Original Article

Update on Psychotropic Medications for Cancer-Related Fatigue

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Key Words

Cancer, fatigue, psychotropic medications, psychostimulants, antidepressants, wakefulness-promoting agents.

Abstract

Fatigue is a common and highly distressing symptom of cancer associated with reduced quality of life and considerable psychological and functional morbidity. The reported prevalence of cancer-related fatigue ranges from 4% to 91%, depending on the specific cancer population studied and the methods of assessment. Cancer-related fatigue has typically been underreported, underdiagnosed, and undertreated. Fatigue and depression may coexist in cancer patients, and considerable overlap of symptoms occurs. This is partly the reason for the interest in examining the role of psychotropic medications in treating fatigue. Clarifying the relationship between depression and fatigue is necessary to effectively evaluate and treat cancer-related fatigue. Even with International Classification of Diseases criteria, differentiating cancer-related fatigue is difficult. Psychotropic drugs that have been studied for cancer-related fatigue include psychostimulants, wakefulness-promoting agents, and antidepressants. Methylphenidate has been studied most and seems to be effective and well tolerated despite common side effects. Some preliminary data support using modafinil in cancer-related fatigue with less concern about tolerance or dependence. Antidepressant studies have shown mixed results. Paroxetine seems to show benefit for fatigue primarily when it is a symptom of clinical depression. Bupropion, a norepinephrine/dopamine reuptake inhibitor, may have psychostimulant-like effects, and therefore may be more beneficial for treating fatigue. However, studies are currently limited. Randomized, placebo-controlled trials with specific agents are needed to further assess the efficacy and tolerability of psychotropic medications in the treatment of cancer-related fatigue. (*JNCCN* 2007;5:1081–1091)

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Fatigue is a highly prevalent and distressing symptom of cancer, associated with reduced quality of life and considerable psychological and functional morbidity.[1–4] Cancer-related fatigue has typically been underreported, underdiagnosed, and undertreated.[5] Patients often perceive fatigue as the most distressing symptom associated with cancer and its treatment, even more distressing than pain, nausea, and vomiting.[3] The reported prevalence of cancer-related fatigue ranges from 4% to 91%, depending on the cancer population studied and the methods of assessment.[6] Fatigue is present at diagnosis in approximately 50% of cancer patients and occurs in up to 75% of patients with bone metastases. Approximately 60% to 96% of patients with cancer experience fatigue during treatment.[7] Chemotherapy, radiation therapy, and biologic and hormonal therapies have all been found to exacerbate fatigue. A 4% rate of fatigue reported by women with early-stage breast cancer before chemotherapy increased to 28% after 4 cycles of chemotherapy.[8] A study in men with localized prostate cancer showed that the fatigue rates increased from 4% to 25% after radiation treatment.[9] Fatigue is reported months or even years after cancer treatment has been completed, ranging from 17% to 53% depending on the diagnostic criteria used to define fatigue.[6,10,11]

Fatigue is a poorly defined symptom that may involve physical, mental, emotional, and motivational components. The NCCN Cancer-Related Fatigue Clinical Practice Guidelines in Oncology define cancer-related fatigue 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."[5] Cancer-related fatigue is more severe and distressing than fatigue experienced by healthy individuals and is less likely to be relieved with rest.[5] Recognizing the need for a standardized definition of fatigue, a group of expert clinicians[4]

proposed a set of diagnostic criteria that have been included in the Tenth Revision of the International Classification of Disease (ICD-10; Table 1). A standardized interview guide was designed and studied for its reliability and validity to assess the proposed clinical syndrome, with results suggesting its usefulness in identifying patients experiencing clinically significant cancer-related fatigue.[12]

Fatigue is not only difficult to define but also challenging to quantify. Various standardized self-report scales are available, most of which were developed in the context of cancer. Different scales may measure fundamentally different aspects or even potentially distinct conceptions of fatigue. The challenge for clinicians or researchers is to choose a reliable and valid tool for measuring fatigue that most adequately suits their purposes.

The oldest scales assessing fatigue are dichotomous. Other scales have taken a unidimensional approach (e.g., Visual Analogue Scale for Fatigue,[13] Karnofsky Performance Status).[14] One limitation of these scales is the presence of confounding factors, such as pain. Multidimensional scales include the Fatigue Symptom Inventory,[15] the Brief Fatigue Inventory (BFI),[16] The Piper Fatigue Scale,[17] and the Multidimensional Assessment of Fatigue.[18] Given the multifactorial nature of fatigue, accessory scales (e.g., depression scales) and measurements of biologic parameters should be used with fatigue assessment tools to obtain the most complete evaluation of a patient's fatigue.

Cancer-related fatigue is a multidimensional syndrome that can be caused by several physical and psychosocial factors, including tumor byproducts, 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.[2,5,19–21] Cancer-related fatigue has been related to pain, depression, emotional distress, sleep deprivation, and reduced physical activity.[22] Cytokines (interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]-α) also have a role in the development of cancer-related fatigue,[23] which has led researchers to consider cytokine-antagonist drugs, such as the TNF receptor etanercept and the TNF-α antagonist thalidomide, to improve tolerability of chemotherapy regimens and potentially to treat cancer-related fatigue and cachexia.[24,25]

To effectively evaluate and treat cancer-related fatigue, the relationship between mood disturbances and fatigue must be clarified. Many symptoms are common to both fatigue and depression, such as decreased energy and motivation, sleep disruptions, diminished concentration and attention, and problems with short-term memory. Clinicians 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 these symptoms to the consequences of fatigue. Depression, on the other hand, occurs more likely in the presence of hopelessness, feelings of worthlessness or guilt, suicidal ideation, and a family history of depression. Fatigue and depression may coexist. The nature of any causal relationship between cancer-related fatigue and depression remains unclear. Studies have not consistently shown relief of fatigue with treatment of depression and visa versa. However, a bidirectional relationship has been suggested, with fatigue occurring as a symptom of depression or depression being caused by fatigue from its interference with mood, work, and leisure activities.[10,26]

Treatment of Cancer-Related Fatigue

All patients should be screened for fatigue at initial visit, at regular intervals during and after treatment, and as clinically indicated.[5] Education is an important initial step, particularly because patients tend not to report fatigue unless directly asked. Precipitating factors, such as acute physical and psychological stresses, should be identified, as should perpetuating factors such as physical inactivity and ongoing psychological or social stresses. Given the multidimensional nature of cancer-related fatigue, a biopsychosocial approach is recommended for treating it.

The NCCN Cancer-Related Fatigue Clinical Practice Guidelines in Oncology recommend using numerical self-report or verbal scales to assess the severity of fatigue. If fatigue is shown to be moderate or severe (a score of 4–10 on a scale of 0–10, with higher numbers indicating increased severity), a focused history and clinical examination and an evaluation of the pattern of fatigue, associated symptoms, and interference with normal functioning are recommended.[5]

Potentially reversible causes of fatigue (e.g., pain, emotional distress, sleep disturbance, anemia,

Table 1 ICD-10 Criteria for Cancer-Related Fatigue

A.	Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, with at least 1 symptom (A1) being significant fatigue:
	A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
	A2. Complaints of generalized weakness or limb heaviness
	A3. Diminished concentration or attention
	A4. Decreased motivation or interest to engage in usual activities
	A5. Insomnia or hypersomnia
	A6. Experience of sleep as unrefreshing or nonrestorative
	A7. Perceived need to struggle to overcome inactivity
	A8. Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued
	A9. Difficulty completing daily tasks attributed to feeling fatigued
	A10. Perceived problems with short-term memory
	A11. Postexertional malaise lasting several hours
B.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C.	Evidence from the history, physical examination, or laboratory findings shows that the symptoms are a consequence of cancer or cancer therapy.
D.	The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

Adapted from Cella D, Peterman A, Passik S, et al. Progress toward guidelines for the management of fatigue. Oncology 1998;12:369–377; with permission.

hypothyroidism) should be identified and treated, and nonessential centrally acting drugs should be eliminated.[5] If anemia is the main cause of fatigue, physicians should determine the necessity of a transfusion. Clinical trials have shown that patients with anemia have improved energy and less fatigue after erythropoietin treatment.[27] Depression also should be carefully screened for and treated because of its high prevalence in cancer patients.[5]

Nonpharmacologic Interventions

The NCCN Cancer-Related Fatigue Guidelines recommend nonpharmacologic approaches for treating cancer-related fatigue.[5] Activity enhancement and psychosocial interventions (e.g., education, support groups, individual counseling, stress management training) have been well supported by research. Dietary management, attention-restoring therapy, and sleep therapy have also been recommended.[5,28,29]

Pharmacologic Interventions

Several pharmacologic interventions are being evaluated in clinical trials for treating fatigue in cancer patients (http://clinicaltrials.gov/). This article focuses on psychotropic medications, with an emphasis on psychostimulants (Table 2). Table 3 presents a review of studies using psychotropic medications to treat cancer-related fatigue.

Psychostimulants: Psychostimulants are defined as drugs that increase alertness or motivation. The term is commonly used to refer to methylphenidate, dextroamphetamine, and pemoline (withdrawn from the U.S. market).

Methylphenidate and dextroamphetamine are sympathomimetic drugs. They both stimulate adrenergic receptors directly as agonists and indirectly cause the release of dopamine and norepinephrine from presynaptic terminals. They have been scheduled as controlled drugs because of their rapid onset of action, immediate behavioral effects, and propensity for users to develop tolerance, which lead to increased risk for abuse and dependence in vulnerable individuals (i.e., patients with personal or family history of substance abuse or dependence). Neuropharmacologic data suggest that methylphenidate has pharmacokinetic properties that reduce its abuse potential compared with stimulant drugs of abuse, such as cocaine.[43]

Table 2 Psychotropic Medications Used in Cancer-Related Fatigue

Medication	Starting Dose	Dose Range	Comments
Psychostimulants			
Methylphenidate	2.5–5 mg daily or twice daily	5–30 mg/d, usually divided as twice daily	Longer-acting formulations are available; capsule forms can be sprinkled in food.
Dextroamphetamine	2.5–5 mg daily or twice daily	5–30 mg/d, usually divided as twice daily	Longer-acting formulations are available; capsule forms can be sprinkled in food.
Wakefulness-Promoting Agents			
Modafinil	50–100 mg daily	50–400 mg daily, may be divided as twice daily	Better tolerated than psychostimulants because of favorable side effect profile.
Antidepressants*			
Selective serotonin reuptake inhibitors (SSRIs)			Well-tolerated; citalopram, escitalopram, and sertraline seem to have the least drug–drug interactions.
Fluoxetine†	10–20 mg/d	10–60 mg/d	
Paroxetine	10–20 mg/d	10–40 mg/d	
Citalopram†	10–20 mg/d	10–40 mg/d	
Escitalopram†	5–10 mg/d	5–20 mg/d	
Sertraline†	25–50 mg/d	25–200 mg/d	
Serotonin/norepinephrine reuptake inhibitors			Well-tolerated. Monitor blood pressure, especially at higher doses.
Venlafaxine	37.5–75 mg/d	37.5–225 mg/d	
Duloxetine	20–30 mg/d	20–60 mg/d	
Norepinephrine/dopamine reuptake inhibitor			Doses higher than 300 mg/d should be used twice daily to minimize the risk for seizures.
Bupropion	75 mg/d	75–450 mg/d	
Tricyclic antidepressants			Drug–drug interactions are more common compared with SSRIs.
Secondary amines			
Desipramine	25–50 mg/d	25–200 mg/d	
Nortriptyline†	10–25 mg/d	10–150 mg/d	
Tertiary amines			
Amitriptyline	10–25 mg/d	10–150 mg/d	
Doxepin†	25–50 mg/d	25–300 mg/d	
Imipramine	10–25 mg/d	10–200 mg/d	
α-2 Antagonist/5-HT2/ 5HT3 Antagonist			May help to improve appetite and insomnia. Well-tolerated.
Mirtazapine	7.5–15 mg/d	7.5–45 mg/d	

*No antidepressant medications have been proven to be efficacious in treating cancer-related fatigue in the absence of diagnosed clinical depression.
†Available in liquid formulations.

Table 3 Review of Studies with Psychotropic Medications for Treating Cancer-Related Fatigue

Study	Sample	Design	Intervention	Results	Comments
Methylphenidate					
Sarhill et al.[30]	Advanced cancer patients (*n* = 11)	Prospective, open-label	Methylphenidate 10 mg twice daily	Decreased fatigue in 9 of 11 patients, with sedation and pain improving in some	More than half of patients experienced side effects such as insomnia, agitation, anorexia, nausea, vomiting, dry mouth
Sugawara et al.[31]	Advanced cancer patients (*n* = 16)	Prospective, open-label	Methylphenidate 5–30 mg/d, mean duration of treatment 8 d	Decreased fatigue scores (*P* = .01)	Two patients dropped out due to insomnia; visual analogue scale used for assessment of fatigue
Schwartz et al.[32]	Melanoma patients receiving interferon (*n* = 12)	Prospective, open-label	Exercise and methylphenidate 20 mg/d	Decreased fatigue scores	Unclear whether positive effect was from exercise, methylphenidate, or both
Bruera et al.[33]	Advanced cancer patients (*n* = 30)	Prospective, open-label	Patient-controlled methylphenidate, 5 mg every 2 h, max 4/d	Decrease in fatigue, depression, and overall well-being	No patients discontinued medication
Hanna et al.[34]	Breast cancer patients who are cancer-free longer than 6 mo shorter than 5 y (*n* = 37)	Open-label, phase II	Methylphenidate 5 mg twice daily for 6 wk	54% responded with a decrease in Brief Fatigue Inventory score of more than 2 points	19% of the patients withdrew from the study because of minor side effects
Bruera et al.[21]	Advanced cancer patients (*n* = 52 medication, *n* = 53 placebo)	Randomized, double-blind, placebo-controlled	Patient-controlled methylphenidate (5 mg every 2 h to 4 capsules/d) vs. placebo for 7 d	Fatigue scores improved both in placebo and medication arms on day 8	Open-label phase of the study past 15 days showed continued improvement in fatigue
Roth et al.[35]	Ambulatory prostate cancer patients (*n* = 14 medication, *n* = 15 placebo)	Randomized, double-blind, placebo-controlled	Methylphenidate vs. placebo	13 patients in placebo arm and 8 in methylphenidate arm completed the study; 73% of patients in medication arm and 23% in placebo arm showed improved fatigue scores	Preliminary analysis of the study shows remarkable placebo effect; 43% of patients dropped out because of cardiac side effects
Dexmethylphenidate					
Lower et al.[36]	Adult cancer patients who completed chemotherapy 2 mo previously (*n* = 77 dexmethylphenidate, *n* = 75 placebo)	Randomized, placebo-controlled, phase III	Dexmethylphenidate 10–50 mg/d for > 2 wk	Medication found to be more effective compared with placebo in improving fatigue	Final data analysis has not been published yet
Modafinil					
Morrow et al.[37]	Women with breast cancer, all completed treatment 2 y previously (*n* = 51)	Prospective, open-label	Modafinil 200 mg/d for a month	86% reported improvement in fatigue	Final data analysis has not been published yet

Table 3 Continued

Kaleita et al.[38]	Adult brain tumor patients (*n* = 30)	Phase III trial, open-label extension phase	Modafinil, mean dose 225 mg/d at week 8, 258 mg/d at week 12	Mean fatigue score change at weeks 8 and 12 was significantly higher in the intervention arm; well-tolerated	Only results from the open-label extension phase were reported; final data analysis not yet published
Paroxetine					
Capuron et al.[39]	Malignant melanoma (*n* = 40)	Randomized, double-blind, placebo-controlled	Paroxetine vs. placebo 2 wk before start of interferon therapy	Paroxetine did not have an effect on prevention of fatigue	Risk for depression was significantly reduced in the intervention arm
Morrow et al.[40]	Breast cancer patients undergoing chemotherapy (*n* = 479)	Randomized, double-blind, placebo-controlled, multicenter	Paroxetine 20 mg/d vs. placebo for 8 wk	No significant difference detected in fatigue improvement between placebo and intervention arms	A significant difference was seen between groups in the mean level of depression
Roscoe et al.[26]	Breast cancer patients undergoing chemotherapy (*n* = 94)	Randomized, double-blind, placebo-controlled	Paroxetine 20 mg/d vs. placebo	No significant difference between placebo and intervention arms	Paroxetine was effective in treating depression, but not cancer-related fatigue
Bupropion					
Cullum et al.[41]	Adult cancer patients (*n* = 15)	Prospective open-label	Bupropion 100–150 mg/d	13 patients reported improvement in fatigue	Small sample size; placebo-controlled studies are needed to confirm the results
Moss et al.[42]	Adult cancer patients (*n* = 21)	Prospective open case series (*n* = 21)	Bupropion 100–300 mg/d	Well-tolerated; both depressed and nondepressed patients reported improvement in fatigue	Small sample size; placebo-controlled studies are needed to confirm the results

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 not recommended for patients with uncontrolled hypertension, underlying coronary artery disease, and tachyarrhythmias.

Psychostimulants have shown great promise in the treatment of medically ill fatigued patients with cancer, multiple sclerosis, Parkinson's disease, opioid-induced sedation, and HIV.[44–47] Psychostimulants have also been used to treat fatigue-related conditions such as pain, depression, and cognitive impairment.[30,48]

Methylphenidate: Methylphenidate has been used since 1954 to treat attention deficit hyperactivity disorder in children. It is usually administered twice a day, at breakfast and lunch, to minimize insomnia. Peak plasma concentration occurs within 1 to 3 hours, with an average half-life of 2 hours. Sustained-release formulations have approximately 4 to 6 hours of clinical action. Newer sustained-release formulations have an early peak followed by 8 hours of action. Close monitoring for common side effects, such as agitation and insomnia, is recommended, especially in the first few days.

Breitbart et al.[44] conducted the first randomized, double-blind, placebo-controlled trial of 2 psychostimulants for the treatment of fatigue in ambulatory patients with HIV disease. They found that methylphenidate and pemoline were equally effective and significantly superior to placebo in decreasing fatigue severity with minimal side effects. Of 109 ambulatory patients with HIV randomized to treatment with methylphenidate, pemoline, or placebo, 15 of 37

(41%) taking methylphenidate and 12 of 33 (36%) taking pemoline experienced clinically significant improvement, compared with 6 of 39 (15%) taking placebo. Improvement in fatigue also was associated with improved quality of life, decreased depression, and decreased psychological distress. Jitteriness and hyperactivity, the only side effects that occurred significantly more frequently in the medication arm, were reported by 31.8% of subjects taking methylphenidate and 25.6% of subjects taking pemoline.

It should be noted that because pemoline was linked with cases of liver failure and resultant death, this agent is no longer be available in the United States for treatment of fatigue.

In their prospective, open-label pilot study in which fatigue was the primary outcome, Sarhill et al.[30] showed that 9 of 11 consecutive patients with advanced cancer were successfully treated with methylphenidate. Notably, more than half of the patients experienced side effects, such as insomnia, agitation, anorexia, dry mouth, nausea, and vomiting.

In an open-label study examining the efficacy of methylphenidate for treating fatigue among 16 patients with advanced cancer, 2 patients withdrew because of insomnia. The remaining 14 patients completed a mean of 8 days of treatment with methylphenidate, showing a statistically significant decrease in fatigue scores (P = .01). In this study, researchers only used the visual analog scale for assessing fatigue.[31]

A pilot study examined the effects of exercise and methylphenidate on fatigue, functional ability, and cognitive function in patients with melanoma and compared results with historical controls who underwent usual care only while on interferon (IFN)-α. Twelve patients with melanoma entered and completed the study. Patients were instructed to take 20 mg/d sustained-release methylphenidate and follow an aerobic exercise program 4 days a week for 15 to 30 minutes. Fatigue was lower for the exercise and methylphenidate group than for historic controls. The researchers concluded that the combination of aerobic exercise and methylphenidate may have a positive effect on fatigue, cognitive function, and functional ability. A larger sample size and randomized trial is needed to more rigorously evaluate the results of exercise and methylphenidate alone or in combination.[32]

A phase II study was performed to evaluate the effects of methylphenidate on cancer-related fatigue in breast cancer survivors with less-than-moderate depression on the Brief Zung Self-Administered Depression Scale and fatigue as evidenced by a score of 4 or more on the BFI. Patients received methylphenidate, 5 mg orally, twice daily, for 6 weeks, with a dose escalation on week 2 if the BFI score remained 4 or more and no significant toxicities were reported. On weeks 4 and 6, 20 of 37 patients (54%) responded with a decreased BFI score greater than 2 points, averaging a decrease of 3.5. Six patients (19%) withdrew because of minor adverse events.[34]

Because of its rapid onset of action and short half-life, Bruera et al.[33] suggested that methylphenidate may be effective in relieving fatigue when taken on an as-needed basis throughout the day, also called patient-controlled dose administration. These investigators initially conducted an open-label pilot study using patient-controlled methylphenidate to manage cancer-related fatigue. In 30 patients, methylphenidate was temporarily associated with improvement in fatigue, overall well-being, and depression. It was well tolerated, and no patients discontinued because of toxicity.

After the open-label study, Bruera et al.[21] conducted a double-blind, randomized, placebo-controlled trial comparing patient-controlled methylphenidate with placebo (5 mg methylphenidate or placebo every 2 hours as needed, to 4 tablets a day for 7 days), and fatigue assessments were made at baseline and days 8, 15, and 36. All patients were offered open-label methylphenidate for 4 weeks. Fatigue intensity improved significantly on day 8 in both the methylphenidate and placebo groups. However, no significant difference was seen in fatigue improvement among the intervention (n = 52) and placebo (n = 53) groups. Approximately 90% of patients receiving methylphenidate or placebo chose to continue the medication beyond 8 days. Improvement in fatigue scores were sustained during the open-label methylphenidate phase at days 15 and 36. Researchers concluded that, without a placebo-controlled group, whether these findings reflect an independent result or extension of placebo effect is difficult to determine. The mean daily number of capsules of methylphenidate and placebo taken by the patients between days 1 and 8 were 2.3 (± 1.0) and 2.1 (± 1.0), respectively (P = not significant).

In their double-blind, randomized, placebo-controlled study evaluating the benefits of methylphenidate compared with placebo in ambulatory patients with prostate cancer, Roth et al.[35] recruited

29 patients (15 in the placebo group, 14 in the methylphenidate group), with 21 completing the study (13 in the placebo arm, 8 in the intervention arm). Preliminary data indicated that 73% of the patients in the intervention group reported a clinically significant reduction in fatigue compared with 23% in the placebo group. A significant placebo effect was seen for fatigue. Among men in the methylphenidate arm, 43% dropped out because of cardiovascular side effects.

Dexmethlyphenidate is the *d*-isomer of methylphenidate, with a longer duration of action (about 6 hours). It was found to be well tolerated and more effective than placebo in improving fatigue in adult patients with cancer (75 in the placebo arm, 77 in the intervention arm) who completed chemotherapy more than 2 months before study entry. Significant improvement was seen in the Functional Assessment of Chronic Illness Therapy–Fatigue Subscale total score at weeks 1, 5, 6, 7, and 8 ($P < .05$) in the intervention group compared with placebo.[36]

Dextroamphetamine: Dextroamphetamine is the *d*-isomer of amphetamine and is more potent than methylphenidate. Although dextroamphetamine does not seem to have been studied for the treatment of cancer-related fatigue, it is commonly used by clinicians for this indication. It has been studied in the treatment of HIV-related fatigue with favorable results.[46]

Pemoline: Pemoline has been linked with cases of liver failure and resultant death. As a result, Abbott Laboratories announced in March 2005 that pemoline would no longer be available in the United States, and in October 2005 manufacturers of generic pemoline agreed to stop selling these products. This action was based on advice from the Food and Drug Administration (FDA) that the overall risk of liver toxicity with pemoline outweighed the benefits of the drug.

Wakefulness-Promoting Agents: Modafinil, a novel psychostimulant, is a wakefulness-promoting agent approved by the FDA in December 1998 to treat excessive daytime sleepiness in patients with narcolepsy.[49] It has been used to augment antidepressants and in patients with persistent fatigue and sleepiness despite antidepressant treatment,[50] and has been indicated as treatment for shift-work sleep disorder. Compared with other psychostimulants, modafinil has a novel mechanism of action and less abuse potential. It is well tolerated and has a good safety profile. The mechanism of action is largely unknown. 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 approximately 15 hours, and a steady state is reached after 2 to 4 days of dosing. Higher doses (200–400 mg/d) of modafinil may be more effective for sleepiness; however, lower doses (50–200 mg/d) seem to be better for concentration problems and fatigue.

It is currently used as a first-line agent for treating severe fatigue in multiple sclerosis.[51] In a 1-month open-label trial of modafinil, 200 mg/d, involving 51 women who completed breast cancer treatment an average of 23.5 months previously and were reporting persistent fatigue, Morrow et al.[37] found that 86% reported reduction of fatigue. Based on a numeric scale of 0 to 10, the mean fatigue severity level of 6.9 at baseline decreased to 3.7 ($P < .1$) after treatment with modafinil. Kaleita et al.[38] reported the fatigue outcomes of the unblinded open-label extension part of their phase II clinical trial. In their sample of 30 patients with brain tumors (malignant and benign), statistically significant differences ($P \leq .005$) were observed in the mean score changes at weeks 8 and 12 compared with baseline on all fatigue self-ratings measures. The mean modafinil dose was 225 mg/d (range, 50–400 mg/d) at week 8 and 258 mg/d (range 50–600 mg/d) 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 treating cancer-related fatigue.

Antidepressants: Underlying depression should be treated with selective serotonin reuptake inhibitors (SSRIs), which are generally better tolerated than tricyclic antidepressants in patients with cancer. When prescribing these medications, clinicians should remember that, because fatigued patients are generally more sensitive to antidepressant side effects, treatment should be initiated with small doses. Drug interactions should be carefully monitored also.

The benefits of antidepressants are not clear in patients with cancer-related fatigue without a depressive mood disorder. Research has suggested a common pathophysiologic mechanism, such as serotonin insufficiency, in the development of both fatigue and depression. Based on that evidence, Morrow et al.[40]

conducted 2 studies to examine whether an SSRI could treat fatigue through increasing serotonin in the synaptic space. In a multicenter, randomized, double-blind, placebo-controlled study, 479 breast cancer patients undergoing chemotherapy were randomly assigned to receive either 20 mg/d of oral paroxetine or placebo for 8 weeks.[40] No difference was detected in fatigue between the placebo and intervention groups at end of study, although a significant difference was seen in the mean level of depression. Notably, 32% of patients in both arms had significant depression at study entry, and approximately half reported fatigue scores of 5 or more on a 10-point scale.

In a single-institution, double-blind clinical trial, the same group randomized 94 women with breast cancer who were undergoing chemotherapy to receive 20 mg of paroxetine or placebo. Depression was significantly reduced in the 44 patients receiving paroxetine compared with the placebo group; however, no significant difference was seen in fatigue measures. The researchers concluded that, although paroxetine is effective at reducing depression, it is not efficacious in relieving cancer-related fatigue among women with breast cancer undergoing chemotherapy.[26]

In a double-blind, randomized, placebo-controlled trial, 40 patients with malignant melanoma were assigned to paroxetine or placebo 2 weeks before initiation of IFN-α treatment. Although the risk for major depression was significantly reduced in patients treated with paroxetine, fatigue was not affected by the intervention.[39]

Bupropion is an antidepressant with a different mechanism of action from SSRIs. It acts as a norepinephrine/dopamine reuptake inhibitor, and thus may have stimulant-like effects. Sustained-release bupropion at a dose of 100 to 150 mg/d was evaluated in an open-label trial of 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, but 13 patients reported that their fatigue improved and 8 that their fatigue was much improved. Controlled studies are required to determine whether the effect of bupropion on fatigue is independent of its antidepressant effects.[41]

A recent study investigated whether sustained-release bupropion improved symptomatic fatigue, depression, and quality of life in cancer patients and their caregivers.[42] The sample consisted of a prospective open-case series of 21 cancer patients with fatigue and with or without depression at moderate to severe levels, referred for psychiatric assessment from a tertiary care cancer center. Both patient symptom and caregiver ratings were measured before and after 4 weeks of treatment with the maximally tolerated dose of bupropion in the range of 100 to 300 mg/d. At trial completion, significant improvement was found for symptoms of fatigue and depression. Subjects were divided into 2 groups: depressed and nondepressed (based on a cutoff score of 17 on the Hamilton Depression Rating Scale). Both groups reported improvement in fatigue and depressive symptoms. Depressed subjects and their caregivers did not experience any change in quality of life, whereas the nondepressed subjects and their caregivers reported improvements. Results from this small group of patients suggest that bupropion may have potential as an effective pharmaceutical agent for treating cancer-related fatigue. However, a randomized, placebo-controlled trial with this medication is indicated.

Other Medications to Treat Fatigue: Various pharmacologic agents have been studied and used to treat fatigue, including corticosteroids, megestrol acetate, L-carnitine, donepezil, and amantadine.

Although corticosteroids have been used to treat cancer-related fatigue, current evidence is anecdotal and responses to corticosteroids seem to be temporary. In their prospective, randomized, double-blind study, Bruera et al.[52] observed that 40 patients undergoing palliative care and given 2 weeks of treatment with methylprednisolone showed an increase in activity that became nonsignificant after 4 weeks of treatment.

Megestrol acetate, a progestational agent that has been found to improve appetite in cancer-related cachexia, also has been suggested to have a role in the treatment of cancer-related fatigue. The effects of megestrol acetate on fatigue are unclear, but probably involve anticytokine and corticosteroid-type effects.[53]

L-carnitine is a cofactor that binds free long-chain fatty acids to transport them across mitochondrial membrane for fatty acid oxidation. L-carnitine supplements were shown to improve fatigue and depression in a group of patients with cancer and L-carnitine deficiency.[54]

Donepezil is a reversible acetylcholinesterase inhibitor used to treat Alzheimer's dementia. Donepezil, 5 mg/d, was evaluated in an open-label trial of 27 patients with various tumor sites. Fatigue improved significantly after a 7-day course of treatment.

However, dose-limiting side effects were observed in approximately 25% of the sample. The open-label design and small sample size of this study calls for further research to assess the efficacy and tolerability of donepezil in treating cancer-related fatigue.[55]

Amantadine, an anti-influenza agent with dopaminergic effects used in Parkinson's disease and as an adjunct to IFN-based therapies for chronic hepatitis C, has been used to treat fatigue associated with multiple sclerosis.[56] Although no studies involving amantadine for treating cancer-related fatigue were found, this agent could be of interest for future research.

The potential role of cytokine antagonists in the treatment of cancer-related fatigue is discussed earlier. Nonsteroidal anti-inflammatory drugs, selective cyclooxygenase 2 inhibitors (i.e., celecoxib), monoclonal antibodies (i.e., infliximab), and bradykinin antagonists could also be considered potential treatments for cancer-related fatigue through their direct and indirect cytokine antagonistic effects.[57]

The NCCN guidelines conclude that sufficient evidence does not currently exist to recommend pharmacologic therapy for cancer-related fatigue, recommending more research in this area.[5]

Conclusions

Fatigue is a serious clinical problem in patients with cancer. It is highly prevalent in this population and associated with decreased quality of life. Patients should describe their fatigue specifically so that different causes can be explored. Several simple, reliable, and valid measurement scales exist to assess fatigue. Discrete medical causes of fatigue should be treated directly. Certain psychiatric syndromes, particularly mood disorders, can cause acute fatigue in the absence of cancer; thus, diagnosis and treatment of these disturbances are also necessary. Several therapeutic strategies can benefit fatigued patients with cancer, although further research is warranted.

References

1. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000;5:353–360.
2. Hwang SS, Chang VT, Rue M, Kasimis B. Multidimensional independent predictors of cancer-related fatigue. J Pain Symptom Manage 2003;26:604–614.
3. Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. Semin Hematol 1997; 34:4–12.
4. Cella D, Peterman A, Passik S, et al. Progress toward guidelines for the management of fatigue. Oncology 1998;12:369–377.
5. Mock V, Atkinson A, Barsevick A, et al. NCCN Practice Guidelines for Cancer-Related Fatigue. Oncology (Williston Park) 2000;14:151–161.
6. Lawrence DP, Kupelnick B, Miller K, et al. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. J Natl Cancer Inst Monogr 2004;32:40–50.
7. Flechtner H, Bottomley A. Fatigue and quality of life: lessons from the real world. Oncologist 2003;8(suppl 1):5–9.
8. Jacobsen PB, Hann DM, Azzarello LM, et al. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. J Pain Symptom Manage 1999;18:233–242.
9. Monga U, Kerrigan AJ, Thomby J, Monga TN. Prospective study of fatigue in localized prostate cancer patients undergoing radiotherapy. Radiat Oncol Investig 1999;7:178–185.
10. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 2000;18:743–753.
11. Cella D, Davis K, Breitbart W, et al. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J Clin Oncol 2001;19:3385–3391.
12. Sadler IJ, Jacobsen PB, Booth-Jones M, et al. Preliminary evaluation of a clinical syndrome approach to assessing cancer-related fatigue. J Pain Symptom Manage 2002;23:406–416.
13. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res 1991;36:291–298.
14. Schag CC, Heinrich RL, Ganz PA. Karnofsky Performance Status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2:187–193.
15. Hann DM, Jacobsen PB, Azzarello LM, et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. Qual Life Res 1998;7:301–310.
16. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer 1999;85:1186–1196.
17. Piper B, Lindsey A, Dodd M, et al. Development of an instrument to measure the subjective dimension of fatigue. In: Funk SG, Tornquist EM, Champagne MT, et al., eds. Key Aspects of Comfort: Management of Pain, Fatigue and Nausea. New York: Springer; 1989:199–208.
18. Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol 1995;22:639–643.
19. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. Lancet 2003;362:640–650.
20. Barnes EA, Bruera E. Fatigue in patients with advanced cancer: a review. Int J Gynecol Cancer 2002;12:424–428.
21. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 2006;24:2073–2078.
22. Reineke-Bracke H, Radbruch L, Elsner F. Treatment of fatigue: modafinil, methylphenidate, and goals of care. J Palliat Med 2006;9:1210–1214.
23. Kurzrock, R. The role of cytokines in cancer-related fatigue. Cancer 2001;92(suppl 6):1684–1688.
24. Monk JP, Phillips G, Waite R, et al. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. J Clin Oncol 2006;24:1852–1859.
25. Hussein MA. Research on thalidomide in solid tumors, hematologic malignancies, and supportive care. Oncology (Williston Park) 2000;14(suppl 12):9–15.

26. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat 2005;89:243–249.
27. Savonije JH, van Groeningen CJ, Wormhoudt LW, Giaccone G. Early intervention with epoetin alfa during platinum-based chemotherapy: an analysis of the results of a multicenter, randomized, controlled trial based on initial hemoglobin level. Oncologist 2006;11:206–216.
28. Mock V. Evidence-based treatment for cancer-related fatigue. J Natl Cancer Inst Monogr 2004;32:112–118.
29. Mitchell SA, Beck SL, Hood LE, et al. Putting evidence into practice: evidence-based interventions for fatigue during and following cancer and its treatment. Clin J Oncol Nurs 2007;11:99–113.
30. Sarhill N, Walsh D, Nelson KA, et al. Methylphenidate for fatigue in advanced cancer: a prospective open-label pilot study. Am J Hosp Palliat Care 2001;18:187–192.
31. Sugawara Y, Akechi T, Shima Y, et al. Efficacy of methylphenidate for fatigue in advanced cancer patients: a preliminary study. Palliat Med 2002;16:261–263.
32. Schwartz AL, Thompson JA, Masood N. Interferon-induced fatigue in patients with melanoma: a pilot study of exercise and methylphenidate. Oncol Nurs Forum 2002;29:E85–90.
33. Bruera E, Driver L, Barnes EA, et al. Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: a preliminary report. J Clin Oncol 2003;21:4439–4443.
34. Hanna A, Sledge G, Mayer ML, et al. A phase II study of methylphenidate for the treatment of fatigue. Support Care Cancer 2006;14:210–215.
35. Roth AJ, Nelson CJ, Rosenfeld B, et al. Randomized controlled trial testing methylphenidate as treatment for fatigue in men with prostate cancer [abstract]. Presented at 2006 ASCO Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 275.
36. Lower E, Fleishman S, Cooper A, et al. A phase III, randomized placebo-controlled trial of the safety and efficacy of d-MPH as new treatment of fatigue and "chemobrain" in adult cancer patients [abstract]. J Clin Oncol 2005;23(suppl 16):729s. Abstract 8000.
37. Morrow GM, Gillies LJ, Hickok JT, et al. The positive effect of the psychostimulant modafinil on fatigue from cancer that persists after treatment is completed [abstract]. J Clin Oncol 2005;23(suppl 16):732s. Abstract 8012.
38. Kaleita TA, Wellisch DK, Graham CA, et al. Pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors [abstract]. J Clin Oncol 2006;24(suppl 1):58s. Abstract 1503.
39. Capuron L, Gumnick JF, Musselman DL, et al. Neurobehavioral effects of interferon alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsycho-pharmacology 2002;26:643–652.
40. Morrow GR, Hickok JT, Roscoe JA, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. J Clin Oncol 2003;21:4635–4641.
41. Cullum JL, Wojciechowski AE, Pelletier G, Simpson JS. Bupropion sustained release treatment reduces fatigue in cancer patients. Can J Psychiatry 2004;49:139–144.
42. Moss EL, Simpson JS, Pelletier G, Forsyth P. An open-label study of the effects of bupropion SR on fatigue, depression and quality of life of mixed-site cancer patients and their partners. Psychooncology 2006;15:259–267.
43. Kollins SH. Comparing the abuse potential of methylphenidate versus other stimulants: a review of available evidence and relevance to the ADHD patient. J Clin Psychiatry 2003;64(suppl 11):14–18.
44. Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. Arch Intern Med 2001;161:411–420.
45. Holmes VF, Fernandez F, Levy JK. Psychostimulant response in AIDS-related complex patients. J Clin Psychiatry 1989;50:5–8.
46. Wagner GJ, Rabkin R. Effects of dextroamphetamine on depression and fatigue in men with HIV: a double-blind, placebo-controlled trial. J Clin Psychiatry 2000;61:436–440.
47. Bruera E, Brenneis C, Paterson AH, MacDonald RN. Use of methylphenidate as an adjuvant to narcotic analgesics in patients with advanced cancer. J Pain Symptom Manage 1989;4:3–6.
48. Homsi J, Walsh D, Nelson KA. Psychostimulants in supportive care. Support Care Cancer 2000;8:385–397.
49. Prommer E. Modafinil: is it ready for prime time? J Opioid Manag 2006;2:130–136.
50. Thase ME, Fava M, DeBattista C, et al. Modafinil augmentation of SSRI therapy in patients with major depressive disorder and excessive sleepiness and fatigue: a 12-week, open-label, extension study. CNS Spectr 2006;11:93–102.
51. MacAllister WS, Krupp LB. Multiple sclerosis-related fatigue. Phys Med Rehabil Clin N Am 2005;16:483–502.
52. Bruera E, Roca E, Cedaro L, et al. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep 1985;69:751–754.
53. Bruera E, Ernst S, Hagen N, et al. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. Cancer Prev Control 1998;2:74–78.
54. Cruciani RA, Dvorkin E, Homel P, et al. Safety, tolerability and symptom outcomes associated with L-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: a phase I/II study. J Pain Symptom Manage. 2006;32:551–559.
55. Bruera E, Strasser F, Shen L, et al. The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study. J Pain Symptom Manage 2003;26:1049–1054.
56. Pucci E, Branas P, D'Amico R, et al. Amantadine for fatigue in multiple sclerosis. Cochrane Database Syst Rev 2007;(1):CD002818.
57. Burks TF. New agents for the treatment of cancer-related fatigue. Cancer 2001;92(suppl 6):1714–1718.