Management of Common Symptoms in Terminally Ill Patients: Part II.
Constipation, Delirium and Dyspnea

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In addition to pain, patients who are approaching the end of life commonly have other symptoms. Unless contraindicated, prophylaxis with a gastrointestinal motility stimulant laxative and a stool softener is appropriate in terminally ill patients who are being given opioids. Patients with low performance status are not candidates for surgical treatment of bowel obstruction. Cramping abdominal pain associated with mechanical bowel obstruction often can be managed with morphine (titrating the dosage for pain) and octreotide. Delirium is common at the end of life and is frequently caused by a combination of medications, dehydration, infections or hypoxia. Haloperidol is the pharmaceutical agent of choice for the management of delirium. Dyspnea, the subjective sensation of uncomfortable breathing, is often treated by titration of an opioid to relieve the symptom; a benzodiazepine is used when anxiety is a component of the breathlessness. (Am Fam Physician 2001;64:1019-26.)

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.

Physical symptoms other than pain often contribute to suffering at the end of life. Part I of this two-part article reviewed the management of fatigue, anorexia, cachexia, nausea and vomiting in patients with cancer, acquired immunodeficiency syndrome (AIDS) and other terminal illnesses. Part II discusses measures to alleviate constipation, delirium and dyspnea. With appropriate diagnosis and management, many of these symptoms can be alleviated in patents who are approaching the end of life.

Constipation

Constipation is a frequent cause of nausea and vomiting in terminally ill patients. Management depends on assessment and manipulation of the four major components required for normal bowel movements: intestinal solids, water, motility and lubrication *(Table 1)*.[1]

Constipation resulting from opioids is dose-related, and patients do not develop tolerance to this side effect. Prophylaxis is crucial because opioid-induced constipation is much easier to prevent than to treat. All patients for whom opioids are prescribed should be given a prophylactic gastrointesti-

This is part II of a two-part article on the management of common symptoms in terminally ill patients. Part I, "Fatigue, Anorexia, Cachexia, Nausea and Vomiting," appeared in the September 1 issue (Am Fam Physician 2001; 64:807-14).

nal motility stimulant laxative and a stool softener, unless use of these agents is contraindicated. A stool softener alone is usually not sufficient to alleviate opioid-induced constipation.

BOWEL OBSTRUCTION

Mechanical bowel obstruction occurs in approximately 3 percent of patients with cancer who are receiving hospice care.[2] It is most frequently associated with ovarian and colon cancers. In terminally ill patients with low performance status, surgical treatment of bowel obstruction is not appropriate because of high mortality and recurrence rates.[2]

Cramping abdominal pain associated with mechanical bowel obstruction primarily results from the accumulation of secreted bowel fluid. This problem can often be managed with titration of the morphine dosage to manage pain, along with the administration of octreotide (Sandostatin), a synthetic somatostatin that inhibits the intraluminal secretion of intestinal fluid.

Treatment with medications commonly used to manage nausea and vomiting (e.g., haloperidol [Haldol], diphenhydramine [Benadryl], octreotide) should also be considered. (Use of these drugs is discussed in

> *All patients for whom opioids are prescribed should be given a prophylactic gastrointestinal motility stimulant laxative and a stool softener, unless use of these agents is contraindicated.*

part I of this two-part article.) The exception is the prokinetic agent metoclopramide (Reglan), which may worsen symptoms of mechanical obstruction. Stool softeners and osmotic agents may be useful in patients with partial mechanical obstruction.

Delirium

Delirium is a disturbance of consciousness and cognition with a sudden onset that may be accompanied by increased psychomotor activity.[3] This symptom occurs in 25 to 85 percent of terminally ill patients.[4,5] Mental status changes can be very distressing to the family, who observe agitation, apparent fear or what they believe to be uncontrolled pain in the patient. Delirium often heralds the end of life and may require active sedation in up to 25 percent of patients.[4]

TABLE 1

End-of-Life Care: Treatment of Constipation by Manipulation of Factors Affecting Bowel Movements

Factor	Etiologic event	Correction or treatment	Comments
Low intestinal solids	Low-fiber diet	Psyllium	Caution is advised in patients with low fluid intake, as psyllium may cause impaction
Low stool water content	Dehydration, reduced intestinal secretion, slow transit time of stool	Hyperosmolar nonabsorbable agents	
		Magnesium salts	Contraindicated in patients with renal failure
		Phosphorous salts	Contraindicated in patients with renal failure
		Glycerin suppositories	
		Sorbitol (30 mL every 2 to 4 hours until stool)	Sickly sweet taste; may cause cramps
		Lactulose (30 mL orally every 4 to 6 hours)	
Low gastrointestinal motility	Bed-ridden patients; neurodegenerative disorders; drugs, including morphine, tricyclic antidepressants, scopolamine (Transderm Scop), diphenhydramine (Benadryl), vincristine (Oncovin), verapamil (Calan) and other calcium channel blockers, iron, aluminum and calcium salts	Senna	Stimulates myenteric plexus
		Bisacodyl	
		Prune juice	Inexpensive, effective
		Casanthranol	
Poor gastrointestinal lubrication	Dehydration	Dioctyl sodium sulfosuccinate	Inadequate alone to counteract opioid-induced constipation
		Mineral oil enemas	Do not give mineral oil by mouth, as aspiration may cause pneumonitis.
		Glycerin suppositories	

Adapted with permission from Hallenbeck J, Weissman D. Fast fact and concepts #15: Constipation—what makes us go. June, 2000. End-of-Life Physician Education Resource Center. Retrieved April 23, 2001, from: http://www.eperc.mcw.edu.

As one investigator noted, "All episodes of delirium . . . interfere with meaningful interpersonal contact with loved ones due to clouding of consciousness."[4] Because the period before death can be a last chance for the patient and family members to mend relationships, share dreams and say good-bye, it is imperative that measures be instituted to control delirium.

Common causes of delirium near death include hypoxia, infections (e.g., simple urinary tract infection), fever, dehydration and opioid or benzodiazepine withdrawal. As the time of death approaches, hepatic and renal function deteriorates, and patients become more vulnerable to delirium, particularly delirium caused by medications. Discontinuing unnecessary drugs or prolonging the dosing interval for necessary drugs may help to clear the sensorium.

A recent study[5] found that despite a high incidence (88 percent), delirium was reversible in approximately 50 percent of dying patients. In this study, opioids, other psychoactive medications and dehydration were the most frequent causes of reversible delirium. Dehydration is usually asymptomatic in terminally ill patients; however, when dehydration results in delirium, gentle rehydration may be beneficial if there is a need for the patient to be more alert.

Another study[6] identified factors associated with an increased risk of delirium in patients older than 80 years. These risk factors included impaired vision (Snellen test score worse than 20/70), severe illness (Acute Physiology and Chronic Health Evaluation II score higher than 16), cognitive impairment (Mini-Mental State Examination score lower than 24) and dehydration (blood urea nitrogen level higher than 18 mg per dL [6.5 mmol per L]).

In addition to reducing risk factors for delirium, the physician may be able to prevent its onset in an elderly patient by avoiding five precipitating conditions: the use of physical restraints, malnutrition, the addition of more than three new medications in one day,

In patients with delirium, discontinuing unnecessary drugs or prolonging the dosing interval for necessary drugs may help to clear the sensorium.

the use of bladder catheterization, and iatrogenic events such as frequent room or staff changes or a disruptive environment with excess noise that may disrupt sleep.[6,7]

Altered mental status may be precipitated by a combination of therapies. Anesthetics, analgesics, antibiotics, anticholinergics, antihypertensives, antiarrhythmics, anticonvulsants, histamine H_1 and H_2 antagonists, and other drugs have been associated with the onset of delirium in patients treated in intensive care units (ICUs).[7] According to one group of investigators,[7] what has been called "ICU psychosis (or syndrome)" is actually a true delirium caused by organic stressors; as such, it should be promptly noted and aggressively managed, rather than tolerated or ignored.

The two goals of symptomatic care in the dying patient are to determine the cause of the mental status symptoms and to institute measures to control these symptoms as they affect the quality of life for the patient and family. Hospice workers often observe "terminal restlessness" as a sign that death is approaching.[8] If delirium occurs close to the time of death, the patient's agitation may simply be observed, with attention given to preventing physical harm. Alternatively, the patient may require sedation for the comfort of all involved in care. Terminal sedation is a treatment of last resort and is beyond the scope of this article. Full discussions of this subject are available in the literature.[9-11]

Hospice workers have noted that a changed mental status is more pronounced in patients who have been undergoing a significant psychosocial or spiritual struggle. They would argue that sedation is not appropriate in this setting. For families, however, the open, star-

ing eyes and agitated movement of a patient may not be emotionally tolerable, resulting in a request for something to "quiet" the patient.

Haloperidol is the agent of choice for the management of delirium associated with hyperactivity at the end of life. A well-designed, double-blind study[8] comparing haloperidol (a high-potency neuroleptic), chlorpromazine (a low-potency neuroleptic) and lorazepam (a benzodiazepine) in the treatment of delirium in hospitalized patients with AIDS found haloperidol to be the preferred drug. Greater improvement of mental status symptoms occurred within 24 hours after the initiation of haloperidol in a low dosage (2.8 mg per day)[8,12] than with neuroleptics given in previous trials.[13] No extrapyramidal side effects were noted. The benzodiazepine arm was terminated before the end of the trial[8] because of paradoxic agitation or oversedation. Studies have not been completed in other patient populations; thus, it is not clear whether these findings are true for all terminally ill patients. Medications commonly used to manage delirium are listed in *Table 2*.[14]

Nonpharmacologic interventions for delirium can also be of benefit. For example, a family member or other person (e.g., a sitter) might remain with the patient to keep the patient calm and prevent physical harm. Use of physical restraints should be avoided unless absolutely necessary; if required, restraints should be used in conjunction with sedation.

Patients' descriptions of "visits" by loved ones who have died before them should not be mistaken for delirium or confusion. Although labeled by some as hallucinations, these encounters usually appear to be comforting to dying patients and consequently may not require medical treatment.

Dyspnea

Dyspnea, which is a subjective experience of difficult or distressed breathing, has been described in patients with cancer (70 percent), AIDS (11 to 62 percent) and other terminal

illnesses.[15(pp295-308)-20] One study[21] noted that family physicians find dyspnea to be the most distressing symptom in dying patients.

Objective findings may not adequately reflect the distress experienced by patients with dyspnea. The original hospice studies[20] conducted during the late 1980s found that 75 percent of patients with cancer and lung involvement had dyspnea; however, of those with dyspnea who were entered in hospice programs, only 39 percent had primary lung problems. In the same studies, fully 24 percent of patients with dyspnea had no obvious etiology for the symptom. Hence, not all patients with dyspnea have severe pulmonary pathology or tachypnea, and vice versa. This distinction is important because symptomatic treatments are directed toward the end point of relieving the symptom (dyspnea), not the sign (tachypnea).

The pathophysiology of dyspnea can reflect the regulation of breathing (central, psychiatric), the act of breathing (weakened intercostal muscles) or the need to alter breathing patterns because of increased activity or hypoxia.[22,23] Tools for measuring dyspnea include the Medical Research Council method,[24] the Support Team Assessment Schedule[25] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; used in many cancer studies).[26] In addition, a visual analog or numeric scale can be employed at the bedside to record the degree of dyspnea experienced by the patient.

The treatment of dyspnea is best directed at the underlying cause (if known). Some causes and appropriate interventions are listed in *Table 3*.[15(pp295-308)] The most common reversible causes of dyspnea are bronchospasm (52 percent), hypoxia (40 percent) and anemia (20 percent).[27]

When dyspnea is not reversible by specific cause-directed treatment, symptomatic treatment is given *(Table 4)*. Opiates, titrated to achieve the desired effect with acceptable toxicity, are considered the mainstay of the symp-

Objective findings may not adequately reflect the distress experienced by patients with dyspnea. One quarter of patients have no obvious etiology for the symptom.

tomatic treatment of dyspnea. In some studies,[28,29] opiates have been reported to increase exercise tolerance and reduce the perception of breathlessness in patients with chronic obstructive pulmonary disease. Other studies[30-32] have not been able to substantiate this benefit. More clinical trials are needed.

A recent study[33] at St. Christopher's Hospice in London found that titrated oral morphine

TABLE 3

Recommended Treatments for Dyspnea in End-of-Life Care Based on Etiology*

Etiology	Treatment
Anemia	Transfusion, erythropoietin†
Hypoxia	Increase fraction of inspired oxygen.
Superior vena cava compression	Radiation; corticosteroids in high dosage
Lymphangitic tumor spread	Corticosteroids in high dosage (short term only)
Pleural effusion	Thoracentesis, chest tube, pleurodesis
Pericardial effusion	Aspiration, pericardial window
Cardiovascular disease	Diuretic, possible irradiation
Pulmonary embolus	Anticoagulation, possible filter (antibiotics)
Chronic obstructive pulmonary disease	Bronchodilators (aerosolized), corticosteroids, antibiotics
Infections	Antibiotics, antifungals or antivirals; corticosteroids
Anxiety	Benzodiazepines, environmental interventions

*—See also Table 4.

†—The physician can decide if it is reasonable to use erythropoietin in a terminally ill patient. Although treatment can be beneficial in relieving fatigue and improving quality of life, it is expensive and must be given for 4 to 6 weeks before benefits become apparent. Giving a dosage of 10,000 units daily for two weeks may reduce this time.

Adapted with permission from Berger A, Portenoy RK, Weissman DE, eds. Principles and practice of supportive oncology. Philadelphia: Lippincott-Raven, 1998: 295-308.

improved dyspnea in 60 percent of patients with terminal cancer. However, significant short-term adverse effects (particularly sedation) occurred, causing some patients to drop out of the trial. The authors of the study advised physicians to inform patients with dyspnea about the side effects of opioids and to monitor carefully for such effects.

Given these caveats, many physicians who provide palliative care manage dyspnea with opioids administered by oral, subcutaneous and inhaled (nebulizer) routes, with the dosage titrated to a level at which the symptom is relieved. Benzodiazepines, titrated until dyspnea is relieved, are commonly added to the opioid regimen to alleviate the anxiety associated with breathlessness.

Nonpharmacologic measures can also be of great value. Interventions include providing good air movement near the patient, keeping cool room temperatures, and proposing and instituting measures to minimize the patient's exertion or anxiety. Movement of air by a fan may calm the patient. The administration of oxygen or air can significantly reduce dyspnea in patients with advanced cancer.[34]

Measures designed to minimize stress can be useful in treating dyspnea. Exertion on the part of the patient can be limited by providing a bedside commode, using a wheelchair for transport and avoiding exposure to hot, humid weather or extreme temperatures. Postural drainage techniques may be helpful. Family members should be taught to inquire specifically about the patient's comfort, in that external signs may appear quite distressing to the family but may not seem unusual to the patient. Family members and friends can lessen the patient's distress by avoiding disagreements in front of the patient.

Patients with dyspnea often prefer sitting with their body leaning forward and their arms resting on a table. Prolonged use of this position may result in muscle aches and soreness, which can be relieved with opioids. Some patients appreciate massage or other distractions, such as listening to music or to a book being read aloud.

A visit from the physician to offer care and reassurance is invaluable to the patient and family. An interdisciplinary approach, such as that provided by hospice, can be very helpful.

Final Comment

This two-part article has focused on some of the most common symptoms patients may experience at the end of life. Dying patients

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TABLE 4

Symptomatic Management of Dyspnea in End-of-Life Care

Nonpharmacologic therapy

Promote good air movement around the patient.

Provide cool room temperature, as tolerated by the patient.

Explain to the family that external signs (e.g., tachypnea) may not indicate patient discomfort.

Humidify the air that the patient breathes.

Maintain the patient in a sitting position.

Minimize the patient's distress by encouraging the family to avoid having disagreements in front of the patient.

Minimize the patient's exertion by providing a bedside commode and transporting the patient by wheelchair; avoid exposure to hot, humid weather and extreme temperatures.

Provide postural drainage.

Have the nursing staff or family give the patient massages and provide distraction with music or by reading aloud to the patient.

Provide oxygen, or a fan in the patient's room.

Visit the patient.

Consult the hospice team.

Pharmacologic therapy

Opioids*

  Mild dyspnea

    Hydrocodone, 5 mg orally every 4 hours

    Acetaminophen-codeine (Phenaphen; 325 mg/30 mg), one capsule orally every 4 hours

  Severe dyspnea

    Morphine, 5 mg orally; titrate dose every 4 hours.

    Oxycodone (Roxicodone), 5 mg orally; titrate dose every 4 hours.

    Hydromorphone (Dilaudid), 0.5 to 2 mg orally; titrate dose every 4 hours.

Benzodiazepines: titrate dosage to reduce anxiety component.

Bronchodilators

Corticosteroids

*—In opiate-naïve patients, use the listed starting dosage and titrate until symptoms are relieved.

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may also suffer from other symptoms, including pressure sores, edema, ascites, bowel impaction, diarrhea, hemoptysis, pleural effusions, incontinence, urinary retention, hematuria and fever. The management of these disorders is discussed in various palliative care textbooks and training programs.[15,35-39]

The End-of-Life Physicians Education Resource is a superb Internet source for palliative care–related educational materials (http://www.eperc.mcw.edu). For no charge, the entire Education for Physicians on End-of-Life Care Participant's Handbook can be downloaded from the Internet (http://www.epec.net/content/participantshandbook.html).

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

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