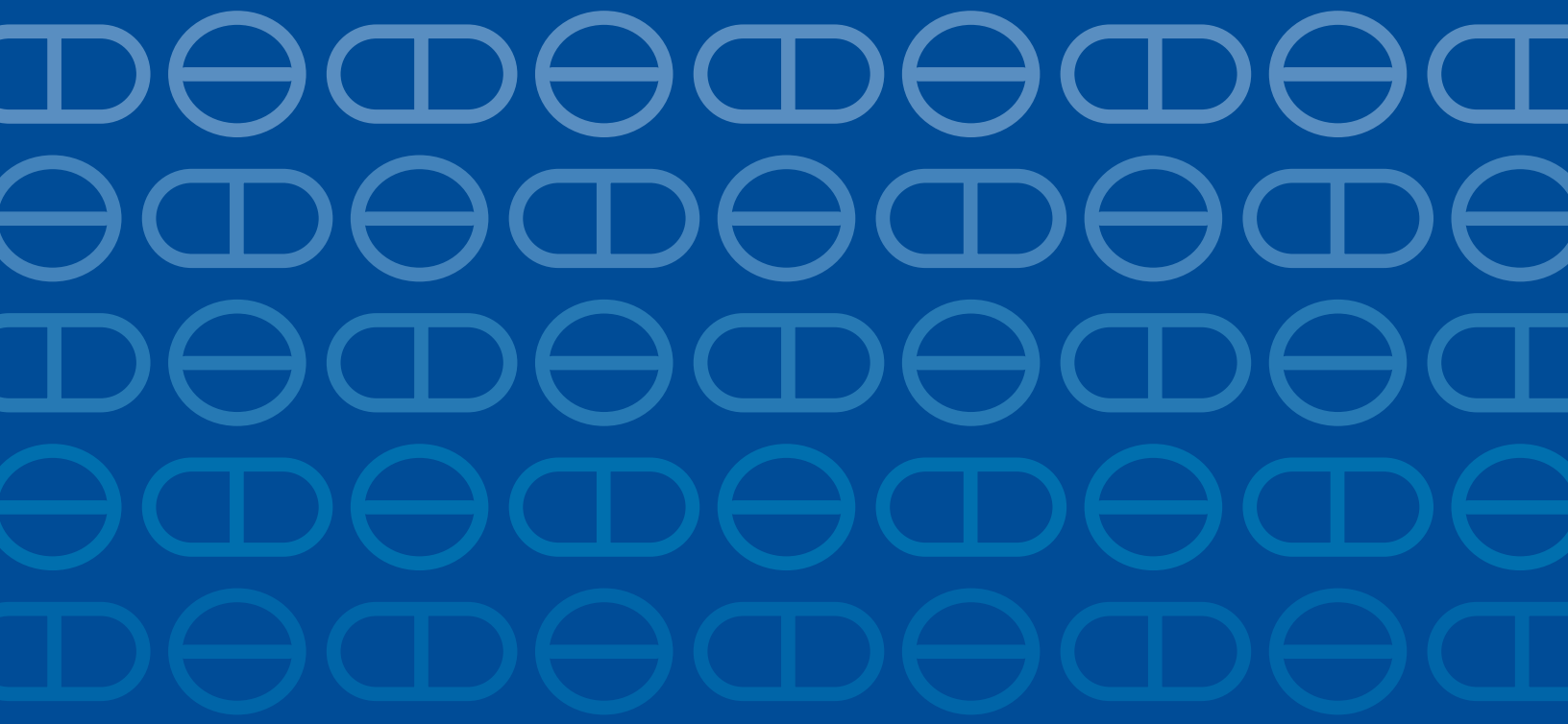
PACE Pharmaceutical Assistance Contract for the Elderly

Alosa Health
Balanced information for better care

Integrating palliative care into primary care



Integrating palliative care into primary care

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Alosa Health

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Accreditation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education and American Nurses Credentialing Center through the joint providership of Harvard Medical School and Alosa Health. The Harvard Medical School is accredited by the ACCME to provide continuing medical education for physicians and the ANCC to provide CNE credit hours to nurses.

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Harvard Medical School is accredited as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation. This activity was approved for 0.50 contact hours, of which 0.25 is eligible for pharmacology credit. Contact hours are awarded commensurate with participation and completion of the online evaluation and attendance attestation.

Activity Overview:

The goal of the educational program is to provide primary care clinicians with tools and techniques to facilitate advance care planning discussions in patients with serious illness, including transitions to specialized palliative care services and hospice, and to be able to relieve common symptoms of serious illness in primary care settings.

The education program has several components, which include:

1. Written evidence report (print monograph)
2. Summary document of 4-5 key messages
3. "Academic detailing" educational sessions with trained outreach educators (pharmacists, nurses, physicians)
4. Reference cards for easy access to key materials
5. Patient education information (brochure/tear off sheets)

The program will critically review and synthesize the most current clinical information on these topics into accessible, non-commercial, evidence-based educational materials to be taught interactively to providers by specially trained clinical educators.

Target Audience:

The educational program is designed for clinicians practicing internal medicine, primary care, family medicine, and geriatrics, as well as nurses and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Describe the population of patients with serious illness who may benefit from palliative care, their relevant disease characteristics, patterns of end-of-life care, and racial/ethnic disparities in care.
- Explain patient-centered approaches for communicating prognoses to patients with serious illnesses.
- Support patients and their surrogates in advance care planning conversations early in the course of a serious illness.
- Identify the most common symptoms among patients with serious illness and describe evidence-based approaches of managing such symptoms at the end of life.
- Integrate practices for using an interprofessional team, palliative care specialists, and hospice at appropriate times for appropriate patients.

Disclosure Policy:

Harvard Medical School has long held the standard that its continuing medical education courses be free of commercial bias.

In accord with the disclosure policy of the Medical School as well as standards set forth by the Accreditation Council for Continuing Medical Education, course planners, speakers, and content reviewers have been asked to disclose any relevant relationship they, or their spouse or partner, have to companies producing, marketing, re-selling or distributing health care goods or services consumed by, or used on, patients. In addition, faculty have been asked to list any off-label uses of pharmaceuticals and/or devices for investigational or non-FDA approved purposes that they plan to discuss. Such disclosure is not intended to suggest or condone bias in any presentation, but is elicited to provide the course director and participants with information that might be of potential importance to their evaluation of a given presentation.

Disclosures:

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Media used:

Printed educational material.

Instructions for Participation and Credit:

No fees are required to participate in this activity. To receive credit, participants must (1) read the statements on target audience, learning objectives, and disclosures, (2) study the educational activity, and (3) complete the post−test and activity evaluation. To receive *AMA PRA Category 1 Credit*™, or CNE nursing credit hours, participants must receive a minimum score of 70% on the post−test.

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Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

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The evolution of palliative care

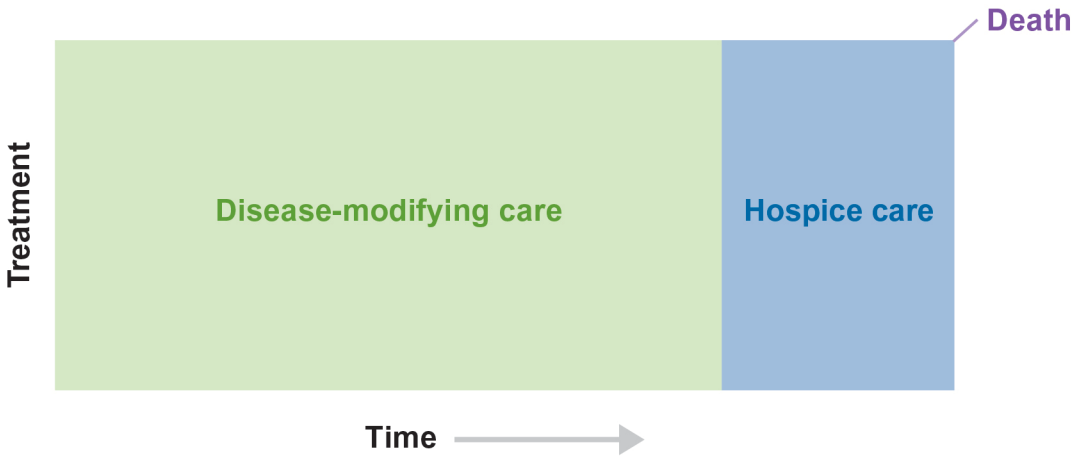
In the early 1990s, a handful of teaching hospitals established palliative care consult services for patients with terminal illnesses. Since then, palliative care programs have grown significantly, spurred by evidence that specialty palliative care improves outcomes for seriously ill patients and their families.[1,2]

The 2015 Institute of Medicine report *Dying in America* recommended that everyone with advanced serious illness have access to palliative care specialists.[3] Not enough specialists exist, however, to care for all patients with serious life-threatening illnesses, a need that is increasing as the population ages.[4] It is now recognized that all clinicians, including primary care clinicians, can benefit from training in palliative care. Palliative care is appropriate at any age and at any stage in a serious illness and can be provided along with curative or otherwise routine disease treatment.[4]

Palliative care is specialized medical care for people with serious illness focused on relieving symptoms and improving quality of life for both the patient and the family. Palliative care involves three key areas: symptom management (e.g., pain, nausea, constipation), supporting patients and their loved ones as they cope with illness and death, and communication and education about the illness through advance care planning (ACP).[5] These care areas overlap considerably with those provided by primary care clinicians, who can play an important role in delivering palliative care. As in other areas, however, primary care clinicians may need to consult palliative care specialists as the complexity of the patient's illness increases. This is similar to how primary clinicians provide cardiac care—they commonly manage blood pressure and cholesterol levels and diagnose and treat a number of cardiac ailments. When cardiac care becomes complicated, however, they request the support of cardiologists for expertise and targeted, longitudinal treatment.

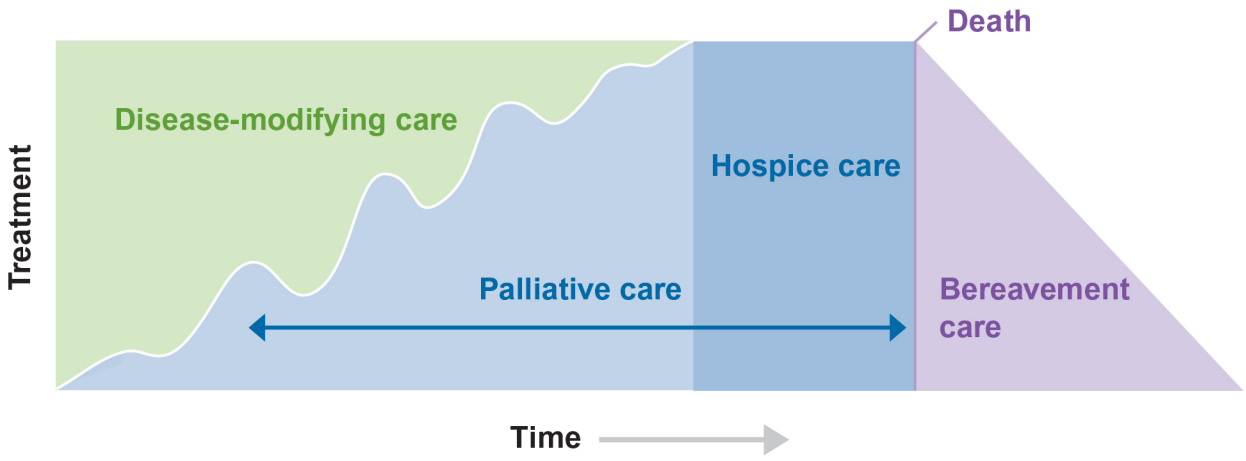
The field of palliative care emerged from a hospice tradition where non-curative, symptom-based treatment was reserved for patients at the end of life—the "transition" model depicted in Figure 1.

Figure 1: Transition model of care[6]



But in the past decade a more nuanced model of care (the "Trajectory" model) has been introduced, which integrates palliative care with disease-modifying care across the duration of an illness and includes consideration of those affected by the death of the individual (Figure 2).

Figure 2: Trajectory model of care[6]



Palliative care can be provided across the spectrum of settings, from homes to hospice facilities to hospitals, and such care is typically provided by interprofessional teams (IPTs) of caregivers. A systematic review of 21 mostly observational studies found that IPTs contribute to staff satisfaction, performance, and effectiveness; patient satisfaction, participation, and safety; that they reduced health system costs and improved communication and productivity among health care workers.[7,8] A team approach can be valuable when challenging issues arise, such as for sedation, blood product transfusion, and the need for artificial nutrition in a patient with multiple comorbidities and a complex medication regimen. Nurse practitioners and social workers can play important roles in palliative care by managing medical comorbidities, managing physical and psychological symptoms, encouraging family engagement, coordinating care, and pronouncing death.[9,10] Chaplains (non-denominational spiritual counselors) and clergy can help patients address the spiritual dimension of palliative care and can facilitate treatment decision-making, perform spiritual assessments, and bridge communication between the patient and family members or caregivers and medical staff.[11,12]

This evidence document summarizes core palliative care principles and many specific treatment approaches that can be readily adopted by primary care clinicians and integrated into the care they already provide to their patients with serious illnesses.

BOTTOM LINE: palliative care can be integrated with disease-modifying care across the duration of an illness and can include care and support of all those affected by serious illness from diagnosis through bereavement.

What is serious illness?

"Serious illness" is any health condition carrying a high risk of death in the next year and that either negatively impacts a person's daily function or quality of life, or excessively strains their caregivers.[13]

Major diagnostic indicators of serious illness include:

- metastatic cancer

- advanced chronic obstructive pulmonary disease (COPD)
- advanced heart failure
- end-stage liver or renal disease
- dementia

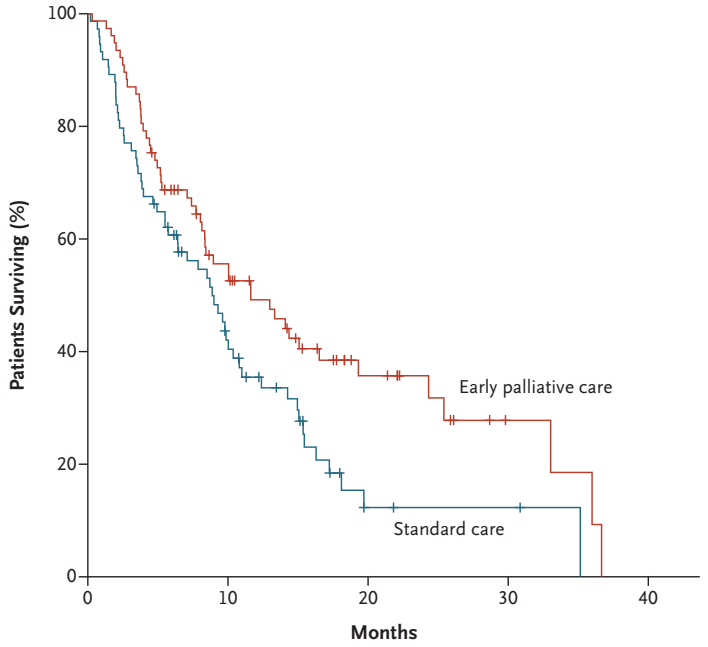
Major functional indicators of serious illness include:

- frequent hospitalizations
- poor mobility
- poor appetite/weight loss
- caregiver stress

Benefits of palliative care

The potential advantages of early palliative care were demonstrated in a trial that randomized 151 patients with newly-diagnosed metastatic lung cancer to early palliative care integrated with standard oncologic care or standard oncologic care alone.[1] Quality of life and mood were assessed at baseline and at 12 weeks. Among the 107 patients alive at follow-up, those assigned to early palliative care had better quality of life than did patients assigned to standard care (mean score on the Functional Assessment of Cancer Therapy-Lung scale 98.0 vs. 91.5; P=0.03). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs. 38%, P=0.01). Despite the fact that fewer patients in the early palliative care group than in the standard care group received intensive end-of-life care (33% vs. 54%, P=0.05), median survival (a secondary outcome) was longer among patients receiving palliative care (11.6 months vs. 8.9 months, P=0.02), suggesting that, at the very least, palliative care does not shorten life.

Figure 3: Survival in patients randomized to early palliative care vs. standard care[1]



In another demonstration of the benefits of palliative care, a retrospective study compared 176 patients at high risk for overmedicalized end-of-life care enrolled in a community-based palliative care program vs. 570 patients who received standard care.[14] Patients getting palliative care showed a statistically significant 20% reduction in total medical costs, a 38% reduction in intensive care unit (ICU) admissions, a 33% reduction in hospital admissions, and a 12% reduction in hospital days.

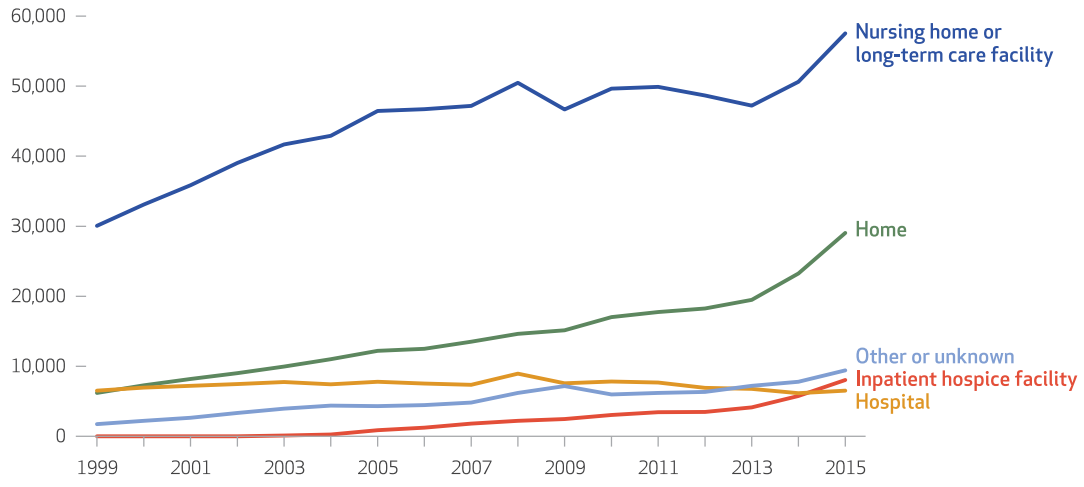
BOTTOM LINE: palliative care is associated with increased quality of life, reduced physical and psychological symptoms, and reduced medical costs.

Trends in serious illness and end-of-life care

In recent years end-of-life care has been characterized by an increasing diversity in the causes of death, increases in multimorbidity and illness complexity among people with terminal illnesses, and shifts in patterns of care and in sites of death.[15,16] Older patients with chronic conditions and functional limitations use a large percentage of healthcare resources. Patients aged 65 years and older represent approximately 7.1% of the population and yet they consume approximately 33.4% of healthcare costs, much of it spent in the last 6 months of life.[3]

In recent years increasing numbers of people have been dying at home or in inpatient hospice facilities (Figure 4).

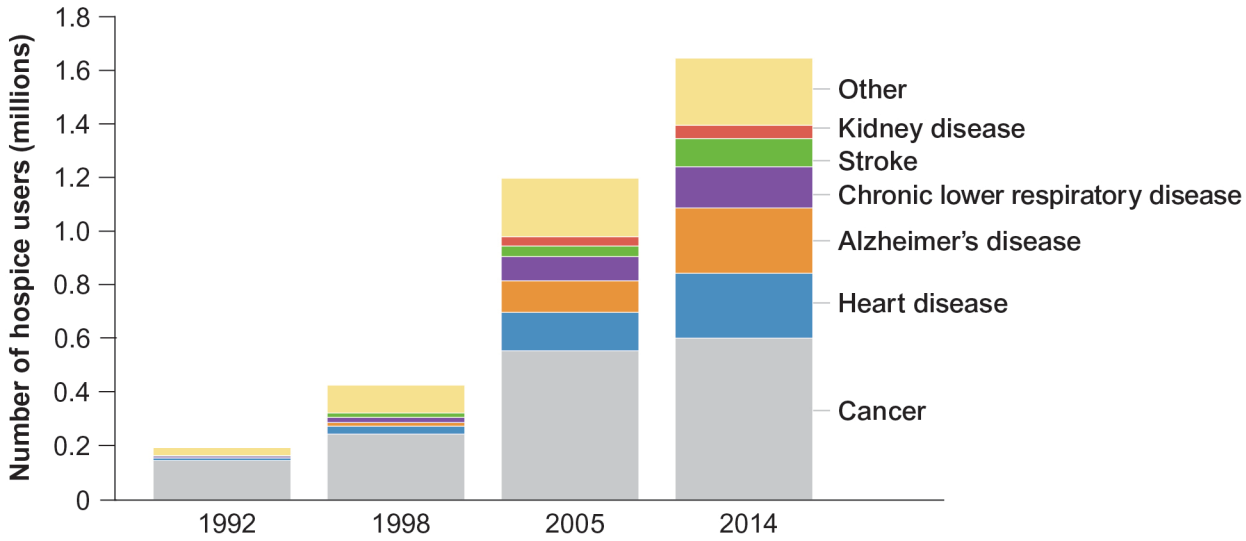
Figure 4: Trends in site of death among U.S. decedents, 1999-2015[15]



SOURCE Authors' analysis of data from: Centers for Disease Control and Prevention, CDC WONDER (Note 1 in text). **NOTE** Percentages were computed from CDC data that the authors grouped by year and site of death.

The proportion of patients with Alzheimer's disease, heart disease, and chronic lower respiratory disease among those in hospice programs has been increasing (Figure 5).

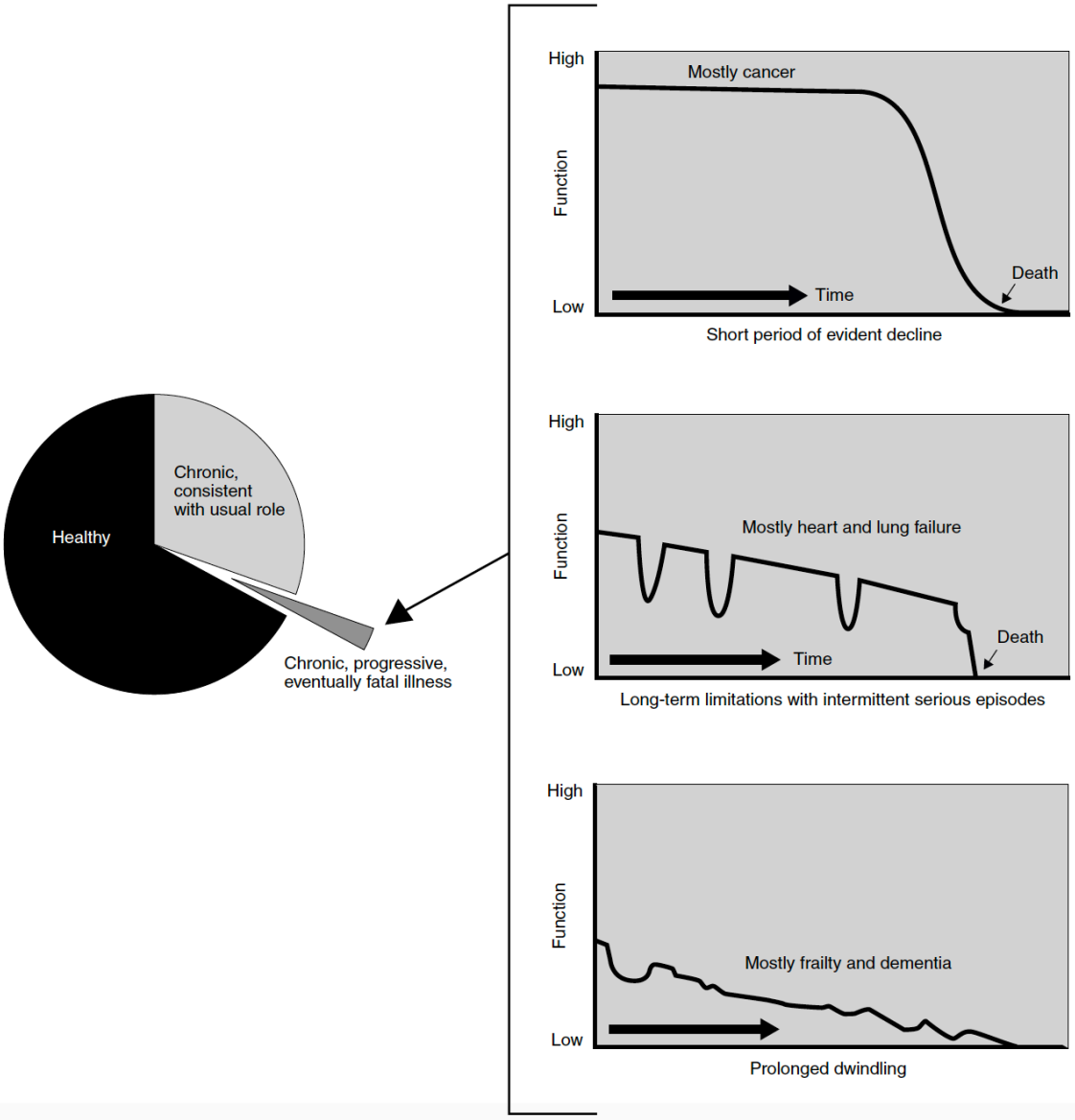
Figure 5: Numbers of hospice users by condition in selected years[15]



Illness trajectories

Different kinds of serious illness have different trajectories of decline towards death (Figure 6). Cancer is characterized by a short period of rapid functional decline, and organ failures (e.g., heart and lungs) are characterized by repeated bouts of decline and recovery. Frailty and dementia are characterized by a gradual decline, although the course can be unpredictable, which is why early palliative care in these populations is particularly important.

Figure 6: Illness trajectories[6]



BOTTOM LINE: end-of-life care is characterized by an increasing diversity in the primary diagnoses of decedents, increases in multimorbidity and illness complexity, and a shift toward dying at home or in-patient hospice facilities. The changing picture of end-of-life and hospice care in the United States places new demands on primary care providers as they manage more older adults with complex illnesses or dementia. Concurrently, the palliative care and hospice workforce is also shifting to accommodate these changes, moving away from cancer-centered care delivered in hospitals and toward broader care of all serious illnesses delivered in a range of settings.

Disparities in serious illness care

Disparities by race, ethnicity, socioeconomic status, and gender exist for many aspects of health care and medical outcomes. For example, Black patients have been found to experience greater pain intensity and pain-related disability than White patients,[17] and Black and Hispanic patients are more likely than White patients to have untreated or undertreated pain.[18]

In a study of 3,789 men with prostate cancer, Black patients had fewer treatments (e.g., chemotherapy, OR 0.59) and more intensive end-of-life care (e.g., ICU admission OR 1.27, and initiation of cardiopulmonary resuscitation, OR 1.72) compared to White patients.[19] Racial minority patients with lung cancer had more ICU and hospital days, more emergency room (ER) visits, and were less likely to use hospice.[20]

Data on the use of palliative or hospice care for racial minorities are mixed. Although one study of 6,288 patients with metastatic cancer found that Black patients were more likely to have inpatient palliative care consultation than White patients,[21] another study of patients with end-stage renal disease found that Black and Hispanic patients were *less* likely to receive inpatient palliative care consultation (adjusted ORs 0.72 and 0.68, respectively).[22]

The role of primary care clinicians

Primary care clinicians can provide a continuum of care as a disease progresses and a patient's needs change.

Table 1: The changing roles for primary care as end-of-life approaches.

Health Status	Goal of care	Primary care role
Diagnosis of serious illness	Use disease modifying treatments and manage symptoms.	Provide overall health care and coordinate specialist input. Advance Care Planning: initiate serious illness conversations and identify a health care proxy.
Advancing serious illness	Reassess the risks and benefits of disease-modifying treatments in accordance with patient's goals and preferences.	Assess and manage common symptoms. Link patients and families to additional supports (e.g., social work). Coordinate with specialist as needed to clarify the prognosis. Advance Care Planning: continue serious illness conversations and encourage the patient to complete a POLST.

Hospice	Provide comfort-focused care for the patient and family as the end of life approaches.	Work with hospice to enroll patient. Continue to serve as patient's PCP.
Bereavement	Support loved ones through their bereavement.	If applicable, screen for complicated grief and refer if necessary. Family members of patients enrolled in hospice care are eligible for bereavement support for one year after death.

Hospice

Primary care clinicians involved in decisions about placement into hospice care need to be aware of some potential complications with this move. For example, patients in hospice typically are not eligible for total parenteral nutrition, blood transfusions, or chemotherapy (although "open access" policies may allow these services in some cases). In-home hospice care is not typically 24-hour care so this may need to be provided by family members or some other kind of caregiver. Visiting nurses may provide more regular but less specialized care, but typically the patient must be homebound to qualify. Note that when the patient chooses to enter hospice, they waive their rights to Medicare Part B payments for other services that are related to the treatment or management of their terminal illness, with the exception of care provided by their own attending physician.

BOTTOM LINE: primary care clinicians play a central role in the care of patients with serious illness, including the transition to hospice care, which may involve trade-offs in treatment availabilities.

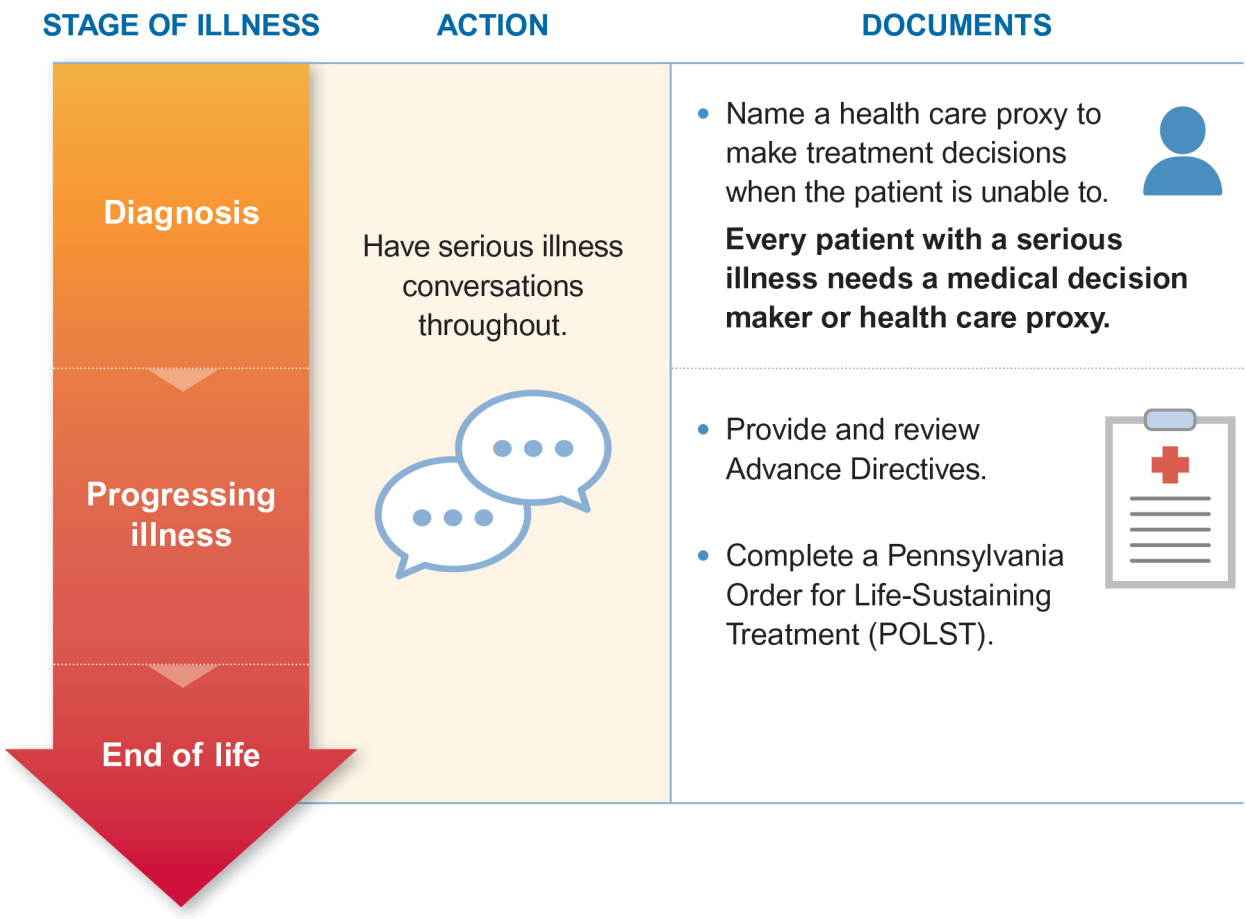
Advance care planning

ACP helps adults at any age or stage of health understand and share their personal values, life goals, and preferences regarding future medical care. It is a continuous, dynamic process of reflection and communication (Figure 7). It is not typically a "one and done" process. Primary care clinicians should lead ACP discussions, regardless of specialist contributions to the effort.

The goal is to help ensure that people receive medical care consistent with their values, goals, and preferences during serious and chronic illnesses and to ensure that treatments align with patients' priorities.[23]

ACP differs from shared decision-making in that ACP is focused on future treatment and care, whereas shared decision making is focused on making decisions about current treatment options.

Figure 7: Stages of advance care planning activities[24]



The potential benefits of having iterative conversations about end-of-life care include: improved end-of-life communication, documentation of care preferences, patients feeling more prepared for death and less anxious, dying in a preferred place, reduced burden and stress on loved ones, and increased satisfaction with care.[25-28] A randomized trial of 986 primary care patients aged 55 years and older compared the online PREPARE program plus an advance directive vs. the advance directive alone.[29] Using PREPARE resulted in a higher rate of ACP documentation (43.0% vs. 32.0%; P<0.001) and higher self-reported scores on ACP engagement (98.1% vs. 89.5%; P<0.001). Results remained significant among English speakers and Spanish speakers.

Although many patients, and practically all health care providers, know about ACP, most patients have not completed the most common documents involved in this process. A systematic review of 150 studies with 795,909 patients found that only 37% had completed advance directives, 29% had a living will, and 33% had named health care proxies.[30] The completion rate for advance directives was similar between those with chronic illnesses and healthy adults.

The primary documents involved in ACP are listed below:

- a living will, which states preferences for life-sustaining treatment and decisions about care in situations where a patient is terminally ill and unable to communicate

- healthcare proxy, which is a surrogate who can make, or participate in, clinical decisions involving situations not covered by a living will
- medical directives (e.g. Physician/Pennsylvania Orders for Life-Sustaining Treatment [POLST] or Medical Orders for Life-Sustaining Treatment [MOLST])[31]
- durable power of attorney, which is a designee to oversee decisions involving finances, estate distributions, and administrative matters

Some evidence suggests that having a POLST is associated with delivery of goal-concordant care involving the use of procedures such as CPR, antibiotics, intravenous (IV) fluids, and feeding tubes. A retrospective cohort study in 1,711 nursing home residents aged 65 years and older found that residents with POLST forms restricting medical interventions were less likely to be given life-sustaining treatments than those who did not.[32] There were no differences in symptom management or assessment. The findings suggested that the POLST program was superior to traditional methods for communicating preferences about life-sustaining treatments.

Reimbursement for ACP conversations

Clinicians can be reimbursed for advance care planning as either an optional element of a patient's wellness visit (same day/same provider) or as a separate Medicare Part B "medically necessary service" (deductibles and coinsurance apply).[33] No additional co-pay is required for ACP conversations held as part of an annual wellness visit. Billable advance care planning can be provided in any setting, including telephone or telehealth visits, and the patient does not have to be present (i.e., discussions can be with a family member of surrogate). Special rules apply for Federally Qualified Health Centers and other Critical Access Hospitals.

Table 2: CPT codes for advance care planning

CPT Codes	Billing Code Descriptors
99497	Advance Care Planning including the explanation and discussion of advance directives such as standard forms (including the completing of such forms, when performed), by the physician or other qualified health professional; first 30 minutes, face-to-face with the patient, family members, and/or surrogate
99498	(add-on) Each additional 30 minutes

Here are some tips for documenting ACP conversations:

- There are no limits on the number of times you can report ACP for a given patient in a given time period – but reimbursement for annual wellness visits are limited to once per year
- Briefly summarize the conversation
- The amount of detail needed is proportional to the length and complexity of the conversation
- Document the starting and stopping times and names of participants
- Note any ACP forms that were completed
- No diagnosis is required, but reference the diagnostic code for a serious illness if applicable

BOTTOM LINE: ACP is a dynamic, continuous process to ensure goal-concordant care for patients. Start conversations early, discuss the expected clinical course, and solicit treatment preferences and goals-of-care. ACP is reimbursable by Medicare.

Five steps to more effective communication

To make informed choices about care in the context of serious illness, patients and their loved ones need clear, timely information about their diagnosis, prognosis, and treatment options. These communications can provoke strong emotions, which can be challenging for clinicians. Palliative care training includes a focus on evidence-based communication strategies that can help clinicians effectively facilitate necessary conversations and prioritize conversations based on prognosis.

Step 1: Enable the discussion

Introduce the conversation with a clear and patient-centered rational to help allay anxiety. For example, you might say: "I'd like to talk in advance about what is ahead and what is important to you so we can make sure to provide you with the care you want—is that okay?"

Step 2: Assess understanding and preferences

Many patients don't document or readily discuss their wishes.[30] The Ask-Tell-Ask approach is one way of giving control over the flow of information to patients or their surrogates:[34]

1) **Ask** for understanding; **Tell** information; **Ask** for verification of understanding
   - "Can you tell me what you understand about where things are with your illness?"
   - "Because your disease isn't responding, I think we need to try something different."
   - "Who will you share this information with; how will you explain it to them?"
2) **Ask** for permission to share information; **Tell** information; **Ask** for verification of understanding
   - "Can I share with you some information about what may be ahead?"
   - "I wish this wasn't the case, but I'm worried that treatments for your COPD are not working well."
   - "I want to make sure I explained things clearly; can you tell me what you understood?"

"Tell me more" is a simple phrase to elicit additional information that helps avoid the assumption that you've heard everything important when asking questions.[34]

Step 3: Share the prognosis

Share a prognosis with a patient using clear, direct language that reflected the patient's stated information preferences. Formulating a prognosis can be challenging, but three validated tools can help with this process:

- ePrognosis (a set of online tools developed by the University of California San Francisco)[35]
- Palliative Performance Scale (10-levels of patient function and consciousness correlated with expected length of survival)[36]

- "Surprise question" (i.e., "Would you be surprised if this patient died in the next 12 months?") A meta-analysis of 22 studies found that this question, when answered by physicians, had a pooled accuracy of 74.8% (sensitivity 73%, specificity 74%)[37]

One useful construct for helping patients understand their prognosis is a framework of "hope/worry," which conveys empathy, acknowledges uncertainty, and helps promote planning.[38]

- "It can be difficult to predict what will happen with your illness. I **hope** you will continue to live well for a long time, but I'm **worried** that you could get sick quickly, and I think it is important to prepare for that possibility."

It's important to expect and respond to emotions. The NURSES framework is one approach to structuring an empathetic response to a patient's emotional reactions.[34,39]

Name the emotion: *"I can see this was really upsetting." "You seem sad."*

Understand: *"How does all this make you feel?"*

Respect: Praise coping skills and validate emotions. *"I really admire the strength you've shown."*

Support: *"This can be really frightening. I'll do whatever I can to help you get through this."*

Explore: *"Tell me more"* about…

Silence: Provide adequate silence for response.

Step 4: Explore key topics

Attempt to solicit from patients their preferences for end-of-life care, which can range from "comfort only" (symptomatic treatments and palliative care/hospice) to "life prolongation" (hospitalization and life support) or some in-between level of care. Recognize that these preferences may change with time and require repeated inquiries.

Table 3: Goals of care applied to two common end-of-life issues[40]

Goals of care	Pneumonia	Eating problems
Comfort	Antipyretics and oxygen	Palliative hand feeding (may not provide sufficient calories)
Life prolongation	Hospitalize for life-prolonging treatment	Tube feeding (note: professional societies recommend against tube feeding because it does not improve survival, malnutrition, or rate of aspiration)
In-between	Antibiotics, while avoiding hospitalization	Palliative hand feeding with aspiration precautions

A number of tools can support ACP conversations:

- PREPARE for your care (online tool at PREPAREforyourcare.org)
- Go Wish[41,42] (free tool available at gowish.org)
- What Matters to Me Workbook (available at: theconversationproject.org/get-started)
- Five Wishes (an advance planning tool and document for creating valid advance directives; see fivewishes.org)
- Serious Illness conversation guide (See Appendix I)

Additional information is available at AlosaHealth.org/Serious_illness

Step 5: Make recommendations and formulate a plan

Use the patient's prognosis and the information they have shared to formulate a patient-centered recommendation covering treatment options, additional supports, and/or additional conversations.

BOTTOM LINE: patients and their loved ones need clear, timely, empathetically-delivered information about their diagnosis and the future with their illness. They, along with their clinicians, need to explore together what matters most to them—their goals, worries, and strengths—while together considering treatment preferences and options. These communications can provoke strong emotions, which can be addressed with a range of strategies including "Ask/Tell/Ask," "Tell me more," and the "hope/worry" framework.

Communicating with patients who have dementia

A diagnosis of dementia does not mean a patient has lost so much mental capacity that a conversation about advance care is not possible. Clinicians should assume full mental capacity if they are unsure since dementia as a progressive condition situated on a continuum of mental functioning.[43] Discussions about advance care should include descriptions of the kinds of issues common in dementia, such as loss of cognition, reduced physical functioning, swallowing problems, and infections.

Explore the person's disease awareness and expectations and their ideas about their disease trajectory. If the person is reluctant to talk about end-of-life issues, do not insist. Instead, explore their perceptions of what quality of life means to them, and ask if they have any fears or concerns about the future.

Providing patients with clear, visual information about the realities of advanced dementia and the differences between comfort care and life prolongation care may improve the patient experience. A 2017 trial randomized 302 dyads of nursing home residents with advanced dementia and their decision makers to either a video focused on goals-of-care and a structured discussion about ACP vs. a general information video and usual care.[44] After nine months follow-up, those in the intervention group reported better quality of communications, greater goal concordance (88.4% vs. 71.2%, P=0.001), and fewer hospital transfers (RR 0.47; 95% CI: 0.26-0.88).

Managing common symptoms of serious illness

Caring for seriously ill patients involves understanding their physical, functional, emotional, and spiritual needs. Assessment and care plans typically focus on relieving symptoms and improving or maintaining functional status and quality of life with the use of pharmacological, non-pharmacological, interventional, behavioral, and complementary treatments. Acute and chronic symptom management is best accomplished as a collaborative effort between all of the clinicians involved in patient care, including primary and specialty care providers. The most common symptoms of serious illnesses are summarized in Table 4.

Table 4: Most common symptoms among 3,030 patients referred to for palliative care[45]

Symptom	Frequency
Pain*	80.4%
WHO I	12.3%
WHO II	16.4%
WHO III	51.7%
Generalized weakness	50%
Fatigue	48%
Anxiety	28%
Anorexia	26%
Constipation	18%
Focal weakness	18%
Depression	18%
Shortness of breath	15%

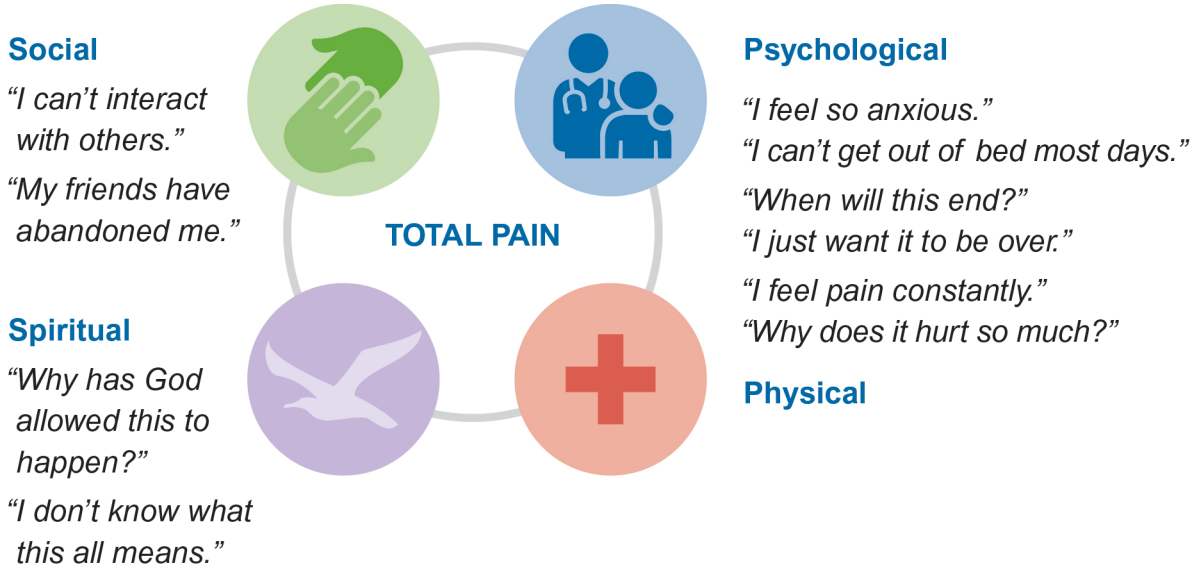
* World Health Organization pain levels I (mild), II (moderate), III (severe)

Pain

Pain control is a central focus of palliative care, but the goal of pain management is not simply the elimination of all pain, it is the control of pain sufficient for a given patient to achieve his or her highest quality of life in the moment.[46] What “quality of life” means will vary between individuals and between different phases of illness within a single individual. For many patients, for example, mental alertness sufficient to allow meaningful interactions with loved ones can be more important than physical comfort.[46] This requires a sensitive, flexible, and adaptive approach to pain management.

A core concept in palliative care is a biopsychosocial perspective on pain that recognizes four dimensions affecting how pain is perceived (Figure 8).

Figure 8: Biopsychosocial model of pain



Pain is defined by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience associated with, or resembling, that associated with actual or potential tissue damage."[47] Pain is always a personal experience influenced to varying degrees by biological, psychological, and social factors. Importantly, pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons. Through their life experiences, individuals learn the concept of pain. A person's report of an experience as pain should be respected. Although pain usually serves an adaptive role, it can easily erode function and social and psychological well-being.

In the palliative care setting, clinicians may need to manage acute pain (e.g., post-surgical or post-treatment pain) or chronic pain (defined as pain lasting longer than 3 months or past the time of normal healing) or both types of pain simultaneously.

Assessment tools

Many tools have been developed to document and assess pain. Initial approaches to assessing pain severity use a visual analog scale rating pain from 0 (no pain) to 10 (worst pain you can imagine) (some scales use a 0 to 100 scale) or the Wong-Baker "FACES" scale, which uses pictorial depictions of pain severity. Such scales are often used in clinical trials of pain therapies, and the minimal clinically important difference using these scales is generally considered a 20%-30% change from baseline (e.g., 2-3 points on a 0-10 scale).[48] Another tool is the OPQRSTU paradigm depicted in Table 5.

Table 5: OPQRSTU pain assessment mnemonic

OPQRSTU	Example questions
Onset	*When did the pain start?*
Provokes/palliates	*What makes it worse?* *What makes the pain better?*
Quality	*How would you describe your pain – is it sharp, achy, burning?*
Region and radiation	*Where is your pain located?* *Does it move from one place to another?*
Severity	*How would you rate your pain on a scale of 0-10?* *Is it mild, moderate, or severe?*
Timing and treatment	*Are there times of day when the pain is worse?* *How long does it take for pain medication to kick in? How long does it last?*
Understanding impact	*How does this pain affect your ability to do things?* *What would be a tolerable level of pain?*

Treatment options

Clinicians can avail themselves of a wide range of pharmacologic and non-pharmacologic approaches for pain management, which should be employed using the following general principles:

- Identify and treat the source of the pain, if possible, although pain treatment can begin before the source of the pain is determined
- Select the simplest approach first. This generally means using non-pharmacologic approaches as much as possible and/or trying medications with the least severe potential side effects, and at the lowest effective doses
- Establish a function-based management plan if treatment is expected to be long-term

Managing pain

Use a multimodal approach, including non-pharmacologic options (e.g., yoga, massage, acupuncture, exercise).

Match the pain mechanism to the medication:

- Neuropathic pain responds best to duloxetine (Cymbalta) or anticonvulsants (e.g., gabapentin [Neurontin], pregabalin [Lyrica]).
- Musculoskeletal pain is best managed with acetaminophen or NSAIDs, and any pain with an inflammatory component is best managed with an NSAID. Acetaminophen can be used as an adjunct.

If opioids are needed, use medication agreements, drug testing, and other best practices as appropriate.

Approaches to chronic pain management

A range of non-pharmacological treatments may help patients manage chronic pain, which can be used alone or in combination with pharmacological treatments:

- physical therapy
- yoga
- acupuncture
- massage
- transcutaneous electrical nerve stimulation
- cognitive behavioral therapy
- mindfulness meditation
- weight loss

Medications used to treat chronic pain include:

- acetaminophen
- non-steroidal anti-inflammatory drugs (NSAIDs)
  - oral
  - topical
- antidepressants
  - serotonin and norepinephrine reuptake inhibitors
  - tricyclic antidepressants (TCAs)
  - selective serotonin reuptake inhibitors
- anticonvulsants
- topical lidocaine or capsaicin
- cannabinoid-based therapies
- opioids

Opioids are classified by the Drug Enforcement Agency according to their presumed abuse and addiction potential, although the evidence base for making these differentiations continues to evolve. Tramadol, for example, is now known to have as much potential for abuse as opioids in more restrictive classes.[49]

Table 6: Opioids by schedule[50]

Schedule*	Description	Opioid
Schedule I	No medical use, lack of accepted safety, and a high potential for abuse	Heroin
Schedule II	High potential for abuse, which may lead to physical or psychological dependence	Hydrocodone Oxycodone Morphine Hydromorphone Tapentadol Methadone Fentanyl
Schedule III	Less potential for abuse than schedules I and II, low to moderate physical dependence and high psychological dependence	Buprenorphine Codeine + acetaminophen
Schedule IV	Lower potential for abuse than schedule III medications	Tramadol
*Note: DEA schedules may not accurately reflect the actual abuse or dependence potential for these medications.		

Relative effectiveness

For chronic pain, the evidence that opioids reduce pain and improve function more than placebo is weak. A 2018 systematic review and meta-analysis of 96 trials comparing various opioids vs. placebo or non-opioid analgesics in 26,169 patients with chronic non-cancer pain found that opioids may slightly reduce pain and increase physical functioning compared to placebo, but not compared to non-opioids.[51] In 76 trials comparing opioids vs. placebo with median follow-up of 60 days (range 30-84 days), the reduction in pain scores with opioids (on a 10-point scale) was only 0.69 points, which is below the generally-accepted minimum clinically important difference for pain. Physical function scores (on a 100-point scale) improved with opioids by 2.04 points, which, again, may not be clinically important. The risk of vomiting with opioids, however, was more than four times higher than with placebo (RR 4.12; 95% CI: 3.34-5.07).[51] There were no significant differences in emotional functioning or role functioning.

The same meta-analysis compared opioids to non-opioid analgesics included NSAIDs, TCAs, anticonvulsants, and synthetic cannabinoids. No significant differences were found in physical functioning scores for any of the comparisons, and no significant differences were found in pain scores for comparisons with NSAIDs (9 trials), TCAs (3 trials), or cannabinoids (1 trial). As compared to anticonvulsants, opioids were associated with slightly lower pain scores, although the confidence interval includes differences that may not be clinically significant (weighted mean difference -0.9 points; 95% CI: -1.65 points to -0.14 points).[51]

The Strategies for Prescribing Analgesics Comparative Effectiveness **(SPACE) trial** randomized 240 patients with moderate to severe chronic low back pain or knee or hip osteoarthritis to regimens of morphine, oxycodone, or hydrocodone or non-opioid analgesics (e.g., acetaminophen, NSAIDs, antidepressants, anti-epileptics) and followed them for one year.[52] The primary outcome was score for pain-related functioning using the 0-10 Brief Pain Inventory (BPI) scale (lower score indicates better function). At 3, 6, 9, and 12 months there were no significant differences in BPI scores (overall P=0.58). At one year, pain intensity was significantly better in the non-opioid group (P=0.03). No differences in treatment response were seen in analyses by pain condition. The authors concluded that their results “do not support initiation of opioid therapy for moderate-to-severe chronic back pain or hip or knee osteoarthritis pain.”[52]

Opioid formulations

Prescription opioids are available in immediate-release and extended-release/long-acting (ER/LA) formulations. Immediate-release agents are recommended in opioid-naïve patients and for all acute pain conditions, with ER/LA agents reserved for patients or conditions in which the longer duration of action (and, hence, less frequent dosing) are preferred.[53] A trial comparing immediate release to an ER/LA opioid did not find evidence that the continuous, time-scheduled use of ER/LA opioids was more effective or safer than intermittent use of the immediate-release opioid.[54] According to the FDA, ER/LA opioids should only be used for patients who tolerate 60 morphine milligram equivalents per day (MMED) for at least one week.[55]

Efforts to create formulations with lower risks of abuse have met with limited success. For example, Opana ER was removed from the market after reports of intravenous abuse of the oral formulation.[56] Abuse-deterrent or tamper-resistant formulations do not prevent users from becoming addicted or taking too much of an opioid by mouth, which is the most common route for abuse.[57,58] No prospective randomized clinical trials or rigorous observational studies have measured the impact of abuse-deterrent opioids on the risk of abuse or misuse. As of August, 2018, eight opioids with abuse-deterrent properties have been approved by the FDA: OxyContin, Targiniq ER, Embeda, Hysingla ER, MorphaBond ER,

Xtampza ER, Arymo ER, and RoxyBond.[59] Recent evidence suggests that abuse-deterrent formulations may confer greater risks to patients. A 2020 cohort study of more than 70 million patients with indications for an oral opioid analgesic found that with a 1-year follow-up the risk of opioid use disorder was more than twice as high among patients on an abuse-deterrent formulation compared to standard formulations (OR 2.02; 95% CI: 1.83-2.23) as was risk for opioid poisoning (OR 1.64; 95% CI: 1.35-1.99).[60]

Tramadol and tapentadol are mu receptor agonists and norepinephrine reuptake inhibitors. Their exact mechanisms of action are unknown, but their analgesic effects are similar to morphine. Tramadol is classified as Schedule IV, which has led some to view it as less potent or safer than other opioids. The 2016 National Survey on Drug Use and Health, however, found that 1.7 million people in the U.S. aged >12 years reported misusing tramadol products (e.g., Ultram, Ultram ER, Ultracet) in the previous year.[49] In addition, a 2019 cohort study of 88,902 patients with osteoarthritis (mean age 70 years) showed increased risks of death at one year compared to NSAIDs naproxen (HR 1.7; 95% CI: 1.4-2.1), diclofenac (HR 1.9; 95% CI: 1.5-2.6), and celecoxib (HR 1.7; 95% CI: 1.3-2.2).[61] In that study, the hazard ratio for death at one year was not significantly different between tramadol and codeine (HR 0.94; 95% CI: 0.83-1.1).

Tapentadol, an opioid with potency and side effect profiles similar to other common opioids such as oxycodone, is FDA-approved for treating neuropathic pain, although it is also used for musculoskeletal pain. A 2015 Cochrane review of four randomized trials with 4,094 patients with osteoarthritis or back pain found modest reductions in pain with tapentadol vs. placebo (mean difference -0.56 points on 11-point scale; 95% CI: -0.92 to -0.2 points), although the CI includes differences that may not be clinically important.[62]

Approaches to acute pain management

A commonly-recommended way to manage acute pain is with multimodal analgesia, in which several therapeutic approaches are used, each acting at different sites of the pain pathway, which can reduce dependence on a single medication and may reduce or eliminate the need for opioids and associated risks/side effects.[63]

Multimodal analgesia (e.g., using drugs from two or more classes, or a drug plus a non-drug treatment) can produce synergistic effects, reduce side effects, or both. One example of multimodal analgesia is the use of both a non-steroidal anti-inflammatory drug (NSAID) and acetaminophen, plus physical approaches (e.g., cold, compression, or elevation) to manage postoperative pain. Demonstrated benefits of multimodal analgesia include earlier ambulation, earlier oral intake, and earlier hospital discharge for postoperative patients, as well as higher levels of participation in activities necessary for recovery (e.g., physical therapy).[63]

Non-pharmacological methods of acute pain management can be helpful in all phases of care, including immediately after tissue trauma (e.g., rest, application of cold, compression, elevation) and later in the healing period (e.g., exercises to regain strength and range of motion).

Non-pharmacologic methods can include:[64]

- relaxation exercises
- distraction/guided imagery
- acupuncture
- massage
- electroanalgesia (e.g., transcutaneous electrical nerve stimulation)
- physical therapy

- yoga

The same range of pharmacological treatments used for chronic pain can be used for acute pain. In general, mild-to-moderate acute pain responds well to oral non-opioids (e.g., acetaminophen, NSAIDs, and topical agents). Although many patients perceive them to be weaker analgesics than opioids, evidence supports the notion that pain relief from acetaminophen and NSAIDs is equal to and sometimes superior to that of opioids. Acetaminophen and NSAIDs are often added to an opioid regimen for their opioid-sparing effect. Because non-opioids relieve pain via different mechanisms than opioids, combination therapy can provide improved relief with fewer side effects.

The choice of medication may be driven by patient risk factors for drug-related adverse effects (e.g., NSAIDs increase the rate of gastrointestinal, renal, and cardiovascular events). If acetaminophen or NSAIDs are contraindicated or have not sufficiently eased the patient's pain or improved function despite maximal or combination therapy, other drug classes are sometimes used, e.g., anticonvulsants or opioids.

Topical capsaicin and salicylates can both be effective for short term pain relief and generally have fewer side effects than oral analgesics, but their long-term efficacy is not well studied.[65,66] Topical NSAIDs and lidocaine may also be effective for short-term relief of superficial pain with minimal side effects. Topical agents can be simple and effective for reducing pain associated with wound dressing changes, debridement of leg ulcers, and other sources of superficial pain.[67]

Anticonvulsants, such as gabapentin, pregabalin, oxcarbazepine, and carbamazepine, are often prescribed for both chronic and acute neuropathic pain (e.g., post-herpetic neuralgia and diabetic neuropathy), although evidence for efficacy in acute pain conditions is weak.[68] A 2017 trial, for example, randomized 209 patients with sciatica pain to pregabalin 150 mg/day titrated to a maximum of 600 mg/day vs. placebo for 8 weeks.[69] There was, however, no significant difference in pain between groups at 8 weeks (mean leg pain intensity on a 0-10 scale 3.7 with pregabalin vs. 3.1 with placebo, P=0.19).

Potential side effects of anticonvulsants include sedation, dizziness, and peripheral edema. Gabapentanoids have been associated with an increased risk of respiratory depression when combined with opioids,[70] and some epidemiological studies have shown an increased risk for opioid-related death with co-prescription of opioids and gabapentanoids (OR 1.99; 95% CI: 1.61-2.47 compared to patients who did not have co-prescription.[71]

Although a short course of an opioid analgesic is common for post-surgical or post-treatment pain, opioids should still be used cautiously. A randomized trial of 416 patients with acute extremity pain found no clinically important differences in pain reduction at two hours after single-dose treatment with ibuprofen and acetaminophen vs. three different combinations of opioid and acetaminophen analgesics.[72]

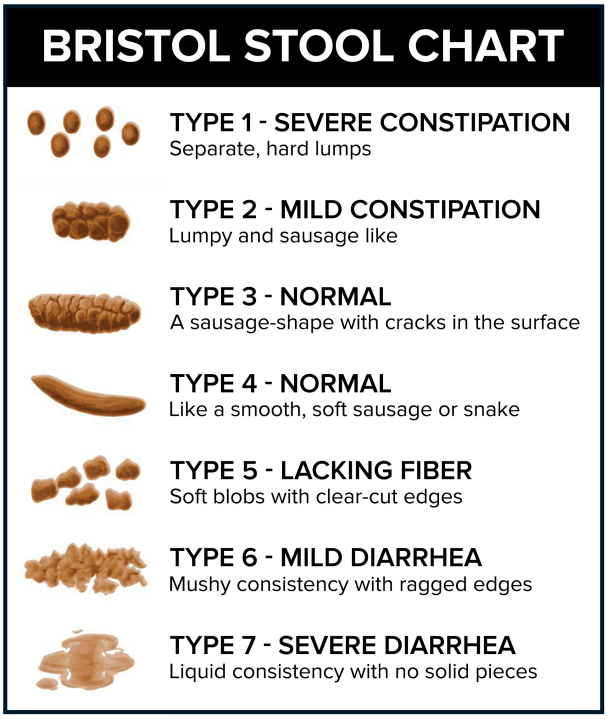
Physical dependence can readily occur after use of opioids for just a few days. In addition, side effects of opioid use include constipation, confusion/gait instability, respiratory depression, pruritus, erectile dysfunction, and fractures, all of which may be more problematic in older patients and occur at higher rates than with non-opioid analgesics. High-intensity prescribing of opioids (high doses or high numbers of pills prescribed) for acute pain may be associated with greater likelihood of long-term opioid use.[73,74] In a retrospective analysis of a national sample of opioid-naïve Medicare beneficiaries who received emergency treatment from 2008 through 2011, initial exposure to an opioid was a strong predictor of subsequent long-term use.[13]

Constipation

Constipation is a common problem among palliative care patients, especially those receiving opioid analgesics, and can cause extreme suffering and discomfort.[75] Broadly, constipation is the passage of small, hard feces infrequently and with difficulty, but patients vary in their perceptions of these components and may put more weight on other factors such as pain and discomfort when defecating, flatulence, bloating, or a sensation of incomplete evacuation. Because of this, constipation is best defined by the patient and inflexible rules about what frequency of evacuation requires intervention should be avoided. That said, if a patient is defecating less than three times per week an assessment is usually warranted.[75]

A number of constipation assessment scales are available, such as the Bristol Stool Chart (Figure 9), which may be helpful to patients for assessing their own bowel movements or when communication between a clinician and patient is difficult for some reason.

Figure 9: Bristol stool chart[76]



To reduce the risk of constipation, patients should be encouraged to be physically active within their limits and to use a mild stimulant laxative such as senna or bisacodyl and increase the dosage in 48 hours if no bowel movement occurs. Consider a rectal examination if no bowel movement occurs in 72 hours. If there is no impaction, consider other therapies such as an enema, suppository, or magnesium citrate.[78] Medications for refractory, opioid-induced constipation include naloxone derivatives: naloxegol (Movantik), methylnaltrexone (Relistor), or naldemedine (Symproic). Naloxegol is an oral tablet that is used daily while methylnaltrexone is a subcutaneous injection or oral tablet used daily. Naldemedine is taken by mouth daily (0.2 mg) and may cause side effects such as abdominal pain or discomfort, diarrhea, and nausea.[79] In the COMPOSE-1 trial, patients on naldemedine had significantly more

spontaneous bowel movements (defined as ≥3 per week) than those on placebo (47.6% vs. 34.6%, P=0.002).[80]

Although commonly used, the evidence base for docusate (Colace) is very weak, particularly among those with serious illness. A systematic review of 9 studies of docusate in patients with chronic illness found significant clinical heterogeneity (preventing a meta-analysis) and only a small trend toward increased stool frequency with use of docusate, leading to the conclusion of "inadequate experimental evidence" for the use of this drug in this population.[81]

Table 7: Management of opioid-induced constipation

Prevent – NO opioid prescription without laxative prescription	
Senna Polyethylene Glycol (Miralax)	8.6 mg 1 tabs orally every 12 hours 17 grams orally daily (up to 34 grams twice daily)
Non-pharmacologic	Increase fluids and activity Discontinue constipating medications Ensure privacy for defecation Correct electrolytes (e.g., calcium, potassium)
Titrate	
1. Senna (multiple forms) and/or Polyethylene glycol (Miralax) **THEN ADD (in order)**	1-3 tabs orally every 12 hours 17-34 grams orally once or twice daily
2. Lactulose	15 mg orally daily, up to 30 mg orally four times daily
3. Milk of magnesia	30 mL orally
4. Bisacodyl (e.g., Dulcolax)	10 mg orally or rectally daily
5. Magnesium citrate	½ to 1 bottle daily
Evacuate (if >5 days, consider mechanical evacuation as first line)	
Enema (Fleet, soap-suds) Manual disimpaction	Can be repeated

Shortness of breath

Dyspnea has been defined as "an uncomfortable sensation of breathing" and is a common symptom associated with many physical and psychological disorders or conditions.[82] The range of sensations a patient feels when experiencing dyspnea arise from the combined effects of at least four physiological systems:

- j-receptors at the junction of capillaries and alveoli, which respond to alveolar fluid or microemboli
- mechanoreceptors in the lungs, airway, and chest wall, which respond to stretch
- peripheral chemoreceptors in the aorta and carotid bodies, which respond to hypoxemia
- central chemoreceptors, which respond to increased CO_2

Patients experience shortness of breath when breathing requires increased effort (e.g., with pleural effusions), when the blood is hypercapnic, when the muscles controlling the diaphragm are weakened (e.g., in some forms of ALS), or when the brain perceives less ventilation that it expected. Anxiety can produce shortness of breath, but shortness of breath can also provoke anxiety, which can set up a positive feedback loop exacerbating symptoms.

One approach to a patient experiencing breathlessness is the COMFORT algorithm summarized in Table 8.

Table 8: The COMFORT algorithm[83]

C	**Call for help.** Calm the person.
O	**Observe** the person closely. Evaluate how severe their shortness of breath has become.
M	**Medication** like morphine, inhaled bronchodilator and/or medication for anxiety may help.
F	**Fan** to create air movement on the face. Open a window. Cool the room.
O	**Oxygen**. Increase the amount of oxygen or give oxygen if ordered.
R	**Reassure.** Help the person relax, provide reassurance.
T	**Take** your time, don't rush.

Pharmacologic approaches to managing dyspnea include:

- opioids
  - morphine 5 – 15 mg orally, although hyperconcentrated morphine (20 mg/ml) may be useful because the low volume is easier to take when feeling short of breath
  - other opiate at equivalent dose
- benzodiazepines
  - lorazepam 0.5 – 2 mg orally or sublingual (avoid alprazolam due to short duration of action)

Non-Pharmacologic approaches include:

- relaxation techniques
- increase air circulation with a fan or by opening a window
- thoracentesis or Pleurex catheterization
- radiotherapy (for obstructive masses)

Fatigue

Fatigue is the most common symptom affecting people with cancer and is, generally, a very common symptom at the end of life.[84] It can seriously erode a patient's quality of life and interfere with nearly every aspect of daily life. Fatigue is associated with many physical and psychological disease states including anemia, cancer, cancer treatments, and depression.

Non-pharmacologic approaches to fatigue, which generally have a weak evidence base but are also low-risk, include:

- increasing activity or exercise as tolerated
- nutrition counseling
- psychosocial measures such as cognitive behavioral therapy, relaxation, hypnosis, and biofeedback
- improving sleep hygiene (i.e., limiting naps, regular awakening and bedtimes, etc.)

Psychostimulants are recommended by the National Cancer Institute for cancer-related fatigue, an approach supported by a 2010 Cochrane systematic review of 31 studies with 7,104 participants that found that methylphenidate provided clinically meaningful improvements in fatigue vs. placebo.[85] A 2011 trial randomized 30 hospice patients with fatigue to 5 mg methylphenidate at 8 a.m. and 1 p.m. vs. placebo for two weeks. Patients in the methylphenidate group had significantly lower scores on measures of fatigue and depression at 14 days, with no significant toxicities observed.[86]

The recommended dose of methylphenidate for fatigue is 2.5 – 10 mg orally twice daily (morning and early afternoon).[86] Modafinil 200 mg orally daily is another option for pharmacologic management of fatigue.

Nausea and vomiting

Nausea and vomiting are common near the end of life and can significantly erode quality of life for patients and their families. Unfortunately, the pathophysiology of nausea and vomiting is complex, involving a host of potential physical or psychological factors (e.g., medications, fear, motion, bacteria, blood-borne emetics) acting on a wide range of endogenous receptors, which can make management decisions difficult.[87] Opioids, chemotherapeutics, antidepressants, and antibiotics frequently contribute to nausea and vomiting, as can recent or rapid discontinuation of corticosteroids.[88]

Taking a thorough history, physical examination, and review of medications is essential to guide treatments, which can focus on prescribing the appropriate antagonist to the receptors suspected to be involved in the symptoms. (Some clinicians, however, suggest starting an empirical antiemetic regimen with a D_2 antagonist regardless of the suspected origin of the nausea.)[89] Since oral administration of medications is often not feasible, alternative routes such as subcutaneous infusions, rectal suppositories, buccal films, or orally dissolvable tablets can be considered.

Table 9: Treatments for nausea and vomiting[87]

Indication/Medication	Dose	Considerations
Anxiety		
Lorazepam (Ativan)	0.5-1 mg orally every six hours	Avoid in those at high risk of delirium, caution in hepatic disease.
Vestibular (e.g., Vertigo)		
Meclizine (Antivert)	25-50 mg orally every 12-24 hours	
Scopolamine (Transderm Scop)	1 mg transdermally every 72 hours	Crosses blood-brain barrier – avoid in those at high risk of delirium
Chemical / Metabolic (e.g., opioid-related, chemotherapy-induced nausea/vomiting)		
Prochlorperazine (Compazine)	5-10 mg orally every 6-8 hours	Dopamine-2 antagonist; risk of extrapyramidal symptoms (EPS)
Ondansetron (Zofran)	8 mg orally every 8 hours	Can be very constipating
Metoclopramide (Reglan)	10 mg orally every 6-8 hours	Promotility agent AND dopamine-2 antagonist; risk of EPS
Olanzapine (Zyprexa)	5 mg orally/sublingually every 6-8 hours	Atypical antipsychotic; Zydis formulation dissolves sublingually
Dronabinol (Marinol)	10-20 mg orally every 2-4 hours	Effective for chemotherapy-induced nausea/vomiting

Medical cannabis	Form dependent	Avoid smoke inhalation for those with lung disease
Abdominal / Visceral (e.g., gastroparesis, bowel obstruction)		
Metoclopramide (Reglan)	10 mg orally every 6-8 hours	Avoid if suspected complete bowl obstruction; risk of EPS
Famotidine (Pepcid) or other H2 blocker	20 mg orally every 6 hours	If gastroesophageal reflux disease or hypersecretory condition suspected
Ondansetron (Zofran)	8 mg orally every 8 hours	Can be very constipating
Unknown etiology		
See chemical/metabolic		
• In general, schedule for 24-48 hours, then as needed • If unable to take orally, refer to emergency department for evaluation and IV medication (if on hospice, consider subcutaneous administration of IV medications		

Often overlooked as treatments for nausea and vomiting are low-dose antipsychotics (e.g., haloperidol 0.5 mg orally every 6 hrs. or olanzapine 2.5-5 mg orally every 6-8 hrs.) which can be very effective although they require more patient counseling due to lingering stigma about these agents.

Anxiety and depression

Stressful life events, such as serious illness in oneself or a loved-one, can impact one's mental health, with anxiety and/or depression being the most common symptoms. Anxiety and depression can both have synergistic and bidirectional effects. For example, shortness of breath can induce anxiety, but anxiety can also induce shortness of breath. Fatigue can exacerbate depression due to a reduction in a patient's level of physical activity, but depression can increase fatigue. These self-reinforcing patterns underscore the important of early assessment and management of anxiety and depression symptoms, which, if left untreated, may intensify to anxiety or depressive disorders.

A related disorder of emotions and mood, adjustment disorder, may also be present in patients at the end of life, or their loved ones. The Diagnostic and Statistical Manual 5th Edition (DSM-5) defines an adjustment disorder as the development of emotional or behavioral symptoms in response to an identifiable stressor occurring within 3 months of the onset of the stressor(s) and which are not associated with normal bereavement.[90] The symptoms must be "clinically significant" such as marked distress out of proportion to the severity or intensity of the stressor, or featuring significant impairment in social, occupational or other important areas of functioning. Although adjustment disorder is generally less severe than clinical depression it can be burdensome and should be taken seriously by clinicians.[91] Although research on treatments for adjustment disorder are sparse, psychotherapies such as interpersonal therapy and brief dynamic psychotherapy may be useful.[91]

Treatment options for anxiety or depression in the palliative care setting depend on the severity and urgency of symptoms. If symptoms are non-urgent (i.e., mild to moderate) and the patient's prognosis is on the order of weeks to months, then treatment with psychotherapy and/or a selective serotonin reuptake inhibitor (SSRI) antidepressant (but not paroxetine or fluoxetine due to potential for withdrawal symptoms, anticholinergic effects or drug/drug interactions) are suggested (Table 10). If symptoms are severe or prognosis is relatively imminent, the following are recommended:

- For anxiety: benzodiazepines (e.g., lorazepam 0.5-1mg every 4 hours) plus referral to psychiatry. (Avoid alprazolam due to its short duration of action and the potential for rebound symptoms.)
- For depression: methylphenidate 2.5 (start) – 10 mg orally twice daily or PRN, or amphetamine/dextroamphetamine 5 mg orally twice daily or PRN (dosed in morning and early afternoon)

Table 10: Treatment options for anxiety and depression in palliative care[92,93]

Medication	Dose*	Considerations
Citalopram (Celexa)	10 mg → 40 mg daily	May reduce anxiety
Escitalopram (Lexapro)	10 mg → 20 mg daily	May reduce anxiety
Mirtazapine (Remeron)	15 mg → 45 mg daily	May cause sedation (at lower doses) and increase appetite
Sertraline (Zoloft)	50 mg → 200 mg daily	Can cause diarrhea
Venlafaxine (Effexor**, Effexor XR)	75 mg → 225 mg daily	Can cause nausea/vomiting
* In general, start at lowest dose and titrate every week to maximum dose for trial of 6-8 weeks, unless side effects prohibit ** Divided doses (e.g., twice or three times daily)		

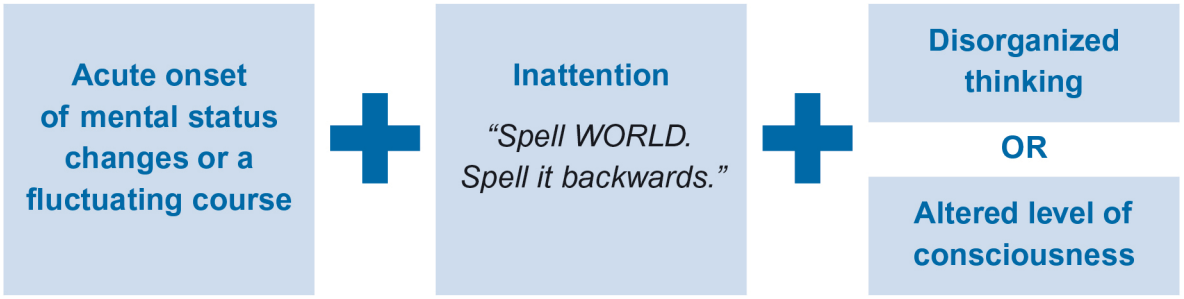
Delirium

Delirium is an acute, frequently reversible, mental disorder affecting up to an estimated 88% of people with a terminal illness in the last days of life, and between 26% and 44% of hospitalized patients with advanced cancer.[94] Delirium is characterized by disorganized thinking and a reduced ability to maintain attention in a rapidly waxing and waning course. Other symptoms include: disorientation to time, place, and person; sensory misperceptions; psychomotor agitation or retardation; sleep disturbances; and memory impairment. Delirium is associated with greater hospital length of stay, increased 30-day and 1-year mortality, hospital readmissions, and caregiver distress.[95] Risk factors include older age, dementia, hospitalization, acute illness, dehydration, and uncontrolled physical symptoms (e.g., constipation).[96]

It is important to distinguish delirium from dementia; delirium is often caused by reversible medical conditions such as infection (including urinary and respiratory tract infections), pain, drug intoxication or withdrawal, seizures, head trauma, and metabolic disturbances such as hypoxia, hypoglycemia, fluid/electrolyte disturbance, and hepatic, cardiac or renal impairment. Management of the precipitating medical problem will often result in clearing of the delirium.

One of the most widely-used instruments to assess delirium is the Confusion Assessment Method (CAM) (Figure 10) consisting of four items: 1) acute onset and fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness. The algorithm requires the presence of the first and the second criteria and of either the third or the fourth criterion.

Figure 10: CAM diagnostic algorithm[97]



The ability of a patient to pay attention can be assessed several ways, such as having them say the days of the week or the months of the year backwards, spell the word "world" backwards, having them count backwards from 100 by 7s, or, for patients with low educational attainment, having them count backwards from 20 by 2s.

Addressing any underlying reversible causes of delirium is key, and it is imperative not to use sedating medications that may "cover up" agitative behaviors instead of dealing with its actual cause. Risperidone and other second–generation APMs may be effective but they are not clearly better or safer than haloperidol, which can be given IM or IV.[98] A recent review underscored the inconsistent findings of the few placebo-controlled studies undertaken. Quetiapine produced a more rapid resolution of delirium than placebo in two studies, whereas haloperidol and ziprasidone did not.[99] However, these differences were likely to be due to differences in subject characteristics. Benzodiazepines should be avoided in the management of delirium.

Evidence-based non-pharmacologic strategies to manage delirium include:[100]

- cognition/orientation
  - cognitive stimulation activities
  - orientation board with names of care team and daily schedule
  - orienting communication
- early mobility
  - ambulation or active range-of-motion exercises
  - minimizing use of immobilizing equipment
- hearing
  - portable amplifying devices and special communication techniques with daily reinforcement
  - ear wax cleaning as needed
- sleep-wake cycle preservation
  - warm milk or herbal tea, relaxation recordings or music, back massage
  - noise reduction strategies and schedule adjustments to allow uninterrupted sleep
- vision
  - glasses, magnifying lenses, and/or adaptive equipment to allow reading
- hydration
  - encourage fluids
  - feeding assistance and encouragement during meals

The symptoms or behaviors associated with delirium should be identified prospectively, and methodically documented both before and following medication initiation for at least two weeks, with regular review for response, adverse effects and drug interactions.[101]

BOTTOM LINE: Multiple, common symptoms occur in patients as they approach end-of-life. Physical pain can be managed with a stepped approach. A bowel regimen should be prescribed alongside any opioid to avoid constipation. Breathlessness can be managed with a combination of non-pharmacologic and low dose opioids or benzodiazepines. Stimulants may help fatigue related to opioid use. Treat anxiety and depression based on prognosis and severity. Substance abuse and misuse is still possible in palliative care settings. Ask about patient and family substance use. Monitor side effects and for signs of misuse.

Cannabis in palliative care

Although still inadequately researched and poorly understood as a pharmacologic class, cannabis has been widely used to treat many symptoms common at the end of life, including pain, nausea, loss of appetite, and mood. Cannabis contains more than 60 cannabinoids, with Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the two of primary interest to patients and clinicians. *C. sativa* strains tend to be generally elevating while *C. indica* strains are generally sedating, although many hybrids of the strains exist which may have variable effects.

Exogenous cannabinoids act on cannabinoid receptors located throughout the body, primarily in the brain and spinal cord, to inhibit release of multiple neurotransmitters (e.g., acetylcholine, dopamine, and glutamate) with indirect effects on opioid, serotonin, and other receptors. Activation of cannabinoid receptors can reduce pain, and some exogenous cannabinoids also function as an antiemetic and have anti-spasticity and sleep-promoting effects.[102] Cannabinoids may also cause side effects of euphoria, psychosis, cognitive impairment, reduced locomotor function, and increased appetite.

A systematic review of 47 randomized trials and 57 observational studies in patients with chronic non-cancer pain found moderate evidence that cannabinoids can exert analgesia.[103] Across RCTs, the overall number needed to treat to obtain a 30% reduction in pain was relatively high (NNT 24; 95% CI: 15-61), while the number needed to harm (for all-cause adverse events) was 6 (95% CI: 5-8).

Cannabis preparations may pose both short-term and long-term risks. Short-term effects include impaired memory, motor coordination, and judgment. Paranoid ideation and psychotic symptoms, while rare, may occur with high doses of THC. Abrupt cessation of marijuana in long-term users may cause withdrawal symptoms such as anxiety, irritability, craving, dysphoria, and insomnia. There is an increased risk of chronic bronchitis, respiratory infections, and pneumonia with inhaled products.[102]

The use of cannabis may have an opioid-sparing effect. The use of medical cannabis has been associated with a 25% reduction in opioid overdose mortality in states that legalized medical use.[104]

FDA-approved cannabinoids include dronabinol (Marinol), indicated for second-line treatment of chemotherapy-induced nausea and vomiting, and anorexia-associated weight loss in patients with HIV. Nabilone (Cesamet) is indicated for chemotherapy-induced nausea and vomiting. Common side effects include dizziness/vertigo and euphoria.[102,105,106]

Substance use disorders

Because controlled substances such as opioids, stimulants, and benzodiazepines are commonly employed in palliative care, it is important for clinicians to be aware both of the potential to exacerbate existing substance use disorders. The potential for palliative care medications to induce a substance use disorder is also possible, although given the short life expectancy of most palliative care patients, this is not the concern it is for patients without serious illness.

Patients with serious illnesses may worry they will become "addicted" to medications used to treat symptoms, without understanding the difference between "addiction" (i.e., a substance use disorder) and medication dependence and tolerance, which are to be expected with chronic use of opioids, benzodiazepines, and other controlled substances.[107]

- Dependence is a state of physiologic adaptation manifested by a drug class-specific withdrawal syndrome that can be precipitated by abrupt cessation, rapid dose reduction, and/or administration of an antagonist.[108]
- Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.
- Substance use disorders occur when continued use a drug causes clinically significant impairment, including health problems, disability, or failure to meet major responsibilities at work, school, or home.
- Chemical coping describes intake of a drug to cope with psychological or spiritual distress ranging from normal non-addictive use to total dependence with accompanying compulsive or destructive behaviors.[109]

Several instruments can be used to assess a patient's risk of aberrant drug-related behavior. The Screening, Brief Intervention, and Referral to Treatment (SBIRT) algorithm can help clinicians identify patients with problematic opioid use or potential opioid use disorder (OUD). SBIRT assesses the severity of opioid use, is brief (typically 5-10 minutes), and targets behaviors specific to substance use. Specific screening tools such as CAGE, a 4-question tool to assess alcohol use, and CAGE-AID (adapted to include drug use) can provide a formal assessment of substance use or misuse within the construct of SBIRT.

Tips for safe prescribing and monitoring of controlled substances:[110]

- Initial prescription of opioids is always on a "trial basis" (helps set expectations)
- Assess the 4 As: Analgesia, Activities of daily living, Adverse events, Aberrant behavior
- Risk of aberrant use is not a reason to withhold prescription but is a rationale for increased monitoring
- The higher the risk or presence of aberrant drug related behaviors, the more frequent the visits and the lower the number of pills prescribed
- Routine and universal use of medication use agreements and urine drug screening
- Always consult a Prescription Drug Monitoring Program prior to a first prescription, and afterwards as part of monitoring

Conclusions

The time between diagnosis of a serious illness and death for any patient is a journey of widely varying lengths, difficulties, and medical challenges, but it is a journey along which primary care clinicians can play the role of steady, supportive, and trusted guides. This evidence document is a reminder that the tools and approaches of palliative care, which formerly were conceived of as appropriate only at the very end of life after “curative” approaches had run their course, are, in fact, invaluable across the course of illness and even after a patient has died. By integrating palliative care techniques into their general practice, primary care clinicians can significantly improve their patients’ quality of life even to the point of death across all of the relevant physical, emotional, social, and spiritual dimensions of a patient’s experience. The key takeaways from this document:

- Engage patients and their surrogates in ACP conversations early in the course of a serious illness.
- Use the tools described above to facilitate dialog that will clarify the patient’s values and preferences.
- Create a structure for discussing prognosis, patients’ goals and values, and medical options.
- Ensure that the patient has completed the necessary documents such as naming a health care proxy and advance health care directives.
- Reduce symptom burden by managing pain, constipation, nausea, shortness of breath, and fatigue.

Resources

Serious Illness Care Program: ariadnelabs.org/areas-of-work/serious-illness-care

VitalTalk: vitaltalk.org/resources

The Conversation Project: theconversationproject.org/get-started

PREPARE for your care: prepareforyourcare.org

Five Wishes: fivewishes.org

Go Wish: gowish.org

POLST: Papolst.org

Palliative Care Network of Wisconsin, Fast Facts and Concepts: mypcnow.org/fast-facts

COVID-specific communication resources:

- VitalTalk Covid Ready Communication toolkit
  vitaltalk.org/guides/covid-19-communication-skills/
- Serious Illness Care Program Covid-19 Response Toolkit
  covid19.ariadnelabs.org/serious-illness-care-program-covid-19-response-toolkit/

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Appendix I: Serious Illness Conversation Guide

Serious illness conversation guide

ENABLE

"I'd like to talk about what is ahead with your illness and do some thinking in advance about what is important to you so that I can make sure we provide you with the care you want— **is this okay?**"

ASSESS

"What is **your understanding** now of where you are with your illness?"

"How much **information** about what is likely to be ahead with your illness would you like from me?"

SHARE

"I want to share with you my understanding of where things are with your illness..."

Uncertain: "It can be difficult to predict what will happen with your illness. I hope you will continue to live well for a long time but I'm worried that you could get sick quickly, and I think it is important to prepare for that possibility."

OR

Time: "I wish we were not in this situation, but I am worried that time may be as short as ___ *(express as a range, e.g. days to weeks, weeks to months, months to a year)*."

OR

Function: "I hope that this is not the case, but I'm worried that this may be as strong as you will feel, and things are likely to get more difficult."

EXPLORE

"What are your most important **goals** if your health situation worsens?"

"What are your biggest **fears and worries** about the future with your health?"

"What gives you **strength** as you think about the future with your illness?"

"What **abilities** are so critical to your life that you can't imagine living without them?"

"If you become sicker, **how much are you willing to go through** for the possibility of gaining more time?"

"How much does your **family** know about your priorities and wishes?"

PLAN

"I've heard you say that ___ is really important to you. Keeping that in mind, and what we know about your illness, I **recommend** that we ___. This will help us make sure that your treatment plans reflect what's important to you."

"How does this plan seem to you?"

"I will do everything I can to help you through this."

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About this publication

These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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