CHAPTER 32

Fatigue

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INTRODUCTION

Fatigue is a highly prevalent and distressing symptom of cancer, associated with decreased quality of life, as well as significant psychological and functional morbidity.[1-6] Fatigue in cancer patients has been significantly associated with depression, hopelessness, and overall psychological distress.[7] Fatigue has been shown to predict desire for hastened death among cancer patients.[8] Patients with cancer perceive fatigue as the most distressing symptom associated with cancer and its treatment, more distressing than pain, nausea, and vomiting.[3] As outlined in the National Comprehensive Cancer Network (NCCN) Practice Guidelines for Cancer-Related Fatigue,[9,10] "fatigue most commonly occurs with other symptoms, such as pain, distress, anemia, and sleep disturbances," thus cancer patients presenting with fatigue should be screened for all these symptoms.[9-11] Despite its impact on patients and their caregivers, cancer-related fatigue is underreported, underdiagnosed, and undertreated.[9,10] As growing attention is given to symptom management and quality of life in cancer patients, clinicians treating such patients should be familiar with major issues in assessment and management of fatigue. This chapter reviews the definition, prevalence, and assessment of cancer-related fatigue, as well as evidence-based strategies for treatment.

DEFINING CANCER-RELATED FATIGUE

Fatigue is a poorly defined symptom that may involve physical, mental, and motivational components. Cancer-related fatigue is defined by the NCCN[9,10] practice guidelines as "a distressing, persistent, subjective sense of physical, emotional, and cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." Cancer-related fatigue is more severe and more distressing than fatigue experienced by healthy individuals and is less likely to be relieved by rest.[9,10] Recognizing the need for a standardized definition of fatigue, a group of expert clinicians[4] proposed a set of diagnostic criteria, which are included in the 10th edition of *International classification of diseases (ICD-10)* (Table 32–1). A standardized interview guide has been designed and validated for use in identifying patients with cancer-related fatigue.[12]

PREVALENCE OF FATIGUE

The reported prevalence of cancer-related fatigue ranges from 4% to 100%, depending on the specific cancer population studied and the methods of assessment.[13,14] Fatigue is present at the time of diagnosis in approximately 50% of patients with cancer. In a study of 179 cancer patients, 23.5% of patients reported "severe fatigue" at the time of diagnosis, before the start of therapy.[15]

Fatigue occurs in up to 75% of patients with bone metastases, and approximately 60%–96% of patients undergoing treatment for cancer report fatigue.[16] A national survey of 197 oncologists, 200 caregivers, and 419 cancer patients with various cancers, at various stages of illness, and treatment noted that more than 78% of patients experienced fatigue during the course of their disease and treatment. Thirty-two percent of patients experienced fatigue daily and 32% felt that fatigue significantly affected their daily routines. Sixty-one percent of patients said fatigue affected everyday life more than pain. Among the oncologists, 80% believed that fatigue was undertreated and that fatigue was infrequently discussed between patients and oncologists.[3] Chemotherapy, radiation therapy, and biologic and hormonal therapies have been shown to exacerbate fatigue.[9] Women with early-stage breast cancer before chemotherapy have reported a 4% rate of fatigue, which increased to 28% after four cycles of chemotherapy.[11] Fatigue was estimated to be a distressing symptom in up to 67% of hospitalized and ambulatory prostate cancer patients.[17] A study in men with localized prostate cancer showed that the fatigue rates increased from 4% to 25% after radiation treatment.[18] In a cross-sectional survey of 814 cancer patients receiving chemotherapy and/or radiotherapy, 80% of patients reported fatigue as a side-effect of cancer treatment. Female patients, younger and unemployed patients, and those with higher levels of depression and fatigue experienced more fatigue.[19]

Fatigue is a disruptive symptom months or even years after completion of cancer treatment, which ranges from 17% to 53% in different prevalence studies depending on the diagnostic criteria used to define fatigue.[10,13,20,21] A systematic review of fatigue among breast cancer survivors concluded that survivors experienced significant fatigue up to 5 years after completion of adjuvant chemotherapy.[22]

Fatigue is most common among cancer patients in palliative care settings reported by 84%–100% of patients in palliative care units.[23,24]

As evidenced by the prevalence studies, fatigue is a common symptom in cancer patients and survivors of cancer, from diagnosis through all stages of treatment and beyond.

PATHOPHYSIOLOGY OF FATIGUE

The exact mechanisms involved in the cancer-related fatigue are unknown. Studies have focused on understanding factors that contribute to fatigue, including the cancer itself, cancer-related treatments, and a variety of physical and psychological co-morbidities (e.g., anemia, pain, depression, anxiety, cachexia, sleep disturbances, and immobility).[4,25] Production of cytokines, abnormal accumulation of muscle metabolites, changes in neuromuscular function, abnormalities in adenosine triphosphate synthesis, serotonin dysregulation, disruption of the hypothalamic-pituitary-adrenal axis, modulation of the circadian rhythm, and vagal nerve activation have been proposed as possible mechanisms in the development of fatigue.[25–27] The role of cytokines in fatigue[25] has led researchers to consider cytokine-antagonist drugs, such as tumor necrosis factor (TNF) receptor etanercept, TNF-α antagonist thalidomide, to improve tolerability of chemotherapy regimens and potentially to treat fatigue and cachexia in cancer patients.[28–30] Genetic variables have also been implicated to play a role in the development of fatigue among cancer patients. Advanced colorectal cancer patients with two variant forms of the *DPYD* gene were significantly less likely than those patients with a form of the gene known as *DPYD*5* to report fatigue following treatment with a chemotherapy regimen of 5-fluorouracil, irinotecan, and oxaliplatin.[31]

The pathogenesis of fatigue among cancer survivors is unclear and most likely multifactorial.[10,27] A study comparing breast cancer survivors with and without fatigue (n = 20 in each group) has found significantly higher levels of interleukin-1 receptor antagonist, soluble TNF type II, and higher numbers of T lymphocytes among breast cancer survivors with fatigue suggesting a chronic inflammatory process involving the T-cell compartment in this group of patients.[32]

Table 32–1. 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, and at least one of the symptoms is (A1) 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 (eg, 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. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.

D. The symptoms are not primarily a consequence of co-morbid psychiatric disorders, such as major depression, somatization disorder, somatoform disorder, or delirium.

SOURCE: Adapted from[4] Cella D, Peterman A, Passik S, Jacobsen P, Breitbart W. Progress toward guidelines for the management of fatigue. *Oncology (Williston Park).* 1998;12:369–377.

ASSESSMENT OF FATIGUE

All cancer patients should be screened for fatigue at their initial visit, at regular intervals during and following cancer treatment, and as clinically indicated.[9,10] The NCCN practice guidelines on cancer-related fatigue recommend the use of numerical self-report scales or verbal scales to assess the severity of fatigue. As fatigue is a symptom that is perceived by the patient, like pain, it is most accurately described by self-report. If the severity is measured as moderate or severe (a score of 4 or more on a scale of 0 to 10 with higher numbers indicating increased severity) a focused history and physical examination; evaluation of the pattern, onset, and duration of fatigue; associated symptoms; and interference with normal functioning is recommended.[9,10] Description of patient behavior by family members and other caregivers is an important part of assessment among children and elderly patients. 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. Age specifications have been included in the NCCN practice guidelines for screening fatigue and assessing the severity of it highlighting the importance and variability of fatigue across the lifespan.[9,10]

Assessment of etiologies. The etiologies of fatigue are complex and varied, including tumor by-products, opioids or other drugs (such as antidepressants, β-blockers, benzodiazepines, antihistamines), hypogonadism, hypothyroidism, cachexia, anemia, malnutrition, pain, myopathy, nausea, hormonal therapy, chemotherapy, radiation therapy, bone marrow transplantation, and treatment with biological response modifiers (Table 32–2).[2,7,9,10,33] Potentially reversible causes of fatigue (such as pain, emotional distress, sleep disturbance, anemia, hypothyroidism) should be identified and treated, and nonessential centrally acting drugs (including prescription drugs, over-the-counter medications, and supplements) should be eliminated.[9,10] Clinicians should consider the possibility of depression due to its high prevalence in patients with cancer and provide treatment.[9,10] If anemia is the main cause of fatigue, the physician should determine the necessity of a transfusion in severely symptomatic patients. Clinical trials have shown that patients with anemia have improved energy and less fatigue after erythropoietin treatment.[34] Co-morbid conditions such as cardiac, pulmonary, renal, hepatic, endocrine, and neurologic dysfunction, and infections should be ruled out as potential causes of fatigue. Several chemotherapy agents and radiation therapy have been associated with endocrine abnormalities, including hypothyroidism and hypogonadism.[35,36] Assessment of nutrition (weight, caloric intake, fluid-electrolyte imbalances) and activity level are also important elements of assessment.[9,10] Anemia, polypharmacy, cognitive impairment, malnutrition, and cachexia are the most likely etiologies of fatigue in palliative care settings.[37]

Table 32–2. Etiologies of cancer-related fatigue

Preexisting conditions
–Congestive heart failure, chronic obstructive pulmonary disease
Direct effects of cancer, "tumor burden"
Effects of cancer treatment
–Surgery, radiation therapy, chemotherapy, biological therapies
Psychological factors
–Depression, anxiety
Immobility
Sleep disturbances (insomnia, excessive daytime sedation with or without narcolepsy, restless leg syndrome, obstructive sleep apnea)
Cancer-related symptoms
–Pain, nausea
Conditions related to cancer or its treatment
–Anemia, dehydration, malnutrition, infections, electrolyte abnormalities, cytokine production, myopathy
Medications and drugs
–Opioid analgesics, psychotropic agents, β-blockers, alcohol

Assessment Instruments. Fatigue is not only difficult to define but also difficult to assess and quantify. Nonetheless, reliable and valid tools for assessment are crucial for improved management and research progress. Various standardized self-report scales exist, developed mostly in the context of cancer.[38,39] Different scales may measure fundamentally different aspects or even potentially distinct conceptions of fatigue.

The oldest scales assessing fatigue are dichotomous. These include Pearson-Byers Fatigue Checklist, Profile of Mood States, Fatigue and Vigor Subscale, the Fatigue Severity Scale, and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Fatigue Subscale.[38,39] Other scales have taken a unidimensional approach, namely the Visual Analogue Scale for Fatigue (VAS-F)[40] and the Karnofsky Performance Status.[41] VAS-F is organized into energy

and fatigue dimensions and has good psychometric properties. The Karnofsky Performance Status probes mainly fatigue consequences. The limitations of such unidimensional scales include the presence of confounding factors such as pain.

Multidimensional fatigue instruments have been developed to assess a wide range of symptom domains that fatigue may present with.[39] Multidimensional scales include the Fatigue Symptom Inventory,[42] the Brief Fatigue Inventory,[43] The Piper Fatigue Scale (PFS),[44] and the Multidimensional Assessment of Fatigue (MAF).[45] PFS,[44] is comprised of affective, cognitive, sensory, and severity subscales. Its major shortcomings include the fact that it takes a long time to complete and is often difficult for patients to understand. The MAF[45] scale is a revision of the PFS developed for use in patients with rheumatoid arthritis.

The Patient-Reported Outcomes Management Information System (PROMIS) is a databank of survey questions, currently under development, designed to measure common symptoms in clinical trials.[46,47] The PROMIS includes 72 questions on fatigue that have been validated in cancer patients. A 1-minute short-version, cancer-specific fatigue short form, containing seven questions has recently been validated.[46,47]

Given the multifactorial nature of fatigue, accessory scales (e.g., depression scales) and measurements of certain biological parameters should be used in addition to fatigue assessment tools to evaluate a patient's fatigue comprehensively.[9,10,39] In particular, the complex interrelationship between fatigue and psychiatric disturbances such as depression and anxiety merit special attention.

Fatigue and depression. Depression is commonly co-morbid in patients with cancer-related fatigue. It is necessary to clarify the relationship between depression and fatigue to effectively evaluate and treat cancer-related fatigue. There is considerable overlap of symptoms in these two conditions, such as decreased energy and motivation, sleep disturbances, diminished concentration, attention, and memory. Depressive symptoms caused by fatigue are typically less severe and patients tend to attribute such symptoms to the consequences of fatigue. Depression, on the other hand, is more likely present with hopelessness, feelings of worthlessness and/or guilt, suicidal ideation, and a family history of depression.[9,10,39] It is also important to note that fatigue and depression may coexist in the same patient. In a study of chronic fatigue syndrome in primary care settings, a temporal relationship was found between depression and fatigue.[27,48] The nature of any causal relationship between cancer-related fatigue and depression remains unclear. In a study with 987 lung cancer patients, 33% were found to have depression; fatigue was identified as an independent predictor of depression.[49] In another study of 201 cancer patients, fatigue was found to be the most common symptom, with 25% of these patients experiencing depression.[50] A possible bidirectional relationship between fatigue and depression exists, with fatigue occurring as a symptom of depression or with depression occurring because of fatigue, due to interference with mood, work, and leisure activities.[9,10,20,51]

Fatigue and pain. Two most commonly reported symptoms among cancer patients, fatigue and pain, share several common features. Both symptoms are complex and multidimensional, largely based on subjective patient report, and require clear communication between patients and clinicians for timely recognition and treatment of these symptoms. Coexistence of pain and fatigue has been shown to worsen the overall symptom experience among elderly cancer patients, suggesting a synergistic effect between these two symptoms.[52]

MANAGEMENT OF FATIGUE

Given the multidimensional nature of fatigue, a biopsychosocial approach is recommended for treatment of fatigue. Interdisciplinary teams addressing needs of individual patients while implementing the treatment guidelines are critical to management of cancer-related fatigue.[9,10] Interventions can be tailored based on the stage of illness (e.g., active treatment phase, survivorship, and end-of-life). A three-stage hierarchy for the management of fatigue was proposed, namely to identify and treat any underlying causes of fatigue; to treat fatigue directly; and finally to address and manage the consequences of fatigue.[4]

General strategies for management of fatigue. Self-monitoring of fatigue levels; energy conserving strategies such as setting priorities, scheduling activities at times of peak energy, postponing nonessential activities, structuring daily routine, attending to one activity at a time, and limiting naps to 45 minutes or less to minimize interference with nighttime sleep quality; and using distraction have been recommended by the NCCN practice guidelines for management of cancer-related fatigue.[10]

Nonpharmacologic Interventions. Nonpharmacological approaches have been recommended by the NCCN guidelines for the treatment of cancer-related fatigue.[9,10] Increased physical activity and psychosocial interventions (i.e., education, support groups, cognitive-behavioral therapy, individual counseling, stress management training) in the treatment of fatigue have been well-supported by research.[9,10,53–56] There is also evidence supporting dietary management, attention-restoring therapy, and sleep therapy (e.g., sleep restriction, sleep hygiene, and stimulus control) in the treatment of fatigue.[9,10,55,56] Alternative therapies such as massage therapy, yoga, muscle relaxation, and mindfulness-based therapies have been evaluated pilot studies with results suggesting benefit in lowering fatigue in cancer patients.[9,10]

Pharmacologic Interventions. A number of studies examined the efficacy and tolerability of different classes of pharmacologic agents for cancer-related fatigue, primarily psychostimulants and antidepressants. A recent meta-analysis of pharmacological treatment options for cancer-related fatigue has concluded that methylphenidate (a psychostimulant) might be effective for treating fatigue. There was also evidence that treatment with hematopoietic agents relieved fatigue due to chemotherapy-induced anemia.[57] Following is a review of pharmacologic interventions used in the treatment of cancer-related fatigue. Table 32–3 provides a list of commonly used psychostimulants and antidepressants in the treatment of cancer-related fatigue.

Psychostimulants. Psychostimulants are drugs that increase alertness and/or 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. Dexmethylphenidate is the d-isomer of methylphenidate, has a longer duration of action (approximately 6 hours) than methylphenidate. Psychostimulants are scheduled controlled drugs because of their rapid onset of action, immediate behavioral effects, and development of tolerance, which leads to an increased risk of abuse and dependence in vulnerable individuals. Existing neuropharmacologic data suggest that methylphenidate has pharmacokinetic properties that reduce its abuse potential as compared with stimulant drugs of abuse, such as cocaine.[58]

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.[28] 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's disease, opioid-induced sedation, and human immunodeficiency virus (HIV).[59–64] Breitbart and colleagues[59] conducted the first randomized, double-blind, placebo-controlled trial of two psychostimulants for the treatment of fatigue in ambulatory patients with HIV disease. They found that both methylphenidate and pemoline (no longer available) were equally effective and significantly superior to placebo in decreasing fatigue severity with minimal side effects. Psychostimulants also have been used in the treatment of fatigue-related conditions, such as pain, depression, opioid-related sedation, and cognitive impairment. Table 32–4 is a summary of the psychotropic medication trials for the

Table 32–3. Psychotropic medications used in the treatment of cancer-related fatigue

Medication	*Starting dose*	*Dose range*	*Comments*
Psychostimulants			
Methylphenidate	2.5–5 mg daily or twice daily	5–30 mg/day, usually divided as twice daily	Longer-acting forms are available Capsule forms can be sprinkled on food
Dextroamphetamine	2.5–5 mg daily or twice daily	5–30 mg/day, usually divided as twice daily	Longer-acting formulations are available Capsule forms can be sprinkled on food
Wakefulness-promoting agents			
Modafinil	50–100 mg daily	50–400 mg daily, may be divided as twice daily	Favorable side-effect profile
Antidepressants			
Selective serotonin reuptake inhibitors			Well-tolerated Citalopram, escitalopram, and sertraline have the least drug-drug interactions
Fluoxetine[a]	10–20 mg/day	10–60 mg/day	
Paroxetine	10–20 mg/day	10–40 mg/day	
Citalopram[a]	10–20 mg/day	10–40 mg/day	
Escitalopram[a]	5–10 mg/day	5–20 mg/day	
Sertraline[a]	25–50 mg/day	25–200 mg/day	
Serotonin-norepinephrine reuptake inhibitors			Well-tolerated Monitor blood pressure regularly
Venlafaxine	37.5–75 mg/day	37.5–225 mg/day	
Duloxetine	20–30 mg/day	20–60 mg/day	
Norpinephrine-dopamine reuptake inhibitor			Doses higher than 300 mg a day should be administered twice daily to minimize the risk of seizures
Bupropion	75 mg/day	75–450 mg/day	
α-2 antagonist/5-HT2/5HT3 antagonist			Most helpful in patients with insomnia and anorexia
Mirtazapine	7.5–15 mg/day	7.5–45 mg/day	

ABBREVIATION: 5HT, 5-hydroxytryptamine.
[a]Available in liquid formulations.

Table 32–4. Psychotropic medication trials for the treatment of cancer-related fatigue

	Sample	*Intervention*	*Results*	*Comments*
Methylphenidate				
Sarhill et al. 2001[64]	Patients with advanced cancer Prospective, open-label design (n = 11)	Methylphenidate 10 mg twice daily	Decreased fatigue in 9 out of 11 patients, with sedation and pain improving in some patients	More than half of the patients experienced side effects, such as insomnia, agitation, anorexia, nausea, vomiting, and dry mouth
Sugawara et al. 2002[66]	Patients with advanced cancer Prospective, open-label study (n = 16)	Methylphenidate 5–30 mg/day, mean duration of treatment 8 days	Decreased fatigue scores ($p = 0.01$)	Two patients dropped out due to insomnia Visual analog scale was used for assessment of fatigue
Schwartz et al. 2002[67]	Patients with melanoma receiving interferon Prospective, open-label study (n = 12)	Exercise and methylphenidate 20 mg/day	Decreased fatigue scores	Unclear whether the positive effect was due to exercise or methylphenidate or both
Bruera et al. 2003[68]	Patients with advanced cancer. Prospective open-label (n = 30)	Patient-controlled methylphenidate 5 mg every 2 hours with a maximum of 4 caps in a day	Decrease in fatigue, depression, and overall well-being	None of the patients discontinued the medication

(*Continued*)

Table 32–4. Continued

	Sample	*Intervention*	*Results*	*Comments*
Hanna et al. 2006[69]	Patients with breast cancer, who were cancer free longer than 6 months but less than 5 years. Open-label, phase II study (n = 37)	Methylphenidate 5 mg twice daily for 6 weeks	54% of the patients responded with a decrease in BFI score of more than 2 points	16% of the patients withdrew from the study due to minor side effects
Bruera et al. 2006[70]	Patients with advanced cancer (n = 52 in medication arm, n = 53 in placebo arm). Randomized, double-blind, placebo-controlled trial	Patient-controlled methylphenidate (5 mg every 2 hours up to 4 caps a day) versus placebo for a total of 7 days	Fatigue scores improved both in placebo and medication arm on day 8	Open-label phase of the study following the randomized trial showed continued improvement in fatigue
Roth et al. 2006[71]	Ambulatory patients with prostate cancer Randomized, placebo-controlled, phase III trial (n = 15 in the placebo arm, n = 14 in the medication arm)	Methylphenidate versus placebo	13 patients taking placebo and 8 patients taking methylphenidate completed the study 73% of the patients in the methylphenidate arm, 23% of the patients in the placebo arm showed improvement in fatigue scores	Remarkable placebo effect was observed in the preliminary analysis of the study 43% of the patients dropped out due to cardiac side effects
D-methylphenidate				
Lower et al. 2005[72]	Adult patients with cancer, 2 months after chemotherapy Randomized, placebo-controlled, phase III trial (n = 75 placebo, n = 77 medication arm)	D-methylphenidate 10–50 mg/d for more than 2 weeks	Medication was found to be more effective compared to placebo in improving fatigue	Final data analysis has not been published yet
Butler et al. 2007[73]	Adult patients with primary or metastatic brain tumors on radiation therapy Double-blind, randomized, placebo-controlled trial (n=34 in each arm)	D-threo-methylphenidate 15 mg twice daily for 4–12 weeks	Prophylactic use of d-threo-methylphenidate did not result in improvement of fatigue scores or quality of life	Researchers concluded that therapeutic rather than prophylactic d-methylphenidate was recommended for patients undergoing brain RT who develop fatigue or cognitive dysfunction
Mar Fan et al. 2008[74]	Women with breast cancer undergoing adjuvant chemotherapy Randomized, double-blind, placebo-controlled trial (n = 29 on medication, n = 28 on placebo)	D-methylphenidate up to 10 twice daily for 20–140 days	There were no significant differences between the FACT-F scores of the randomized groups	Greater number of patients discontinued study drug in the d-MPH arm than the placebo arm, on the other hand equal numbers in each group required dose reduction for presumed d-MPH toxicity
Modafinil				
Morrow et al. 2005[79]	Women with breast cancer, 2 years after treatment Prospective, open-label study (n = 51)	Modafinil 200 mg/day for a month	86% reported improvement in fatigue	Final data analysis has not been published yet
Kaleita et al. 2006[80]	Adult patients with brain tumor. Phase III, open-label trial (n = 30)	Modafinil, mean dose 225 mg/day at week 8, 258 mg/day at week 12	Well-tolerated; mean fatigue score change at week 8 and 12 was significantly higher in the intervention arm	Only results from the open-label extension phase were reported in this abstract. Final data analysis has not been published yet

	Sample	Intervention	Results	Comments
Paroxetine				
Capuron et al. 2002[81]	Patients with malignant melanoma Double-randomized controlled trial (n = 40)	Paroxetine versus placebo 2 weeks before the start of interferon therapy	Paroxetine did not have an effect on the prevention of fatigue	Risk of depression was significantly reduced in the paroxetine arm
Morrow et al. 2003[82]	Patients with breast cancer receiving chemotherapy Randomized, double-blind, placebo-controlled trial (n = 479)	Paroxetine 20 mg/day versus placebo for 8 weeks	No significant difference was detected in fatigue improvement between placebo and paroxetine arms	There was a significant difference between groups in the mean level of depression
Roscoe et al. 2005[51]	Patients with breast cancer undergoing chemotherapy. Randomized, double-blind, placebo-controlled trial (n = 94)	Paroxetine 20 mg/day versus placebo	No significant difference was observed in fatigue scores between the placebo and paroxetine arms	Paroxetine was effective in treating depression, but not cancer-related fatigue
Sertraline				
Stockler et al. 2007[83]	Patients with advanced stage cancer (n = 189) without major depressive disorder Randomized, double-blind, placebo-controlled trial	Sertaline 50 mg/day (n = 95) versus placebo (n = 94)	No significant difference was observed in depression, anxiety, fatigue, and overall well-being	Sertraline was kept at the starting dose throughout the study duration of 8 weeks
Bupropion				
Cullum et al. 2004[84]	Adult patients with cancer Open-label, prospective design (n = 15).	Bupropion sustained release 100–150 mg/day	13 patients reported improvement in fatigue	Small sample size, open-label design
Moss et al. 2006[85]	Adult patients with cancer Prospective, case series (n = 21)	Bupropion sustained release 100–300 mg/day	Well-tolerated; both depressed and nondepressed patients reported improvement in their fatigue	Small sample size. Placebo-controlled studies are needed to confirm the results
Donepezil				
Bruera et al. 2003[90]	Adult patients with cancer Open-label trial (n=27)	Donepezil 5mg/day for 7 days	All of the 20 patients who completed the trial showed significant improvement in fatigue	7 patients dropped out. Open-label design limits the significance of positive results
Shaw et al. 2006[91]	Adult patients with brain tumor Open-label, phase II trial (n = 34).	Donepezil 5 mg/day for 24 weeks	Fatigue subscale of the Profile of Mood States scale showed improvement short of statistical significance, "trend toward significance" as noted by the researchers	Improvement in cognitive functioning and health-related quality of life were observed
Bruera et al. 2007[92]	Adult patients with advanced cancer Randomized, double-blind, placebo-controlled trial with donepezil (n = 47) versus placebo (n = 56)	Donepezil 5 mg/day for 7 days	There was no significant difference in fatigue scores between the donepezil and placebo groups	Improvement in sedation observed both in the placebo and donepezil arms. Open-label phase of the study with donepezil showed sustained improvement in fatigue scores

ABBREVIATIONS: BFI, brief fatigue inventory; d-MPH, dexmethylphenidate hydrochloride; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; RT, radiation therapy.

treatment of cancer-related fatigue. While open-label studies with psychostimulants have shown improvements in cancer-related fatigue, placebo-controlled randomized trials have found a remarkable placebo effect among cancer patients as well as improved fatigue scores with Psychostimulants.[28]

The Food and Drug Administration (FDA) approved the use of wakefulness-promoting agent modafinil in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder.[75] It has been used to augment antidepressants in major depressive disorder, and as an adjunct treatment for bipolar

depression.[76,77] Compared to the 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.

Modafinil is commonly used for the treatment of severe fatigue in multiple sclerosis[78] and has been studied as a treatment option for cancer-related fatigue with improvement of fatigue in open-label trials.[79,80] Well-designed, randomized, controlled clinical trials are necessary to further clarify the role of modafinil in the treatment of cancer-related fatigue.

Antidepressants. The phenomenological similarities and the possibility of a bidirectional relationship between fatigue and depression have led clinicians to consider antidepressants in the treatment of cancer-related fatigue.

The benefits of antidepressant use are not clear in patients with cancer-related fatigue in the absence of a depressive mood disorder. Research has suggested a common pathophysiological mechanism, such as serotonin insufficiency, in the development of both fatigue and depression.

Studies have examined the role of paroxetine,[51,81,82] sertraline,[83] and bupropion[84,85] in the treatment of cancer-related fatigue. Paroxetine[51,81,82] and sertraline[83] were effective in improving fatigue among cancer patients with co-morbid depressive symptoms. Bupropion was found to be effective and well-tolerated in both depressed and nondepressed cancer patients in open-label trials.[84,85] However controlled studies are required to determine whether the effect of bupropion on fatigue is independent of its antidepressant effects.

Underlying depression treated with selective serotonin-reuptake inhibitors (SSRIs) is generally better tolerated than tricyclic antidepressants in patients with cancer. Medications should be initiated at lower doses and drug-drug interactions should be carefully monitored among patients with cancer-related fatigue.[28]

Corticosteroids. Corticosteroids have been used in the treatment of cancer-related fatigue. In a survey among Swedish palliative care physicians, 40% of the clinicians reported using corticosteroids to treat fatigue, and 80% reported "very "or "some effect" of corticosteroids on fatigue.[86] Bruera and colleagues in their prospective, randomized, double-blind study observed that 40 palliative care patients who received a 2-week treatment with methylprednisolone demonstrated an increase in activity that became nonsignificant after 4 weeks of treatment.[87] This study suggests that the positive effects of corticosteroids in the treatment of fatigue may be transient. It is important to note that corticosteroids may have detrimental side effects such as muscle wasting with long-term use.

Megestrol acetate. Megestrol acetate, a progestational agent, which has been found to improve appetite in cancer-related cachexia, may have a role in the treatment of cancer-related fatigue. A double-blind crossover study comparing megestrol acetate (160 mg 3 times daily for 10 days) to placebo in the treatment of cachexia among patients with advanced cancer (n = 84, total number of patients) has shown significant improvement in overall fatigue scores measured by the PFS.[88] The effects of megestrol acetate on fatigue are not clear but probably involve anticytokine and corticosteroid-type effects.[88]

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.[89] Although the use of L-carnitine in cancer-related fatigue is preliminary, carnitine supplementation shows some promise for management of fatigue.

Donepezil. Donepezil is a reversible cholinesterase inhibitor used in the treatment of Alzheimer's dementia. Studies have explored the role of donepezil in the treatment of cancer-related fatigue.[90-92] A double-blind randomized controlled trial has failed to show any difference between donepezil and placebo in improving fatigue among cancer patients.[92]

Other medications. Amantadine, an antiinfluenza agent with dopaminergic effects, used in Parkinson's disease and as an adjunct to interferon-based therapies for chronic hepatitis C. Amantadine has been utilized in the treatment of fatigue associated with multiple sclerosis, however it has not been studied in cancer-related fatigue.[93,94] Nonsteroidal anti-inflammatory drugs, selective cyclooxygenase 2 inhibitors (e.g., celecoxib), monoclonal antibodies (e.g., infliximab), cytokine antagonists, and bradykinin antagonists have been considered as potential treatments for cancer-related fatigue through their direct and indirect cytokine antagonistic effects.[30,95]

CONCLUSIONS

Fatigue is highly prevalent among patients with cancer, and is associated with decreased quality of life. Fatigue should be recognized, assessed, monitored, and treated promptly for all age groups, at all stages of cancer, before, during, and following treatment as outlined by the NCCN Practice Guidelines on cancer-related fatigue.[9,10] Several nonpharmacologic and pharmacologic treatment options are available for management of fatigue. Increased physical activity, various types of psychosocial interventions, dietary management, and sleep hygiene are well-supported by research in the treatment of fatigue. Psychostimulants and antidepressants have been studied the most in the treatment of cancer-related fatigue. Psychostimulants are well-tolerated and appear to have a role in the improvement of fatigue despite a large placebo effect. Antidepressants are most effective in patients with underlying depression. Activating antidepressants such as bupropion may be more effective in the treatment of fatigue symptoms. However, it is important to emphasize that more research is needed to evaluate the efficacy of pharmacologic interventions, as current evidence falls short of providing sufficient evidence to recommend medications for treating cancer-related fatigue.

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