Pharmacologic Pearls for End-of-Life Care

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As death approaches, a gradual shift in emphasis from curative and life prolonging therapies toward palliative therapies can relieve significant medical burdens and maintain a patient's dignity and comfort. Pain and dyspnea are treated based on severity, with stepped interventions, primarily opioids. Common adverse effects of opioids, such as constipation, must be treated proactively; other adverse effects, such as nausea and mental status changes, usually dissipate with time. Parenteral methylnaltrexone can be considered for intractable cases of opioid bowel dysfunction. Tumor-related bowel obstruction can be managed with corticosteroids and octreotide. Therapy for nausea and vomiting should be targeted to the underlying cause; low-dose haloperidol is often effective. Delirium should be prevented with normalization of environment or managed medically. Excessive respiratory secretions can be treated with reassurance and, if necessary, drying of secretions to prevent the phenomenon called the "death rattle." There is always something more that can be done for comfort, no matter how dire a situation appears to be. Good management of physical symptoms allows patients and loved ones the space to work out unfinished emotional, psychological, and spiritual issues, and, thereby, the opportunity to find affirmation at life's end. (*Am Fam Physician*. 2009;79(12):1059-1065. Copyright © 2009 American Academy of Family Physicians.)

ILLUSTRATION BY MARK E. SCHULER

▶ **See related editorial on page 1050.**

▶ **Patient information:** A handout on care for people with a severe or complicated illness, written by the authors of this article, is available at http://www.aafp.org/afp/20090615/1059-s1.html.

The aging population calls for an increasing emphasis on palliative care (interdisciplinary care that focuses on quality of life in the context of advanced, complex, and severe illness). This recently recognized medical subspecialty includes hospice as a subset of care focused on the latter few months of life. Palliative care is delivered across the continuum of care from office to hospital, nursing home, and home hospice. As death approaches, a gradual shift in emphasis from curative and life prolonging therapies toward palliative therapies can relieve significant medical burdens and maintain a patient's dignity and comfort. Pharmacologic symptom management can improve the quality of life of patients with a severe life-limiting illness. This article is intended as a primer on pharmacologic symptom management. More comprehensive sets of recommendations for end-of-life care can be found at the End of Life/Palliative Education Resource Center (http://www.eperc.mcw.edu/ff_index.htm) and the National Cancer Institute (http://www.cancer.gov/cancertopics/pdq/supportivecare), as well as in recent reviews.[1-4]

Pharmacotherapy is only one component of end-of-life care. Quality palliative care is delivered by a team of caregivers and focuses on careful individualization of holistic care based on patient and family goals. The evidence base supporting interventions at the end of life is limited, but growing.

Symptom Management at the End of Life

Symptoms are often best controlled by elucidating and treating their causes. However, any intervention should be consistent with the patient's preferences and goals, especially in the context of palliative care. If test results cannot possibly lead to a change in management, the test is not indicated. Medical management of symptoms should follow the palliative care principles to start low and go slow, and treat to effect or adverse effect, recognizing the risks of polypharmacy.[5]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Opioids should be used for dyspnea at the end of life.	A	6, 7	Multiple studies have shown that nebulized opioids have no benefit over systemic administration in terms of effect or adverse effects.
Opioids should be used for pain at the end of life.	C	12	The ethical limitations of withholding opioids have limited the study of opioids versus placebo, except in neuropathic pain.
Stimulant laxatives are effective for prevention and treatment of constipation in persons on opioids.	C	20, 25	There is no clear benefit of one regimen over another.
Methylnaltrexone (Relistor) can be used for treatment of opioid bowel dysfunction.	B	22, 23	Methylnaltrexone has recently been added as a treatment option.
Corticosteroids can be used for malignant bowel obstruction.	B	33	—
Haloperidol (formerly Haldol) is effective for nausea and vomiting.	B	34, 35	—
Hyoscyamine (Levsin) should be used for the "death rattle" (excessive respiratory secretions).	C	40	—

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

PAIN AND DYSPNEA

Pain and dyspnea are treated based on severity, with stepped interventions, primarily opioids. Dyspnea that persists despite optimal respiratory treatment is sensed in the same central nervous system structures as pain and should be considered as if it were "lung pain." Moderate to severe dyspnea and pain may be treated with oral or parenteral opioids.[1,6,7] Proven nonpharmacologic strategies should be optimized.[8] Using one of many validated scales, physicians can support patients' efforts to set realistic goals for function and pain or dyspnea levels. Recommended scales should include assessment of intensity and quality of pain, as well as function.

Scales that include a nonverbal 0 to 10 line, faces scales, and intensity descriptive scales have proven reliable in persons with Mini-Mental State Examination scores averaging as low as 15.3 out of 30.[9] For nonverbal patients, other scales, such as the Pain Assessment in Advanced Dementia scale, are necessary *(Table 1)*.[10]

Nonopioid pain therapies should be optimized; nonsteroidal anti-inflammatory drugs, steroids, and bisphosphonates are particularly effective for bone pain.[1,4,6] A variety of medications are also available for neuropathic pain, a subject beyond the scope of this article.

The fear that opioids will hasten death is an inappropriate barrier to their use, assuming proper dose initiation and escalation are used.[11] Opioids are a central part of pain treatment in palliative care, including treatment of nonmalignant and neuropathic pain.[12] Titration for effective pain management should be rapid and consistent, using parenteral or oral short-acting medications, with dosing intervals set according to peak effects rather than duration of action.[13]

Breakthrough dosing must be proportionate to the total 24-hour dose of opioids. It should be 10 to 20 percent of the 24-hour oral morphine equivalent (or 50 to 150 percent of the hourly intravenous rate). A common error is the administration of 5 to 10 mg of oxycodone (Roxicodone) for breakthrough pain when a patient is tolerating high long-acting doses. For example, if a patient requires 1,000 mg of oral morphine equivalent every 24 hours, the appropriate breakthrough dose would be 60 to 120 mg of oxycodone. Breakthrough doses should treat unpredictable spikes in pain and prevent breakthrough pain when predictable, such as before necessary turning or transfers. Increases in the basal dose should be 25 to 50 percent for mild to moderate pain and 50 to 100 percent for severe pain. To control symptoms, breakthrough doses should be administered each time an increase in a basal dose is initiated. Preparations that combine an opioid with acetaminophen, aspirin, or ibuprofen should be avoided because of the risk of toxicity above established dose ceilings of the nonopioid.[14]

Many patients with terminal illnesses and their families are reluctant to begin opioid therapy because of the stigma associated with addiction. Preparatory reassurance, education of the patient and family, and use of the term "opioids" instead of "narcotics" helps. If a persistent objection is raised to initiating one opioid, another can be substituted. Failure of one opioid at the highest tolerated

dose may be treated by rotation to another opioid. Reduce dose equivalents by 50 to 75 percent when rotating opioids in the context of well-controlled pain to compensate for incomplete cross-tolerance. Dose ceilings of opioids are variable and often high. Methadone is among the most difficult and dangerous to use, but has advantages in cost and effectiveness. Physicians should consider consultation with a palliative care specialist before using methadone, unless they are familiar with its interactions, variable duration of effect, adverse effects, unique comparative potency with morphine, and risk of toxicity, including QT interval prolongation. The New Hampshire Hospice and Palliative Care Organization's opioid use guidelines (http://www.nhhpco.org/opioid.htm) provide a quick reference card that reviews opioid management and includes equianalgesic tables, opioid rotation guidelines, and a methadone and morphine nomogram.[13]

Common causes of a partial response or lack of response to opioids include: neuropathic pain; social, psychological, or spiritual pain; substance use disorders; and misinterpretation of symptoms for pain, particularly in persons who are cognitively impaired.

Sometimes, aggressive therapies for pain control, such as surgery, radiation, regional nerve blocks, and intraspinal or epidural delivery devices, are appropriate and necessary when basic measures fail and interventions are consistent with patient goals.

Throughout treatment, physicians must evaluate the "total pain syndrome" and align treatment with the causes of pain as much as possible, optimizing psychological, social, and spiritual treatments and avoiding inappropriate pharmacologic management of psychosocial or spiritual pain.

OPIOID ADVERSE EFFECTS

Nausea and vomiting, sedation, and mental status changes are common with opioid initiation and most often fade within a few days. When initiating an opioid, prophylactic use of an antiemetic for three to five days can be effective in the susceptible patient.[15] Persistent nausea and vomiting is related to chemoreceptor trigger zone stimulation, and can be treated with a combination of dose reduction, opioid rotation, and antiemetics.[16] Undesirable sedation can be addressed with low-dose methylphenidate (Ritalin), which can be rapidly tapered when no longer needed.[17] Allergy to opioids usually amounts to nothing more than sedation or gastrointestinal adverse effects, and can be managed expectantly. Localized urticaria or erythema at the site of an injection of morphine is caused by local histamine release and is not necessarily a sign of systemic allergy.

Constipation is one adverse effect of opioids that does not extinguish with time *(Table 2)*.[18] An important principle of pain management is that, when writing opioid prescriptions, physicians also need to write orders for the bowel preparation. Increasing fiber or adding detergents

Table 1. Pain Assessment in Advanced Dementia Scale

Item	*0*	*1*	*2*	*Score*
Breathing independent of vocalization	Normal	Occasional labored breathing; short period of hyperventilation	Noisy, labored breathing; long period of hyperventilation; Cheyne-Stokes respiration	
Negative vocalization	None	Occasional moan or groan; low level speech with a negative or disapproving quality	Repeated troubled calling out; loud moaning or groaning; crying	
Facial expression	Smiling or inexpressive	Sad; frightened; frowned	Facial grimacing	
Body language	Relaxed	Tense; distressed pacing; fidgeting	Rigid; fists clenched; knees pulled up; pulling or pushing away; striking out	
Consolability	No need to console	Distracted or reassured by voice or touch	Unable to console, distract, or reassure	
			Total:* _____	

**—Total scores range from 0 to 10, with a higher score indicating more severe pain (0 = no pain to 10 = severe pain).*

Adapted with permission from Warden V, Hurley AC, Volicer I. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J Am Med Dir Assoc. *2003;4(1):14.*

Table 2. Treatment of Constipation in Patients Receiving Opioids

Treatment	*Dosage*
Lactulose	15 to 30 mL orally two or three times per day
Magnesium hydroxide	30 to 60 mL orally at bedtime
Polyethylene glycol (Miralax)	One or more tablespoons dissolved in 4 to 8 oz of fluid orally per day
Senna with docusate	One to two tablets orally two to four times per day

Information from reference 18.

(e.g., forms of docusate) is not sufficient. Like pain, constipation is more easily prevented than treated. Start a conventional combination of a stimulant laxative with a stool softener (e.g., senna with docusate) or osmotic agent (e.g., polyethylene glycol solution [Miralax]) at the same time as the opioid.[19] There is no good evidence of superiority of any one regimen over another.[20] Polyethylene glycol solutions are easy to titrate, with no maximal dose; can be given once daily; and are particularly effective with the addition of a stimulant, such as senna. With increases in opioid dose, or with other risks of worsening constipation (e.g., change in environment, declining performance status), the laxative dose should be doubled or therapy stepped up by adding a stronger agent. Dosing can be ordered with the notation "hold for diarrhea" or a stepped action plan can be developed based on consistency and frequency of stool. Overflow diarrhea can occur with fecal impaction. Patients nearing death decrease their intake of solids, which is often expected to cause the cessation of bowel movements. However, 70 percent of the dry weight of stool consists of bacteria, so bowel activity can and should be maintained for comfort.[21]

Opioid bowel dysfunction that is unresponsive to aggressive conventional medications, removal of anticholinergic or other contributing medications, enemas, opioid dose rotation, and opioid reduction may be carefully treated with methylnaltrexone (Relistor).[22] It reverses mu-opioid receptor-mediated bowel paralysis without crossing the blood-brain barrier. In a recent industry-sponsored phase 3 trial, subcutaneous methylnaltrexone at 0.15 mg per kg led to a bowel movement within four hours in 48 percent of terminally ill patients with opioid bowel dysfunction versus 15 percent with placebo, with a median time of 45 minutes to first bowel movement versus 6.3 hours with placebo.[23] A more recent study found a dose of 5 mg to be effective, but did not find a dose response above 5 mg.[24] Methylnaltrexone is approved by the U.S. Food and Drug Administration for this indication.

Toxic effects of opioids at higher dose ranges or with rapidly escalating doses include forms of neuroexcitation, such as hyperalgesia, delirium, and myoclonus.[25] A common pitfall is to confuse these symptoms with worsening pain and further escalate the dose, which may worsen neuroexcitation and increase hyperalgesia, thereby exacerbating total pain. Opioid reduction or rotation, with the addition of adjuncts for pain control, is indicated instead. Ketamine (Ketalar) can be an effective adjunct in severe cases, but requires experience or consultation.[26]

Unintentional overdose of an opioid can usually be managed expectantly; however, if partial reversal is necessary, very low-dose naloxone (formerly Narcan) can be quickly administered by giving 0.01- to 0.04-mg (or 1.5 mcg per kg) intravenous or intramuscular boluses every three to five minutes, titrated to respiratory rate or mental status (mix one 0.4 mg per mL ampule of naloxone with saline to make 10 mL, which equals 0.04 mg per mL).[27] Continued close monitoring is necessary because duration of opioid effect may outlast naloxone.

BOWEL OBSTRUCTION, NAUSEA, AND VOMITING

Mechanical bowel obstruction is commonly associated with ovarian[28] and colon cancers.[29] If this cause is known or suspected, it is acceptable to opt not to proceed to invasive intervention urgently.[30] Surgery or venting gastrostomy tube insertion should be undertaken only after careful consideration, because of potential procedural complications, lack of evidence for life prolongation, and recurrence rates up to 50 percent.[31] Endoscopic bowel stenting can be a reasonable option for esophageal or duodenal obstruction. Standard conservative therapies may include cessation of oral intake, transient nasogastric suction, antiemetics, octreotide (Sandostatin), and corticosteroids. Octreotide inhibits the accumulation of intraluminal intestinal fluid and can be administered subcutaneously or intravenously at 50 to 100 mcg every six to eight hours and titrated rapidly to effect.[32] It is also available in an intramuscular depot form, but this form costs more. Dexamethasone six to 16 mg intravenously daily may resolve a bowel obstruction caused by edema from gastrointestinal or ovarian cancer.[33] Although there is no change in mortality at one month, a review of 10 trials confirmed that corticosteroids shrink swelling around

Table 3. Antiemetics Used in Palliative Care by Category

Category	*Action*	*Drug examples*
5-HT_3 receptor antagonists	Block serotonin receptors in the CNS associated with chemoreceptor trigger zone and "vomiting center"	Ondansetron (Zofran) 4 to 8 mg orally or IV every four to eight hours Granisetron (Kytril) 1 mg orally or IV twice daily
Anticholinergics	Block acetylcholine receptors, slow bowel function, dry secretions	Scopolamine one to two patches (1.5 mg) applied topically and changed every 48 to 72 hours
Antihistamines	Block histamine release, have anticholinergic properties	Diphenhydramine (Benadryl) 12.5 to 50 mg orally, rectally, or IV every four to 12 hours Promethazine (Phenergan) 25 to 50 mg orally, rectally, or IV every six hours
Benzodiazepines	CNS anxiolytic effects; enhances gamma-aminobutyric acid action, slowing neuronal function	Lorazepam (Ativan) 0.5 to 2 mg orally or IV every six hours
Cannabinoids	Brainstem cannabinoid receptor agonists, CNS anxiolytic effects	Nabilone (Cesamet) 1 to 2 mg orally every 12 hours Dronabinol (Marinol) 5 to 10 mg orally, rectally, or under the tongue every six to eight hours Marijuana (only where legal for medical use)
Corticosteroids	Anti-inflammatory, reduces tumor-related swelling centrally or peripherally	Dexamethasone 2 to 8 mg orally or IV every four to eight hours
Dopamine receptor blockers		
Benzamides	Peripheral (more than central) dopamine D2 receptor blocker, with some 5-HT antagonism and cholinergic stimulation at bowel level improving gastric emptying and increasing lower esophageal sphincter tone	Metoclopramide (Reglan) 5 to 20 mg orally or IV every six hours as needed
Butyrophenones	Central (more than peripheral) dopamine D2 receptor blocker, with antimuscarinic activity	Haloperidol (formerly Haldol) 0.5 to 2 mg orally or IV every four to eight hours Droperidol 1.25 to 2.5 mg IV (one to three doses)
Phenothiazines	Dopamine D2 receptor blocker, with some antimuscarinic and antihistaminic activity	Prochlorperazine (formerly Compazine) 5 to 10 mg orally or IV every six to eight hours; or 25 mg rectally every 12 hours Chlorpromazine 12.5 to 25 mg IV every six to eight hours; or 25 to 50 mg orally every eight hours

5-HT = 5-hydroxytryptamine; CNS = central nervous system; IV = intravenously.

Information from reference 34.

the tumor and can allow resumption of oral intake with reinstatement of normal bowel activity (number needed to treat = 6).[33] Tapering off corticosteroids should not be undertaken in this circumstance unless indicated for other reasons.

Persistent nausea and vomiting (without bowel obstruction) should be carefully investigated and treatment directed to the underlying cause, most commonly in the central nervous system or the gastrointestinal tract *(Tables 3 and 4)*.[34] If one medication fails, substitute another drug from a different class. Promethazine (Phenergan), a sedating antihistamine, is relatively ineffective in palliative care and is overused. As noted in a comprehensive review,[34] off-label use of haloperidol (formerly Haldol), a low-cost antiemetic, can be at least as effective as ondansetron (Zofran).[35] It is best used at lower doses than for psychosis and can be combined with other interventions.

DELIRIUM AND THE "DEATH RATTLE"

Up to 85 percent of patients experience delirium in the last weeks of life, up to 46 percent with agitation.[36] It manifests as a sudden onset of worsened mental status with agitation. This distressing symptom often occurs in those with rapidly escalating opioid requirements and can be challenging for all. Prevention can be undertaken in all patients

Table 4. Choice of Antiemetic Based on Cause of Nausea and Vomiting

Cause of nausea and vomiting	*Antiemetic*
Anxiety, anticipatory, psychologic	Benzodiazepines, canniboids
Bowel obstruction	Octreotide (Sandostatin; see text)
Gastroparesis	Metoclopramide (Reglan)
Increased intracranial pressure, central nervous system pain	Dexamethasone
Inner ear dysfunction (rare in palliative care)	Anticholinergics, antihistamines
Medication (primarily chemotherapy)	5-HT_3 and dopamine receptor blockers
Metabolic (e.g., uremia, cirrhosis)	5-HT_3 and dopamine receptor blockers, antihistamines, steroids
Opioid bowel dysfunction	Methylnaltrexone (Relistor)

5-HT = 5-hydroxytryptamine.

Information from reference 34.

Table 5. Treatment of Excessive Respiratory Secretions

Treatment	*Dosage*
Atropine eye drops 1%	One to two drops orally or under the tongue; titrate every eight hours
Glycopyrrolate (Robunil)	1 mg orally or 0.2 mg subcutaneously or intravenously every four to eight hours as needed
Hyoscyamine (Levsin)	0.125 to 0.5 mg orally, under the tongue, subcutaneously, or intravenously every four hours as needed
Scopolamine	One to two patches applied topically and changed every 48 to 72 hours

Information from reference 40.

at risk by providing continuity of care; keeping familiar persons at the bedside; limiting medication, room, and staff changes; limiting unnecessary catheterization; and avoiding restraints. Causes such as polypharmacy, opioid toxicity, urinary retention, constipation, and infection should be ruled out. For mild to moderate cases, add haloperidol.[37] More severe terminal delirium can be managed with midazolam infusion or other forms of sedation. These interventions, which in conjunction with high-dose opioids can induce "double effect" (the outcome of hastening death when the intention is purely to relieve symptoms), require expertise and can lead to ethical controversy.[38,39] Consultation with a palliative care specialist is recommended when delirium, pain, or any other symptoms appear to be intractable.

As mental status changes occur during the dying process, patients lose the capacity to clear upper respiratory secretions ("death rattle"). Nonpharmacologic interventions, such as positioning to facilitate drainage and very gentle anterior suctioning (not deep), are an appropriate initial response. Pharmacologic interventions may include hyoscyamine (Levsin), glycopyrrolate (Robinul), scopolamine, octreotide, and the oral use of atropine eyedrops *(Table 5)*.[40] Patients do not report experiencing these sounds to be as distressing as family members or caregivers find them, and education regarding this issue may be as effective as positioning and medication.[41] A randomized trial is presently underway comparing the effectiveness of different strategies.

Final Comment

The end of life is a sacred time in every human culture, a final opportunity to promote and experience spiritual growth. However, spiritual work is difficult, if not impossible, when in pain, when short of breath, or when in a wet bed. Family physicians who care for patients at the end of life have a profound influence on the quality of patients' lives and the dying experience for families. There is always something more that can be done for comfort, no matter how dire a situation appears to be. Palliative care can provide an environment of comfort, healing, and affirmation near the end of life, something that is deeply appreciated by patients and their families, as well as the entire health care team.

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Author disclosure: Nothing to disclose.

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