

DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition >

Chapter e28: Palliative and End-of-Life Care

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KEY CONCEPTS

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- 1 Palliative care may be provided to any patient with a serious illness, at any point in the course of the illness, including while a patient receives curative or disease-focused therapy.
- 2 Hospice is a form of palliative care, which has been defined by Medicare to encompass care solely focused on comfort and quality of life for patients with a likely prognosis of 6 months or less.
- 3 Pain is a common symptom among patients receiving palliative care and may be managed safely and effectively using nonopioid, adjuvant, and/or opioid therapies.
- 4 Opioids are the drug of choice for the management of dyspnea.
- 5 Constipation, nausea, vomiting, anxiety, and delirium are common symptoms among patients receiving palliative care and may be managed effectively with drug and nondrug therapies.
- 6 End-of-life care can be provided to patients in the last days of their lives through palliative or hospice care and provides the management of common terminal symptoms.
- 7 Identifying a patient's goals and structuring care to achieve these goals is a key component of palliative care. Identifying a patient's goals of care involves communication with patients, their families and/or caregivers, as well as other healthcare professionals.
- 8 Addressing nonphysical needs—including spiritual, faith, and psychosocial—is a key component of providing quality palliative care.

PATIENT CARE PROCESS

Patient Care Process for Cancer Pain



Collect

- Patient-specific information (age, sex, goal of care, patient and family beliefs/preferences regarding pain management)
- Past medical history, concurrent disease states
- Social history (alcohol or other substance use)
- Current medications
- Subjective data
 - Pain score/severity (eg, at best, at worst, at rest, with movement)
 - Time course (acute vs chronic and intermittent vs persistent) of pain
 - Patient description of pain quality (eg, achy, sharp, localized, diffuse)
 - Associated symptoms
 - Precipitating or palliating factors
 - Impact on patient's ability to function
- Objective data
 - Respiratory rate
 - Labs: serum creatinine (SCr), estimated glomerular filtration rate (eGFR), liver function tests (ALT, AST)
 - Electrocardiogram (ECG), QTc interval

Assess

- Etiology of pain
- Type of pain
 - Nociceptive, neuropathic, inflammatory, mixed
- Why are symptoms presenting now?
- Severity of symptoms
- Is pain stable/unstable?
- State prescription drug monitoring program data

Plan*

- Pain management regimen including drug and nondrug therapy, consider scheduled versus “as needed” or PRN therapy
 - Consider both adjuvant and/or opioid medications
- Monitoring parameters for efficacy (pain severity and patient functioning) and safety (adverse effects such as sedation, constipation, nausea, and other drug-specific adverse effects)
- Frequency of monitoring and follow-up
- Patient and caregiver education (eg, expectations improvement in pain severity and function, medication use, and expected adverse effects and management)
- Appropriate use of “as needed” or PRN medications
- Safe medication storage and disposal
- Referrals to other providers, if appropriate (eg, physical therapy, behavioral health, chaplain)

Implement*

- Provide education to patient, caregivers, and family members regarding treatment plan using the teach-back method
- Schedule follow-up labs and appointments as applicable

Follow-Up: Monitor and Evaluate

- Improvement in pain symptoms (severity, patient function)
- Presence of adverse effects (eg, sedation, constipation, nausea)
- Changes in renal/hepatic function
- Medication adherence

* *Collaborate with patient, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

Navigate to the website <http://www.graduate.umaryland.edu/palliative>, then click on “Palliative Care Chat Podcast” on the left-hand side. Scroll down to Episode 15: “Ten Tips Palliative Care Pharmacists Want the Palliative Care Team to Know When Caring for Patients.” Select any two tips discussed in the podcast and critically think through why the tip is an important one for the rest of the hospice or palliative care team. This podcast is useful to enhance your understanding regarding the PLAN and MONITORING and FOLLOW-UP steps in the patient care process.

INTRODUCTION

1 Palliative care, or palliative medicine, is specialized care provided to patients with serious illness with a goal of managing symptoms and helping patients to cope with their illnesses.¹ It is provided by an interdisciplinary team of healthcare professionals, including physicians, pharmacists, nurses, nurse practitioners, social workers, chaplains, and others.² Palliative care is appropriate for any patient with a serious or potentially life-limiting illness, at any point during the time course of that illness. Common diseases for which palliative care is appropriate include cancer, heart failure, advanced lung disease such as chronic obstructive pulmonary disease (COPD), organ failure such as liver or renal failure, and neurologic diseases such as dementia and Parkinson disease.² Patients may receive palliative care throughout the course of a serious illness, including while the patient receives treatment aimed at managing or curing the disease. If or when the serious illness progresses and disease-focused therapies are no longer helpful or desired, palliative care continues to be provided to manage symptoms and maximize quality of life.

Provision of palliative and end-of-life care to patients with limited prognoses has been shown to improve patient and caregiver satisfaction,³⁻⁵ reduce healthcare utilization,^{3,4} and decrease healthcare costs.^{3,4,6} In addition to providing symptom management, improving patient and caregiver satisfaction, and reducing healthcare costs, early integration of palliative care has been shown to increase survival among patients with advanced cancer.^{7,8}

Because of the evidence supporting the benefits of palliative care, clinical practice guidelines for serious illnesses incorporate palliative care into treatment recommendations. Both the American Society of Clinical Oncology and National Comprehensive Cancer Network recommend palliative care as a component of oncology management.^{9,10} In addition, the American College of Cardiology Foundation/American Heart Association practice guideline for the management of heart failure supports the incorporation of palliative care into the management of patients with advanced heart failure due to its effectiveness in increasing quality of life.¹¹

WHAT IS HOSPICE?

2 In the United States, hospice care is a Medicare-defined insurance benefit and is a form of palliative care that is focused on caring for patients with a life expectancy of 6 months or less.¹² Hospice care is generally provided when a patient is no longer pursuing disease-focused therapies and the decision has been made to focus solely on comfort and quality of life.^{12,13} Although commonly associated with end-stage cancer, the frequency of noncancer diagnoses among hospice patients more than doubled between 1998 and 2008.¹⁴ In 2014, the most recent year for which data are available, the most common hospice diagnoses were as follows: noncancer diagnoses (63.4% of hospice admissions) such as dementia (14.8%), heart disease (14.7%), and lung disease (9.3%). Cancer diagnoses accounted for 36.6% of hospice admissions.¹⁴

SYMPTOM MANAGEMENT IN PALLIATIVE CARE

Based on the diseases frequently encountered in hospice and palliative care, the most common symptoms managed by palliative care practitioners include pain, dyspnea, constipation, nausea and vomiting, anxiety, and delirium. The management of these symptoms is discussed below.

Pain

3 Pain is a common symptom among patients receiving palliative care, and providing effective pain management is a high priority of palliative care

practitioners. A systematic review found that among studies of patients with cancer (any stage), 53% of patients experienced pain.¹⁵ Among studies of patients with advanced cancer, 64% of patients experienced pain and more than 30% of patients who experienced cancer-related pain rated it as moderate or severe.¹⁵ In an observational study of adults in the last 2 years of life with a variety of terminal diagnoses (eg, cardiac disease, cancer), the prevalence of moderate or severe pain was 26%, which increased to 46% during the last month of life.¹⁶

Developing an effective plan for pain management first requires pain assessment. The components of a pain assessment are timing, severity, patient description, location, palliative factors, precipitating factors, whether or not it radiates, and impact on patient function.

Ascertaining the time course of a patient's pain can help to distinguish acute from chronic pain. In addition, assessing the severity of pain at its best and worst throughout the day, as well as with movement and at rest, can provide helpful information in determining a treatment plan.¹⁷ Patient descriptions of pain, such as its quality, precipitating or palliating factors, region affected, radiation of the pain (if any), temporal factors associated with the pain (ie, worse at night), and impact on the patient's ability to function can be extremely helpful in identifying the cause of pain and appropriate treatment. In noncommunicative patients, palliative care practitioners should assess patients for nonverbal indicators of pain such as grimacing, agitation, restlessness, or resistance to personal care.^{17,18} Family members or caregivers can also provide useful information when assessing pain, as can validated tools such as the Pain Assessment in Advanced Dementia (PAINAD), Checklist of Nonverbal Pain Indicators (CNPI), and the Mahoney Pain Scale.^{17,18} When assessing a patient's complaint of pain, a key distinction is between nociceptive pain and neuropathic pain, as drug therapy selection requires an understanding of pain pathophysiology.

Nociceptive pain is commonly described by patients as achy, throbbing, and dull.¹⁷ Traditionally, nonopioid analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are often considered first line for pain management. However, among the palliative care patient population, the severity of pain or contraindications to nonopioid agents often necessitate the use of opioid agents such as morphine, oxycodone, or hydromorphone.¹⁷ For example, acetaminophen is contraindicated in patients with severe hepatic impairment, while NSAIDs can increase the risk of cardiovascular events and gastrointestinal bleeding and should not be used in patients with renal impairment.¹⁷ In patients without contraindications, NSAIDs are helpful for mild-to-moderate nociceptive pain, especially pain due to inflammatory processes such as pain from bony metastases in advanced cancer.¹⁸ Opioids are frequently required for the management of moderate-to-severe pain in palliative care.¹⁸ Although the World Health Organization ladder recommends weak opioid agonists such as tramadol and codeine as an intermediate step between nonopioid analgesics and strong opioids such as morphine and oxycodone, current evidence supports using lower initial doses of strong opioids in place of weak opioids to achieve better results in the management of cancer pain.^{19,20} Opioid agents do not have a maximum ceiling dose and should instead be titrated to achieve acceptable pain relief while minimizing unacceptable adverse effects such as sedation and respiratory depression. After initiating opioid therapy, patients should be re-evaluated and doses titrated as required. For patients continuing to experience moderate pain, a dose increase of 25% to 50% is appropriate, while a dose increase of 50% to 100% is reasonable for patients experiencing severe pain.¹⁷

Patients often describe neuropathic pain as tingling, sharp, burning, electric shock-like, or numbness. Neuropathic pain is caused by damage to the central or peripheral nervous system itself, rather than actual or potential tissue damage, which is a characteristic of nociceptive pain.²¹ The distinct pathophysiology underlying neuropathic pain necessitates a different approach to treatment, where adjuvant agents (drugs not originally developed for use as analgesics) are considered first line for pharmacologic management. Evidence-based recommendations for drug treatment of neuropathic pain identify tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and calcium channel alpha-2-delta ligands (gabapentin and pregabalin) as first-line therapies.^{17,22} Traditional analgesics, such as opioids, are recommended as second-line (tramadol) or third-line therapy (morphine, oxycodone).²²

When designing an analgesic regimen, the palliative care practitioner should first conduct a thorough assessment of the patient's pain to identify the pathophysiology whenever possible. For patients with persistent nociceptive pain, particularly that which is not expected to resolve (eg, pain due to advancing metastatic cancer without targeted interventions such as radiation), scheduling around-the-clock analgesics, rather than as-needed analgesics only is preferable. For patients receiving opioid therapy who require dosing throughout the day to maintain pain control, palliative care practitioners should consider initiation of a long-acting (LA) or extended-release (ER) formulation of an opioid.¹⁷ Short-acting opioids should continue to be available for the management of "breakthrough" pain, which the patient may experience despite the LA or ER opioid.¹⁷ When designing an opioid regimen consisting of LA and short-acting opioids, the basal, or LA, opioid is typically started at a dose representing 50% to 75% of a patient's total 24-hour opioid requirement, while the breakthrough, or short-acting, opioid is started at a dose representing 10% to 20% of the 24-hour opioid

requirement.^{17,23} If a patient's description or reason for pain is consistent with a neuropathic pathophysiology, adjuvant agents should be considered, and these agents should always be dosed around-the-clock.

When using opioid therapy as part of an analgesic regimen, palliative care practitioners must diligently monitor for and manage opioid adverse effects. Adverse effects frequently associated with opioid therapy include constipation, sedation, and confusion.¹⁸ Adverse effects such as nausea, pruritus, urinary retention, and myoclonus may also occur with opioid therapy, although they are less common.¹⁸ Respiratory depression, the most severe and worrisome opioid adverse effect, is always preceded by sedation and thus can typically be caught early with careful monitoring and slow dose titration. While tolerance occurs to most opioid adverse effects after the initial days of therapy or after an increase in dose, tolerance to opioid-induced constipation never develops.²⁴ Therefore, all patients receiving opioid therapy must be simultaneously initiated on a bowel regimen containing a stimulant laxative.^{18,19} Although opioid adverse effects are typically similar for all agents within the class, individual patients may respond more or less favorably to a particular drug. If patients experience unacceptable adverse effects with one opioid agent, rotation to another agent within the class may provide analgesia while minimizing adverse effects.^{19,24}

Dyspnea

4 Dyspnea, or the subjective sensation of breathlessness, is a common symptom in the palliative care patient population.²⁵ Although common among patients with advanced cancer, particularly those with lung tumors, dyspnea also occurs in patients with advanced cardiac and pulmonary disease such as heart failure and COPD.²⁶ Whenever possible, treating and reversing the underlying cause of dyspnea is preferred.²⁶ However, in patients with end-stage disease, reversing the underlying cause may no longer be possible, in which case symptoms should be controlled through pharmacologic and nonpharmacologic treatment.^{25,26}

Opioids are first-line agents for the pharmacologic management of refractory dyspnea.^{25,26} When used for the management of dyspnea, opioids are equally effective given through either the enteral or parenteral route. However, less evidence supports their use through the nebulized route of administration.^{25,26} The beneficial effect of opioids on dyspnea is postulated to occur through multiple mechanisms: a vasodilatory effect on the pulmonary vasculature, a decrease in oxygen consumption during rest and exertion, and changes in the effects of carbon dioxide, oxygenation, and inspiratory flow resistive loading on ventilation.²⁵

Benzodiazepines have been studied for the management of dyspnea. A 2011 Cochrane review found no evidence of benefit for benzodiazepines in the management of dyspnea.²⁷ Benzodiazepines are considered second- or third-line agents and are likely most useful in combination with opioid therapy in patients experiencing both dyspnea and related anxiety.^{25,27}

Nonpharmacologic treatment strategies for dyspnea include use of a fan to create air movement across a patient's face, repositioning, pulmonary rehabilitation, and complementary therapies such as relaxation strategies. Although commonly requested by patients due to the symptoms of breathless, supplemental oxygen has not been beneficial for patients without hypoxia ($\text{PaO}_2 < 55 \text{ mm Hg}$ [7.3 kPa]).²⁵

Constipation

5 Constipation is a common symptom among patients receiving palliative care, due to both disease processes themselves (eg, tumor obstruction due to gastrointestinal cancers, electrolyte abnormalities, and impaired venous flow due heart failure) and the drugs used to manage other symptoms (eg, opioids, TCAs, antiemetics, and anticholinergics).²⁸ Estimates of the incidence of constipation vary widely, from 18% to 90% of patients, due to varying definitions of constipation.²⁸ Constipation generally includes the following symptoms: bowel movements that are difficult, painful, and/or infrequent; hard stools; and a sense of incomplete bowel evacuation.²⁸ The Rome III Criteria define functional constipation as "a functional bowel disorder that presents as persistently difficult, infrequent, or seemingly incomplete defecation, which do not meet [irritable bowel syndrome (IBS)] criteria."²⁹

Constipation can be managed through nonpharmacological therapies such as increased intake of fluid and fiber, and increased physical activity. However, among the palliative care patient population, pharmacologic therapy with laxatives is generally required. Bulk-forming laxatives such as psyllium are generally not preferred for palliative care patients due to the risk of bowel obstruction or fecal impaction with inadequate fluid intake.²⁸ In a review of randomized controlled trials evaluating laxatives in patients receiving palliative care, no differences in efficacy were found among lactulose,

senna, magnesium hydroxide plus liquid paraffin, and docusate plus senna.²⁸ All patients receiving opioids for the management of pain or dyspnea should receive prophylactic stimulant laxatives to prevent opioid-induced constipation.^{18,19}

When designing a therapeutic regimen for a palliative care patient experiencing constipation, it is reasonable to consider agent availability, patient preference, and onset of action, as the evidence does not support increased efficacy of one agent over another. Combination laxative therapy with agents having different mechanisms of action is likely more effective than restricting therapy to a single laxative.¹⁹ Peripheral opioid antagonists such as methylnaltrexone, naloxegol, and alvimopan should be reserved for opioid-induced constipation that does not respond to traditional laxative therapy.¹⁹

Nausea and Vomiting

Although less common than pain and dyspnea, nausea and vomiting are distressing symptoms frequently encountered in the palliative care patient population.³⁰ When evaluating a patient's complaint of nausea and/or vomiting, the palliative care practitioner should attempt to identify the cause of nausea and/or vomiting to identify potentially reversible causes such as those due to hyperglycemia, electrolyte abnormalities, constipation, or medications.³¹ Although the evidence base for the treatment of nausea and vomiting in the palliative care population is limited, identification of causative factors can also guide rational drug therapy selection.^{30,31} Causes of nausea and vomiting, and cause-directed therapies, are shown in [Table e28-1](#). If the cause of nausea and/or vomiting is not identifiable or is multifactorial, dopamine antagonists such as haloperidol should be considered for the first-line therapy because most symptoms of nausea and vomiting are due to gastroparesis or irritation of the chemoreceptor trigger zone.³⁰ Little evidence supports the use of 5-HT₃ receptor antagonists outside of chemotherapy-induced and postoperative nausea/vomiting, and thus, these agents have a limited role in palliative care.³⁰ Because patients may have multiple causes of nausea and vomiting that respond differently to different agents, use of more than one antiemetic from different classes may be required.³⁰ If symptoms are refractory to first- or second-line therapy, olanzapine may be useful due to its effect on multiple neurotransmitters involved in the emetic pathway.³⁰ Nonpharmacologic therapies for nausea and vomiting include relaxation therapy and distraction, provision of small, frequent meals with adequate liquids, and acupuncture.¹⁸

TABLE e28-1

Causes of Nausea and Vomiting and Treatment

Cause of Nausea and Vomiting	Receptor Target	First-Line Treatment	Alternative Treatment
Chemical <ul style="list-style-type: none"> • Drugs: opioids, antimicrobials, antidepressants, antipsychotics • Metabolic: end-organ failure, electrolyte abnormalities • Toxins: disease-related (cancer), infection 	<ul style="list-style-type: none"> • D₂ • 5-HT₃ • NK₁ 	Haloperidol	Ondansetron
Impaired Gastric Emptying <ul style="list-style-type: none"> • Drugs: opioids, tricyclic antidepressants, anticholinergics, phenothiazines • Ascites • Hepatomegaly • Tumor infiltration 	<ul style="list-style-type: none"> • 5-HT₄ • D₂ 	<ul style="list-style-type: none"> • Metoclopramide • Discontinuation of causative drugs (if possible) 	
Visceral or Serosal <ul style="list-style-type: none"> • Bowel obstruction • Constipation • Metastatic disease 	<ul style="list-style-type: none"> • 5-HT₃ • ACh 	<ul style="list-style-type: none"> • Promethazine • Diphenhydramine • Meclizine 	Prochlorperazine
Cranial <ul style="list-style-type: none"> • Increased intracranial pressure • CNS tumors • Radiation therapy 	<ul style="list-style-type: none"> • H₁ • ACh • 5-HT₃ • 5-HT₄ • NK₁ • Mu 	Chlorpromazine promethazine	<ul style="list-style-type: none"> • Haloperidol • Dexamethasone
Vestibular <ul style="list-style-type: none"> • Drugs: opioids • Motion sickness 	<ul style="list-style-type: none"> • H₁ • ACh 	<ul style="list-style-type: none"> • Chlorpromazine • Promethazine • Diphenhydramine 	<ul style="list-style-type: none"> • Scopolamine • Prochlorperazine
Cortical <ul style="list-style-type: none"> • Pain • Anxiety 	<ul style="list-style-type: none"> • GABA • H₁ 	<ul style="list-style-type: none"> • Lorazepam • Treatment of underlying pain or anxiety, if applicable 	

D₂, dopamine type 2 receptor; 5-HT₃, serotonin type 3 receptor; NK₁, neurokinin 1 receptor; 5-HT₄, serotonin type 4 receptor; ACh, acetylcholine receptor; H₁, Histamine type 1 receptor; Mu, μ-opioid receptor.

Data from References 30 and 31.

Anxiety

Anxiety is a common symptom among palliative care patients, and may be an underlying condition, caused by the serious illness itself or exacerbated by physical symptoms such as pain and dyspnea.¹⁸ Communication with patients about their goals of care, and addressing spiritual concerns, discussed later in this chapter, are both essential components of managing anxiety in palliative care patients.¹⁸ Other nonpharmacologic tools for managing anxiety, including relaxation techniques and psychotherapy, may also be useful.¹⁸

First-line pharmacologic therapy consists of benzodiazepines.¹⁸ These agents may be combined with selective serotonin reuptake inhibitors (SSRIs), which have an anxiolytic effect in addition to their antidepressant activity. Because SSRIs do not achieve efficacy until 4 to 6 weeks after initiation, they are not appropriate for patients with a life expectancy of less than 1 month.¹⁸

Delirium

Delirium is an acute decline in attention and consciousness combined with cognitive dysfunction and is a common symptom among patients receiving palliative care.¹⁸ Among palliative care patients, 13% to 42% of patients have delirium upon admission to a palliative care unit, 26% to 62% of patients have delirium at some point during their admission to a palliative care unit, and 59% to 88% of patients experience delirium during the final weeks preceding death.³² While delirium may be of a hyperactive, hypoactive, or mixed subtype, hypoactive delirium is most common and also more difficult to detect.³²

Although often considered an indicator that a patient is approaching the final weeks to days of life, it is important to note that nearly half of delirium cases may be caused by reversible factors and these causes should be assessed and reversed if possible.^{18,32} Potentially reversible causes of delirium among palliative care patients include the following: uncontrolled pain; constipation; infections; electrolyte abnormalities; withdrawal from opioids, benzodiazepines, or alcohol; medication adverse effects; and lack of sleep.¹⁸ When present, delirium can often be successfully managed or reversed; however, its presence is distressing to patients and caregivers, and can interfere with the assessment and management of other symptoms, such as pain.³² Thus, the assessment of delirium is critical to provide good palliative care. Tools such as the Bedside Confusion Scale (BCS), Confusion Assessment Method (CAM), Delirium Rating Scale, and Memorial Delirium Assessment Scale are available to assist in the recognition of delirium and have been validated in the palliative care patient population.³²

Nonpharmacologic management of delirium includes patient reorientation, maintenance of a sleep-wake cycle, provision of a familiar environment (presence of family), and provision of assistive devices such as a patient's glasses and hearing aids.³³ Pharmacologic management should begin with avoiding medications that can precipitate or worsen delirium such as benzodiazepines, opioids, anticholinergics, corticosteroids, and beta blockers, as well as correcting reversible causes of delirium.^{18,33} Drug therapy for the prevention and treatment of delirium has not been supported by existing evidence.³³ While some pharmacologic therapies reduce the rates of delirium among hospitalized patients, an impact on clinical outcomes, such as length of stay and mortality, has not been demonstrated.³³ First- and second-generation antipsychotics are widely used for the management of delirium symptoms among palliative care patients which are not reversible; however, more evidence is required to fully support their place in therapy.^{18,33}

MEDICATION MANAGEMENT

An essential component of providing quality palliative care is ensuring that the treatments a patient receives are consistent with his or her wishes and goals of care. Palliative care providers also have a responsibility to ensure that the benefits of any therapy provided outweigh the risks and burdens associated with that treatment.

Deprescribing, the process of discontinuing drug therapy with a goal of improving care and minimizing unnecessary polypharmacy is the one tool palliative care practitioners can use to achieve this aim.³⁴ Successfully applied, deprescribing can reduce the burden to patients due to the adverse effects of individual agents and also decrease the risks associated with polypharmacy such as drug interactions and use of potentially inappropriate medications.³⁴⁻³⁷ When combined with palliative care, deprescribing has been shown to result in reduced medication burden, decreased mortality, reductions in hospitalizations, and improvements in patient-reported overall health.³⁴

When evaluating medication regimens for candidates for deprescribing, practitioners should consider all drugs in a patient's regimen and the indication for each (if known).³⁴ Drug candidates for deprescribing include those without an indication, those whose potential harms outweigh potential benefits, drugs initiated to control adverse effects associated with another drug that may not be required, and preventive drugs whose benefit is unlikely to be realized given the patient's life expectancy.³⁴

END-OF-LIFE CARE

6 As discussed earlier, palliative care can and should be provided in concert with curative efforts in patients with serious illnesses. At some point, curative therapies are no longer viable, but aggressive palliative care efforts should continue to the point of death.

The final days of life present special challenges for pharmacotherapy specialists. First, recognizing when the end is near is important. The “Investigating the Process of Dying” study evaluated physical signs in more than 350 terminally ill cancer patients.³⁸ Looking at 10 target physical signs, three were considered “early” signs (high frequency and moderate predictive value of death within 3 days): decreased level of consciousness (Richmond Agitation Sedation Scale score of -2 or lower), decreased performance status (Palliative Performance scale less than or equal to 20%), and dysphagia of liquids.³⁸ Associated symptoms include pulselessness on the radial artery, respiration with movement, decreased urine output, Cheyne-Stokes breathing, death rattle, periods of apnea, and peripheral cyanosis.

The National Cancer Institute provides a superb overview of the “Last Days of Life (PDQ)—Health Professional Version.”³⁹ Much of this information is also applicable to imminent death for patients with noncancer diagnoses. This review covers those symptoms seen in the final months, weeks and days of life, care decisions during this time period, forgoing potentially life-sustaining treatments, and more. Issues of particular relevance for pharmacotherapy specialists include attention to symptoms likely to arise or worsen such as delirium, dyspnea, fatigue, pain, cough, death rattle, myoclonus, fever, and palliative care emergencies such as catastrophic hemorrhage.

Medication management issues at this point in the patient's life clearly include elimination of medications unlikely to provide benefit, and switching to nonoral routes of medication administration that are least likely to be invasive. For example, several opioids, lorazepam, dexamethasone, and haloperidol, are available as “intensol” formulations. An intensol is a highly concentrated oral solution of a medication, such as morphine 20 mg/mL oral solution. Generally speaking, up to 1 mL can be instilled in the buccal cavity even if the patient is unconscious (the upper body should be propped up to 30° from horizontal to prevent aspiration). Medication management needs during final days should be anticipated and discussed with the family members and caregivers well in advance.

GOALS OF CARE

7 A critically important part of all patient care, but particularly while providing palliative care is to determine the patient's goals of care. As a matter of fact, the most common reason for referral to palliative care services is to have the “goals of care” discussion.⁴⁰ Meaningful conversations about the goals of care lead to significantly better patient and family outcomes including enhanced quality of life, less use of nonbeneficial medical care near death, better goal-consistent care, positive family outcomes, and reduced costs.⁴¹

Determining the patient's and family's wishes and goals of care requires excellent communication among healthcare providers, the patient, and the patient's family. There are many models that may be used to facilitate these discussions. Bernacki and colleagues provide an excellent review and synthesis of best practices for communication about serious illness care goals.⁴¹ They suggest a “conversation guide” that includes probing the patient's understanding of their illness (“What is your understanding now of where you are with your illness?”) and determining how much information that patient would like to know about their illness (“How much information about what is likely to be ahead with your illness would you like from me?”). The model continues with questions that help shape goals, solicit patient/family fears and worries, assess important functional goals, determine how much information the patient wants to share with others, and explore the idea of “trade-offs.” One suggested trade-off question is, “If you become sicker, how much are you willing to go through for the possibility of gaining more time?” This question may include advance directives such as “do not resuscitate” or “do not intubate” but also includes the patient's willingness to undergo potentially aggressive therapies such as continued chemotherapy, radiation, surgery, and hospitalization including intensive care unit admission. This conversation helps shape pharmacotherapy, frequently shifting from often futile curative therapies to supportive/palliative measures.

Kaldjian and colleagues reviewed the literature regarding goals of care at the end of life. They determined six overarching comprehensive goal categories most often brought up by patients: be cured, live longer, improve or maintain function/quality of life/independence, be comfortable, achieve life goals, and provide support for family/caregiver.⁴² Again, the wish to “be comfortable” is highly relevant to pharmacotherapy specialists. Specific comfort goals that frequently populate a “top 10 wish list” for patients with a serious illness and may be related to drug therapy include: to be free from pain (number 1), to be mentally aware, not being short of breath, not being connected to machines, and to be free from anxiety.⁴³ Understanding the advanced illness patient’s goals of care, and cultural beliefs is critically important in the medication management process.

SPIRITUAL CONSIDERATIONS

8 While physical comfort is paramount in caring for patients with advanced illnesses, nonphysical complaints such as spiritual concerns are an important component of total patient care. Palliative care providers span a range of healthcare disciplines, and it is critically important that all providers work collaboratively to achieve physical, psychological, social, and spiritual goals established by the patient. Spirituality is “the aspect of humanity that refers to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to nature, and/or to the significant or sacred.”⁴⁴

Research has shown that a patient’s religion and spirituality play an important role in coping with disease-related symptoms and affect the quality of life and medical decision making.⁴⁵ The National Consensus Project (NCP) provides “Clinical Practice Guidelines for Quality Palliative Care,” emphasizing spiritual, religious, and existential aspects of advanced illness care as one of the key elements of palliative care.⁴⁶ Pharmacotherapy specialists should be competent to perform an initial spiritual screening, with subsequent referral to a board-certified chaplain as appropriate. One instrument that has been developed to assist primary care practitioners and other nonspecialists perform a spiritual assessment is the FICA (F—faith and belief; I—important; C—community; A—address in care) tool developed by Puchalski and colleagues.⁴⁷

CONCLUSION

Palliative care provides patients with serious illness with symptom management, attention to quality of life, and alignment of treatment with patient-identified goals. Providing palliative care requires healthcare practitioners to be competent in the management of pain, dyspnea, constipation, and other symptoms using pharmacologic and nonpharmacologic treatments. Practitioners are also challenged to address the nonphysical needs of patients with serious illness including spirituality and faith. Lastly, palliative care practitioners must continually strive to ensure that all treatments provided to patients with serious illness are consistent with the patients’ goals of care and are not associated with burdens that outweigh potential benefits.

ABBREVIATIONS

5-HT ₃	serotonin type 3 receptor
5-HT ₄	serotonin type 4 receptor
ACh	acetylcholine receptor
ASCO	American Society of Clinical Oncology
BCS	bedside confusion scale
CAM	Confusion Assessment Method
CNPI	Checklist of Nonverbal Pain Indicators
COPD	chronic obstructive pulmonary disease
D ₂	dopamine type 2 receptor
ER	extended-release
FICA	F—faith and belief; I—important; C—community; A—address in care
H ₁	histamine type 1 receptor
IBS	irritable bowel syndrome
LA	long-acting
Mu	μ-opioid receptor
NCCN	National Comprehensive Cancer Network
NCP	National Consensus Project
NK ₁	neurokinin 1 receptor
NSAIDs	nonsteroidal anti-inflammatory drugs
PAINAD	Pain Assessment in Advanced Dementia
SNRIs	serotonin-norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors
TCAs	tricyclic antidepressants

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is false regarding the concept of palliative care?
 - A. Palliative focuses on pain and symptom management and other needs of the patient to achieve an optimal quality of life.
 - B. Palliative care should not be combined with active or curative treatment of a serious or life-threatening illness.
 - C. Palliative care often intensifies as a patient gets closer to end of life.
 - D. Palliative care is a team approach that includes social, psychological, and spiritual support for the patient, caregiver, and family.
2. Nociceptive pain is best described by which of the following statements?
 - A. Nociceptive pain is specific and well-localized.
 - B. Nociceptive pain is described as a gnawing, cramping, aching, squeezing, pressure-like sensation.
 - C. Opioids are useful in treating nociceptive pain.
 - D. A and B

- E. B and C
3. Which of the following statement(s) is/are *true* regarding dyspnea?
- A. Dyspnea is a common end-of-life symptom that may evoke distress and anxiety in a patient.
 - B. Dyspnea may be defined as an unpleasant or uncomfortable sensation of breathing.
 - C. Dyspnea is objective and involves the patient's perception of the sensation and his or her reaction to it.
 - D. A and B only.
 - E. A, B, and C.
4. Respiratory sedatives are used to manage dyspnea at the end of life. Which of the following statements is/are false?
- A. Opioids alter the perception of breathlessness.
 - B. Opioids decrease the ventilatory response to high oxygen and low carbon dioxide levels.
 - C. Benzodiazepines help to relieve anxiety associated with dyspnea.
 - D. Opioids cause vasodilation and can improve cardiac function.
5. Which of the following statements regarding dyspnea in patients receiving palliative care is false?
- A. Dyspnea is difficult to manage at the end of life because the underlying cause can no longer be reversed.
 - B. Typical palliative treatments are opioids and benzodiazepines.
 - C. Nonpharmacologic approaches can be useful.
 - D. Oxygen therapy is useful unless hypoxia is present.
6. Which of the following is a preferred agent in patients in palliative care with nausea and vomiting of unknown etiology?
- A. Metoclopramide
 - B. Haloperidol
 - C. Promethazine
 - D. Lorazepam
7. When selecting an appropriate antiemetic, which of the following factors should be taken into account?
- A. The etiology of nausea and vomiting
 - B. Available routes of administration of therapy which are best for the patient
 - C. Potential adverse effects of medications
 - D. All of the above
8. A patient begins experiencing symptoms of delirium, including decreases in attention and cognition. Which of the following statements regarding delirium in patients receiving palliative care is correct?
- A. Delirium cannot generally be controlled.

- B. Delirium is frequently caused by reversible factors.
 - C. Delirium is rarely present in the final weeks of life.
 - D. Pharmacologic treatment of delirium is preferred over nondrug measures.
 - E. Hyperactive delirium occurs more frequently than hypoactive delirium.
9. Symptoms occurring in the last hours to days of life include which of the following?
- A. Dysphagia, even with liquids
 - B. Delirium
 - C. Decreased level of consciousness
 - D. All of the above

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Rationale: Patients may receive palliative care throughout the course of a serious illness, including while the patient receives treatment aimed at managing or curing the disease.
2. **E.** Rationale: In comparison to the sharp pain associated with neuropathic conditions, nociceptive pain is commonly described by patients as achy, throbbing, and dull. Traditionally, nonopioid analgesics such as acetaminophen and nonsteroidal anti-inflammatory agents are often considered first line for pain management. However, among the palliative care patient population, the severity of pain or contraindications to nonopioid agents often necessitate the use of opioid agents such as morphine, oxycodone, or hydromorphone.
3. **D.** Rationale: Dyspnea is a subjective symptom that is common in the palliative care patient population.
4. **B.** Rationale: The beneficial effect of opioids on dyspnea is postulated to occur through multiple mechanisms: a vasodilatory effect on the pulmonary vasculature, a decrease in oxygen consumption during rest and exertion, and changes in the effects of carbon dioxide, oxygenation, and inspiratory flow resistive loading on ventilation.
5. **D.** Rationale: Oxygen is frequently requested by patients for symptoms of breathlessness, but it has not been shown useful for those without hypoxia. When underlying causes can be identified, they can be addressed, but reversal in patients at the end of life may not be possible. Opioids are first-line treatments for pharmacologic management of dyspnea, and benzodiazepines are second- or third-line agents. Nonpharmacologic approaches include fans, repositioning the patient, pulmonary rehabilitation, and complementary therapies.
6. **B.** Rationale: If the cause of nausea and/or vomiting is not identifiable or is multifactorial in the patient receiving palliative care, dopamine antagonists such as haloperidol should be considered for first-line therapy because most symptoms of nausea and vomiting are due to gastroparesis or irritation of the chemoreceptor trigger zone.
7. **D.** Rationale: When evaluating a patient's complaint of nausea and/or vomiting, the palliative care practitioner should attempt to identify the cause of nausea and/or vomiting to identify potentially reversible causes such as those due to hyperglycemia, electrolyte abnormalities, constipation, or medications. Although the evidence base for treatment of nausea and vomiting in the palliative care population is limited, identification of causative factors can also guide rational drug therapy selection. See [Table e28-1](#) for medications useful for specific types of nausea and vomiting.
8. **B.** Rationale: In the final weeks of life, 59% to 88% of patients experience delirium. It is most often of the hypoactive type, which is more difficult to recognize than the other types of delirium. Because delirium is caused by reversible factors: uncontrolled pain; constipation; infections; electrolyte abnormalities; withdrawal from opioids, benzodiazepines, or alcohol; medication adverse effects; and lack of sleep—about half the time, these should be addressed when present. Delirium can often be successfully managed or reversed.
9. **D.** Rationale: Early signs of the end of life include decreased level of consciousness, decreased performance status, and dysphagia of liquids. Issues

identified in an NCI review of terminal symptoms that are of particular importance to pharmacotherapists include delirium, dyspnea, fatigue, pain, cough, death rattle, myoclonus, fever, and palliative care emergencies such as catastrophic hemorrhage.