacologic Interventions for Cancer-Related Fatigue

Exercise

Strong evidence supports the benefits of exercise for CRF management. Numerous randomized, controlled clinical trials have evaluated exercise during and after treatment in patients with various malignancies; and the data have been the subject of several comprehensive meta-analyses and review articles (Courneya & Friedenreich, 1999; Galvao & Newton, 2005; Knols, Aaronson, Uebelhart, Fransen, & Aufdemkampe, 2005; Mitchell, Beck, Hood, Moore, & Tanner, 2007). Exercise can effectively reduce CRF in various settings. During palliative care, for example, low-intensity exercise matched to patients’ comfort levels was associated with improved quality of life (Oldervoll, Kaasa, Knobel, & Loge, 2003; Porock, Kristjanson, Tinnelly, Duke, & Blight, 2000). For patients receiving marrow or stem cell transplantations, positive studies have been conducted using aerobic interval training with appropriate monitoring (Dimeo, 2001). During chemotherapy and radiation therapy, home-based exercise programs have proven beneficial (Mock et al., 1994, 1997). Strength-resistance exercise has been used effectively in men with prostate cancer undergoing androgen-deprivation therapy (Segal et al., 2003; Stevinson et al., 2004).

Carefully considering which types of exercise may be beneficial is important. The current NCCN recommendation is to...
begin with low intensity and duration of exercise and to then progress slowly and modify the exercise plan as conditions change (Mock et al., 2007). Timing, at least initially, might be 20- to 30-minute sessions, three to five times per week. One study showed that patients with cancer who exercised more than one hour per day reported an increase in fatigue (Schwartz, Mori, Gao, Nail, & King, 2001). The appropriate intensity of exercise will vary depending on individual patient circumstances.

Exercise risks and benefits should be weighed and used cautiously in patients with bone metastases, neutropenia, low platelet counts, anemia, and fever. A modified exercise regimen can be recommended in some cases. For example, a patient with neutropenia should avoid environments with high infection risk, such as gyms and swimming pools (NCCN, 2007).

Exercise is the only strategy that ONS guidelines for CRF classify as recommended for clinical practice. However, additional research still is needed regarding both safety and customization of exercise regimens (e.g., type, intensity, frequency, duration) in different patient populations (Mitchell & Friese, 2007).

**Education**

Education and counseling, which should be used for all patients with cancer, are particularly beneficial for those beginning fatigue-inducing treatments. Data from several studies support the role of educational interventions (i.e., providing physical sensory information, anticipatory guidance, coping skills training, and coaching) to reduce CRF levels (Allison et al., 2004; Fawzy, 1995; Given et al., 2002; Yates et al., 2005). Consultation may be useful regarding nutritional deficiencies that may result from anorexia, diarrhea, nausea, and vomiting associated with cancer or its treatment (Brown, 2002).

Strategies that can be taught for coping with fatigue include energy conservation and activity management. Energy conservation is the deliberate and planned management of one’s activities and personal energy resources. The goal is to balance rest and activity so that valued activities can be maintained.

Initiatives include planning, delegating, prioritizing activities, pacing, and resting. Randomized clinical trials have shown that patients with cancer benefited from learning energy conservation (Barsevick et al., 2004). ONS guidelines describe energy conservation as likely to be effective.

**Cognitive-Behavior Interventions**

Distress can result in fatigue. According to NCCN guidelines, distress represents a complex, multifactorial experience that may include anxiety and depression (Holland et al., 2007; Mock et al., 2007). Complicating matters more, distress can interfere with sleep; which can worsen fatigue.

For moderate to severe distress (a score of 4 or higher on the 0–10 scale), NCCN guidelines recommend referral to a specialist. The oncology team can provide supportive care if distress is mild (Holland et al., 2007; Mock et al., 2007).

Stress reduction and management of depression and anxiety can be useful in reducing fatigue (Stark et al., 2002). Randomized trials have shown that cognitive-behavior strategies, such as progressive muscle relaxation or relaxed breathing, may improve fatigue in patients with cancer receiving radiation therapy or hematopoietic stem cell transplantation (Decker, Cline-Elsen, & Gallagher, 1992; Kim & Kim, 2005). Use of these strategies to improve sleep also could be effective in relieving fatigue; the strategies are classified by ONS guidelines as likely to be effective in reducing fatigue (Mitchell et al., 2007).

Studies support the role of a cognitive-behavior approach to improve sleep quality to reduce fatigue (Berger et al., 2003; Quesnel, Savard, Simard, Ivers, & Morin, 2003; Savard, Simard, Ivers, & Morin, 2005). Important components of the cognitive-behavior approach include having the patient set and maintain a schedule of regular sleep and wake times. Patients also should place themselves in an environment that is conducive to sleep and not stay in bed any longer than they intend to sleep. Caffeine, nicotine, and alcohol should be avoided, particularly in the evening or within several hours before intended sleep (Mitchell et al., 2007).

**Strategies for Pharmacologic Management of Cancer-Related Fatigue Based on Associated Factors**

**Anemia**

Published data suggest that the use of recombinant erythropoietic agents (epoetin or darbopoetin) to increase hemoglobin levels in patients with cancer with disease- or treatment-related anemia (hemoglobin < 10 g/dl) may improve vigor, fatigue, and other quality-of-life outcomes (Crawford et al., 2002; Djulbegovic, 2005; Fallowfield et al., 2002; Vansteenkiste et al., 2002). However, several major concerns have arisen regarding potential risks associated with the use of recombinant erythropoietins, including increased risk of death, thrombotic events, red blood cell aplasia (from anti-erythropoietin antibodies), and growth stimulation of certain tumor types (Rosenzweig, Bender, Lucke, Yasko, & Brufsky, 2004; Stasi et al., 2005; Steensma & Loprinzi, 2005; Verhelst et al., 2004). ONS guidelines for fatigue management emphasize
that clinicians and patients should carefully evaluate potential benefits and harmful effects of recombinant erythropoietins for individual patients (Mitchell et al., 2007).

**Pain**

Pain also can be a contributing factor to fatigue. According to ONS guidelines, pain management is likely to be effective in reducing fatigue in patients with cancer. NCCN guidelines for pain in adult patients with cancer have been developed by experts from comprehensive cancer centers across the United States. The guidelines recommend universal screening to quantify pain intensity and to describe the quality and anatomical locations. A more comprehensive pain assessment is indicated if pain is reported (Swarm et al., 2007).

NCCN guidelines for pain management recommend a non-steroidal anti-inflammatory drug or acetaminophen (without an opioid) or a short-acting opioid for patients with low pain levels (pain score of 1–3 out of 10). For moderate pain (score of 4–6) or severe pain (score of 7–10), an opioid may be prescribed with a coanalgesic as needed. Reassessment is recommended every 24 hours for patients with severe pain and every one to three days for patients with moderate or mild pain (Mock et al., 2007).

**Sleep Disturbances and Insomnia**

ONS guidelines for pharmacologic management of sleep-wake disturbances specify that clinicians and patients should carefully weigh the benefits and potential harmful effects of pharmacologic sleep interventions (Page, Berger, & Johnson, 2007). In general, little research exists on the effects of sleep drugs on patients with cancer; a systematic assessment is needed regarding efficacy, safety, and possible drug interactions. Pharmacologic agents used for inducing sleep and improving sleep maintenance include benzodiazepines and nonbenzodiazepines. Other drugs prescribed for sleep disturbance management are the tricyclic antidepressants and antidepressants such as bupropion sustained release. Antihistamines, chlorohydrates, and chlorpromazine also have been used. The general recommendation for sleep drugs is that they not be used for more than 7–10 days (Page et al.). Many patients with cancer also use herbal supplements to help with side effects related to their treatment or to induce sleep. However, minimal evidence exists to support the effectiveness of herbal supplements and concern has been noted regarding potential drug interactions with such agents (Berger et al., 2005; Block, Gyllenhaal, & Mead, 2004).

**Emotional Distress—Depression**

When depression has been identified as a contributing factor to fatigue, pharmacologic management of depression may be effective in controlling CRF (NCCN, 2007). Patients may benefit from a combination of medication and counseling. Medications for depression include selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors. Counseling methods include behavior therapy, education, and preparatory information and have been used primarily when fatigue was observed in association with depression, but many issues surrounding the relationship between the two symptoms and potential treatment options have not been addressed in clinical studies and require further investigation. However, Morrow et al. (2003) and Roscoe et al. (2005) used the selective serotonin reuptake inhibitor paroxetine in patients with cancer and found no significant effect on fatigue in the absence of depressed mood.

**Future Options for Management of Cancer-Related Fatigue**

Several other agents have been used or are being evaluated for the management of CRF (see Table 2). However, the efficacy and safety of these agents for this indication have not been established (Mitchell et al., 2007). The use of psychostimulants for fatigue is being evaluated currently in a number of research studies; however, more data are necessary before the use of these drugs can be recommended (Mock et al., 2007). Breitbart and Alici (2008) discuss investigational agents for CRF management in an article beginning on page 27 in this supplement.

**Summary**

CRF management strategies have been described in clinical practice guidelines. Education and counseling are essential for

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**Table 2. Potential Pharmacologic Options for Cancer-Related Fatigue**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>DRUG CLASS</th>
<th>APPROVED INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>Central nervous system stimulant</td>
<td>Attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Cholinesterase inhibitor</td>
<td>Alzheimer disease</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Central nervous system stimulant</td>
<td>Daytime sleepiness associated with narcolepsy</td>
</tr>
<tr>
<td>Bupropion sustained release</td>
<td>Antidepressant</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Levocarnitine</td>
<td>Amino acid supplement</td>
<td>–</td>
</tr>
<tr>
<td>Adenosine 5'-inosine triphosphate</td>
<td>Nutraceutical</td>
<td>–</td>
</tr>
</tbody>
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*Note. Based on information from Mitchell et al., 2007.*
helping patients with cancer anticipate and cope with fatigue that may be associated with their disease or related to their cancer treatment. Effective strategies for coping with fatigue include energy conservation, activity management, optimizing restful sleep, and relaxation techniques. Strong evidence supports physical exercise as a means of reducing CRF, although patient limitations must be considered. Management of some of the etiologic factors known to be associated with CRF, including pain, insomnia, and distress, also may be effective in helping to reduce these symptoms in selected patients. Effective CRF management may result in improved patient quality of life.

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References


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