Management of Common Symptoms in Terminally Ill Patients: Part I.
Fatigue, Anorexia, Cachexia, Nausea and Vomiting

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Physical symptoms other than pain often contribute to suffering near the end of life. In addition to pain, the most common symptoms in the terminal stages of an illness such as cancer or acquired immunodeficiency syndrome are fatigue, anorexia, cachexia, nausea, vomiting, constipation, delirium and dyspnea. Management involves a diagnostic evaluation for the cause of each symptom when possible, treatment of the identified cause when reasonable, and concomitant treatment of the symptom using nonpharmacologic and adjunctive pharmacologic measures. Part I of this two-part article discusses fatigue, anorexia, cachexia, nausea and vomiting. Fatigue is the most common symptom at the end of life, but little is known about its pathophysiology and specific treatment. Education of the patient and family is the foundation of treatment, with the possible use of adjunctive psychostimulants. Anorexia and cachexia caused by wasting syndromes are best managed with patient and family education, as well as a possible trial of appetite stimulants such as megestrol or dexamethasone. For appropriate pharmacologic treatment, it is helpful to identify the pathophysiologic origin of nausea in each patient. (Am Fam Physician 2001;64:807-14.)

This is part of a series of articles and features on issues in end-of-life care. Coordinator of this series is Caroline Wellbery, M.D., assistant deputy editor of AFP.

This is part I of a two-part article on the management of common symptoms in terminally ill patients. Part II, "Constipation, Delirium and Dyspnea," will appear in the next issue.

Although pain is commonly associated with end-of-life distress, other physical symptoms often contribute to the suffering of terminally ill patients.[1-5] In patients who have cancer, fatigue and anorexia rank as the top two reasons for emotional and physical distress, with pain ranked third. Nausea, constipation, altered mental state (e.g., delirium) and dyspnea are the next most common symptoms.[3,4] This two-part article focuses on the more prevalent nonpain physical symptoms found in patients who have cancer, acquired immunodeficiency syndrome (AIDS) or other terminal illnesses.

In managing a nonpain symptom at the end of life, the physician should search for the cause of the symptom by obtaining the proper historical, physical and laboratory data (to the extent that is appropriate in terminally ill or hospice patients). Efforts are directed at alleviating the symptom, as well as preventing or treating the underlying cause when possible or reasonable. Effective management requires that the physician be thoroughly familiar with the drugs and treatments prescribed. Frequent re-evaluation of the patient is also important.

Treatments often change as the patient approaches the end of life. The continued presence of physicians and a steadfast commitment to ameliorating symptoms are particularly important when it is impossible to cure or even slow the progression of an underlying disease process.

Fatigue

The terms "asthenia" and "fatigue" are often used interchangeably. Used in relation to a terminal illness, however, the word "fatigue" has multiple components, including the symptoms of tiredness, a general lack of energy not relieved by rest, diminished mental capacity and the subjective weakness associated with difficulty in performing activities of daily living.[6] When conducting a review of systems, the physician is advised to use terms that are more familiar to patients than "asthenia." In addition to "fatigue," appropriate terms include "tiredness" and "lack of energy."

Dexamethasone, 2 to 20 mg taken orally once daily in the morning, can bring about feelings of well-being and increased energy, although these effects may diminish after the drug has been used for four to six weeks.

Fatigue can be extremely debilitating and may have a severe negative impact on quality of life. This symptom is a problem in 75 to 90 percent of patients with cancer or other chronic illnesses.[4-7] Even survivors of cancer and other life-threatening illnesses report chronic fatigue lasting months to years after the completion of treatment. Despite the high prevalence of fatigue, little is known about its pathogenesis. Consequently, treatment for fatigue may be less successful than treatment for other symptoms at the end of life.

In medical practice, fatigue is frequently undiagnosed or ignored. Recent reports indicate that patients with cancer seldom discuss this symptom with their oncologist.[6,8,9] A number of multidimensional fatigue assessment tools have been validated,[10-13] but family physicians may be most interested in recently proposed practical criteria for the bedside diagnosis of cancer-related fatigue.[6,8] The Brief Fatigue Inventory is a straightforward diagnostic tool *(Figure 1)*.[13] (This inventory can also be obtained from the Internet at http://prg.mdanderson.org/bfi.pdf.)

Pathologic fatigue can arise from both physical and psychologic stresses.[6] Physical causes include the direct consequences of a disease process, such as diminished oxygen-carrying capacity as a result of anemia or heart failure. Cancer, hepatic or renal failure, and many chronic illnesses (including chronic pain) can cause fatigue. In addition, treatments such as cancer therapy or antihypertensive and cardiac therapy can cause this symptom. Psychologic causes of fatigue include anxiety and depression.

Determining the severity of a patient's fatigue is important. The physician should note the factors that worsen or relieve fatigue, the presence of potentially treatable causes (i.e., anxiety or depression, concurrent medications, anemia, pain, infection, cancer, sleep disorder) and the impact of fatigue on the patient's daily activities and quality of life.[6]

The management of fatigue with an unidentified underlying treatable cause is summarized in *Table 1*.[6,14] Patient and family education can be of great value. For example, family members may interpret fatigue to mean that the patient is "giving up," when the symptom is actually beyond the patient's control. To decrease pressure on the patient to be more energetic, the physician may need to give the patient "permission" to rest.[14]

Medications, notably corticosteroids and psychostimulants, are sometimes beneficial adjuncts to nonpharmacologic interventions directed at relieving fatigue in patients nearing the end of life. Dexamethasone (Decadron), 2 to 20 mg taken orally once daily in the morning, can bring about feelings of well-being and increased energy, although these effects may diminish after the drug has been used for four to six weeks.[14] In the end-of-life setting, the long-term side effects of morning doses of corticosteroids are usually not an issue. Of the psychostimulants, methylphenidate (Ritalin) is most commonly prescribed, although dex-

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Brief Fatigue Inventory

Date: _____ Time: _____

Name: _____
Last First Middle initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the past week? Yes _____ No _____

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue *right now*.

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your *usual* level of fatigue during the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your *worst* level of fatigue during the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal work (includes work outside the home and daily chores at home)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

FIGURE 1. Brief Fatigue Inventory. Family physicians may find this tool useful for evaluating fatigue in patients who are approaching the end of life.

Adapted with permission from Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer 1999;85:1186-96.

Treatable causes of anorexia and cachexia in patients who are near the end of life include chronic pain, mouth conditions, gastrointestinal motility problems and reflux esophagitis.

troamphetamine (Dexedrine) and pemoline (Cylert) also are used.

Antidepressants have been used empirically in patients without clinical depression who have fatigue that does not respond to nonpharmacologic interventions, corticosteroids or psychostimulants. In addition to elevating mood, antidepressants (particularly selective serotonin reuptake inhibitors) can have an energizing effect.[6]

Erythropoietin therapy can be beneficial in relieving fatigue and improving quality of life in patients with chronic anemia who have human immunodeficiency virus (HIV) infection/AIDS or end-stage renal disease, and in those who are undergoing cancer chemotherapy.[15,16] However, erythropoietin therapy is expensive, and beneficial effects may not become apparent for four to six weeks. The expense and "time to effect" for this treatment should be compared with the cost and inconvenience of transfusions in patients who have symptomatic anemia at the end of life.

TABLE 1

Anorexia and Cachexia

Systemic illnesses such as cancer, chronic organ failure, infections or AIDS sometimes cause wasting syndromes. These syndromes are characterized by lack of appetite (anorexia) and weight loss (cachexia), frequently accompanied by fatigue.[17-19]

Little is known about the pathogenesis of wasting syndromes. In cancer, humoral factors elaborated by the tumor appear to be involved, because cachexia can be transferred from cancer-bearing to noncancer-bearing animals in parabiotic experiments.[20] It is likely that elevated levels of cytokines, notably interferons and tumor necrosis factors, play a role in the metabolic alterations observed in patients with wasting syndromes.[20,21] There is no relationship between tumor size and the degree of cachexia.[17]

Despite the appearance of malnutrition, the wasting syndrome associated with cancer and hypermetabolic states is caused by the underlying disease process and is usually not reversible with improved nutrition. Orally or parenterally administered nutrition frequently results in increased body fat, not increased protein. The findings of a number of studies indicate that aggressive alimentation in patients with a wasting syndrome related to cancer may actually increase their discomfort.[22,23] This differs for patients with AIDS.

The physician can be of particular assistance in helping the patient and family understand that cachexia is an expected con-

sequence of the underlying disease process. Frequently, family caregivers believe that wasting is the result of their provision of inadequate care and nutrition. They can be taught to replace their "need to feed" with behaviors that alleviate symptoms, such as moistening the patient's lips and oral cavity with a sponge, offering small amounts of food as desired by the patient, providing light massage, reading to the patient or playing soft music for the patient.

Treatable causes of anorexia and cachexia in patients who are near the end of life include chronic pain, mouth conditions (dryness, mucositis resulting from chemotherapy, and infections such as oral candidiasis or oral herpes), gastrointestinal motility problems (e.g., constipation) and reflux esophagitis. In patients with cancer who are being treated with chemotherapy, radiation therapy and/or medications such as opioids or nonsteroidal anti-inflammatory drugs, an attempt should be made to determine whether anorexia and weight loss are due to mucositis, changes in gastrointestinal motility and nausea as the effects of treatment, rather than progressive disease.

In the absence of specific treatable causes, symptomatic management of cachexia at the end of life includes both nonpharmacologic and pharmacologic interventions *(Table 2)*.[14] It is important to emphasize that cachexia is part of the "normal" end-of-life process. Wasting in dying patients may result in the natural release of endorphins, causing euphoria.

Nausea and Vomiting

Nausea and vomiting can be extremely debilitating symptoms at the end of life. With available methods, effective control of these symptoms can be achieved in most patients.

The brain (chemoreceptor trigger zone, cerebral cortex, vestibular apparatus and vomiting center) and the gastrointestinal tract are the key organs involved in nausea and vomiting. Neurotransmitter receptors that mediate nausea and vomiting include those for serotonin, dopamine, acetylcholine and histamine.[14] Identification of the pathophysiologic origin of nausea is helpful in prescribing effective pharmacologic interventions.

If patients have persistent nausea and treatable causes have been ruled out, haloperidol, 0.5 to 2 mg given orally, intravenously or subcutaneously every six hours, can be very effective. The dosage can be titrated, if necessary, to a total of 10 to 15 mg daily.

The common causes, pathophysiology and treatments of nausea and vomiting in terminally ill patients are summarized in *Table 3*.[14] Medications frequently used in the treatment of these symptoms are listed in *Table 4*,[14] along with typical dosage schedules.

TABLE 2

Management of Weight Loss Once Treatable Causes Have Been Ruled Out

Nonpharmacologic therapy
Provide patient and family education about the pathophysiology of the anorexia and cachexia in terminal illness, and the ineffectiveness of forced feeding and hydration.
Eliminate dietary restrictions: allow the patient to choose favorite foods and fluids, and to have them when desired and in the amount desired.
Reduce portion size and eliminate foods whose odor the patient finds unpleasant.
Explore the emotional and spiritual issues related to the patient's weight loss.
Pharmacologic therapy*
Dexamethasone (Decadron), 2 to 20 mg taken orally each morning; effect may diminish after 4 to 6 weeks of use.
Megestrol (Megace), 200 mg taken orally every 6 to 8 hours; titrate dosage to achieve and maintain desired effect.
Dronabinol (Marinol), 2.5 mg taken orally two or three times daily; titrate dosage to patient tolerance and to achieve and maintain desired effect.
Androgens (e.g., oxandrolone [Oxandrin], nandrolone [Durabolin]) are currently under investigation for their effects on appetite and weight.

**—Pharmacologic therapy should be considered an adjunct to general nonpharmacologic measures; a drug should be discontinued if no benefit occurs after two to six weeks of treatment.*

Information from Module 10: Common physical symptoms. In: Education for physicians on end-of-life care. Chicago: EPEC Project, The Robert Wood Johnson Foundation, 1999.

TABLE 3
Management of Nausea and Vomiting—the 11 M's

Etiology	*Pathophysiology*	*Treatment*
Metastases		
Cerebral	Increased intracranial pressure, direct chemoreceptor trigger zone effect	Corticosteroids, mannitol, dopamine antagonists, histamine antagonists
Liver	Toxin buildup	Dopamine antagonists, histamine antagonists
Meningeal irritation	Increased intracranial pressure	Corticosteroids
Movement	Vestibular stimulation (may be worse with morphine)	Acetylcholine antagonists
Mentation (e.g., anxiety)	Cerebral cortex	Anxiolytics (e.g., benzodiazepines, dronabinol [Marinol])
Medications		
Opioids	Chemoreceptor trigger zone, vestibular effect, gastrointestinal tract	Dopamine antagonists, histamine antagonists, acetylcholine antagonists, prokinetic agent, stimulant laxatives
Chemotherapy	Chemoreceptor trigger zone, gastrointestinal tract	Serotonin antagonists, dopamine antagonists, corticosteroids
Others (e.g., NSAIDs)*	Chemoreceptor trigger zone	Dopamine antagonists, histamine antagonists
Mucosal irritation		
NSAIDs	Gastrointestinal tract, gastritis	Cytoprotective agents
Hyperacidity, gastroesophageal reflux	Gastrointestinal tract, gastritis, esophagitis, duodenitis	Antacids
Mechanical obstruction		
Intraluminal	Constipation, obstipation	Manage with laxatives, stool softeners, lubricants, etc.
Extraluminal	Tumor, fibrotic stricture	Reversible: surgery Irreversible: manage fluids, administer corticosteroids, inhibit secretions with octreotide (Sandostatin) or scopolamine (Transderm Scop)
Motility		
Ileus, opioids and other medications	Gastrointestinal tract, central nervous system	Prokinetic agent, stimulant laxatives
Metabolic imbalance		
Hypercalcemia, hyponatremia, hepatic or renal failure	Chemoreceptor trigger zone	Dopamine antagonists, histamine antagonists, corticosteroids; correct electrolyte imbalance
Microbes		
Local irritation (e.g., esophagitis, gastritis caused by infection with Candida species, *Helicobacter pylori*, herpesvirus, cytomegalovirus)	Gastrointestinal tract	Antibacterials, antivirals, antifungals, antacids
Systemic sepsis	Chemoreceptor trigger zone	Dopamine antagonists, histamine antagonists, antibacterials, antivirals, antifungals
Myocardial dysfunction		
Ischemia, congestive heart failure	Vagal stimulation, cerebral cortex, chemoreceptor trigger zone	Oxygen, opioids, dopamine antagonists, histamine antagonists, anxiolytics

NSAIDs = nonsteroidal anti-inflammatory drugs.

**—See mucosal irritation.*

Adapted with permission from Module 10: Common physical symptoms. In: Education for physicians on end-of-life care. Chicago: EPEC Project, The Robert Wood Johnson Foundation, 1999.

TABLE 4
Medications Commonly Used in the Treatment of Nausea and Vomiting

Medication	*Dosage and usual routes of administration*
Dopamine antagonists	
Haloperidol (Haldol)	0.5 to 2 mg orally, IV or SC every 6 hours; then titrate the dosage
Prochlorperazine (Compazine)	10 to 20 mg orally every 6 hours, 25 mg rectally every 12 hours, or 5 to10 mg IV every 6 hours
Droperidol (Inapsine)	2.5 to 5 mg IV every 6 hours
Thiethylperazine (Torecan)	10 to 20 mg orally every 6 hours
Perphenazine (Trilafon)	2 to 8 mg orally or IV every 6 hours
Histamine H_1 receptor blockers (antihistamines)	
Diphenhydramine (Benadryl)	25 to 50 mg orally every 6 hours
Meclizine (Antivert)	25 to 50 mg orally every 6 hours
Hydroxyzine hydrochloride (Atarax), hydroxyzine pamoate (Vistaril)	25 to 50 mg orally every 6 hours
Promethazine (Phenergan)	12.5 to 25 mg IV or IM every 4 to 6 hours, or 25 mg orally or rectally every 4 to 6 hours
Acetylcholine antagonist (anticholinergic)	
Scopolamine (Transderm Scop)	1 to 3 transdermal patches every 72 hours
Serotonin antagonists	
Ondansetron (Zofran)	8 mg orally three times daily
Granisetron (Kytril)	1 mg orally once or twice daily
Dolasetron (Anzemet)	100 mg orally once daily
Prokinetic agent	
Metoclopramide (Reglan)	10 to 20 mg orally every 6 hours
Antacids	
Liquid antacids (various)	1 to 2 tablespoons every 2 hours as needed
Histamine H_2 receptor blockers	800 mg orally at bedtime for ulcers; 800 mg orally twice daily
Cimetidine (Tagamet)*	for gastroesophageal reflux
Ranitidine (Zantac)	150 mg orally twice daily or 300 mg orally at bedtime; decrease dosage by 50% if creatinine clearance is less than 50 mL per minute (0.84 mL per second)
Famotidine (Pepcid)	20 to 40 mg orally at bedtime for ulcers; 20 to 40 mg orally twice daily for gastroesophageal reflux
Proton pump inhibitors	
Omeprazole (Prilosec)	20 mg orally once daily; dosage should be reduced in Asian patients
Lansoprazole (Prevacid)	15 mg orally once daily
Cytoprotective agents	
Misoprostol (Cytotec)	200 µg orally two to four times daily
Proton pump inhibitors	Same as above
Other medications	
Dexamethasone (Decadron)	6 to 20 mg orally once daily
Dronabinol (Marinol)l	2.5 to 5 mg orally three times daily
Lorazepam (Ativan, Intensol)	0.5 to 2 mg orally, sublingually or SC every 4 to 6 hours
Octreotide (Sandostatin)	50 to 150 µg IV or SC every 8 to12 hours; titrate dosage every 24 to 48 hours to achieve and maintain desired effect

IV = intravenous; SC = subcutaneous; IM = intramuscular.

**—Note that liquid antacids impair the absorption of cimetidine.*

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If patients have persistent nausea and treatable causes have been ruled out, haloperidol (Haldol), 0.5 to 2 mg given orally, intravenously or subcutaneously every six hours, can be very effective. The dosage can be titrated, if necessary, to a total of 10 to 15 mg daily. If needed, an antihistamine or a prokinetic agent may provide additional benefit.[24] Severe symptoms may require a judicious combination of agents, based on mechanism of action.

Note that health care providers should use clinical judgment and consult official prescribing information before any pharmaceutical product mentioned in this article is used.

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