

Palliative Management of Fatigue at the Close of Life

"It Feels Like My Body Is Just Worn Out"

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THE PATIENT'S STORY

Mrs D is an 82-year-old retired nurse with a history of interstitial lung disease, hypertension, coronary disease, osteoporosis, gastroesophageal reflux disease, and anemia, with a recent admission for pneumonia. Her surgical history includes a colectomy secondary to a perforated diverticulum and gastrointestinal bleeding.

Mrs D's most pervasive complaint over the past 3 years has been fatigue—often profound, debilitating fatigue that is functionally and cognitively limiting. Mrs D describes her symptom as "fatigue," "exhaustion," and "sleepiness." Mrs D lives alone; she is very close to her daughter, who attends most clinic visits and helps her at home. She has a living will, she has asked to not undergo attempted resuscitation, and her daughter is her durable power of attorney for health care. Mrs D's goals of care generally focus on comfort. She will not pursue diagnostic testing unless it will help to identify therapy that improves her quality of life. Her primary care physician, Dr K, who is also a palliative care specialist, suspects that her fatigue stems from a combination of factors. These include her underlying diseases: interstitial lung disease; anemia resulting from chronic low-grade blood loss, likely at her prior surgical site (vs an undiagnosed gastrointestinal cancer); depression, increasing social isolation, and a growing sense of apathy; medications, including opioids and antihistamines; deconditioning (increasing weakness resulting from decreased daily activity); and other symptoms, including intermittent pain (related to vertebral and rib fractures due to osteoporosis and intermittent angina), progressive dyspnea, chronic diarrhea, and dizziness. When symptoms worsen, her fatigue seems to worsen. She also has anorexia and weight loss (from 101 to 84 lb in 2 years), which distresses her greatly. Dr K thinks the weight loss might be related to the short bowel syndrome but

Fatigue is the most common chronic symptom associated with cancer and other chronic progressive diseases. The assessment and treatment of fatigue at or near the end of life can be complex. Some of the challenges include its subjective nature, with great variability in its source, how it is expressed, and how it is perceived, requiring treatment to be based on patient report of frequency and severity; its multidimensional character; and the limited understanding of its pathophysiology. Using the case of an 82-year-old retired nurse with fatigue that could be explained by a number of concurrent conditions, including anemia, weight loss, depression and isolation, dyspnea, deconditioning, and medications, the authors illustrate the clinical approach to assess and treat fatigue at the end of life.

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also harbors some suspicion of an underlying gastrointestinal malignancy.

Pulmonary function tests reveal severe restrictive lung disease, with a forced vital capacity of 34% of predicted. A previous pulmonary evaluation excluded reversible or modifiable causes. Since having a recent episode of pneumonia, Mrs D has been more dependent on oxygen both for dyspnea and for daily activities. Using the oxygen makes her feel anxious and self-conscious. She also has chronic dizziness resistant to vestibular training (prior evaluation suggested Ménière disease) and vitamin B₁₂ deficiency. Her current daily medications are lisinopril, alendronate, isosorbide, omeprazole, and acetylsalicylic

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acid; as needed medications are albuterol inhalations, oxycodone or acetaminophen, diphenoxylate, megestrol acetate, nitroglycerin, and meclizine.

A number of symptomatic interventions have been attempted, including exercise or physical therapy, increased socialization, methylphenidate, megestrol acetate, blood transfusions, vitamin B₁₂ replacement, a course of sertraline (25 mg titrated upward to 100 mg) for 1 year and fluoxetine (10 mg titrated to 40 mg) for 8 months for depression, as well as other therapies to control concurrent symptoms (eg, opioids for pain). Each has yielded only partial and short-lasting relief.

PERSPECTIVES

A Perspectives editor interviewed Mrs D and Dr K in April 2005.

DR K: *Sometimes, she would come in saying she was very, very tired. At other times she would . . . say she was sleepy.*

Sometimes she would say she was weak. . . . [S]he was quite open to the idea of doing blood tests and other tests. . . . She drew the line when we talked about the idea that she might have an underlying cancer. . . . [S]he consistently made the decision to do “easier tests” that would not require hospitalization, including colonoscopy or anything more invasive.

MRS D: *I was in the Army Corps . . . during World War Two. Then I went into the VA . . . most of my patients there were paraplegics. I had to pull them up . . . and turn them over . . . Then I was about 110 pounds, but now 82 is a long way from that. It feels like my body is just worn out.*

The assessment and treatment of fatigue near or at the end of life can be complex. Some of the challenges include its subjective nature, with great variability in its source, how it is expressed, and how it is perceived, requiring that

Table 1. Assessment Tools for Fatigue in Patients With Cancer and Other Conditions

Measure	Reliability, Cronbach Coefficient	Population Base	No. of Items	Comments
Multidimensional Fatigue Inventory ^{24,25}	0.80 Validity (r ≤0.78)	Cancer patients receiving radiotherapy, patients with chronic fatigue syndrome, psychology students, medical students, army recruits, and junior physicians	20-Item self-report instrument	Multidimensional scale including: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity
Multidimensional Assessment of Fatigue ²⁶	0.93	Adults with rheumatoid arthritis, human immunodeficiency virus-positive adults, multiple sclerosis, coronary heart disease, or cancer	16 Items, self-administered, 5 min	Subjective aspects of fatigue including quantity, degree, distress, impact, and timing are assessed
Multidimensional Fatigue Symptom Inventory (short form) ²⁷	0.87-0.96	Patients with different types of cancer	30-Item instrument	Global, somatic, affective, cognitive, and behavioral symptoms of fatigue
Revised Piper Fatigue Scale ²⁸	0.85- 0.97	Patients with cancer-related fatigue; or chronic hepatitis C infections	22-Item measure	Multidimensional, assesses global fatigue severity to evaluate the efficacy of intervention strategies
Revised Schwartz Cancer Fatigue Scale ²⁹	0.82-0.93; Validity, overall α = .96	Patients with cancer and receiving treatment	6 Items	Multidimensional fatigue questionnaire
Brief Fatigue Inventory ³⁰	0.82-0.97	Patients with cancer and receiving treatment	9 Items, self-administered, 5 min	Severity and effect of fatigue on daily functioning in the past 24 h
Fatigue Symptom Inventory ³¹	0.90	Patients with cancer and receiving treatment	13 Items, self-administered	Fatigue intensity and duration and interference in quality of life in the past week
Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) ³²	0.93-0.95, Test-retest reliability r = 0.87 over 3-7 d	Patients with cancer and receiving treatment	41 Items, self-administered or interview, 10 min	Multidimensional fatigue subscales of Functional Assessment of Cancer Therapy, assesses global fatigue severity and quality of life
Edmonton Symptom Assessment Scale ^{33,34}	0.79, Test-retest reliability 0.65	Elderly patients receiving palliative care	Patients rate the severity of 9 symptoms including fatigue on visual analog scales, self-administered or interview, 5 min	Global fatigue severity
Profile of Mood States (vigor and fatigue) ³²	0.89, Test-retest reliability r = 0.65	Patients with cancer and many chronic conditions	8 Items for vigor, 7 Items for fatigue	Global fatigue severity
Short Form-36-Version 1 Vitality (Energy/Fatigue) Subscale ³⁵	0.87	Adults with cancer and other populations	1-2 min for 4-item subscale	Vitality, energy level, and fatigue

treatment be based on the patient's report of its frequency and severity; its multidimensional character; and an incomplete understanding of its pathophysiology. In addition, the evidence base for treatment is limited.

This article aims to provide clinicians with a definition of fatigue and a clinical approach to its evaluation and management at the end of life.

Definition and Prevalence of Fatigue

Physiologically, *fatigue* is defined as a "decrement in performance of either physical or psychological tasks."¹ *Cancer-related fatigue* is defined by the National Comprehensive Cancer Network (NCCN) 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."² In contrast to muscle fatigue, clinical fatigue includes 3 major components: (1) generalized weakness, resulting in inability to initiate certain activities; (2) easy fatigability and reduced capacity to maintain performance; and (3) mental fatigue resulting in impaired concentration, loss of memory, and emotional lability.^{3,4}

Chronic fatigue is defined as persistent fatigue present at least 50% of the time over a period of at least 6 months. Chronic fatigue syndrome is an illness predominantly affecting young adults. It is characterized by disabling fatigue of at least 6 months' duration, accompanied by several other symptoms (such as sore throat, adenopathy, muscle pain, multijoint pain, and headache) that cannot be attributed to any alternative condition. Its prevalence in the general population varies from 0.2% to 0.7%.^{5,6}

Fatigue is the most common chronic symptom associated with cancer and other chronic diseases, such as multiple sclerosis, systemic lupus erythematosus, heart failure, rheumatoid arthritis, and renal disease.⁷⁻¹¹ It is the one symptom most likely to interfere with physical and social activities.¹² In patients with cancer or those undergoing cancer-related treatment, its frequency exceeds 75%.^{2-4,13} In elderly patients with chronic disease states, its frequency ranges from 47% to 99%.¹⁴ In the palliative-care setting, the prevalence ranges from 48% to 78%.¹⁵

Causes of Fatigue

Fatigue is a multidimensional syndrome, often with multiple contributing causes.^{16,17} Physiological, psychological, and situational factors can contribute to fatigue, as exemplified by Mrs D's anemia, weight loss, depression, dyspnea, deconditioning, isolation, and polypharmacy. Chronic diseases can produce factors such as circulating cytokines, inflammation, and autonomic failure that may mediate fatigue.¹⁸⁻²⁰

Although few published studies have correlated fatigue and cytokines near or at the end of life, several lines of evidence implicate cytokines in the pathophysiology of fatigue.²¹ First, cytokine levels are increased in nononcologic conditions characterized by fatigue, such as chronic fatigue syndrome.²² Second, fatigue is a major adverse effect of cytokines adminis-

tered for therapeutic purposes including interleukins, tumor necrosis factor α , and interferon.¹⁸ Finally, up-regulation of proinflammatory cytokines is correlated with fatigue in several malignancies.²³

Evaluation of Fatigue

DR K: *[A] combination of her depression, her anorexia, and some of her other symptoms, her interstitial lung disease, and probably her growing isolation, were all contributing factors . . . and the possibility of anemia or B₁₂ deficiency . . . as well as some of the medications and opioids. If I could identify some of those top sources, I might be able to do something to reverse those. [H]er goals centered around using interventions that would allow her fatigue to be decreased.*

Fatigue's multidimensional character makes systematic evaluation essential.³ Fatigue assessment involves characterizing its severity, temporal features (onset, course, duration, and daily pattern), exacerbating and relieving factors, associated distress, and impact on daily life⁴; and identifying treatable causes. Several scales have been developed to quantify fatigue in initial assessment as well as to monitor symptoms over time (TABLE 1). Although most scales were developed for patients with cancer, the Edmonton Symptom Assessment Scale has been validated in elderly palliative care patients and has reliability similar to the other tools.²⁴⁻³⁵

Unfortunately there are few studies to inform the evaluation of fatigue. However, evaluation should include a detailed history and focused physical examination and laboratory investigations based on clinical suspicion (BOX).

Patients who present with obvious findings of hepatic, cardiac, or respiratory disease may simply have fatigue as a disease manifestation, with treatment focused on the underlying disease. As with Mrs D, in cases in which there are no obvious findings, clinicians may evaluate patients for the presence of medication adverse effects, cognitive impairment, anemia, metabolic abnormalities, disease treatments, malnutrition, and infections, all of which are associated with fatigue.^{36,37} TABLE 2 presents components of such an evaluation. Unfortunately, no controlled trials have been conducted to definitively support the use of these tests to improve fatigue at the end of life.

For patients, such as Mrs D, who at the end of life wish to focus solely on interventions that may improve her symptoms rather than underlying conditions, evaluation of common, potentially treatable causes of fatigue is appropriate. Such evaluation is described below.

Pain and Opioid-Induced Neurotoxicity Contributing to Fatigue

DR K: *[S]he struggles with chronic pain from vertebral fracture and osteoporosis. [A]fter increasing the dosage of low-dose acetaminophen and oxycodone to improve pain control, she was describing additional somnolence . . . over a course of days to weeks, that complaint continued. So, we talked about trying something to combat the somnolence.*

Box. Evaluation of Fatigue in Elderly Patients**History****Assess Symptoms**

Self-report: Intensity of fatigue, its onset and duration, and its effect on patient function and overall quality of life using bedside tools, including 0-to-10 visual analog scales.

Identify Causes

Major reversible contributing factors: mood disorder (specifically depression and anxiety), cognitive disorder (dementia and delirium), pain, anemia, malnutrition, and deconditioning.

Other Important Factors

Sleep pattern, weight change, prescribed medications, self-medication (over-the-counter preparations, tobacco and alcohol use, other drug use), precipitating factors, chronic pain conditions, bereavement, recent viral infections, recent trauma, dietary history, social changes, such as retirement. Environmental assessment should be considered if necessary.

Physical Examination

Individualized, including orthostatic changes, mucous membranes for pallor or icterus, lymphadenopathy, hepatosplenomegaly, murmurs, bruits. Perform detailed neurological examination, including cognition.

Laboratory Investigations

The prudent use of laboratory investigations may include both blood tests and diagnostic imaging tests as suggested by clinical suspicion.

Fatigue is frequently noted in studies of chronic low back pain and neck pain.³⁹ In a structured, evidence-based study of the pain-fatigue literature, Fishbain et al³⁹ reviewed high-quality studies enrolling patients with many kinds of chronic pain, including pain due to osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, fibromyalgia, cancer, chronic headache, and chronic low back pain. In these studies, “grade A” evidence (highly consistent findings from multiple studies) indicated an association between pain and fatigue and suggested that at least in some patient populations, persistent pain can be considered a causative factor.

In elderly patients, pain is common in the period before death and is frequently managed with opioids.^{40,41} Prospective studies of patients with advanced cancer who are taking opioids often reveal evidence of neurotoxicity.⁴¹ Because symptom assessment is based on self-report, it is difficult if not impossible to distinguish between opioid-induced somnolence, delirium, and neurotoxicity from the subjective symptom of fatigue. Opioid-induced neurotoxicity may manifest in drowsiness, myoclonus, and cognitive dysfunction, such as delirium.⁴¹ Potential risk factors

include dose escalation for neuropathic pain and incidental pain (pain that occurs only with a certain activity or event) or for opioid tolerance, somatization of psychologic distress, and prior drug or alcohol abuse, as well as renal insufficiency or dehydration causing elevation of opioid metabolites. Mrs D’s somnolence following a dose increase of oxycodone and acetaminophen may be a manifestation of such opioid-induced neurotoxicity. Recognition of opioid-related cognitive dysfunction is improved by objective screening using tools such as the Mini-Mental State Examination and delirium screening tools.^{42,43} In suggesting treatment, it is important for physicians to set specific goals regarding comfort, function, and cognition with the patient and family.

Undertreated or overtreated pain may contribute to fatigue. In some older patients with preexisting cognitive dysfunction, such as dementia, the development of an acute or chronic pain syndrome may result in the development of delirium and consequent fatigue. Untreated pain must be in the differential diagnosis of recent onset of delirium and fatigue among nursing home patients and elderly patients in general.⁴⁴

Psychological Disorders Contributing to Fatigue. MRS D: *[It makes me feel] very sad. I want to do things that I know that I can’t do any more.*

DR K: *The more I learned about her fatigue, the more she related it to her sense of depression and isolation.*

One prospective cohort study of elderly patients with cancer found a significant association between intensity of fatigue and psychological symptoms, such as anxiety and depression.³⁶ However, few studies have described the prevalence of depression among patients complaining of fatigue at the end of life.

For patients with advanced cancer, the classic somatic symptoms of depression, such as anorexia and weight loss, are often a function of the disease or its treatment and therefore are less useful in diagnosis of depression.⁴⁵ Frequently, a simple screening question, such as “Are you depressed?” or rating depression on a 0-to-10 scale may provide clinicians with useful information.⁴⁶ For Mrs D, as for all patients who complain of chronic fatigue, a thorough assessment of mood is extremely important. In addition to her own report of depression, she has a past history of treatment trial with selective serotonin reuptake inhibitors (SSRIs) with some improvement (as well as adverse effects), and likely she is depressed.

Delirium, Cognitive Dysfunction, and Fatigue. MRS D: *My thinking is very fuzzy. I’ll go from one room to another room for something, and by the time I’ve gotten there, I’ve forgotten. I credit that to age.*

Although Mrs D has no defined features of cognitive dysfunction or delirium, patients at the end of life have a high prevalence of both conditions and both may be associated with fatigue.⁴⁷ Delirium is frequently underrecognized, misdiagnosed (as either depression or dementia),⁴⁸ and undertreated. Delirium may arise from such diverse factors as dehydration, medications, infections, hypoxia, renal and hepatic failure, advanced age, illness severity, and comorbidities.⁴⁷

A prospective study of palliative care patients revealed a high occurrence of delirium in patients with advanced cancer: 42% of patients on admission, 45% of patients after admission, and 88% of patients dying of advanced cancer.⁴⁷ Despite its prevalence, few studies have evaluated the relationship between delirium and fatigue at the end of life. A prospective cohort study of 54 patients with acute myelogenous leukemia found that cognitive dysfunction and fatigue were correlated.⁴⁸ Cognitive dysfunction is also associated with fatigue in noncancer conditions, such as anemia⁴⁸ and chronic fatigue syndrome.⁴⁹ Common mediators of both cognitive dysfunction and fatigue include inflammatory cytokines, such as interleukin 6, interleukin 1, and tumor necrosis factor α .⁵⁰

Screening tools for delirium include the Confusional Assessment Method⁴² and the Memorial Delirium Assessment Scale and, for cognitive impairment, the Mini-Mental State Examination.^{43,51} However, assessment of cognitive dysfunction may require more formal neuropsychological testing.

Weight Loss Contributing to Fatigue. DR K: *[S]he came in and complained of generalized weakness and noted that she was not eating much at all. She said that she wasn't having difficulty swallowing. . . . She just didn't have much of an appetite.*

MRS D: *He put me on a medicine, Megace [megestrol acetate], to give me more strength. I thought I was doing pretty well, but I was still losing weight.*

Weight loss at the end of life is often multifactorial. It may be due to anorexia-cachexia (with cancer and other illnesses), impaired food intake (nausea, dysphagia, or dental problems), decreased nutrient absorption (malabsorption), associated comorbidities (chronic heart failure, chronic lung disease), psychiatric disorders (depression), metabolic disorders (hyperthyroidism or diabetes mellitus), socioeconomic problems (lack of food), and lack of motor and cognitive skills for food preparation.⁵² Fatigue is a common component of cachexia.⁵³

Factors that have been identified as having an etiologic role in cachexia and fatigue in cancer and other nonmalignant conditions include elevated inflammatory cytokines, tumor byproducts, autonomic dysfunction, neuroendocrine dysfunction, and decreased energy intake.^{18,54}

In most cases, the cause of weight loss is identified by a thorough history, targeted physical examination, and simple laboratory evaluation.^{55,56} The Edmonton Symptom Assessment Scale includes measures of both appetite (anorexia) and fatigue.³³ Additional assessment should include evaluation of functional and nutritional status.

Anemia Contributing to Fatigue. Anemia is a major cause of fatigue in elderly patients, occurring in 11% of community-dwelling men and 10.2% of women older than 65 years.⁵⁷ Anemia is associated with increased mortality.⁵⁸ In elderly patients, anemia causes mobility problems and decline in other objective measures of physical performance.⁵⁹ However, studies of this population at the end of life using validated tools are limited. For patients with cancer and cancer treatment, ane-

Table 2. Assessment Modalities for the Causes of Unexplained Fatigue at the End of Life*

Medical Condition	Assessment Modality
Anemia	Complete blood cell count, serum vitamin B ₁₂ , folate, iron, transferrin saturation, ferritin levels, fecal occult blood tests, and, if abnormal test result, further evaluation for blood loss
Medication adverse effects and polypharmacy	Anticholinergics, antihistamines, anticonvulsants, neuroleptics, opioids, central α -antagonists, β -blockers, diuretics, selective serotonin reuptake inhibitors and tricyclic antidepressants, muscle relaxants, and benzodiazepines
Cognitive or functional impairment	Assessments such as ADL, IADL, MMSE, and "get up and go" test
Mood disorders	Assessment of depression and anxiety following the DSM-IV criteria
Adverse effects of primary disease treatment	Recent radiation therapy, chemotherapy, surgery
Malnutrition	Serum albumin, prealbumin, cholesterol
Infections	Blood cultures, urine culture, chest radiography, HIV antibody, RPR, PPD skin test
Other contributing medical conditions	Directed based on clinical finding

Abbreviations: ADL, activities of daily living; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; HIV, human immunodeficiency virus; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; PPD, purified protein derivative; RPR, rapid plasma reagin.

*Evaluations of fatigue is based on Murtagh.³⁸

mia is a predictor of poor quality of life and decreased survival.⁶⁰ Anemia of chronic disease may be a result of elevated inflammatory cytokines.⁶¹ In patients such as Mrs D who have a history of chronic anemia requiring blood transfusion, gastrointestinal malignancy may be a cause.⁶²

Management of Fatigue

Treatment of Specific Sources of Fatigue. DR K: *I try to work with my patients early on so that they understand that "treating fatigue" is better termed as "managing fatigue."*

Treatment strategies for fatigue must be multidimensional and often require interdisciplinary team. When discovery of the specific sources for the cause is not possible, treating the symptoms should be the focus of care (TABLE 3). Dr K identified potential causes and devised treatments for pain, opioid adverse effects, depression, cachexia, dyspnea, and anemia.

Treatment of Pain and Opioid-induced Neurotoxicity. Treatment of pain and of opioid-induced neurotoxicity may be helpful for both patients with chronic disorders and for patients at the end of life. In a prospective cohort study of 208 patients with chronic pain (175 patients with low back pain and 33 patients with chronic neck pain), fatigue improved significantly with multimodal, multidisciplinary treatment of pain.⁷⁵ Successful management requires either dose reduction or change of opioid, in addition to addressing other reversible precipitants, such as dehydration. If opioid-induced sedation is persistent, as with Mrs D, a trial of methylphenidate may be helpful.⁷⁶

As with Mrs D, the combination of opioids with other medications from different classes or interaction between these various classes of medications, such as antihistamines, may contribute to drowsiness and fatigue² (Table 2). It is appropriate to cease or adjust the dose of these medications to improve fatigue.

Treatment of Depression. DR K: *Mrs D had been on antidepressants periodically throughout her life. While her mood (variably) was improved on the SSRIs, she struggled with side effects that included fatigue, "stomach pains," anxiety, and both insomnia and somnolence. She said she generally preferred to be off antidepressants, although when pressed by her daughter, admitted they helped. She continued to describe fatigue while on the SSRIs. [H]er decreasing social interaction was also creating a sense of isolation and depression. . . . [W]e tried her on some low-dose methylphenidate. . . . [H]er daughter noted that she was much more interactive and started to gain some of her prior social interaction. She did not stay on the SSRI when the trial of methylphenidate was undertaken.*

Treatment with antidepressants, counseling, and physical exercise can reduce depression's vegetative symptoms.⁴⁶ Selective serotonin reuptake inhibitors and atypical antidepressants produce fewer adverse effects than do tricyclic antidepressants in frail elderly patients.^{77,78} In addition, clinical observations reveal that antidepressant therapy can produce increases in energy disproportionate to changes in mood.⁴ Methylphenidate has been shown to have benefit in patients with cancer and depression.⁷⁸ In our practice, we consider a brief course of SSRIs or atypical antidepressants and/or methylphenidate for patients who have persistent symptoms of sadness, even if they do not meet full criteria for a major depressive disorder or severe adjustment disorder. Unfortunately, randomized controlled trials have not been conducted to prove

efficacy. Mrs D's depressive symptoms and social isolation abated for several months during the trial of methylphenidate, which also improved her fatigue. Patients with coronary disease, like Mrs D, should be monitored for worsening coronary symptoms and elevated blood pressure.

Treatment of Delirium and Cognitive Dysfunction. Management of delirium and cognitive dysfunction involves identifying and correcting reversible risk factors and treating the symptoms.^{40,41} This approach includes treatment of possible opioid toxicity, dehydration, infection, medication interactions or adverse effects, metabolic disturbances, thyroid dysfunction, and anemia. In the end-of-life setting, both the intensity of diagnostic work up and treatment strategies for cognitive impairment and delirium must be individualized.

Treatment of Weight Loss. Management of weight loss should include both correction of potential causes and nutritional supplementation.⁷⁹ In a double-blind randomized controlled trial in 84 patients with advanced cancer, those receiving 160 mg of megestrol acetate 3 times a day had significantly improved appetite, increased activity ($r=0.24$), and improved overall well-being.⁷¹ The mechanism of megestrol's effects is not known, but the effects are not due to nutritional parameter changes. Megestrol apparently helped Mrs D's appetite and quality of life for more than a year, in turn decreasing her fatigue. In a prospective, randomized, double-blind trial of 31 patients with terminal cancer, methylprednisolone significantly improved appetite and fatigue ($r=0.60$) after 14 days.⁸⁰ Metoclopramide can be useful for chronic nausea and dyspepsia associated with cancer cachexia.⁸¹ Investigational agents for cachexia include thalidomide, omega-3 fatty acids, growth hormone or insulinlike growth factors, androgenic anabolic steroids, cannabinoids, melatonin, β_2 -adrenergic blockers, nonsteroidal

Table 3. Medications With Some Evidence for Symptomatic Treatment of Fatigue at the End of Life

Drug	Use*	Initial Dose	Adverse Effects
Corticosteroids ⁶³⁻⁶⁸	For disease-related fatigue	Dexamethasone, 8 mg/d for 2 wk	Adverse effects include infection, oral thrush, insomnia, mood swings, myalgia, and elevation of blood glucose Prolonged use (more than 1 mo): gastritis (especially with concurrent use of NSAIDs), hiccups, edema, muscle weakness, easy bruising, dizziness, hirsutism, and decreased wound healing
Methylphenidate ^{69,70}	For cancer-related fatigue	5 mg/d	Common adverse effects include loss of appetite, slurred speech, abnormal behavior, and restlessness Serious adverse effects include hypertension, tachyarrhythmias, thrombocytopenia, and hallucinations
Megestrol acetate ⁷¹	FDA labeled for AIDS patients with cachexia, treatment of cancer (breast and endometrial); also used for treatment of cancer cachexia	480-800 mg/d	Common adverse effects include hypertension, sweating, hot flashes, weight gain, dyspepsia, nausea, vomiting, insomnia, mood swings, and impotence Serious adverse effects include thrombophlebitis, adrenal insufficiency, and pulmonary embolism
Modafinil ⁷²	For fatigue related to cancer and multiple sclerosis	200 mg/d	Common adverse effects include diarrhea, nausea, dizziness, headache, insomnia, agitation, anxiety, nervousness, and rhinitis Serious adverse effects include cardiac dysrhythmia, hypertension, and infectious disease
L-Carnitine ^{73,74}	Investigated for the treatment of disease-related fatigue in multiple sclerosis; under study for AIDS and cancer	1 g/d in divided doses	Adverse effects reported include nausea, diarrhea, body odor, hypertension, arrhythmias, headaches, seizure Interactions with acenocoumarol may increase risk of bleeding

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

*None are US Food and Drug Administration-labeled indications unless otherwise indicated.

anti-inflammatory drugs, and adenosine triphosphate.^{52,82-88} Evidence of their effectiveness at the end of life is even more limited. Nutritional supplementation alone is often not able to reverse metabolic cachexia,⁷⁹ although nutritional support can be helpful in the treatment of cachexia when starvation is a major contributor (eg, in patients with severe dysphagia or bowel obstruction).⁵²

Weight loss and concerns about malnutrition often cause severe psychological and social distress to patients and families. Most patients and families believe that cachexia related to cancer, AIDS, and other progressive incurable illness is due to poor caloric intake.⁸⁹ Therefore, in addition to trying pharmacological interventions, clinicians should educate patients and families about the futility of forced feeding and ways to maintain the social value of mealtimes.

Treatment of Anemia. Anemia in elderly patients is best managed by treatment of the underlying cause, such as replacement of iron, folate, or vitamin B₁₂ (as with Mrs D's vitamin B₁₂ replacement). When the cause is obscure or there is no specific remedy, or when patients refuse work up (as did Mrs D), then treatment is supportive. Transfusion of packed red blood cells is the most widely used and rapid way to alleviate symptomatic anemia in cancer patients. However, for those with repeated transfusions, there are risks of blood-borne infection, acute transfusion reaction, transfusion-associated graft vs host disease, subtle immune modulation that occurs with transfusion, and iron overload.⁹⁰ In elderly patients with anemia of chronic disease or chronic kidney disease, erythropoietin therapy improves anemia⁹¹ but does not reduce risk of cardiovascular events and clear guidelines regarding its use are lacking.^{57,92}

For anemia in patients undergoing cancer chemotherapy, treatment with erythropoietin has been found to be effective in improving functional status and quality of life, independent of tumor response.⁹³⁻⁹⁵ Although treatment of anemia has been shown to decrease fatigue of patients receiving chemotherapy,^{92,93} correction of anemia in advanced cancer patients at the end of life was found to have limited impact on the intensity of fatigue,^{14,96,97} likely due to the multifactorial contributors to their fatigue.

Nonspecific Treatments for Fatigue

Exercise. DR K: *She . . . feels somewhat empowered by the use of exercise and physical therapy, though she hasn't sustained that. After she did it, however, she noticed that her ability to get around the house was improved.*

MRS D: *He's just been stringing along with me, he hasn't really helped me in any way, except he sent me to physical therapy and managed to get more use of my arms and legs. . . .*

Until recently, energy conservation was the most frequently recommended treatment for fatigue in palliative care.⁹⁸ However, prospective cohort and randomized controlled trials have shown that the risk of energy conservation is deconditioning, creating the potential for a vicious cycle of fatigue and further deconditioning, subsequently leading to disability.⁹⁹

During the year that Mrs D could maintain her physical therapy and exercise regimen, it helped to improve her mobility at home and restored a sense of independence.

TABLE 4 summarizes various clinical trials and prospective cohort studies on the symptomatic treatment of cancer-related fatigue. In patients with arthritis, cancer, and chronic heart disease, randomized trials have demonstrated that resistance training or aerobic exercise lessens fatigue and improves physical performance.¹⁰⁰⁻¹⁰⁷ In a phase 2 study of elderly terminally ill cancer patients, a 50-minute group exercise program twice a week for 6 weeks showed significant reduction of fatigue and improvement in emotional function (Table 4).¹⁰⁶ Resistance exercise 3 times per week has been shown to reduce interference from fatigue on activities of daily living and lead to higher quality of life.^{103,104}

Pharmacologic Treatments. Palliative care physicians occasionally face a dilemma of having to treat patients with no specific diagnosis, and in those instances, treatment is based on clinical suspicion.^{108,109} Such treatment is not evidence-based because most trials for symptoms of fatigue have been conducted with patients who had a specific diagnosis, such as cancer, AIDS, or multiple sclerosis (Table 3). Mrs D's profound fatigue in the context of chronic progressive illness with accompanying weight loss, anemia, and deteriorating physical function and her reluctance to undergo further investigations prompted Dr K to choose a number of interventions for the symptomatic management of cancer-related fatigue.

Randomized controlled trials have been conducted to evaluate corticosteroids to reduce fatigue of terminally ill cancer patients,⁶³⁻⁶⁸ but the most appropriate type and dose of corticosteroid have not been defined.

As noted with Mrs D, megestrol acetate to treat symptoms of decreased appetite and weight loss may improve fatigue and sense of well-being.⁷¹ As happened with Mrs D, a trial of methylphenidate may improve symptoms of fatigue,⁶⁹ but a recent randomized controlled trial involving patients with cancer found that methylphenidate was not superior to placebo.⁷⁰ More research is required to better define the role of psychostimulants in the management of fatigue associated with chronic illnesses.

Finally, in an open-label pilot study of 27 patients with advanced cancer and cancer pain, administration of donepezil for 7 days significantly improved fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue, $P = .004$).^{110,111} Randomized controlled trials of the effect of donepezil on fatigue are needed. L-Carnitine was found to reduce fatigue in 2 randomized crossover studies: the first involving patients with multiple sclerosis and the second involving patients with chronic fatigue syndrome. Randomized controlled studies are now underway for patients with cancer and AIDS.^{73,74}

Managing Expectations

DR K: *I have a number of patients who suffer from fatigue who I think mostly just want . . . someone to listen to them tell their story. . . . In the case of Mrs D, she was willing to try almost*

Table 4. Studies of Symptomatic Treatment of Fatigue in Patients With Advanced Cancer

Source	Intervention	Total No. of Patients	Diagnosis	Duration	Results	
					Fatigue Change in Study Group	Fatigue-Related Change in Study Group
Crossover Design						
Bruera et al, ⁶³ 1985	32 mg Methylprednisolone vs placebo	31 Methylprednisolone 31 Placebo	Advanced cancer	14 d Crossover 20 d Open label	Change in study group activity score, $r = 0.60$	Mean pain, $r = -0.42$ Depression, $r = -0.37$ Appetite, $r = 0.33$
Bruera et al, ⁷¹ 1998	480 mg Megestrol	84 (53 completed scale)	Advanced cancer	10 d	Overall Piper Fatigue scale, $r = -0.19$ Fatigue (activity), $r = -0.24$	VAS: Nausea, $r = -0.17$ Appetite, $r = -0.23$ Well-being, $r = -0.22$
Randomized Controlled Trials						
Della Cuna et al, ⁶⁴ 1989	125 mg Methylprednisolone vs placebo	207, Methylprednisolone 403 Placebo	Advanced cancer	8 wk	LASA score, $P < .05$	NOSIE for depression, $P < .05$ QOL, $P < .001$
Popiela et al, 1989 ⁶⁵	125 mg Methylprednisolone vs placebo	85, Methylprednisolone 88, Placebo	Advanced cancer	9 wk	LASA weakness score, $P < .10$	Appetite, $P < .05$
Moertel et al, ⁶⁶ 1974	1.5 mg Dexamethasone vs placebo	116	Terminal gastrointestinal cancer	Until death or unable to take oral medication	Strength improved in 2 wks, $P < .05$	Appetite, $P < .05$
Dimeo et al, ¹⁰⁰ 1999	Bed-cycle ergometer to 50% maximum heart rate	59	Cancer	Throughout hospitalization	Decreased increment in fatigue in the treatment group, $r = 0.011$	Decreased psychological distress Increased fatigue and somatic symptoms in control group, $P = .03$
Mock et al, ¹⁰¹ 2001	Home-based walking program	52	Breast cancer, in treatment	For the duration of treatment*	Piper Fatigue Scale, decreased fatigue in high-walk exercise group, $r = 0.52$	Decreased decline in QOL in high-walk exercise group, $P = .02$
Inoue et al, ⁶⁷ 2003	8 mg Dexamethasone vs placebo	68	Advanced gastric or colorectal cancer	4 d	NRS for fatigue, $P = .06$	Anorexia, delayed emesis, $P < .0058$
Courneya et al, ¹⁰² 2003	Laboratory-based cycle ergometer, 3/wk for 15-35 min	53	Early stage breast cancer	15 wk	FACIT-F Fatigue Improvement, $r = 0.315$	Improvement in QOL, $r = 0.12$
Segal et al, ¹⁰³ 2003	Laboratory-based resistance exercise, 3/wk	155	Prostate cancer, in treatment	12 wk	FACIT-F Fatigue Improvement, $r = 0.065$	Improvement in QOL, $r = 0.08$
Mock et al, ¹⁰⁴ 2005	Home-based moderate-intensity walking program	119	Breast cancer, in treatment	For duration of cancer treatment	Piper Fatigue Scale- Significant effect of exercise on pretest to posttest change in fatigue levels	$P = .03$
Bruera et al, ⁷⁰ 2006	5-20 mg Methylphenidate	112	Advanced cancer	7 d	Fatigue 0-10 scale, $r = 0.146$ FACIT-F, $r = 0.098$	The correlation between fatigue as measured by Piper Fatigue Scale and physical function of the Medical Outcomes Study short form (MOS SF-36) was -0.40 $P \leq .01$.
Prospective Survey						
Hardy et al, ⁶⁸ 2001	8-12 mg Dexamethasone	106	Advanced cancer receiving palliative care	Median 40.5 d	NRS, 0-4 scale, weakness 50% improvement	Anorexia, 73% Pain, 86% Mood, 59%
Open Label						
Bruera et al, ⁶⁹ 2003	5-20 mg Methylphenidate	30	Advanced	7 d	Fatigue 0-10 scale, $P < .001$ FACIT-F, $P < .001$	Appetite, $P = .02$; Anxiety, $P < .05$; Appetite, $P < .05$; Nausea, $P < .05$; Depression, $P < .05$; Drowsiness, $P < .05$
Cohort						
MacVicar and Winningham, ¹⁰⁷ 1986	Laboratory-based cycle ergometer, 3 times a wk to 60%-80% maximum heart rate	10	Cancer	10 wk	Decreased fatigue and mood disturbance	Increased functional capacity
Pilot With Comparison						
Schwartz et al, ¹⁰⁵ 2002	20 mg Methylphenidate	12	Cancer	4 mo	Schwartz Cancer Fatigue scale-exercise and fatigue group had decreased fatigue levels vs exercise alone	% change in the 12-min walk from baseline to posttest was not correlated with fatigue scores, $P = .56$

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LASA, linear analog self-assessment scale; NOSIE, nurses' observational scale for inpatient evaluation; NRS, numerical rating scale; QOL, quality of life; VAS, visual analog scale.

*Patients received cytotoxic therapy or radiation therapy.

any pharmacologic or nonpharmacologic intervention . . . to help bring some quality of life. That involves always going to back to see if the things that are being tried are making any difference . . . from the patient's perspective.

MRS D: I'm walking with a cane now, and I can walk up steps. . . . I just started driving last week, I haven't driven all year.

To lessen the burden of fatigue that patients experience at the end of life, it is important to understand the gap between the patient's hopes and expectations and what they are actually experiencing. This gap (termed the *Calman gap*) influences the patient's quality of life.¹¹² Measures that may help adjust patients' expectations include changing the focus from physical functioning to other enjoyable nonphysical activities. Patients may benefit from physical therapy evaluation and orthotics, wheelchairs, walkers, and physical therapy to improve function, which can enhance quality of life.^{106,113} Finally, continued access to the physician on short notice, continued assessment of symptoms, and emphasis on comfort and maximizing function are essential. Excellent patient-physician communication, including expressive supportive therapy and empathic listening, is critical particularly at the end of life. This is particularly so when changes to care setting are necessary so that the patient and family have a sense of stability and continuity. Finally, simply being present can provide patients and families great comfort, even with progressive illness and severe symptoms.

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Resources for End-of-Life Care

Centers for Disease Control and Prevention: Chronic Fatigue Syndrome

<http://www.cdc.gov/ncidod/diseases/cfs>

Online site with information about chronic fatigue syndrome and its diagnoses and treatment.

Edmonton Palliative Care Program

<http://www.palliative.org>

Online resource to assist clinicians in applying the best available research

evidence in clinical decisions and promote common practice of palliative care.

The Center to Advance Palliative Care, Palliative Care Leadership Centers (PCLC)

<http://www.capc.org/pclc>

The Center has funded 6 Palliative Care Leadership Centers throughout the nation to provide health care institutions intensive palliative care service training and assistance tailored to that individual institution's needs.

End of Life/Palliative Education Resource Center (EPEC)

<http://www.eperc.mcw.edu>

Online site with peer-reviewed educational resources, including materials on communication and end-of-life decision-making.

National Cancer Institute: Fatigue

<http://www.cancer.gov/cancertopics/pdq/supportivecare/fatigue/HealthProfessional>

Expert-reviewed information that provides a summary about fatigue as a complication of cancer or its treatment.