

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Comfort Care for Patients Dying in the Hospital

Craig D. Blinderman, M.D., and J. Andrew Billings, M.D.*

FOR HOSPITALIZED PATIENTS WHOSE DEATH IS IMMINENT, PALLIATIVE care can alleviate distressing symptoms that are common during the last few days or weeks of life. The essentials of such care that are presented in this review are intended to provide both generalists and specialists in fields other than palliative care with a practical, evidence-based approach to alleviating these symptoms in patients who are dying in a hospital. Communication skills that are essential to personalized care and goal setting are described briefly; the alleviation of the psychosocial and spiritual suffering that is often faced by terminally ill patients and their families is addressed only incidentally.

The term “comfort care” is used here to describe a set of the most basic palliative care interventions that provide immediate relief of symptoms in a patient who is very close to death. Typically, these measures are used to achieve comfort for the patient rapidly; diagnostic or therapeutic maneuvers that might be appropriate for palliation in earlier stages of the illness are usually not considered in this context. Many elements of this approach can be used to ease patients’ distress in other phases of a life-threatening illness and in nonhospital settings, and they can also be applied to relieve symptoms in patients with less grave conditions.

From the Adult Palliative Care Service, Department of Medicine, Columbia University Medical Center, New York (C.D.B.); and the Division of Palliative Care, Massachusetts General Hospital, the Department of Medicine, Harvard Medical School, and the Harvard Medical School Center for Palliative Care — all in Boston (J.A.B.). Address reprint requests to Dr. Blinderman at Adult Palliative Care Service, Department of Medicine, Columbia University Medical Center, 601 W. 168th St., Suite 38, New York, NY 10032, or at cdb21@columbia.edu.

*Deceased.

N Engl J Med 2015;373:2549-61.

DOI: 10.1056/NEJMra1411746

Copyright © 2015 Massachusetts Medical Society.

THE NEED FOR COMFORT-CARE SKILLS IN HOSPITAL PRACTICE

Although a growing proportion of deaths in the United States now occur at home or in nursing homes, hospitals remain a major site for end-of-life care; in 2010, 29% of deaths occurred in the hospital, and the average terminal admission lasted 7.9 days.¹

Multiple distressing symptoms affect hospitalized patients who have advanced, life-threatening illnesses,^{2,3} and some of these symptoms worsen as the patient approaches death.⁴ Poorly controlled symptoms have been documented in patients with advanced cancer, congestive heart failure, chronic obstructive pulmonary disease (COPD), and many other life-threatening conditions.^{5,6} The meticulous management of distressing symptoms is important in any phase of illness, but it becomes a primary focus near the end of life.⁷

Palliative care services can reduce the distress caused by symptoms and improve the quality of life of patients near the end of life.⁸ However, the current scarcity of board-certified palliative care specialists — a workforce shortage that is projected to continue far into the future — means that the responsibility for ensuring excellent end-of-life care for dying patients will continue to fall primarily on generalists and on specialists in areas other than palliative care.^{9,10} Thus, familiarity with basic comfort measures is an essential skill for all clinicians who are caring for patients whose death is imminent.^{7,11}

Table 1. Guidelines for Physicians in Discussing Values, Goals, and Preferences with Patients Near the End of Life.*

<p>If possible, begin these conversations early in the illness, rather than waiting until a medical crisis occurs or until death is imminent. Revisit these discussions when the patient's condition changes substantially.</p> <p>Ask the patient about his or her understanding of the current medical situation and about additional diagnostic and therapeutic options.</p> <p>Assess the patient's and family's information-sharing preferences. What kinds of information do they wish to have, what would they prefer not to know, and who should be involved in discussions about the patient's care? Similarly, ask about their preferences for decision making. How should important decisions be handled? Will key decisions be made by the patient, family members, or the clinician, or will the decisions be made collaboratively?</p> <p>Answer questions as clearly as possible and provide simple, clear, jargon-free information about the patient's condition, prognosis, and options for treatment. Clarify any misconceptions the patient or family may have. In general, patients cannot make good decisions about their care without some understanding of their prognosis.</p> <p>Inquire about and address the patient's concerns. For example, ask, "What are your main worries or fears about your situation?" Ensure that attention is paid to the patient's comfort.</p> <p>Ask about "unacceptable states" — that is, states of existence or losses of critical functioning that a given patient wants to avoid (e.g., a state in which mechanical ventilation would be required indefinitely or in which the patient would be unable to communicate meaningfully with family members).</p> <p>After the patient has been informed about the situation and prognosis, discuss and clarify the patient's values, goals, and preferences for care.</p> <p>With this shared knowledge about goals for care, recommend a plan for end-of-life care. The clinician should not simply ask, "What do you want?" nor should the clinician offer to use harmful or nonbeneficial treatments (e.g., cardiopulmonary resuscitation that will almost certainly be unsuccessful and will not serve the patient's goals¹⁶). When decisions need not be made urgently, allow time for the patient to reflect on choices, obtain further information, or discuss the matter further with family or other advisors.</p>

* Recommendations in the table are based on published guidelines.¹²⁻¹⁵

SETTING GOALS AT THE END OF LIFE: THE IMPORTANCE OF COMMUNICATION

The broad goals and methods of comfort care near the end of life should reflect the informed patient's wishes. Table 1 briefly summarizes communication techniques that can be used to help terminally ill patients identify their values, goals, and preferences. The plan of care can then be aligned with the patient's wishes.¹² Such conversations about goals of care are essential when the withholding or withdrawing of life-sustaining interventions (e.g., dialysis or cardiopulmonary resuscitation) is being considered and as an aid in choosing appropriate diagnostic tests (e.g., positron-emission tomography-computed tomography or monitoring of vital signs). Discussions about setting goals at the end of life are associated with greater congruence between patients' wishes and the care that they receive during that time, and such discussions are correlated with the use of fewer aggressive, life-extending interventions (e.g., mechanical ventilation and resuscitation), as well as with end-of-life care that is consistent with the patient's prefer-

ences, fewer deaths in the intensive care unit, and earlier referral to a hospice.^{17,18}

UNDERSTANDING COMFORT CARE

Comfort care requires the meticulous palliation of troubling symptoms and offering of skilled psychosocial and spiritual support to the patient and the patient's family (Table 2). However, the term is often used in a misleading or imprecise manner — for example, when such care is automatically considered equivalent to a do-not-resuscitate order and, perhaps even without discussion with the patient,²³ is extrapolated to mean the exclusion of a full range of palliative measures appropriate for a dying patient. Rather than simply writing orders for "comfort care" (or "intensive comfort measures," the term that we prefer), the medical team should review the entire plan of care and enter explicit orders to promote comfort and prevent unnecessary interventions.

Infrequently, a focus on comfort care may include the use of potentially life-sustaining measures, when these are consistent with a patient's goals (e.g., when the patient wants to be

Table 2. Guidelines for Physicians Providing Comfort Care for Hospitalized Patients Who Are Near the End of Life.

<p>Ideally, the dying process should never entail sustained severe pain or other physical suffering. The physician should assure the patient and family that comfort is a high priority and that troubling symptoms will be expertly treated.</p> <p>When possible, involve an interdisciplinary team that offers comprehensive, coordinated care for both the patient and the family. Promote good communication among the members of the clinical team.</p> <p>Nursing interventions (e.g., oral care, skin and wound care, application of heat or cold packs) can be critical in addressing the full range of the patient's and family members' needs, as can attention from mental health providers, social workers, music therapists, volunteers, and others.</p> <p>Inquire about the patient's spiritual and religious needs ("Is religion or spirituality important to you?") and offer chaplaincy services when appropriate.</p> <p>Discontinue diagnostic or treatment efforts that are likely to have negligible benefit or that may cause harm by diminishing the patient's quality of life and his or her ability to interact with loved ones. Monitoring of vital signs is rarely useful in the final days of life, especially when obtaining this information involves the use of noisy, distracting monitors in the patient's room. Unnecessary treatment with medications not intended for comfort (such as statins for hyperlipidemia) should be discontinued.¹⁹ Mouth and skin care and changing the patient's position in bed may enhance comfort in some situations, but in other situations these measures may bother the patient and contribute to suffering and should be discontinued.</p> <p>Prophylactic analgesia or sedation should be administered before distressing procedures are performed (e.g., removal of a chest tube,²⁰ withdrawal of mechanical ventilation in a conscious patient,²¹ or changing the dressing on a pressure sore). Treating the symptoms associated with such procedures only after they occur is likely to lead to unnecessary discomfort until the appropriate medication takes effect.</p> <p>Encourage oral assisted eating for pleasure but respectfully inform patients and families that the administration of intravenous fluids and nutrition through a feeding tube has no benefit in terms of comfort or survival at this phase of illness.</p> <p>Inform the patient and family about any proposed major changes in the management of the patient's condition.</p> <p>Consider home care, rather than care in the hospital, for the patient if appropriate. Most dying patients are more physically comfortable at home, and family members have generally been found to be most satisfied with the experience of relatives who die at home with hospice care.²²</p>

kept alive with mechanical ventilation until a loved one can visit from afar or when withdrawing a treatment conflicts with the patient's religious beliefs or cultural norms).¹¹ In addition, the use of invasive interventional procedures, such as thoracentesis for the treatment of symptomatic pleural effusions, can promote comfort.

EVIDENCE-BASED MANAGEMENT OF SYMPTOMS IN DYING PATIENTS

Here we offer basic guidance regarding the management of common symptoms that affect hospitalized patients whose death is imminent.⁴ Because few high-quality studies address the management of symptoms in this population, we have often turned to investigations involving similar populations or to consensus statements on best practices for information. Our premise is that a brief, primarily pharmacologic, clinical guide should feature only a few essential, relatively inexpensive drugs that the clinician can become familiar with and learn to use confidently. Intravenous drug therapy is emphasized,

since most hospitalized dying patients have an intravenous catheter, but suggestions for oral medications, which may be quite adequate in the hospital setting, are also included. If intravenous access is difficult to obtain, opioids and many other drugs can be administered conveniently by other routes, including through a subcutaneously placed butterfly needle that provides easy access for continuous or intermittent infusion.²⁴

PAIN

Pain is the symptom most feared by patients who have cancer and many other terminal conditions. Approximately 40% of hospitalized dying patients have moderate-to-severe pain in the final 3 days of life.²⁵ Assessment of this symptom should include regularly asking patients whether they have pain and, if so, to rate its severity. For example, "On a scale from 0 to 10, with 0 being no pain and 10 being the worst pain you can imagine, how much pain are you having now?"²⁶ Nonverbal indicators of discomfort (e.g., a patient's grimacing, moaning, or repeatedly rubbing a body part) can help the physician assess the

severity of pain when patients are unable to provide a verbal response (e.g., in cases of advanced dementia).

Patients with mild pain (scores of 1 to 3 on a 10-point verbal reporting scale) should initially be treated with acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If treatment with these agents fails to control pain, a low dose of an opioid can be added (Table 3). If a patient who has been receiving oral opioids can no longer swallow, an equianalgesic intravenous regimen of the same opioid or, in the case of opioids that do not have an intravenous formulation, another agent should be substituted (Table 4).

Opioids are first-line agents for the treatment of moderate-to-severe pain (pain score, 4 to 10 on a 10-point verbal reporting scale).³¹ Morphine sulfate is commonly used; hydromorphone is an alternative. Oxycodone is a valuable oral agent, but there is no intravenous preparation. Various long-acting formulations, such as transdermal fentanyl patches, are appropriate for patients receiving stable opioid doses. Intravenous fentanyl has a number of advantages, primarily in critical care and perioperative settings. Methadone should be used only by clinicians who are familiar with its unique pharmacologic properties.

The initial management of moderate-to-severe pain should consist of frequent bolus doses of an opioid with rapid adjustment until a satisfactory degree of analgesia is achieved (Table 3). When the patient is comfortable, the physician should prescribe a regular (basal) dose — which is typically administered as a continuous infusion — to prevent further pain, as well as intermittent bolus doses as needed for episodic worsening of pain (“breakthrough doses”).

Constipation is a frequent side effect of opioid therapy and should be anticipated and treated prophylactically. Other common side effects of opioid therapy include sedation, confusion, nausea, pruritus, myoclonus, and urinary retention.³² Inappropriate escalation of the opioid dose may result in unnecessary sedation and agitation at the end of life.³³ When opioid doses are adjusted appropriately, respiratory depression that is serious enough to affect survival is encountered only in rare cases.³⁴ Patients with renal failure, including those undergoing dialysis, are susceptible to neurotoxic effects of opioids, and special expertise is therefore needed for management of their care³⁵; dose adjustments may also be re-

quired for patients who have liver failure. Rotation to another opioid should be considered when dose-limiting side effects, toxic effects, or incomplete analgesia occurs.³⁶

Neuropathic pain should be distinguished from somatic or visceral pain, since opioids alone may not provide adequate analgesia for patients with neuropathic pain.³⁷ For patients with only a few days to live, adjuvant analgesics used for neuropathic pain may not have time to take effect; however, glucocorticoids may be of benefit in treating acute neuropathic pain.³⁸ The combination of morphine with gabapentin produces analgesia that is more effective than that provided by either agent alone.³⁹ Other agents (such as transdermal lidocaine, antidepressants, and anticonvulsants) may be considered when longer survival is anticipated.

DYSPNEA

Dyspnea can be a debilitating symptom and may lead to substantial anxiety in the patient about the possibility of suffocating. A search for the underlying cause, especially when the degree of dyspnea changes rapidly, may occasionally be appropriate. However, such investigations should not be allowed to delay the treatment of symptoms.

Opioids, given either orally or intravenously, are the treatment of choice for dyspnea and have been studied thoroughly in patients with COPD^{40,41} and patients with cancer⁴²; they have been found to be effective in alleviating dyspnea and, when used carefully, not to have serious side effects, such as respiratory depression.⁴³ Treating dyspnea with opioids is similar to managing moderate-to-severe pain, although lower opioid doses are typically adequate and safe for dyspnea⁴¹ (Table 5). For acute or severe dyspnea, intravenous morphine boluses should be used initially; after comfort is achieved, a continuous infusion may be started. When the patient is experiencing anxiety, as regularly occurs in association with breathlessness, benzodiazepines can be added, although there is no evidence that they have benefit in the treatment of the dyspnea itself.⁴⁵ Patients are regularly given supplemental oxygen for dyspnea, but systematic reviews have found no benefit for patients with cancer or heart failure who do not have hypoxemia⁴⁶; however, oxygen may provide some relief for patients with COPD who do not have hypoxemia.⁴⁷

Table 3. Guidelines for the Management of Acute Pain at the End of Life.*

Type of Pain and Treatment	Initial Dosage	Notes
Mild-to-moderate pain		
Acetaminophen	1000 mg orally or rectally 3–4 times a day	Do not exceed 4 g per day. Use this agent with caution in the treatment of patients with liver disease.
Ibuprofen	800 mg orally 3–4 times a day	
Codeine	30 mg (with or without 325 mg acetaminophen) orally every 3–4 hr as needed	Do not exceed 360 mg per day.
Oxycodone	5 mg (with or without 325 mg acetaminophen) orally every 3–4 hr as needed	If analgesia is inadequate with initial treatment, adjust the dosage to 10 mg orally every 3–4 hr as needed; for further management, see treatment for moderate-to-severe pain.
Moderate-to-severe pain in patients not currently receiving opioids		
Morphine	Oral: 5–15 mg every 30–60 min as needed Intravenous: 2–5 mg every 15–30 min as needed	For both morphine and hydromorphone:
Hydromorphone	Oral: 2–4 mg every 30 min as needed Intravenous: 0.4–0.8 mg every 15–30 min as needed	If analgesia is inadequate with initial treatment, increase the bolus dose by 25–50% for moderate pain or by 50–100% for severe pain. If the level of analgesia is acceptable, administer continuous infusion (equal to the total daily opioid dose) over 24 hr, with a breakthrough dose every hour equivalent to 10–20% of the total 24-hr opioid dose. If the current drug causes unacceptable side effects to the patient, administer an equianalgesic dose of a different opioid.
Moderate-to-severe pain in patients currently receiving opioids		
	Bolus dose (up to 10–20% of total opioid taken in the previous 24 hr) every 15–60 min as needed	If previously satisfactory analgesia becomes inadequate, increase the basal and bolus dose by 25–50% for moderate pain or by 50–100% for severe pain. For daily follow-up, calculate the total 24-hr dose received (basal plus breakthrough) and adjust the basal rate to equal this 24-hr opioid amount; adjust the bolus dose to 10–20% of this 24-hr total. If the current drug causes unacceptable side effects to the patient, administer an equianalgesic dose of a different opioid.
Neuropathic pain		
Opioids	Adjust dose until analgesia has been achieved (as described above for moderate-to-severe pain)	
Glucocorticoids	For example, 4–16 mg of dexamethasone intravenously daily	Consider especially for acute neurologic injury, such as nerve or spinal cord compression from a tumor.
Transdermal lidocaine patches		Consider especially when allodynia is present.
Short-acting antiepileptic drug (e.g., gabapentin or pregabalin) or tricyclic antidepressant		If survival for more than a few days is anticipated, consider adding one of these agents immediately.

* Guidelines in the table are from Swarm et al.²⁷ and Portenoy.²⁸

Table 4. Relative Potencies (Equianalgesic Doses) and Pharmacologic Properties of Commonly Used Opioids.*

Drug	Intravenous, Intramuscular, or Subcutaneous Dose	Oral Dose	Half-Life	Duration of Action hours
Morphine	10 mg	30 mg	2–3	3–4 (intravenous); 3–6 (oral)
Codeine	120 mg	200 mg	2–4	4–6
Oxycodone	NA	20 mg	2–3	3–6
Hydromorphone	1.5 mg	7.5 mg	2–3	3–4 (intravenous); 3–6 (oral)
Fentanyl†	100 µg	NA	7–12	1–2
Methadone‡	Variable	Variable	12–150	6–8

* Data in the table are from Portenoy and Ahmed.²⁹ When switching (“rotating”) between opioids, decrease the newly calculated dose by approximately 25% because of the risk of incomplete cross-tolerance (i.e., tolerance may have developed with the original drug, but the degree of tolerance of the new drug is not necessarily the same). NA denotes not applicable.

† When rotating from a continuous fentanyl infusion, use an equianalgesic ratio of 100 µg of fentanyl per hour to 4 mg of morphine per hour intravenously. Fentanyl can also be administered as a transdermal patch; when rotating from morphine to transdermal fentanyl, divide the oral morphine equivalent daily dose in milligrams by 2 for the equianalgesic dose of transdermal fentanyl in micrograms per hour.³⁰ The duration of action of transdermal fentanyl is 48 to 72 hours.

‡ Methadone can be a very useful analgesic, but its relative potency is highly variable, and it should be used only by clinicians familiar with its unique pharmacokinetic properties.

Psychosocial support, relaxation, and breathing training can decrease breathlessness and distress.⁴⁸ Facial cooling with a fan reduces breathlessness.⁴⁹ In addition, patients may report benefiting from open windows, a reduction in ambient room temperature, breathing humidified air, and elevation of the head of the bed.⁵⁰

When the withholding or withdrawal of mechanical ventilation is being considered for a patient with progressive dyspnea and this measure would be expected to lead quickly to death, patients and their families need to be reassured that the patient will not experience a sense of suffocation. Prophylactic intravenous bolus doses of both an opioid and a benzodiazepine should be given just before the ventilator is withdrawn, followed by further doses as needed.⁵¹

The presence of tachypnea or irregular breathing in an otherwise unresponsive patient should not be confused with the subjective feeling of dyspnea. Such actively dying patients often have altered respiratory patterns (e.g., Cheyne–Stokes breathing, intermittent apnea, or hyperpnea). The patient’s family should be reassured that these breathing patterns are not distressing to the patient. Indeed, the aggressive use of opioid infu-

sions for aberrant breathing patterns at the end of life can lead to opioid-induced toxic effects.⁵²

COUGH

Cough occurs at the end of life in up to 70% of patients with cancer and has been reported in 60% to nearly 100% of dying patients with various nonmalignant diseases.⁵³ Opioids, which act centrally to suppress the cough center, have been shown to be effective antitussive agents⁵⁴ and may work well at low doses.⁵⁵ Studies have also shown that gabapentin is effective for chronic cough.⁵⁶

XEROSTOMIA

Dry mouth, or xerostomia, is a common issue among patients at the end of life. Its causes include medications (e.g., anticholinergic agents, opioids, and antihistamines), radiotherapy to the head and neck, and dehydration. Strategies to minimize dry mouth include the discontinuation of unnecessary treatment with drugs that may contribute to the problem and the use of saliva stimulants, saliva substitutes, and other treatments (Table 5). Parasympathomimetic medications (e.g., pilocarpine and cevimeline) are effec-

tive for improving xerostomia but are administered orally, so their use may not be practical for many dying patients.⁵⁷

EXCESSIVE ORAL AND PHARYNGEAL SECRETIONS

The inability to clear oral and tracheobronchial secretions is typically observed in the final days of life and can lead to gurgling sounds in the throat, sometimes referred to as a “death rattle.” Although family members and staff are often distressed by these sounds, they are unlikely to be disturbing to the dying patient,⁵⁸ since they typically occur when the patient is unresponsive and lacks an effective cough reflex. The production of “grunting” sounds by the vocal cords is also common in dying patients.⁵⁹ Simply repositioning the head may reduce these sounds and reassure loved ones that the patient is not in distress.

No convincing evidence beyond clinical reports supports the commonly recommended use of antimuscarinic agents (e.g., atropine and glycopyrrolate) in patients with noisy breathing due to terminal respiratory secretions.⁶⁰ A trial of glycopyrrolate can be considered, but we do not recommend its routine use, especially given the risk of such side effects as xerostomia, delirium, and sedation. Rather, clinicians should reassure and counsel family members and staff about the unlikelihood that the patient is experiencing discomfort from excessive secretions and about the lack of benefit and potential harm of treatment.

NAUSEA AND VOMITING

Common causes of nausea and vomiting near the end of life include reactions to opioids and other medications, uremia, bowel obstruction, gastroparesis, ascites, and increased intracranial pressure. Some cases of nausea and vomiting can be treated according to their cause: glucocorticoids when symptoms are due to increased intracranial pressure,⁶¹ metoclopramide in cases caused by gastroparesis,⁶² muscarinic acetylcholine receptor antagonists (such as scopolamine) or antihistamines (such as promethazine) for symptoms of vestibular origin,⁶¹ and perhaps octreotide and glucocorticoids for malignant bowel obstruction.⁶³

Most episodes of nausea and vomiting near the end of life have multifactorial or uncertain causes.⁶⁴ The evidence supporting the efficacy of

various antiemetics or of a single preferred agent in dying patients is limited. Haloperidol is recommended in much of the literature on palliative care, but metoclopramide is also favored.⁶¹ Serotonin antagonists (e.g., ondansetron) are first-line agents in chemotherapy-related nausea and vomiting, and they may also be used alone or added to other dopamine-receptor antagonists, such as haloperidol, metoclopramide, and first-generation or second-generation antipsychotics (e.g., prochlorperazine and olanzapine).⁶¹ Glucocorticoids are used in many situations, although a randomized, controlled trial comparing metoclopramide alone with metoclopramide plus glucocorticoids did not show a greater benefit in association with the latter regimen.⁶⁵ Benzodiazepines are used to prevent or treat anticipatory nausea and vomiting in patients receiving chemotherapy, but they may also have a more general role in treating nausea and vomiting when it is associated with anxiety.⁶¹

CONSTIPATION

Constipation is often multifactorial in terminal illness and typically results from dehydration, immobility, the effects of drugs, or the effects of a tumor on the bowel. Constipation is a predictable side effect of opioid use and needs to be managed prophylactically with a laxative regimen along with the opioid. Patients who can swallow oral medications are typically prescribed a stimulant laxative (such as senna) with a stool softener (such as docusate). No significant benefit has been found with the addition of docusate to senna alone.⁶⁶ Methylnaltrexone, an expensive drug that is indicated for opioid-induced constipation, is given subcutaneously and can be used to treat patients who are unable to swallow or whose conditions do not respond to the usual agents.^{67,68}

ANOREXIA AND CACHEXIA AND THE ROLE OF HYDRATION AND NUTRITION

No drugs effectively treat anorexia and cachexia near the end of life, although glucocorticoid treatment can transiently improve appetite and energy.⁵⁰ The evidence from clinical studies does not support the use of artificial hydration or nutrition to improve symptoms of dehydration, quality of life, or survival in patients at the end of life.^{69,70} Attempts to alleviate dehydration can result in fluid overload in these patients.

Table 5. Management of Symptoms Other Than Pain at the End of Life.

Symptom and Treatment	Typical Starting Dosage	Notes
Dyspnea		
Morphine	Oral: 5–10 mg every 30 min as needed until patient is comfortable Intravenous: 2–4 mg every 30 min to 1 hr as needed until patient is comfortable For patients already receiving opioids, increase the dose by 25–50%	For dose adjustments, follow the guidelines for treating moderate-to-severe pain.
Oxygen	Adjust to achieve satisfactory oxygen saturation and subjective relief of dyspnea	Should be used only for patients with low oxygen saturation; oxygen delivered by a high-flow nasal cannula may be useful for patients with low oxygen saturation, as long as it does not cause discomfort for the patient.
Bilevel positive airway pressure		Use if consistent with patient's goals, as long as it does not cause discomfort for the patient, and if it is subjectively helpful.
Nonpharmacologic approaches		Approaches include psychosocial support, relaxation and breathing training, facial cooling with a fan, keeping windows open for ventilation, keeping the ambient room temperature low, humidifying the air, and keeping the head of the bed elevated.
Cough		
Codeine	30 mg orally every 4–6 hr as needed	Codeine is available in various liquid formulations, often with additional medications, or as a tablet.
Morphine	Oral: 5–10 mg every 60 min as needed until patient is comfortable Intravenous: 2–4 mg every 30 min to 1 hr as needed	For dose adjustments, follow the guidelines for treating moderate-to-severe pain.
Xerostomia		
Pilocarpine	5–10 mg orally 3 times daily (not to exceed 30 mg/day)	Evidence of pharmacologic effectiveness is minimal. This method requires that the patient be able to take medication by mouth.
Mouth care		Approaches include the use of antimicrobial mouthwashes, saliva substitutes, oral hydration, mouth swabs, sugarless gum, lip balm, or a humidifier.
Excessive oral–pharyngeal secretions (“death rattle”)		
Glycopyrrolate	Intravenous or subcutaneous: 0.2 mg every 4 hr as needed, not to exceed 4 doses per day Oral: 0.5 mg 3 times per day	There is insufficient evidence to support the use of anticholinergic agents. Family members and staff should be reassured about the low probability that the patient will have discomfort as a result of the secretions and should be counseled about the potential side effects of treatment.
Nausea and vomiting		
Caused by bowel obstruction		If the patient has complete bowel obstruction, avoid prokinetic drugs.
Octreotide	100–200 µg subcutaneously 3 times per day (or 100–600 µg per day in an intravenous or subcutaneous infusion)	Although this treatment is commonly administered, studies have shown conflicting results regarding its usefulness. ⁴⁴
Dexamethasone	4–8 mg orally or intravenously every day (up to 16 mg per day)	
Caused by gastroparesis		
Metoclopramide	10–20 mg orally or intravenously every 4–6 hr (up to 100 mg per day)	

Caused by increased intracranial pressure		
Dexamethasone	4–8 mg orally or intravenously once a day (up to 16 mg per day)	
Caused by medications, uremia, toxins, or other unspecified or multiple factors		
Metoclopramide	10–20 mg orally or intravenously every 4–6 hr (up to 100 mg total daily dose)	
Haloperidol	Oral: 1.5–5 mg 2–3 times per day Intravenous: 0.5–2 mg every 8 hr	
Ondansetron	8 mg orally every 8 hr as needed	
Dexamethasone	4–8 mg orally or intravenously once a day (up to 16 mg per day)	Dexamethasone is usually combined with other antiemetics. Check for fecal impaction.
Constipation		
Senna	2–4 tablets (8.6 mg sennosides per tablet) or 1–2 tablets (15 mg sennosides per tablet) as a single daily dose or in two divided doses each day (not to exceed 100 mg per day)	
Bisacodyl suppository	10-mg rectal suppository once daily as needed	
Polyethylene glycol	17 g orally once daily as needed	
Methylaltraxone	For patients weighing 38 to <62 kg: 8-mg dose subcutaneously every other day For patients weighing 62 to 114 kg: 12-mg dose subcutaneously every other day For patients weighing <38 kg or >114 kg: 0.15 mg/kg subcutaneously every other day	
Anorexia		
Dexamethasone	2–4 mg orally or intravenously once a day	Counsel the patient and family about the limited long-term value of treatment.
Fever		Cooling blankets, ice packs, and sponging may be helpful; in some cases, however, the patient may find them troublesome.
Acetaminophen	650–1000 mg orally, rectally, or intravenously every 4–6 hr as needed (maximum dose, 4 g per day)	
Naproxen	250–500 mg orally twice daily	Naproxen may be of particular benefit in the treatment of neoplastic fevers.
Anxiety and insomnia		
Lorazepam	0.25–2 mg orally, intravenously, or subcutaneously every 4–6 hr as needed; dose may be increased to 5 mg	Psychosocial interventions may be helpful. Sedation may increase the risk of falls.
Delirium		
Haloperidol	0.5–1 mg orally or intravenously every hour as needed; when symptoms have been relieved, give the total daily requirement in 3 or 4 divided doses per day	If symptoms are refractory, consider a trial of another antipsychotic agent, instead of or in addition to haloperidol. If agitation is refractory to treatment, consider the addition of a benzodiazepine, with careful monitoring.

Even when this information is presented to patients and families, there may be considerable individual, cultural, or religious variation in their views of the acceptability of withholding fluids and nutrition. The physician should respect these personal values when making a recommendation, which must be tailored to the individual patient's situation; compromises are common (e.g., giving small amounts of parenteral water with dextrose despite the lack of evidence of benefit).

FEVER

Dying patients may have troubling fevers in the final days or weeks of life. The cause is often unknown, but they may be due to infection, neoplasm, medication, or neurologic injury. Acetaminophen and NSAIDs are the first-line agents for the treatment of these fevers. Dexamethasone also has antipyretic properties and should be tried when treatment with the first-line agents fails. Antibiotics may have a role when a specific infection is being treated and when their use is consistent with the patient's goals (e.g., for alleviating a cough due to bronchitis), but they have not been shown to be generally effective in relieving fevers in the final week of life.⁷¹

ANXIETY AND INSOMNIA

A host of fears and concerns — about current or anticipated physical, psychological, social, and existential matters, including dying — are common among patients approaching death and may cause serious impairment of the quality of their remaining life or a frank anxiety disorder. Ensuring the patient's comfort will reduce his or her anxiety, but the primary treatment entails eliciting and addressing concerns and providing reassurance and support. Complementary therapies, such as relaxation exercises, may have a role, and mental health consultation should be considered. When symptoms of anxiety interfere with the patient's quality of life, pharmacotherapy may be considered, especially if some sedation is acceptable to the patient and the family. There is insufficient evidence for the recommendation of a pharmacologic treatment for anxiety at the end of life,⁷² although the use of benzodiazepines is supported by consensus expert opinion.⁷³

Sleep disorders are also common in patients

near the end of life.⁷⁴ Physical discomfort is an important remediable cause. Strategies for managing insomnia include nonpharmacologic interventions, such as ensuring that the patient's room is quiet and comfortable at night.⁵⁰ Little information is available to guide physicians in making a wise choice among hypnotic agents for use in the treatment of dying patients, but various shorter-acting benzodiazepines improve sleep⁷⁵ for terminally ill patients in whom anxiety is a principal cause of sleeplessness, among other groups of dying patients.⁵⁰ Nonbenzodiazepine hypnotic agents may also be useful.

DELIRIUM

Confusional states are regularly encountered in patients as death approaches.⁷⁶ The cause is often multifactorial and may include organ failure, effects of medications, inadequately treated pain, disease of the central nervous system, and infection. The major features of these states include acute changes in the patient's level of consciousness (either hyperactive or hypoactive) or attention and disordered thinking, but delirium may also take a great variety of forms, such as restlessness or suspiciousness. Clinicians often overlook subtler forms of delirium, whereas family members unfortunately may misinterpret even moderately aberrant behavior by the patient as a reflection of normal cognitive processing (e.g., they may rationalize the patient's behavior as resulting from a lack of sleep).

There is little or no high-level evidence from meta-analyses or well-designed trials to guide the management of delirium in the terminal phase of life.^{72,77} Antipsychotic agents are regularly used as the initial pharmacologic treatment. Haloperidol has long been the preferred initial treatment for both agitated, or hyperactive, delirium (characterized by agitation, restlessness, or emotional lability) and hypoactive delirium (characterized by flat affect, apathy, lethargy, or decreased responsiveness)⁷⁸ in patients receiving palliative care, but atypical antipsychotics (e.g., olanzapine and quetiapine) have recently been shown to be equally effective.⁷⁹ The familiarity with and versatility of haloperidol — it can be given both orally and parenterally — make it the preferred drug for initial use in patients with delirium (Table 5).

There is insufficient evidence to recommend benzodiazepines for delirium,⁸⁰ except in cases

of alcohol or sedative-hypnotic withdrawal.⁸¹ Benzodiazepines can cause paradoxical reactions that worsen delirium, but they may be added cautiously if treatment with neuroleptic drugs fails to relieve agitation or if more sedation is desired.⁷⁹ Nonpharmacologic treatments for delirium include frequent reorientation to the environment and hospital routine, modification of factors that may precipitate delirium (such as sensory deprivation and pain),⁸² and reductions in noise and other bothersome or stimulating environmental factors.

PALLIATIVE SEDATION TO UNCONSCIOUSNESS AT THE END OF LIFE

Palliative sedation to the point of unconsciousness is a treatment of last resort when distressing symptoms cannot be controlled despite expert consultation.⁸³ It is widely recognized as an ethically appropriate approach in end-of-life care.⁸⁴ The goal is to relieve refractory suffering, not to hasten death, and it should not be confused with physician-assisted dying or voluntary euthanasia. The patient or a legal surrogate must be in agreement that such an approach is justified. Consultation with specialists in palliative

care, ethics, psychiatry, or other areas should be considered before a decision to initiate palliative sedation is made.

CONCLUSIONS

Nearly a half century after the founding in London of St. Christopher's, the first modern hospice, in 1967, palliative care has been recognized throughout the world as an important medical specialty. Considerable advances have been made during that time in our knowledge of the management of symptoms in terminal illnesses — advances that deserve widespread incorporation into the clinical practice of both generalists and specialists. The information presented here should provide clinicians in fields other than palliative care with a framework for delivering basic comfort care to hospitalized patients who are near death.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article is dedicated to the memory of Dr. J. Andrew Billings, who died from lymphoma during the writing of the manuscript.

REFERENCES

- Hall MJ, Levant S, DeFrances CJ. Trends in inpatient hospital deaths: National Hospital Discharge Survey, 2000-2010. *NCHS Data Brief* 2013;118:1-8.
- McCarthy EP, Phillips RS, Zhong Z, Drews RE, Lynn J. Dying with cancer: patients' function, symptoms, and care preferences as death approaches. *J Am Geriatr Soc* 2000;48:Suppl:S110-S121.
- Puntillo KA, Arai S, Cohen NH, et al. Symptoms experienced by intensive care unit patients at high risk of dying. *Crit Care Med* 2010;38:2155-60.
- Hui D, Santos RD, Chisholm GB, Bruera E. Symptom expression in the last seven days of life among cancer patients admitted to acute palliative care units. *J Pain Symptom Manage* 2014 September 19 (Epub ahead of print).
- Levenson JW, McCarthy EP, Lynn J, Davis RB, Phillips RS. The last six months of life for patients with congestive heart failure. *J Am Geriatr Soc* 2000;48:Suppl:S101-S109.
- Elkington H, White P, Addington-Hall J, Higgs R, Edmonds P. The health-care needs of chronic obstructive pulmonary disease patients in the last year of life. *Palliat Med* 2005;19:485-91.
- Institute of Medicine. Dying in America: improving quality and honoring individual preferences near the end of life. Washington, DC: National Academies Press, 2014.
- Higginson IJ, Evans CJ. What is the evidence that palliative care teams improve outcomes for cancer patients and their families? *Cancer J* 2010;16:423-35.
- Lupu D. Estimate of current hospice and palliative medicine physician workforce shortage. *J Pain Symptom Manage* 2010;40:899-911.
- Quill TE, Abernethy AP. Generalist plus specialist palliative care — creating a more sustainable model. *N Engl J Med* 2013;368:1173-5.
- Truog RD, Campbell ML, Curtis JR, et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College [corrected] of Critical Care Medicine. *Crit Care Med* 2008;36:953-63.
- Bernacki RE, Block SD. Communication about serious illness care goals: a review and synthesis of best practices. *JAMA Intern Med* 2014;174:1994-2003.
- Back AL, Arnold RM, Baile WF, Tulsky JA, Fryer-Edwards K. Approaching difficult communication tasks in oncology. *CA Cancer J Clin* 2005;55:164-77.
- Tulsky JA. Interventions to enhance communication among patients, providers, and families. *J Palliat Med* 2005;8:Suppl 1:S95-S102.
- Clayton JM, Hancock KM, Butow PN, et al. Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers. *Med J Aust* 2007;186:Suppl 12:S77, S79, S83-108.
- Blinderman CD, Krakauer EL, Solomon MZ. Time to revise the approach to determining cardiopulmonary resuscitation status. *JAMA* 2012;307:917-8.
- Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008;300:1665-73.
- Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. *J Clin Oncol* 2010;28:1203-8.
- Kutner JS, Blatchford PJ, Taylor DH Jr, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med* 2015;175:691-700.
- Puntillo K, Ley SJ. Appropriately

- timed analgesics control pain due to chest tube removal. *Am J Crit Care* 2004;13:292-301.
21. Billings JA. Humane terminal extubation reconsidered: the role for preemptive analgesia and sedation. *Crit Care Med* 2012;40:625-30.
 22. Teno JM, Clarridge BR, Casey V, et al. Family perspectives on end-of-life care at the last place of care. *JAMA* 2004;291:88-93.
 23. Yuen JK, Reid MC, Fetters MD. Hospital do-not-resuscitate orders: why they have failed and how to fix them. *J Gen Intern Med* 2011;26:791-7.
 24. Parsons HA, Shukkoor A, Quan H, et al. Intermittent subcutaneous opioids for the management of cancer pain. *J Palliat Med* 2008;11:1319-24.
 25. The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients: the study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). *JAMA* 1995;274:1591-8.
 26. Jensen MP. The validity and reliability of pain measures in adults with cancer. *J Pain* 2003;4:2-21.
 27. Swarm RA, Abernethy AP, Angheliescu DL, et al. Adult cancer pain. *J Natl Compr Canc Netw* 2013;11:992-1022.
 28. Portenoy RK. Continuous intravenous infusion of opioid drugs. *Med Clin North Am* 1987;71:233-41.
 29. Portenoy RK, Ahmed E. Principles of opioid use in cancer pain. *J Clin Oncol* 2014;32:1662-70.
 30. Breitbart W, Chandler S, Egel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. *Oncology (Williston Park)* 2000;14:695-705.
 31. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012;13(2):e58-e68.
 32. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic non-cancer pain: a systematic review. *J Pain* 2003;4:231-56.
 33. White C, McCann MA, Jackson N. First do no harm . . . Terminal restlessness or drug-induced delirium. *J Palliat Med* 2007;10:345-51.
 34. Morita T, Tsunoda J, Inoue S, Chihara S. Effects of high dose opioids and sedatives on survival in terminally ill cancer patients. *J Pain Symptom Manage* 2001;21:282-9.
 35. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* 2004;28:497-504.
 36. Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev* 2004;3:CD004847.
 37. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. *Cochrane Database Syst Rev* 2013;8:CD006146.
 38. Haywood A, Good P, Khan S, et al. Corticosteroids for the management of cancer-related pain in adults. *Cochrane Database Syst Rev* 2015;4:CD010756.
 39. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005;352:1324-34.
 40. Marciniuk DD, Goodridge D, Hernandez P, et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. *Can Respir J* 2011;18:69-78.
 41. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014;348:g445.
 42. Ben-Aharon I, Gafter-Gvili A, Paul M, Leibovici L, Stemmer SM. Interventions for alleviating cancer-related dyspnea: a systematic review. *J Clin Oncol* 2008;26:2396-404.
 43. Mahler DA, O'Donnell DE. Recent advances in dyspnea. *Chest* 2015;147:232-41.
 44. Currow DC, Quinn S, Agar M, et al. Double-blind, placebo-controlled, randomized trial of octreotide in malignant bowel obstruction. *J Pain Symptom Manage* 2015;49:814-21.
 45. Simon ST, Higginson IJ, Booth S, Harding R, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev* 2010;1:CD007354.
 46. Cranston JM, Crockett A, Currow D. Oxygen therapy for dyspnoea in adults. *Cochrane Database Syst Rev* 2008;3:CD004769.
 47. Uronis H, McCrory DC, Samsa G, Currow D, Abernethy A. Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011;6:CD006429.
 48. Zhao I, Yates P. Non-pharmacological interventions for breathlessness management in patients with lung cancer: a systematic review. *Palliat Med* 2008;22:693-701.
 49. Galbraith S, Fagan P, Perkins P, Lynch A, Booth S. Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. *J Pain Symptom Manage* 2010;39:831-8.
 50. Dy SM, Apostol CC. Evidence-based approaches to other symptoms in advanced cancer. *Cancer J* 2010;16:507-13.
 51. Brody H, Campbell ML, Faber-Langendoen K, Ogle KS. Withdrawing intensive life-sustaining treatment — recommendations for compassionate clinical management. *N Engl J Med* 1997;336:652-7.
 52. Blinderman CD. Opioids, iatrogenic harm and disclosure of medical error. *J Pain Symptom Manage* 2010;39:309-13.
 53. Bausewein C, Simon ST. Shortness of breath and cough in patients in palliative care. *Dtsch Arztebl Int* 2013;110:563-71.
 54. Chung KF. Drugs to suppress cough. *Expert Opin Investig Drugs* 2005;14:19-27.
 55. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. *Am J Respir Crit Care Med* 2007;175:312-5.
 56. Ryan NM. A review on the efficacy and safety of gabapentin in the treatment of chronic cough. *Expert Opin Pharmacother* 2015;16:135-45.
 57. Villa A, Connell CL, Abati S. Diagnosis and management of xerostomia and hyposalivation. *Ther Clin Risk Manag* 2015;11:45-51.
 58. Lokker ME, van Zuylen L, van der Rijt CC, van der Heide A. Prevalence, impact, and treatment of death rattle: a systematic review. *J Pain Symptom Manage* 2014;47:105-22.
 59. Hui D, Dos Santos R, Chisholm G, Bansal S, Souza Crovador C, Bruera E. Bedside clinical signs associated with impending death in patients with advanced cancer: preliminary findings of a prospective, longitudinal cohort study. *Cancer* 2015;121:960-7.
 60. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *Cochrane Database Syst Rev* 2008;1:CD005177.
 61. Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. *Clin Interv Aging* 2011;6:243-59.
 62. Acosta A, Camilleri M. Prokinetics in gastroparesis. *Gastroenterol Clin North Am* 2015;44:97-111.
 63. Longford E, Scott A, Fradsham S, et al. Malignant bowel obstruction — a systematic literature review and evaluation of current practice. *BMJ Support Palliat Care* 2015;5:119.
 64. Davis MP, Hallerberg G. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation. *J Pain Symptom Manage* 2010;39:756-67.
 65. Bruera E, Moyano JR, Sala R, et al. Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. *J Pain Symptom Manage* 2004;28:381-8.
 66. Tarumi Y, Wilson MP, Szafran O, Spooner GR. Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. *J Pain Symptom Manage* 2013;45:2-13.
 67. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008;358:2332-43.

68. Bull J, Wellman CV, Israel RJ, Barrett AC, Paterson C, Forbes WP. Fixed-dose subcutaneous methylalantrexone in patients with advanced illness and opioid-induced constipation: results of a randomized, placebo-controlled study and open-label extension. *J Palliat Med* 2015;18:593-600.
69. Bruera E, Hui D, Dalal S, et al. Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Oncol* 2013;31:111-8.
70. Good P, Cavenagh J, Mather M, Ravenscroft P. Medically assisted nutrition for palliative care in adult patients. *Cochrane Database Syst Rev* 2008;4:CD006274.
71. Nakagawa S, Toya Y, Okamoto Y, et al. Can anti-infective drugs improve the infection-related symptoms of patients with cancer during the terminal stages of their lives? *J Palliat Med* 2010;13:535-40.
72. Candy B, Jackson KC, Jones L, Leurent B, Tookman A, King M. Drug therapy for delirium in terminally ill adult patients. *Cochrane Database Syst Rev* 2012;11:CD004770.
73. Lindqvist O, Lundquist G, Dickman A, et al. Four essential drugs needed for quality care of the dying: a Delphi-study based on international expert consensus opinion. *J Palliat Med* 2013;16:38-43.
74. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 2001;19:895-908.
75. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ* 2000;162:225-33.
76. Goy ER, Ganzini L. Prevalence and natural history of neuropsychiatric syndromes in veteran hospice patients. *J Pain Symptom Manage* 2011;41:394-401.
77. Bush SH, Leonard MM, Agar M, et al. End-of-life delirium: issues regarding recognition, optimal management, and the role of sedation in the dying phase. *J Pain Symptom Manage* 2014;48:215-30.
78. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry* 1996;153:231-7.
79. Grassi L, Caraceni A, Mitchell AJ, et al. Management of delirium in palliative care: a review. *Curr Psychiatry Rep* 2015;17:550.
80. Lonergan E, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. *Cochrane Database Syst Rev* 2009;4:CD006379.
81. Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med* 2014;371:2109-13.
82. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911-22.
83. Quill TE, Lo B, Brock DW, Meisel A. Last-resort options for palliative sedation. *Ann Intern Med* 2009;151:421-4.
84. Cherny NI, Radbruch L. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliat Med* 2009;23:581-93.

Copyright © 2015 Massachusetts Medical Society.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal's* website at NEJM.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.