Fatigue is a highly distressing symptom of cancer associated with significant psychological morbidity and reduced quality of life. Cancer-related fatigue (CRF) has been underreported, underdiagnosed, and undertreated. Fatigue and depression may coexist in patients with cancer, and considerable overlap of symptoms often occurs. This has led researchers to examine the role of psychotropic medications to treat fatigue. Psychostimulants, wakefulness-promoting agents, antidepressants, and cholinesterase inhibitors have been studied for CRF treatment. Methylphenidate has been studied most and is effective and well tolerated despite common side effects. Some preliminary data support using modafinil for patients with CRF. Antidepressant studies have shown mixed results. Paroxetine shows benefit for fatigue, primarily when it is a symptom of clinical depression. Bupropion sustained release may have psychostimulant-like effects and, therefore, may be beneficial in treating fatigue. Donepezil, a cholinesterase inhibitor, has shown benefit only in open-label trials. Randomized, placebo-controlled trials with specific agents are needed to further assess the efficacy and tolerability of psychotropic medications in CRF treatment.

At a Glance
- Psychostimulants, wakefulness-promoting agents, antidepressants, and cholinesterase inhibitors are the main psychotropic medications that have been studied in the treatment of cancer-related fatigue (CRF).
- Psychostimulant use has been studied and shows promise for CRF treatment.
- Randomized, placebo-controlled trials are needed to further assess the efficacy and tolerability of various medications in CRF treatment.

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Fatigue is a poorly defined symptom that may involve physical, mental, emotional, and motivational components. The National Comprehensive Cancer Network (NCCN) practice guidelines define CRF 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” (Mock et al., 2000, p. 151). CRF is more severe and distressing than fatigue experienced by healthy individuals and is less likely to be relieved by rest (Mock et al.). Recognizing the need for a standardized definition of fatigue, Cella et al. (1998) proposed a set of diagnostic criteria, the International Classification of Diseases-10 Criteria for Cancer-Related Fatigue, that are explained further by Piper et al. (2008) in their article beginning on page 37 of this supplement. A standardized interview guide has been designed and studied for its reliability and validity to assess the proposed clinical syndrome, with results suggesting its use in identifying patients who experience clinically significant CRF (Sadler et al., 2002).

Challenges in Fatigue Assessment

Fatigue is a concept that is not only difficult to define but also challenging to quantify. Various standardized self-report scales exist, developed mostly in the context of cancer. Different scales may measure different aspects or distinct conceptions of fatigue. The challenge facing the clinician or researcher is to choose a reliable and valid tool that is most adequately suited to measure fatigue. Piper et al. (2008) present an overview of the different available scales. Given the multifactorial nature of fatigue, accessory scales (e.g., depression scales) and measurements of certain biologic parameters should be used in addition to fatigue assessment tools to obtain the most complete fatigue evaluation. The oldest scales assessing fatigue are dichotomous. Other scales have taken a unidimensional approach, namely the Visual Analogue Scale for Fatigue (Lee, Hicks, & Nino-Murcia, 1991) and the Karnofsky Performance Status (Schag, Heinrich, & Ganz, 1984). The major limitation of one-dimensional scales is the inability to evaluate confounding factors, such as pain, which can interfere with fatigue assessment. Multidimensional fatigue instruments have been developed to assess a wide range of symptom domains with which fatigue may present and include the Fatigue Symptom Inventory (Hann et al., 1998), the Brief Fatigue Inventory (Mendoza et al., 1999), the Piper Fatigue Scale (Piper et al., 1998), and the Multidimensional Assessment of Fatigue (Belza, 1995).

Determining Treatment Options

CRF is a multidimensional syndrome caused by a number of physical and psychosocial mechanisms, including tumor products, opioids, or other drugs (e.g., antidepressants, beta blockers, benzodiazepines, antihistamines), hypogonadism, hypothyroidism, cachexia, anemia, chemotherapy, radiation therapy, bone marrow transplantation, and treatment with biologic response modifiers (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003; Barnes & Bruera, 2002; Bruera et al., 2006; Hwang et al., 2003; Mock et al., 2000). CRF has been related to pain, depression, emotional distress, sleep deprivation, and reduced physical activity (Reinecke-Bracke, Radbruch, & Elsner, 2006). Cytokines (interleukin-1 [IL-1], IL-6, and tumor necrosis factor-alpha [TNF-α]) play a role in CRF development (Kurzrock, 2001), which has led researchers to consider cytokine-antagonist drugs, such as TNF-receptor etanercept and TNF-α antagonist thalidomide, to improve tolerability of chemotherapy regimens and potentially treat CRF and cachexia (Hussein, 2000; Monk et al., 2006).

Clinicians must clarify the relationship between mood disturbances and fatigue to effectively evaluate and treat CRF. Many symptoms are common to both fatigue and depression, such as decreased energy and motivation, sleep disruptions, diminished concentration and attention, and issues with short-term memory. The clinician seeking to differentiate between depression and fatigue should remember that depressive symptoms caused by fatigue are typically less severe and that patients tend to attribute such symptoms to the consequences of fatigue. Depression, on the other hand, more likely is present with hopelessness, feelings of worthlessness or guilt, suicidal ideation, and a family history of depression. Fatigue and depression may coexist in a patient. The nature of any causal relationship between CRF and depression is unclear. A possible bidirectional relationship between fatigue and depression may exist, with fatigue occurring as a symptom of depression or with depression occurring because of fatigue or interference with mood, work, and leisure activities (Bower et al., 2000; Roscoe et al., 2005).

Treatment of Cancer-Related Fatigue

Given the multidimensional nature of CRF, a biopsychosocial approach is recommended to treat fatigue. Potentially reversible causes of fatigue (i.e., pain, emotional distress, sleep disturbance, anemia, and hypothyroidism) should be identified and treated. Nonessential centrally acting drugs should be eliminated (Mock et al., 2000). The physician should determine the necessity of a transfusion in severely symptomatic patients if anemia is the main cause of fatigue. Clinical trials have shown that patients with anemia have improved energy and less fatigue after erythropoietin treatment (Savonije, van Groeningen, Wormhoudt, & Giaccone, 2006). Physicians also should consider the possibility of depression and provide treatment because of its high prevalence in patients with cancer (Mock et al.).

Nonpharmacologic Interventions

Nonpharmacologic approaches have been recommended by NCCN guidelines for CRF treatment (Mock et al., 2000). Activity
enhancement and psychosocial interventions (i.e., education, support groups, individual counseling, and stress management training) have been supported by research. Dietary management, attention-restoring therapy, and sleep therapy also have been recommended as CRF treatments (Mitchell, Beck, Hood, Moore, & Tanner, 2007; Mock, 2004; Mock et al.). A randomized controlled trial by Armes, Chalder, Addington-Hall, Richardson, and Hotopf (2007) evaluated the effectiveness of a behaviorally oriented intervention for CRF and found significant improvements in physical function following the intervention with a trend toward improved fatigue. The intervention consisted of three individual, face-to-face sessions that lasted one hour and were conducted at three- to four-week intervals using cognitive-behavioral interventions such as goal setting, activity scheduling, graded task management, and cognitive restructuring (Armes et al.). A long-term follow-up study (mean follow-up of 1.9 years) by Gielissen, Verhagen, and Bleijenberg (2007) of cognitive behavior therapy for fatigued cancer survivors found that the positive effects on improving fatigue were maintained at about two years after completion of cognitive behavior therapy. Nonpharmacologic approaches are described in greater detail by Barsevick, Newhall, and Brown (2008) in an article beginning on page 21 in this supplement.

Pharmacologic Interventions

A number of pharmacologic interventions for the treatment of fatigue in patients with cancer are being evaluated in phase II, III, and IV clinical trials. Table 1 outlines research trials with psychotropic medications for CRF treatment.

Psychostimulants

Psychostimulants are drugs that increase alertness and motivation and include methylphenidate, dextroamphetamine, and pemoline (withdrawn from the U.S. market). Methylphenidate and dextroamphetamine are sympathomimetic drugs. They stimulate adrenergic receptors directly as agonists and indirectly cause the release of dopamine and norepinephrine from presynaptic terminals. They are scheduled as controlled drugs because of their rapid onset of action, immediate behavioral effects, and association with tolerance, which leads to an increased risk of abuse and dependence in vulnerable individuals (i.e., patients with a personal or family history of substance abuse or dependence). Existing neuropharmacologic data suggest that methylphenidate has pharmacokinetic properties that reduce its abuse potential compared to commonly abused stimulant drugs, such as cocaine (Kollins, 2003).

Agitation and insomnia are the most common side effects associated with the use of psychostimulants. Reducing the dosage and taking the medication early in the day may help. Rare side effects include hypertension, palpitations, arrhythmias, confusion, psychosis, tremor, and headache. Discontinuation of the medication results in quick reversal of the side effects. Methylphenidate and dextroamphetamine are contraindicated for patients with uncontrolled hypertension, underlying coronary artery disease, and tachyarrhythmias.

Psychostimulants show great promise in the treatment of medically induced fatigue in patients with cancer, multiple sclerosis, Parkinson disease, opioid-induced sedation, and HIV (Breitbart, Rosenfeld, Kaim, & Funesti-Esch, 2001; Bruera, Brennies, Paterson, & MacDonald, 1989; Holmes, Fernandez, & Levy, 1989; Mendoza, Menezes, & Joq, 2007; Wagner & Rabin, 2000). Psychostimulants also have been used in the treatment of fatigue-related conditions, such as pain, depression, and cognitive impairment (Homsi, Walsh, & Nelson, 2000; Sarhill et al., 2001).

Methylphenidate

Methylphenidate has been used since the 1960s in the treatment of attention deficit hyperactivity disorder in children (Connors & Eisenberg, 1965). Methylphenidate usually is administered twice per day, at breakfast and lunch, to minimize insomnia. Peak plasma concentration occurs within one to three hours with an average half-life of two hours. Sustained-release formulations have about four- to six-hour durations of clinical action. Newer sustained-release formulations have an early peak followed by eight-hour durations of action. Close monitoring for common side effects of agitation and insomnia is recommended, particularly during the first few days of treatment.

Breitbart et al. (2001) conducted the first randomized, double-blind, placebo-controlled trial of two psychostimulants for the treatment of fatigue in ambulatory patients with HIV and found that both methylphenidate and pemoline were equally effective and significantly superior to placebo in decreasing fatigue severity with minimal side effects. Fifteen (41%) of 37 patients with HIV taking methylphenidate and 12 (36%) of 33 patients taking pemoline experienced clinically significant improvement, compared to 6 (15%) of 39 patients taking placebo. Improvement in fatigue correlated with improved quality of life, decreased depression, and decreased psychological distress. Jitteriness and hyperactivity, the only side effects to occur significantly more frequently in the medication arm, occurred in 14 (32%) of 44 patients taking methylphenidate and 11 (26%) of 43 patients taking pemoline.

Sarhill et al. (2001) conducted a prospective, open-label pilot study in which fatigue was the primary outcome measure and demonstrated that 9 (82%) out of 11 patients with advanced cancer had successful treatment with methylphenidate. In the study, more than 50% of the patients experienced side effects, such as insomnia, agitation, anorexia, dry mouth, nausea, and vomiting.

An open-label study by Sugawara et al. (2002) examined the efficacy of methylphenidate for fatigue in 14 patients with advanced cancer. The patients completed a mean duration of eight days of treatment with methylphenidate, and researchers observed a statistically significant decrease in fatigue scores (p = 0.01) using only the Visual Analogue Scale for Fatigue.

A pilot study by Schwartz, Thompson, and Masood (2002) examined the effects of exercise and methylphenidate on fatigue, function ability, and cognitive function in patients with melanoma (N = 12) and compared results with historical controls who received usual care while on interferon-α. Patients were instructed to take 20 mg per day of sustained-release methylphenidate and follow an aerobic exercise program four days per week for 15–30 minutes. Fatigue was lower among the exercise and methylphenidate group than among historical controls. Schwartz et al. concluded that the combination of aerobic exercise and
<table>
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<tr>
<td><strong>Methylphenidate</strong></td>
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<td>Sarhill et al., 2001</td>
<td>11 patients with advanced cancer in a prospective, open-label design</td>
<td>Methylphenidate 10 mg twice daily</td>
<td>Decreased fatigue in 9 out of 11 patients with sedation and pain improving in some</td>
<td>More than 50% of patients experienced side effects, such as insomnia, agitation, anorexia, nausea, vomiting, and dry mouth.</td>
</tr>
<tr>
<td>Sugawara et al., 2002</td>
<td>16 patients with advanced cancer in a prospective, open-label design</td>
<td>Methylphenidate 5–30 mg per day; mean treatment duration is eight days.</td>
<td>Decreased fatigue scores (p = 0.01)</td>
<td>Two patients withdrew from insomnia. A visual analog scale was used for fatigue scoring.</td>
</tr>
<tr>
<td>Schwartz et al., 2002</td>
<td>12 patients with melanoma receiving interferon in a prospective, open-label design</td>
<td>Exercise and methylphenidate 20 mg per day</td>
<td>Decreased fatigue scores</td>
<td>Unclear whether the positive effect was from exercise, methylphenidate, or both.</td>
</tr>
<tr>
<td>Bruera, Driver, et al., 2003</td>
<td>30 patients with advanced cancer in a prospective, open-label design</td>
<td>Patient-controlled methylphenidate, 5 mg every two hours, maximum four capsules per day</td>
<td>Decrease in fatigue, depression, and overall well-being</td>
<td>None of the patients discontinued the medication.</td>
</tr>
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<td>Hanna et al., 2006</td>
<td>37 patients with breast cancer, cancer-free more than six months but less than five years, in an open-label, phase II design</td>
<td>Methylphenidate 5 mg twice daily for six weeks</td>
<td>54% responded with a decrease in fatigue score of more than two points.</td>
<td>16% of the patients withdrew from the study because of minor side effects.</td>
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<tr>
<td>Bruera et al., 2006</td>
<td>Patients with advanced cancer (n = 52 in medication arm; n = 53 in placebo arm) in a randomized, double-blind, placebo-controlled design</td>
<td>Patient-controlled methylphenidate (5 mg every two hours, maximum four capsules per day) versus placebo for seven days</td>
<td>Fatigue scores improved both in placebo and medication arm on day 8.</td>
<td>Open-label phase of the study beyond 15 days showed continued improvement in fatigue.</td>
</tr>
<tr>
<td>Roth et al., 2006</td>
<td>Ambulatory patients with prostate cancer (n = 15 in medication arm; n = 14 in placebo arm) in a randomized, placebo-controlled, phase III design</td>
<td>Methylphenidate versus placebo</td>
<td>13 patients in the placebo and 8 in the methylphenidate arm completed the study. Seventy-three percent of the patients in the methylphenidate arm and 23% of the patients in the placebo arm showed improved fatigue scores.</td>
<td>Remarkable placebo effect was observed in this preliminary analysis of the study. Forty-three percent of the patients dropped out because of cardiac side effects.</td>
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<td><strong>Dexmethylphenidate</strong></td>
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<td>Lower et al., 2005</td>
<td>Adult patients who completed chemotherapy two months prior (n = 77 in dexmethylphenidate arm; n = 75 in placebo arm) in a randomized, phase III design</td>
<td>Dexmethylphenidate 10–50 mg per day for more than two weeks</td>
<td>Medication was found to be more effective compared to placebo in improving fatigue.</td>
<td>Final data analysis has not been published to date.</td>
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<td><strong>Modafinil</strong></td>
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<td>Morrow et al., 2005</td>
<td>51 women with breast cancer, all completed treatment two years prior, enrolled in a prospective, open-label design</td>
<td>Modafinil 200 mg per day for one month</td>
<td>86% reported improvement in fatigue.</td>
<td>Final data analysis has not been published to date.</td>
</tr>
<tr>
<td>Kaleita et al., 2006</td>
<td>30 adult patients diagnosed with a brain tumor in a phase III, open-label extension phase trial</td>
<td>Modafinil, mean dose 225 mg per day at week 8; 258 mg per day at week 12</td>
<td>Well-tolerated; mean fatigue score change at weeks 8 and 12 was significantly higher in the intervention arm</td>
<td>Only results from the open-label extension phase were reported in this abstract. Final data analysis has not been published to date.</td>
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*(Continued on next page)*
Table 1. Review of Psychotropic Medication Trials for Cancer-Related Fatigue Treatment (Continued)

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<tr>
<th>DRUG AND REFERENCE</th>
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<td><strong>Paroxetine</strong></td>
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<td>Capuron et al., 2002</td>
<td>40 patients with malignant melanoma in a randomized, double blind, placebo-controlled design</td>
<td>Paroxetine versus placebo two weeks prior to start of interferon therapy</td>
<td>Paroxetine did not have an effect on fatigue prevention.</td>
<td>Risk of depression was significantly reduced in the intervention arm.</td>
</tr>
<tr>
<td>Morrow et al., 2003</td>
<td>479 patients with breast cancer receiving chemotherapy in a randomized, double-blind, placebo-controlled, multicenter design</td>
<td>Paroxetine 20 mg per day versus placebo for eight weeks</td>
<td>No significant difference was detected in fatigue improvement between placebo and intervention arms.</td>
<td>A significant difference was seen between groups in mean level of depression.</td>
</tr>
<tr>
<td>Roscoe et al., 2005</td>
<td>94 patients with breast cancer undergoing chemotherapy in a randomized, double-blind, placebo-controlled design</td>
<td>Paroxetine 20 mg per day versus placebo</td>
<td>No significant difference was observed in fatigue scores between the placebo and intervention arms.</td>
<td>Paroxetine was effective in treating depression, but not cancer-related fatigue.</td>
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<td><strong>Sertraline</strong></td>
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<td>Stockler et al., 2007</td>
<td>Patients with advanced cancer without major depressive disorder (sertraline arm, n = 95; placebo arm, n = 94) in a randomized, placebo-controlled, double-blind design</td>
<td>Sertraline 50 mg per day</td>
<td>No significant difference was observed in depression, anxiety, fatigue, and overall well-being.</td>
<td>Sertraline was kept at the starting dose throughout the study duration of eight weeks.</td>
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<td><strong>Bupropion Sustained Release</strong></td>
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<td>Cullum et al., 2004</td>
<td>15 adult patients with cancer in a prospective, open-label design</td>
<td>Bupropion sustained release 100–150 mg per day</td>
<td>13 patients reported improvement in fatigue.</td>
<td>Small sample size. Placebo-controlled studies are needed to confirm the results.</td>
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<tr>
<td>Moss et al., 2006</td>
<td>21 adult patients with cancer in a prospective, open-case series</td>
<td>Bupropion sustained release 100–300 mg per day</td>
<td>Well tolerated; both depressed and nondepressed patients reported improvement in their fatigue.</td>
<td>Small sample size. Placebo-controlled studies are needed to confirm the results.</td>
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<td><strong>Donepezil</strong></td>
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<td>Bruera, Strasser, et al., 2003</td>
<td>27 adult patients with cancer in an open-label trial</td>
<td>Donepezil 5 mg per day for seven days</td>
<td>20 patients who completed the trial showed significant improvement in fatigue.</td>
<td>Seven patients dropped out. Open-label design limits the significance of positive results.</td>
</tr>
<tr>
<td>Shaw et al., 2006</td>
<td>34 adult patients with brain tumors in an open-label phase II trial</td>
<td>Donepezil 5 mg per day for 24 weeks</td>
<td>Profile of Mood States fatigue subscale showed improvement short of statistical significance with a trend toward significance.</td>
<td>Improvements in cognitive function and health-related quality of life were observed.</td>
</tr>
<tr>
<td>Bruera et al., 2007</td>
<td>Adult patients with advanced cancer (donepezil arm, n = 47; placebo arm, n = 56) in a double-blind, randomized, placebo-controlled trial</td>
<td>Donepezil 5 mg per day for seven days</td>
<td>No significant difference was found between the donepezil and placebo arms.</td>
<td>Improvement in sedation observed in the donepezil and placebo arms. Open-label phase of the study with donepezil showed sustained improvement in fatigue scores.</td>
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Methylphenidate may have a positive effect on fatigue, cognitive function, and functional ability. A larger sample size and randomized trial is necessary to more rigorously evaluate the results of exercise and methylphenidate alone or in combination.

A phase II study by Hanna et al. (2006) evaluated the effects of methylphenidate on CRF in breast cancer survivors with less than moderate depression on the Brief Zung Self-Rating Depression Scale and who scored four or higher on the Brief Fatigue
Inventory. Patients received 5 mg oral methylphenidate twice daily for six weeks, with a dose escalation in the second week if the Brief Fatigue Inventory score remained four or higher with no significant toxicities. On weeks 4 and 6, 20 (54%) of 37 patients responded with a decreased Brief Fatigue Inventory score of more than two points, for an average decrease of 3.5 points. Six patients (16%) withdrew because of minor adverse events.

Because of the rapid onset of action and short half-life of methylphenidate, Bruera, Driver, et al. (2003) suggested that this agent may effectively relieve fatigue when taken as needed throughout the day, also called patient-controlled dose administration. Bruera, Driver, et al. initially conducted an open-label pilot study using patient-controlled methylphenidate for CRF management. Methylphenidate showed a temporary association with improvement in fatigue, overall well-being, and depression in 30 patients. The medication was well tolerated and none of the patients had to discontinue methylphenidate because of toxicity. Following the open-label study, Bruera et al. (2006) conducted a randomized, double-blind, placebo-controlled trial comparing patient-controlled methylphenidate with placebo (methylphenidate 5 mg or placebo every two hours as needed, up to four tablets per day for seven days). Fatigue was assessed at days 8, 15, and 36. All patients were then offered open-label methylphenidate for four weeks. Fatigue intensity decreased significantly on day 8 in both the methylphenidate and placebo groups; however, no significant difference was noted in fatigue improvement between the intervention (n = 52) and placebo (n = 53) groups. About 90% of patients receiving methylphenidate or placebo chose to continue the medication beyond eight days. Improvement in fatigue scores was sustained during the open-label methylphenidate phase at days 15 and 36. Researchers concluded that, in the absence of a placebo-controlled group, determining whether the findings reflect an independent or an extension of placebo effect was unknown. The mean daily number of capsules of methylphenidate and placebo taken by the patients from days 1–8 was 2.3 (± 1.0) and 2.1 (± 1.0), respectively (p was not significant).

In a double-blind, randomized, placebo-controlled study, Roth et al. (2006) evaluated the benefits of methylphenidate compared to placebo in ambulatory patients with prostate cancer. Roth et al. recruited 29 patients (15 in the placebo group, 14 in the methylphenidate group), with 21 patients completing the study (13 in placebo group, 8 in methylphenidate arm). The preliminary data analysis indicated that 73% of the patients in the methylphenidate group reported a clinically significant reduction in fatigue compared to 23% in the placebo group. The placebo response rate was higher than expected. Forty-three percent of the men in the methylphenidate arm withdrew from the study because of cardiovascular side effects.

Dexmethylphenidate is the d-isomer of methylphenidate, with a longer duration of action (about six hours) compared to methylphenidate. Dexmethylphenidate has demonstrated good tolerability and was shown to be more effective than placebo in improving fatigue symptoms in adult patients with cancer (75 patients in placebo arm, 77 patients in intervention arm) who completed chemotherapy more than two months before study entry. The intervention group, compared with the placebo group, showed significant improvement in the Functional Assessment of Chronic Illness Therapy–Fatigue subscale total score at weeks 1, 5, 6, 7, and 8 (p < 0.05) (Lower et al., 2005).

**Dextroamphetamine**

Dextroamphetamine is the d-isomer of amphetamine and is a more pharmacodynamically potent psychostimulant than methylphenidate. Although not studied in CRF treatment, dextroamphetamine is the common choice of clinicians for this indication. Dextroamphetamine has had favorable results in studies for the treatment of HIV-related fatigue (Wagner & Rabkin, 2000).

**Pemoline**

Pemoline is an oral psychostimulant with effects on dopaminergic and, to a smaller degree, sympathomimetic systems. Pemoline’s action is similar to amphetamines and methylphenidate; however, the drug is structurally different. Pemoline is linked with cases of liver failure and resultant death. As a result, Abbott Laboratories announced in March 2005 that Cylert®, the brand name for pemoline, would no longer be available in the United States and, in October 2005, manufacturers of pemoline agreed to stop sales and marketing of the product. This action was based on advice from the U.S. Food and Drug Administration (FDA) that the overall risk of liver toxicity with pemoline outweighed the benefits of the drug.

**Wakefulness-Promoting Agents**

The FDA approved the wakefulness-promoting agent modafinil for improving wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift-work sleep disorder (Prommer, 2006). Modafinil has been used to augment antidepressants in major depressive disorder, as an adjunct treatment for bipolar depression, and in patients with persistent fatigue and sleepiness despite antidepressant treatment (Frye et al., 2007; Thase, Fava, DeBattista, Arora, & Hughes, 2006). Compared to other psychostimulants, modafinil has a novel mechanism of action, has less abuse potential, and is well tolerated with a good safety profile. The mechanism of action is largely unknown, but it presumably enhances activity in the hypothalamic wakefulness center (i.e., tuberomammillary nucleus), activates tuberomammillary nucleus neurons that release histamine, and activates other hypothalamic neurons that release orexin/hypocretin. The half-life of modafinil is about 15 hours, and a steady state is reached after two to four days of dosing. Higher doses (200–400 mg per day) of modafinil may be more effective for sleepiness; however, lower doses (50–200 mg per day) appear to be better for concentration issues and fatigue.

Modafinil is currently a first-line agent for the treatment of severe fatigue in multiple sclerosis (MacAllister & Krupp, 2005) and has been studied as a CRF treatment option. Morrow et al. (2005) enrolled 51 women who had completed breast cancer treatment an average of 23.5 months previously and who had persistent fatigue. In a one-month open-label trial of modafinil (200 mg per day), 86% reported reduction of fatigue. The mean fatigue severity level of 6.9 at baseline (on a scale where 0 indicated “not present” and 10 indicated “as bad as one
can imagine”) decreased to 3.7 (p < 0.1) after treatment with modafinil. Kalela et al. (2006) reported in an unblinded open-label extension of their phase II clinical trial that, of 30 patients with brain tumors (malignant or benign), statistically significant differences (p ≤ 0.005) occurred in the mean score changes at weeks 8 and 12 compared to baseline on all fatigue self-rating measures. The mean modafinil dose was 225 mg per day (range 50–400 mg per day) at week 8 and 258 mg per day (range 50–600 mg per day) at week 12. Modafinil was generally well tolerated with a low incidence of adverse events. Well-designed, randomized, controlled clinical trials are needed to further clarify the role of modafinil in CRF treatment.

**Antidepressants**

The phenomenologic similarities and the possibility of a bidirectional relationship between fatigue and depression have led clinicians to consider antidepressants to treat CRF.

The benefits of antidepressant use are unclear in patients with CRF without a depressive mood disorder. Research has suggested a common pathophysiological mechanism, such as serotonin insufficiency, in the development of both fatigue and depression. Based on that evidence, Morrow et al. (2003) conducted two studies to examine whether a selective serotonin reuptake inhibitor (SSRI) could treat fatigue by increasing serotonin in the synaptic space. In a multicenter, randomized, double-blind, placebo-controlled study (N = 479), patients with breast cancer receiving chemotherapy were randomly assigned to receive either 20 mg per day of oral paroxetine or placebo for eight weeks (Morrow et al., 2003). No difference was detected in fatigue between the placebo and intervention groups at the end of the study; however, a significant difference existed between the groups in the mean level of depression. Of note is that 32% of patients in both arms had significant depression at study entry and about 50% reported fatigue scores of 5 or higher on a 10-point scale. In a second study by the group (Roscoe et al., 2005), a double-blind, placebo-controlled clinical trial of 94 female patients with breast cancer receiving chemotherapy were randomly assigned to receive 20 mg of paroxetine. Depression was significantly reduced in the 44 patients receiving paroxetine compared to the placebo group; however, no significant difference was observed in any of the fatigue measures between the two groups. The researchers concluded that, although paroxetine is effective at reducing depression, it is not efficacious in relieving CRF among women with breast cancer undergoing chemotherapy (Roscoe et al.).

In a double-blind randomized placebo-controlled trial by Capuron et al. (2002), 40 patients with malignant melanoma were assigned to paroxetine or placebo two weeks before initiation of interferon-α treatment. Although the risk of major depression was significantly reduced in patients receiving paroxetine, fatigue was not affected by the intervention.

In a study by Stockler et al. (2007) of patients with advanced cancer without major depressive disorder, 189 patients were randomly assigned to receive 50 mg per day of sertraline, an SSRI (n = 95), or placebo (n = 94) for eight weeks. Sertraline had no significant effect on depression, anxiety, fatigue, or overall quality of life. The authors concluded that antidepressants should be reserved only for individuals with a proven indication.

Underlying depression treated with SSRIs is generally better tolerated than tricyclic antidepressants in patients with cancer. When prescribing such medications, clinicians should remember that fatigued patients are usually more sensitive to antidepressant side effects; therefore, clinicians should initiate treatment with small doses. Drug-drug interactions need careful monitoring.

Bupropion is an antidepressant with a different mechanism of action from the SSRIs. It acts as a norepinephrine dopamine reuptake inhibitor and, therefore, may have stimulant-like effects. An open-label trial by Cullum, Wojciechowski, Pelletier, and Simpson (2004) evaluated bupropion sustained release at a dose of 100–150 mg per day in 15 patients with various cancer diagnoses who were experiencing fatigue or depression with marked fatigue. Whether the rater was blinded to the treatment condition is unclear. Thirteen patients reported their fatigue as improved and eight participants reported their fatigue as much improved. Controlled studies are required to determine whether the effect of bupropion on fatigue is independent of its antidepressant effects.

Moss, Simpson, Pelletier, and Forsyth (2006) investigated whether bupropion sustained release improved symptomatic fatigue, depression, and quality of life in patients with cancer and their caregivers. The sample consisted of a prospective open-case series of 21 patients with cancer, with fatigue and with or without depression at moderate to severe levels, referred for psychiatric assessment from a tertiary care cancer center. Patient symptom ratings and caregiver ratings were measured before and after four weeks of treatment with the maximally tolerated dose of bupropion sustained release in the range of 100–300 mg per day. At trial completion, significant improvement was found for symptoms of fatigue and depression. Subjects were divided into depressed and nondepressed groups (based on a cut-off score of 17 on the Hamilton Depression Rating Scale). Both groups reported improvement for fatigue and depressive symptoms. Depressed subjects and their caregivers did not experience any change in quality of life, although the nondepressed subjects and their caregivers reported improvements. Results from this small group of patients suggest that bupropion sustained release may have potential as an effective pharmaceutical agent for treating CRF; however, randomized, placebo-controlled trials are necessary.

**Corticosteroids**

Corticosteroids have been used in CRF treatment but the current evidence is anecdotal and responses to corticosteroids appear to be temporary. Bruera, Roca, Cedaro, Carraro, and Chacon (1985), in their prospective, randomized, double-blind study, observed that 40 patients in palliative care receiving a two week treatment with methylprednisolone demonstrated an increase in activity that became nonsignificant after four weeks of treatment. Corticosteroids, however, have long-term detrimental side effects, such as muscle wasting.

**Megestrol Acetate**

Megestrol acetate, a progestational agent, has been found to improve appetite in cancer-related cachexia and also may have a role in CRF treatment. A double-blind crossover study by Bruera et al. (1998) (N = 84) compared megestrol acetate (160 mg three
times daily for 10 days) to placebo in the treatment of cachexia among patients with advanced cancer and found significant improvement in overall fatigue scores measured by the Piper Fatigue Scale. The effects of megestrol acetate on fatigue are unclear but probably involve anticytokine and corticosteroid-type effects (Bruera et al., 1998).

L-Carnitine

L-carnitine is a cofactor that binds free long-chain fatty acids to transport them across mitochondrial membrane for fatty acid oxidation. Patients with advanced cancer are at risk for carnitine deficiency because of decreased intake and increased renal loss. L-carnitine supplements improved fatigue and depression in a group of patients with cancer with L-carnitine deficiency (Cruciani et al., 2006). Although use of L-carnitine in CRF is preliminary, carnitine supplementation shows some promise for fatigue management.

Donepezil

Donepezil is a reversible acetylcholinesterase inhibitor used in the treatment of Alzheimer dementia. Donepezil 5 mg per day was evaluated by Bruera, Strasser, et al. (2003) in an open-label trial of 27 patients with various tumor sites. Fatigue improved significantly following a seven-day course of treatment among 20 patients who completed the trial. Side effects included nausea, vomiting, diarrhea, muscle and abdominal cramps, and anorexia. Further research is needed to assess the efficacy and tolerability of donepezil in the treatment of CRF. A prospective, open-label phase II study was conducted by Shaw et al. (2006) to assess the effects of donepezil on cognitive function, mood, and quality of life in patients with irradiated brain tumors (N = 34) and showed improvement in the fatigue subscale of the Profile of Mood States with a trend toward significance following 24 weeks of treatment with donepezil in addition to improvements in cognitive function and health-related quality of life. The most common toxicities were fatigue, diarrhea, and insomnia. A double-blind placebo-controlled trial by Bruera et al. (2007) (47 patients in the donepezil group, 56 patients in the placebo group) assessed the efficacy of donepezil (5 mg per day for seven days) among patients with cancer and failed to show a statistically significant difference between donepezil and placebo in CRF treatment.

Amantadine

Amantadine, an anti-influenza agent with dopaminergic effects used in Parkinson disease and as an adjunct to interferon-based therapies for chronic hepatitis C, has been used in the treatment of fatigue from multiple sclerosis (Kronengerber et al., 2007; Pucci et al., 2007). Studies of amantadine to treat CRF are unknown; however, the agent could be of interest for future research.

Other Medications

The potential role of cytokine-antagonists in the treatment of CRF was discussed earlier in this article. Nonsteroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors (e.g., celecoxib), monoclonal antibodies (e.g., infliximab), and bradykinin antagonists also could be considered as potential CRF treatments through their direct and indirect cytokine antagonistic effects (Burks, 2001). The NCCN practice guidelines conclude that sufficient evidence does not exist to recommend pharmacologic therapy for CRF and suggest that more research in this area is needed (Mock et al., 2000).

Conclusions

Fatigue is a serious clinical issue for patients with cancer, is highly prevalent in this population, and is associated with decreased quality of life. Complaints of fatigue should be described specifically by patients so the healthcare team can explore possible etiologies. Several simple, reliable, and valid measurement scales exist to assess fatigue. Discrete medical causes of fatigue should be directly treated. Certain psychiatric syndromes, particularly mood disorders, can cause acute fatigue in the absence of cancer; therefore, diagnosis and treatment of these disturbances also are necessary. A number of therapeutic strategies exist that can benefit fatigued patients with cancer, although further research is needed.

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