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In the Clinic®

Best Practices in Caring for Seriously Ill Patients

Palliative care (PC) is the art and science of providing goal-concordant care, skillfully managing complex and refractory pain and nonpain symptoms, mitigating suffering, and augmenting quality of life for seriously ill patients throughout the course of the illness trajectory. The primary team should provide generalist PC for all seriously ill patients and know when to refer patients to specialist PC. Specialty-level PC services should be reserved for complex problems beyond the scope of primary PC. This article reviews principles and best practices to support patient-centered PC.

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Palliative care (PC) (1) is specialized medical care that aims to alleviate complex symptoms, identify and deliver goal-concordant care, and facilitate care coordination for people living with serious illness across the lifespan. "Serious illness" is defined as a health condition that carries a high risk for mortality and either negatively affects a person's daily function or quality of life or excessively strains their caregivers (2). PC does not shorten the lifespan; rather, initiating PC in the early stages of a serious illness may provide a survival benefit (3, 4). Quality PC is best provided by an interdisciplinary team that addresses physical, emotional, social, spiritual, and existential aspects of suffering and aims to promote quality of life, hope, and dignity for all seriously ill patients.

What are the distinctions between primary and specialist PC?

Most seriously ill patients are unable to receive specialist PC, as there is a national shortage of these specialists. "Primary PC" refers to the basic elements of PC provided by a primary team (5). All physicians should seek training on the general knowledge and skills needed to provide primary PC for patients in routine practice. Specialty-level PC services should be reserved for complex problems beyond the scope of primary PC.

Which patients should be referred to specialist PC?

Timely referral to PC subspecialists using standard criteria has been shown to improve patients' quality of life, symptom control, mood, illness understanding, end-of-life care, and survival. **Table 1** lists criteria for identifying seriously ill patients who might benefit from specialist PC (6). Clinicians and health care organizations should implement practices that routinely assess and track seriously ill patients' needs for specialist PC so they can make timely referrals for high-quality management of symptoms and psychosocial, spiritual, and existential suffering should these be necessary.

Can patients who receive specialist PC obtain life-prolonging treatments?

Referral to a PC subspecialty does not preclude patients from receiving disease-directed treatments, such as hemodialysis, chemotherapy, radiation therapy, blood transfusions, surgical procedures, and clinical trials. However, many disease-modifying treatments can cause secondary symptoms that negatively affect quality of life (for example, chemotherapy-induced nausea or hemodialysis-induced fatigue). For patients with complex and refractory symptoms or challenging communication issues, ensuring that PC specialists work in

Table 1. **Suggested Criteria for Consideration of Specialist Palliative Care Assessment at the Time of Hospital Admission***

Criterion	*Definition*
Surprise	You would not be surprised if the patient died within 12 months
Frequent admissions	Repeated admission for same condition within several months
Complex symptoms	Admission for difficult symptom or psychological need
Complex care requirement	Functional dependence or complex home support needed
Failure to thrive	Decline in functional status, weight, or ability to care for self
Advance care planning needs	No history of completing an advance care planning document or having a discussion
Limited social support	Family stress, chronic mental illness, lack of caregivers
Limited prognosis	Any of the following may be sufficient to warrant consultation (multiple criteria need not be present): metastatic or locally advanced cancer, hip fracture with cognitive impairment, out-of-hospital cardiac arrest

* *From reference 5.*

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conjunction with primary providers and other subspecialists is critical to ensuring goal-aligned care.

What tools are available to assist in prognosticating or estimating life expectancy?

Although prognostication is challenging, validated scales for specific disease states have been developed to assist in this area (6, 7). Functional status correlates with survival in many chronic diseases (such as heart failure), whereas disease-specific prognostic indicators improve prediction within specific contexts (8). For example, functional status estimation via the Karnofsky Performance Status Scale or the Eastern Cooperative Oncology Group Performance Status Scale helps prognostication in cancer. These scores also provide an estimate of what disease-directed treatments a person may be able to endure. It is important to explain to patients that estimating prognosis is an approximate, inexact, and iterative process. As the patient advances in the trajectory of serious illness, their prognosis is likely to change depending on treatment, treatment response, new illnesses, and other factors. For example, the anticipated lifespan of a patient with cancer may be reduced from years to days due to severe sepsis after chemotherapy.

Why should communication of diagnostic and prognostic information be culturally informed?

Receiving and processing diagnostic or prognostic information about serious illness is stressful for patients. Culture (9) strongly shapes how patients approach decisions about health care and infer the meaning of their illness, death, and dying. Culture also influences how patients cope with serious illness. Many patients, particularly those from communities of color (9) or those with limited English proficiency, prefer discussing serious illness with family present. Conversely, some cultures practice "protective truthfulness" (9), where families ask that diagnostic or prognostic information not be divulged to the patient or vice versa (or both). PC providers must therefore approach cross-cultural encounters with cultural humility. First, they should gauge the patient's information-seeking preferences and whether they are ready to engage in discussion. In some cultures, the patient may prefer not knowing or discussing diagnostic or prognostic information. In such cases, it is important to respect the patient's wishes and ask them to identify a surrogate for these discussions. When the patient is ready to engage in the conversation, the clinician should identify who should be present during the discussion (10, 11). The patient should be asked for their preferences about ongoing communication and how they would like to be involved or include loved ones (9). It is important to remember that a patient who initially chooses to recuse themselves from decision making can change their mind in the course of their illness. When conveying prognosis, clinicians should avoid using specific numbers (for example, "Your life expectancy is 8 months"), as the likelihood of being incorrect is high and patients will perseverate on numbers. Rather, prognosis should be communicated as an estimated range (for example, 6 to 12 months) (5, 12), stressing that the estimates may change as the patient's condition changes. Time, function, and uncertainty are useful domains through which to communicate prognosis (**Figure 1**) (13).

What is hospice care, and who is eligible?

Hospice is a care delivery system that is usually reserved for patients with an anticipated lifespan of 6 months or less. Unlike traditional PC, which is provided in conjunction with disease-directed care, seriously ill patients can receive hospice care if they choose to forgo disease-directed therapies and a physician certifies to Medicare that the patient meets criteria for a life expectancy of 6 months or less (14). Although hospice care is usually delivered in the

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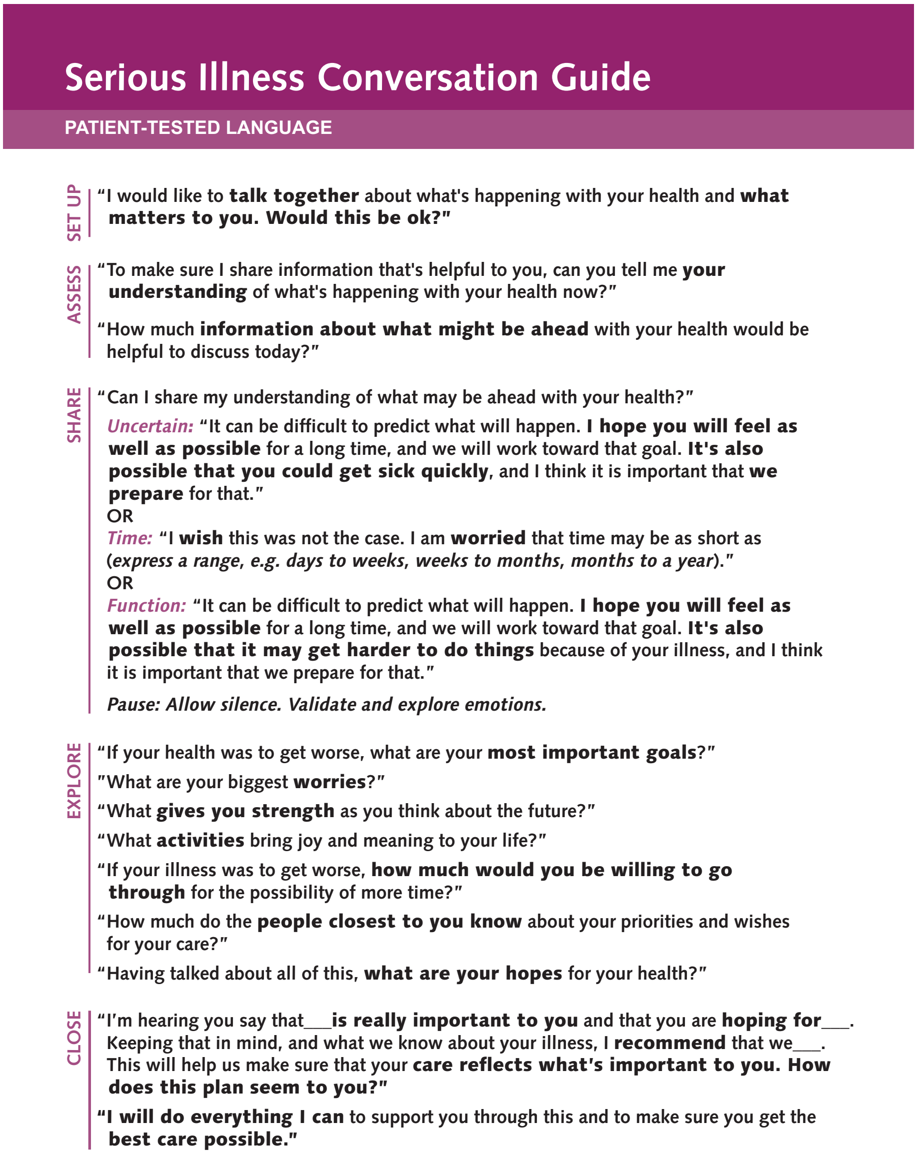
Figure 1. **Serious illness conversation guide.**



Serious Illness Conversation Guide

PATIENT-TESTED LANGUAGE

SET UP

"I would like to **talk together** about what's happening with your health and **what matters to you. Would this be ok?"**

ASSESS

"To make sure I share information that's helpful to you, can you tell me **your understanding** of what's happening with your health now?"

"How much **information about what might be ahead** with your health would be helpful to discuss today?"

SHARE

"Can I share my understanding of what may be ahead with your health?"

Uncertain: "It can be difficult to predict what will happen. **I hope you will feel as well as possible** for a long time, and we will work toward that goal. **It's also possible that you could get sick quickly**, and I think it is important that **we prepare** for that."

OR

Time: "I **wish** this was not the case. I am **worried** that time may be as short as (*express a range, e.g. days to weeks, weeks to months, months to a year*)."

OR

Function: "It can be difficult to predict what will happen. **I hope you will feel as well as possible** for a long time, and we will work toward that goal. **It's also possible that it may get harder to do things** because of your illness, and I think it is important that we prepare for that."

Pause: Allow silence. Validate and explore emotions.

EXPLORE

"If your health was to get worse, what are your **most important goals**?"

"What are your biggest **worries**?"

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

"What **activities** bring joy and meaning to your life?"

"If your illness was to get worse, **how much would you be willing to go through** for the possibility of more time?"

"How much do the **people closest to you know** about your priorities and wishes for your care?"

"Having talked about all of this, **what are your hopes** for your health?"

CLOSE

"I'm hearing you say that___**is really important to you** and that you are **hoping for**___. Keeping that in mind, and what we know about your illness, I **recommend** that we___. This will help us make sure that your **care reflects what's important to you. How does this plan seem to you?"**

"I will do everything I can to support you through this and to make sure you get the **best care possible."**

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home, nursing homes and care facilities also provide hospice services. Hospice can be revoked without penalty for unexpected emergencies (for example, a fall with a hip fracture) or if a patient's goals of care change. If eligible, patients may reenroll if they wish to seek hospice care again.

Managing Common Symptoms

How should pain be evaluated and managed?

A detailed history and physical examination are crucial for pain management. A focused history of past and present opioid and sedative-hypnotic use, a social history of recreational use of opioids and other psychotropic medications, laboratory tests, and imaging can help guide management. Providers

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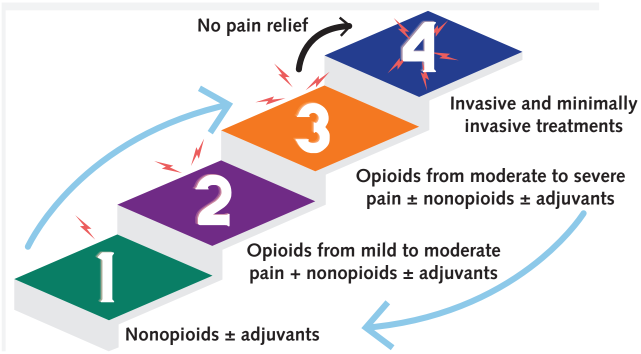
should classify pain as nociceptive (somatic, visceral, or both) and/or neuropathic, understanding that patients may have more than 1 type. Visceral pain is usually dull, colicky, and poorly localized and may be associated with autonomic symptoms, such as nausea or diaphoresis. Visceral pain is typically caused by distention, torsion, or inflammation and often occurs in conjunction with pancreatic, hepatic, renal, or intestinal cancer. It may also be caused by severe constipation due to medications, immobility, and underlying disease. Anticholinergic agents can be used adjunctively for colic but are associated with xerostomia, constipation, and sedation, which may lead to additional symptoms. Surgeons or interventional radiologists can offer interventions to relieve visceral pain caused by bowel obstruction (15). Sympathetic blockade of the celiac plexus or splanchnic nerves may be useful for patients with pain that is refractory to opioids.

Neuropathic pain is usually burning, tingling, stabbing, or shooting. It can be constant or episodic and is often caused by damage to the central or peripheral nervous system. Patients with cancer may experience such pain from nerve root compression or neural encroachment; it may also occur in patients with HIV or diabetes or patients receiving certain types of chemotherapy. In cases of nerve compression, corticosteroids are effective in reducing swelling while increasing appetite and energy levels. Steroids are also useful in management of headaches from increased intracranial hypertension due to peritumoral vasogenic edema (16).

Nonpharmacologic therapies, including cognitive behavioral therapy, acupuncture, and massage therapy, should be considered before medications are instituted. Gabapentin, pregabalin, venlafaxine, and duloxetine can be given as first-line medications for neuropathic pain (17). Tricyclics and medications with anticholinergic activity should be avoided in older adults due to the risk for adverse effects, including confusion, constipation, hallucination, tachycardia, urine retention, and xerostomia. If used as a last resort, dose escalation should

Figure 2. **Choice and route of analgesics.**

By mouth	**When available, the oral route is always preferred over other routes, such as transdermal, intravenous, or subcutaneous.**
By the clock	**Chronic basal pain is usually best treated by scheduling long-acting pain medications (e.g., sustained-action morphine tablets) at specific times.** **Short-acting pain medications can be used on an as-needed basis for incidental or breakthrough pain.**
By the WHO ladder	

The WHO pain ladder is reproduced from Ventafridda V, Saita L, Ripamonti C, et al, WHO guidelines for the use of analgesics in cancer pain, Int J Tissue React, 1985;7:93-96, with permission. WHO = World Health Organization.

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Table 2. **Noninjected Opioids That Are Commonly Used in Palliative Care**

Agent	*Available Form*	*Onset*	*Duration*	*Notes*
Morphine	IR (tablet, liquid, or concentrated liquid)	15–30 min, peak at 60 min	4 h	Can be given rectally; "sublingual" liquid is absorbed in the gut, not in the buccal mucosa; avoid in renal failure
	ER (tablet)	2–4 h	8–12 h	Tablets cannot be crushed; can be given orally or rectally; avoid in renal failure
Oxycodone	IR (tablet, liquid, or concentrated liquid)	15–30 min, peak at 60 min	3–6 h	Safer than morphine, but still may not be tolerated
	ER (tablet)	1 h	8–12 h	Long-acting morphine should be tried first unless contraindicated in light of cost considerations
Fentanyl	IR (buccal tablet, "film" or "lozenge")	5–15 min	4 h (≤4 doses per day)	Not recommended for opioid-naive patients; expert consultation recommended before use
	ER (transdermal patch)	12–18 h (for initial dose)	72 h (less in some patients)	Patients should be taking ≥60 oral morphine equivalents before starting; need 3 days after placement to assess benefit before adjusting; temperature and cachexia can alter absorption (i.e., fever increases absorption, low subcutaneous fat stores decrease absorption); safest in renal failure
Hydromorphone	IR (tablet or liquid)	15–30 min, peak at 60 min	4 h	Safer in kidney and liver failure; can be used orally or rectally
	ER (tablet)	6–8 h	24 h	Only 1 ER form available in the United States; expert consultation recommended before use

ER = extended release; IR = immediate release.

consider age, renal function, or previous titration tolerance (18), and the patient should be carefully monitored.

The 11-point Numerical Rating Scale (NRS) is a valid and simple-to-use metric for cognitively intact patients (19). The World Health Organization (WHO) analgesic ladder provides useful guidance in the choice of analgesics (**Figure 2**) (20). Nonopioid analgesics, including acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), are used for mild pain (score of 1 to 3 on the NRS). Moderate pain (score of 4 to 6 on the NRS) is commonly treated with a combination of opioids and nonopioid analgesics. If these agents are combined in a single pill (such as oxycodone and acetaminophen), clinicians should be mindful of the dose of the acetaminophen component as opioid needs increase. Similarly, clinicians should caution patients about simultaneous use of over-the-counter acetaminophen formulations to avoid overdose. Acetaminophen metabolism is age-dependent, and the daily cumulative dose of acetaminophen (<3 g for people aged >65 years) is the limiting factor in combination opioids, particularly for patients with liver disease, where the dose should not exceed 2 g/d. Similarly, NSAIDs should be used with caution in older adults and those with kidney disease, hypertension, and thrombocytopenia.

Severe pain (score of 7 to 10 on the NRS) in seriously ill patients is best treated with opioids. However, adjuvants such as NSAIDs, corticosteroids, antiepileptics, and antidepressants can be helpful in some pain syndromes, such as neuropathic pain. Commonly used opioids are summarized in **Table 2** (for opioid equivalents, see the **Box**: Morphine Equivalents).

Oral opioid administration is convenient and inexpensive and produces stable blood levels. Intramuscular injections are not recommended because of injection-associated pain, unreliable absorption, and a longer interval to

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Morphine Equivalents

According to the "1:2:3" rule, the following drugs are equivalent:
- 1 mg IV or SQ morphine
- 2 mg PO oxycodone
- 3 mg PO morphine

The "30:20:10:7.5:1.5" rule is a corollary of the "1:2:3 rule" but includes hydromorphone.
- 30 mg PO morphine
- 20 mg PO oxycodone
- 10 mg IV or SQ morphine
- 7.5 mg PO hydromorphone
- 1.5 mg IV or SQ hydromorphone

Rather than memorizing individual drug potencies, using these ratios allows clinicians to calculate equivalent doses using stoichiometry. For example, if a patient is receiving 30 mg of ER oxycodone every 12 hours and 10 mg of IR morphine every 4 hours, 4 times a day, how many OMEs is this?
- Oxycodone 30 mg × 2 doses = 60 mg × (30 mg PO morphine/20 mg PO oxycodone) = 90 OMEs
- Morphine 10 mg × 4 doses = 40 OMEs

The patient is receiving 130 OMEs.

ER = extended release; IR = immediate release; IV = intravenous; OME = oral morphine equivalent; PO = oral; SQ = subcutaneous.

peak drug concentrations. If parenteral administration is needed, intravenous or subcutaneous injection is preferred. Intravenous administration has the most rapid onset but the shortest duration of action. Transdermal opioid patches are reasonable for moderate to severe pain or chronic pain in patients who do not have reliable oral intake. Short-acting opioids alone are insufficient to manage cancer-related pain. Long-acting agents, such as extended-release morphine, extended-release oxycodone, and transdermal fentanyl patches, ensure basal pain control. Shorter-acting opioids should be added to treat breakthrough pain as needed.

To ensure adequate pain control while avoiding overmedication, the dose of long-acting basal pain medication should be determined by calculating the total oral morphine equivalents consumed in a 24-hour period. The initial long-acting dose should be 50% to 75% of this 24-hour total (see the **Box**: Calculating Short- and Long-Acting Opioid Doses), with adjustments every 3 to 4 days if frequent medication is required for breakthrough pain. When calculating a breakthrough opioid dose, clinicians should consider total opioid dose in a 24-hour period and prescribe 10% to 15% of this as an immediate-release medication as needed. It is important to remember that long-acting opioids require 1 to 3 days to take full effect, and using the same agents for breakthrough and basal pain can facilitate dose changes.

Several opioids should be avoided or used with caution under certain circumstances. Tramadol, although marketed as an opioid alternative, is habit-forming. Codeine and meperidine have limited utility due to variable oral bioavailability and differences in speed of metabolism; they are best avoided in the treatment of pain in serious illness. Meperidine metabolites accumulate with prolonged use at high doses and in patients with renal failure, reducing seizure threshold and causing neurotoxicity. Morphine should be used with caution in patients with renal and hepatic insufficiency. Buprenorphine, a mixed opioid agonist-antagonist, may be used for analgesia in patients at risk for opioid use disorder. Although inexpensive, methadone has complex pharmacokinetics and is best prescribed by providers who are skilled in its use.

Opioid misuse, diversion, and addiction have led to heightened scrutiny of

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Calculating Short- and Long-Acting Opioid Doses

1. Sum all doses of opioids the patient is taking in 24 hours; consider converting all doses to OMEs for ease and a common point of reference.
2. If the short-acting agent differs from the long-acting agent, the calculated dose of the short-acting agent in OMEs should be reduced by 50% because of incomplete cross-tolerance.
3. If the long- and short-acting agents are the same, no adjustment for incomplete cross-tolerance is required.
4. Provide a dose for the breakthrough pain between 10%–15% of the combined total daily OME dose; this may be given as a short-acting opioid every 1–2 hours. No reduction in this calculation is required for incomplete cross-tolerance.
5. For example, a patient receiving 20 mg of ER oxycodone PO every 12 hours continues to require 4 mg of hydromorphone PO every 4 hours as needed for breakthrough pain (a total of 4 doses a day). How do we calculate the new long-acting dose for the breakthrough pain dose?

Step 1: Calculate OMEs for each drug:
- Long-acting agent: (2 × 20 mg oxycodone per day) × (30 mg PO morphine/20 mg PO oxycodone) = 60 OMEs
- Short-acting agent: (4 × 4 mg hydromorphone per day) × (30 mg PO morphine/7.5 mg PO hydromorphone) = 64 OMEs

Steps 2 and 3: Here, the short- and long-acting agents are different drugs, so the short-acting daily dose in OMEs should be reduced by 50% (64 × 0.5 = 32 OMEs). Add the short- and long-acting daily doses of OMEs (60 + 32 = 92 OMEs). Calculate the new total daily dose of the long-acting agent to be given: 92 OMEs × (20 mg oxycodone/30 mg PO morphine) = 61 mg oxycodone. This may be given as 30 mg ER oxycodone every 12 hours.

Step 4: Calculate the new breakthrough dose. Use total current OMEs from step 1 (no adjustment): 60 OMEs + 64 OMEs = 124 OMEs. Use 10%–15% for breakthrough: (about 12–18 OMEs) × (20 mg PO oxycodone/30 mg PO morphine) = 8–12 mg PO immediate-release oxycodone as needed every 1–2 hours for breakthrough pain in seriously ill patients (less frequently as pain is controlled). This may be given as 10- to 15-mg tablets of PO immediate-release oxycodone.

ER = extended release; OME = oral morphine equivalent; PO = oral.

prescription practices. The 2022 guidelines from the Centers for Disease Control and Prevention update and expand the previous guidelines and provide recommendations for prescribing opioid pain medication for acute, subacute, and chronic pain for outpatients aged 18 years or older. Although the guidelines exclude pain management related to sickle cell disease, cancer-related pain treatment, PC, and end-of-life care, screening patients for aberrant use behaviors and checking state registry data will augment patient safety (21). Even persons with serious illness can display these behaviors. Ongoing monitoring of opioid use is therefore critical to deter misuse or diversion. Persons at risk for misusing prescription opioids include those with a history of substance use, more severe pain, mental illness, or a history of child abuse. Such patients can be identified using the Opioid Risk Tool (22), a short questionnaire to stratify risk. Clinicians are responsible for safe opioid prescribing and may need to consider misuse-deterrent preparations, limited-quantity prescriptions, frequent pill counts, routine urine drug testing, or use of agents with low risk for aberrant use.

How should adverse effects of opioids be managed?

Opioids have predictable adverse effects, including nausea, constipation, pruritus, and sedation. Sedation usually dissipates over 1 to 2 days as tolerance develops. It can also be alleviated by dose reduction or rotation to another opioid. To avoid opioid-induced constipation, clinicians should prescribe a prophylactic stimulant (such as senna

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or bisacodyl) and adjust the dosage based on the patient's bowel habits. Stool softeners (docusate) alone are ineffective (23). If a prophylactic regimen does not produce bowel movements at least every other day, osmotic laxatives such as polyethylene glycol and sorbitol should be considered. Lactulose should be limited to patients with hepatic issues due to abdominal discomfort (24).

In most cases, opioid-related pruritus and urticaria result from histamine release rather than a true drug allergy. Symptoms may be alleviated by changing the opioid or adding a nonsedating antihistamine. Opioid-induced nausea typically abates in 3 to 5 days (25). It is best treated with antidopaminergic antiemetics, such as metoclopramide or prochlorperazine. Ondansetron may be useful in refractory cases. Some patients experience less nausea if the opioid blood level remains steady rather than peaking intermittently; using immediate-release preparations regularly or at shorter intervals may therefore help nausea. Changing to extended release or the transdermal route may also produce more constant opioid blood levels.

Musculoskeletal manifestations may occur, including referred pain (for example, shoulder pain from a visceral tumor) or gout in patients receiving chemotherapy. Nerve blocks are effective for localized pain. Neuraxial opioid therapy using epidural or intrathecal pumps is effective when pain is refractory to systemic opioids. For bone metastases, radiation therapy, corticosteroids, bisphosphonates, or interventional procedures (such as cryoablation or radiofrequency ablation) may be considered (26).

What treatments are most effective for relieving dyspnea?

Dyspnea is a subjective experience of air hunger or breathing discomfort. Severity correlates poorly with respiratory rate, arterial blood gas levels, oxygen saturation levels, or accessory muscle use. Therefore, symptoms should guide treatment. The first step in management is to identify and address the underlying causes, such as pulmonary effusion, anemia, or ascites. Supplemental oxygen is useful in relieving dyspnea in terminally ill patients with hypoxemia but is no better than medical air in patients without hypoxemia (27). Use of nonpharmacologic interventions (26), including breath training, gait aids, neuroelectric muscle stimulation, chest wall vibration, and fans, is supported by evidence (28, 29). Data are insufficient to support music therapy, relaxation, counseling, or psychotherapy (30). Pulmonary rehabilitation is also effective in reducing chronic dyspnea and exertional tolerance (31).

The American College of Chest Physicians supports aggressive treatment of dyspnea, including with opioids, for seriously ill patients (32). A recent multicenter double-blind randomized clinical trial evaluated the efficacy and safety of regular, low-dose, sustained-release morphine compared with placebo for chronic breathlessness and showed no differences in intensity of breathlessness, fatigue, quality of life, function, or harms. Low-dose oral morphine in a cumulative dose of 10 to 20 mg/d (27, 33) is the current standard pharmacologic treatment for dyspnea in seriously ill patients (34). Regular, low-dose, oral, sustained-release morphine also improved COPD Assessment Test scores, suggesting clinical benefit in these patients (35). Opioids can cause respiratory depression if titrated too quickly in opioid-naive patients. Although benzodiazepines may be effective anxiolytics for patients whose dyspnea is exacerbated by anxiety, concurrent use with opioids may also lead to adverse outcomes and is best done under the auspices of palliative specialists (36).

How should clinicians treat nausea?

Nausea may result from several processes, and understanding its origin helps guide effective therapy (**Table 3**). Most recommendations come from small studies or expert opinion based on putative neurotransmitters (37, 38). Opioid-induced nausea responds best

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Table 3. **Treatment of Nausea, by Origin**

Origin	Treatment
Cortex	GABA: Benzodiazepines (anticipatory nausea only) Behavioral treatments
Gastrointestinal tract	Peripheral D2: Metoclopramide Other: Treat underlying cause (constipation, medical and surgical treatment of obstruction, GERD/PUD) Dexamethasone
Vestibular system	H1>AchM: Promethazine AchM: Scopolamine
Chemoreceptor trigger zone	Central D2: Haloperidol, olanzapine, metoclopramide, prochlorperazine 5HT3: Ondansetron, granisetron, mirtazapine NK1: Aprepitant

GABA = γ-aminobutyric acid; GERD = gastroesophageal reflux disease; PUD = peptic ulcer disease.

to dopaminergic blockage with metoclopramide, prochlorperazine, or haloperidol. Chemotherapy-induced nausea is more often responsive to serotonin antagonists (such as ondansetron) or olanzapine (38, 39). Corticosteroids are additive to other antiemetics in chemotherapy regimens and for primary treatment of nausea due to increased intracranial pressure (37, 38). For incomplete mechanical bowel obstruction, the standard of care is dexamethasone and metoclopramide; findings on the efficacy of octreotide have varied (40). Higher-grade obstructions may require venting gastrostomy tubes in addition to octreotide to alleviate pressure. Reduced gastrointestinal motility can be relieved by metoclopramide, whereas radiation-associated nausea responds best to serotonin antagonists. Anticholinergic antihistamines (such as scopolamine or meclizine) are effective for motion-associated nausea and vomiting or for posterior fossa lesions (for example, cerebellar stroke or metastases) (37).

When should depression and anxiety be treated?

Depression is not normal but is not uncommon in seriously ill patients. Physicians should therefore have a low threshold for assessment and treatment. It can be difficult to differentiate depression from preparatory grief (41, 42), which may be normal in patients facing serious illness. Symptoms persisting for several weeks and meeting diagnostic criteria for depression are neither normal nor expected (see the **Box**: Indicators of Depression in Seriously Ill Patients). Treatment with selective serotonin reuptake inhibitors (SSRIs) is usually safe, but drug–drug interactions should be considered, particularly if the patient is also receiving hormonal agents, such as tamoxifen (43). Psychostimulants, such as methylphenidate, are fast-acting and effective in patients without contraindications (for example, unstable tachyarrhythmia) and are helpful in treating depression in combination with SSRIs (44). Mirtazapine at low doses may be useful in patients with concomitant insomnia or anorexia. Duloxetine or venlafaxine may be considered for depression with neuropathic pain; however, prognosis must be considered because treatment requires weeks to achieve the optimal effect (45). Nonpharmacologic interventions, such as music therapy or future-focused psychotherapy, may also be beneficial (44).

Seriously ill patients with active suicidal ideation, including those requesting hastened death, often fear unmanageable symptoms or loss of control. Such requests should prompt an immediate assessment for suicidality while addressing concerns about the end of life. Referral to a mental health or specialty PC professional may be necessary (45).

Up to one quarter to one half of patients with advanced cancer experience significant anxiety symptoms, and

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Indicators of Depression in Seriously Ill Patients*

Psychological symptoms
- Dysphoria
- Depressed mood
- Sadness
- Tearfulness
- Anhedonia
- Hopelessness
- Helplessness
- Social withdrawal
- Guilt
- Suicidal ideation

Other indications
- Intractable pain or other symptoms
- Somatic preoccupation
- Poor adherence to or refusal of treatment
- Treatment with corticosteroids, interferon, or other agents

Historical indicators
- Personal or family history of psychiatric illness
- Pancreatic cancer

* *From reference 45.*

2% to 14% have anxiety disorders (13). Nonpharmacologic interventions, including mindfulness, relaxation and breathing techniques, and cognitive behavioral therapy, are often effective in these situations.

When and how should providers treat anorexia and weight loss in serious illness?

Reduced appetite and weight loss are common in seriously ill patients. Because eating and enjoying food are essential components of social interaction, many families find lack of interest in food distressing. Patients may feel pressured to eat more, even if it causes discomfort, as caregivers conflate not eating with “giving up.” Educating patients and caregivers about anorexia and cachexia is helpful in relieving guilt and promoting acceptance of altered eating habits. Caregivers should engage the patient in eating for pleasure and participating in the social aspects of meals, realizing that the patient may only enjoy a few bites of a favorite food.

If weight gain is important to the patient (goal-concordant), appetite stimulants may be considered. A small randomized clinical trial (46) showed that mirtazapine was inferior to megestrol in weight gain and appetite improvement. A critical appraisal of systematic reviews (47) showed that anamorelin improved cancer anorexia–cachexia syndrome, while megestrol acetate improved appetite and was associated with weight gain. Use should be carefully balanced against adverse effects, including thromboembolic disease, hyperglycemia, adrenal suppression, and vaginal bleeding. Olanzapine can also stimulate weight gain and reduce nausea but may induce hyperglycemia (48).

Is cannabis appropriate in patients with serious illness?

The WHO estimates that about 2.5% of the world's population uses cannabis (49). Although cannabinoids can improve appetite and sense of well-being, data in patients with serious illness are limited. Synthetic cannabinoids, such as nabilone and dronabinol, are indicated for chemotherapy-induced nausea and vomiting; however, limited evidence supports their use as appetite stimulants. With increased legalization of marijuana in many states, clinicians should be aware of the evidence underpinning cannabis use (50). It is important to ask patients in a gentle and nonjudgmental manner about use of cannabis products, such as edibles. Patients may be unaware of the adverse effects (including agitation, orthostatic hypotension, and tachypnea) of these agents, so education is important.

Are psychedelics appropriate in patients with serious illness?

Conventional psychotherapeutic or pharmacologic interventions have limited effects on patients with an anticipated prognosis of days to weeks who may struggle with existential distress, demoralization, and despair. Research on the effect of psychedelics is outdated, as they were banned in 1968 (51, 52). However, interest in the effectiveness of classic serotonergic psychedelics (LSD and psilocybin) and entactogens or empathogens (methylenedioxymethamphetamine [MDMA]) in alleviating suffering in the last phase of life has reemerged. The U.S. Food and Drug Administration has issued draft guidance (53) for clinical investigations using psychedelics. Although psychedelics are not available for clinical use, patients who feel desperate may experiment with "street drugs," including psychedelics. Clinicians should engage in open and nonjudgmental communication so patients feel safe sharing their experiences with psychedelics and receive guidance to augment their safety.

Do artificial nutrition and hydration help patients at the end of life to live longer or feel better?

Use of enteral and parenteral nutrition in patients approaching the end of life is controversial. Benefits (such as increasing weight or strength) are most pronounced in patients with good functional status or when nutritional intake is limited in aerodigestive cancers (for example, esophageal cancer).

Enteral feeding confers no benefit in patients with advanced dementia in terms of survival, quality of life, or risk for aspiration pneumonia. Parenteral nutrition is associated with risks such as central line–associated bloodstream infection, electrolyte imbalances, and fluid overload. Enteral or parenteral nutrition does not prolong life or improve quality of life for patients in their final weeks and may cause harm (54). Discussing nutritional preferences before extreme weight loss and anorexia occur is important and may help prevent distress for the patient and their family (55). Oral nutritional supplements may be considered if they are consistent with the patient's goals of care (56, 57).

What are common symptoms in the last days of life?

Patients transitioning into the active dying process show less interest in their surroundings and sleep most of the time. Gradual loss of hunger and thirst is expected but may cause distress to family members. Persons in the last days of life can experience terminal delirium, which may manifest as agitation (less common) or hypoactivity and inattention. Urinary obstruction, bowel impaction, and poorly treated pain are common causes of agitation. Nurse-led bedside ultrasound bladder scans to identify urine retention should be considered in the last days of life. Constipation is also a common cause of urine retention, particularly in men. Suppositories and enemas can relieve constipation and may allow for resumption of urination. Some patients, however, may need straight catheterization; use of indwelling catheters is not recommended given the risk for infectious and noninfectious complications (58, 59). Should reversible causes of agitation not be discovered, low-dose haloperidol may be considered.

Irregular breathing patterns (for example, Cheyne–Stokes respiration) are common and do not cause distress to the patient, although family members need reassurance. Death rattle, or "noisy breathing," is caused by the presence of oropharyngeal secretions in the upper airways, which dying patients are unable to clear. Loved ones can misinterpret the death rattle as a sign of suffering. A recent multicenter, randomized, double-blind, placebo-controlled trial showed that prophylactic subcutaneous scopolamine butylbromide significantly reduced occurrence of death rattle compared with placebo (60).

Managing Common Symptoms... Moderate to severe pain and dyspnea in patients with life-limiting illness are best managed with opioids. Careful opioid dosing can eliminate respiratory depression. Treatment of nausea is most effective when it is tailored to associated neurotransmitters. Anxiety may occur, and contributors to distress should be investigated before pharmacotherapy is instituted. Delirium is common in patients approaching the end of life and should be recognized early. Persistent depression in seriously ill patients warrants antidepressant treatment. Encouraging oral intake for enjoyment should take preference over parenteral or enteral nutrition, particularly in late-stage illness. Patients in the last days of life experience multiple distressing symptoms, which should be monitored and palliated.

CLINICAL BOTTOM LINE

Communication and Psychosocial and Ethical Issues

How should clinicians approach discussions about goals of care?

Seriously ill patients may be reluctant to initiate discussions about goals of care and prognosis as they may fear physician abandonment, withdrawal of supportive measures and treatments, and emotional reactions from loved ones. Physicians must facilitate conversations among patients, families, and care providers to address patients' wishes and concerns about life-sustaining technologies, supportive treatments, and desire for care at home versus the hospital (2). Such conversations may evoke emotional responses (61), and often several discussions are necessary to address these issues.

Many physicians and families incorrectly believe that initiating discussions about goals of care "takes away hope" (62, 63). Patients should be assured that these discussions do not imply "giving up," "losing hope," or that there is "nothing left to do." Reminding patients that hope can be preserved by setting achievable goals (such as controlling pain, taking walks, or performing activities that provide enjoyment), which often alleviates anxiety. For patients who seek prognostic information, studies suggest that hope is maintained when patients are given truthful information and treatment options, even if the news is bad (62). Avoiding such discussions may limit evaluation and treatment of important symptoms. Such avoidance may also rob a patient of the opportunity to complete tasks before death (64).

What should clinicians know about health care proxies, advance care planning, and serious illness conversations?

In addition to assessing goals of care and symptom control, patients' preferences for disease-targeted interventions and surrogate decision making should be addressed. State laws vary regarding default surrogate decision makers if one was not previously designated by the patient (65). Appointing a durable health care power of attorney or health care proxy can help prevent conflict or confusion.

Advance care planning originally focused on completion of advance directives; however, most evidence suggests that advance directive completion per se is not effective (66). However, the broader goal of advance care planning is to prepare patients for decision making (67) by identifying values and goals. The optimal timing and content of conversations and who should conduct them remain subjects of investigation (68).

Free online resources to promote serious illness conversations (68) and advance care planning are available and improve documentation rates and well-being (69–71). Surrogates should be informed of and agree to support a patient's care preferences and remember that their role is to represent the patient's expressed wishes as illness progresses. The experience can be positive, therapeutic, and less stressful when the surrogate knows the patient's wishes (72, 73). Patients with medical devices (such as pacemakers or cardioverter-defibrillators) or those receiving long-term, life-sustaining treatments (such as hemodialysis) require special consideration and careful discussions. Ideally, treatments that no longer achieve the patient's goals should be discussed when the patient's functional status and quality of life are still intact.

What are the legal and ethical differences between withholding or withdrawing life-sustaining treatments and euthanasia or aid in dying?

Goal-directed, voluntary withdrawal of medical treatment is ethically and legally sound and differs from physician or medical aid in dying (MAID) or euthanasia (**Table 4**). The U.S. Supreme Court and lower courts have consistently ruled that there is no moral, legal, or ethical difference between withholding or withdrawing life-sustaining treatments versus not initiating them. Because patients ultimately die of their underlying illness, withholding or withdrawing mechanical ventilation, feeding tubes, and hemodialysis is legally allowable and ethically neutral.

MAID is morally different for many because it introduces an intervention with the primary goal of hastening death independent of the terminal disease process. Direct administration of a lethal drug by a clinician is not legal in the United States. However, as more jurisdictions legalize MAID, clinicians should be aware of state laws and how to refer patients should they desire more information. Conscientious objection is permitted regardless of legal status. The American College of Physicians, which is committed to improving care for patients approaching the end of life, does not support MAID (74). Instead, the guidelines suggest that requests for MAID prompt discussion to understand the underlying reasons for the request (75).

Table 4. **Differences Among Withholding and Withdrawing Life-Sustaining Treatment, Palliative Sedation, Medical Aid in Dying, and Euthanasia***

Characteristic	*Withhold Life-Sustaining Treatment*	*Withdraw Life-Sustaining Treatment*	*Palliative Sedation*	*Medical Aid in Dying*	*Euthanasia*
Cause of death	Underlying disease	Underlying disease	Underlying disease†	Treatment prescribed by physician and used by patient	Intervention administered by physician
Goal of treatment	Preclude burdensome intervention	Discontinue burdensome intervention	Treat symptoms	Death	Death
Legal status in the United States	Legal‡§	Legal‡§	Legal	Legal in some states; prohibited in some states; being considered in some states§	Illegal

* Based on Olsen ML, Swetz KM, Mueller PS. Ethical decision making with end-of-life care: palliative sedation and withholding or withdrawing life-sustaining treatments. Mayo Clin Proc. 2010;85:949-954.
† Note "double effect" (see text).
‡ Several states limit the power of surrogate decision makers with regard to life-sustaining treatments.
§ Clinicians should refer to their state's medical guidelines for current policy.

When should clinicians consider palliative sedation?

Palliative sedation with benzodiazepines, barbiturates, or anesthetic agents is justified for alleviation of symptoms that cannot be managed any other way (75). Sedation may unintentionally hasten death due to possible side effects, often referred to as the "double effect" (76). The intent of palliative treatments should be congruent with the patient's wishes to relieve symptoms, must follow standards of care, and must be documented alongside the patient's or surrogate's understanding of potential risks (**Table 4**). Palliative sedation is ethically and legally acceptable because its primary intent is to relieve suffering that is refractory to reasonable treatments. It is also consistent with physicians' responsibility to provide comfort. Palliative sedation is best managed by a PC specialist.

Communication and Psychosocial and Ethical Issues... Early, regular discussions of goals of care among physicians, patients, and families help set expectations about disease progression and facilitate preference-sensitive, high-value care. Serious illness conversations and roles for surrogate decision makers should be addressed. If a patient perceives that the burden of a treatment outweighs the benefits, withdrawing treatment is morally equivalent to having never started it.

CLINICAL BOTTOM LINE

Patient Education

What do patients and their families need to understand about PC?

Patients and their families commonly (and mistakenly) believe that hospice and specialist PC are the same. Misunderstandings about eligibility, purpose (life-prolonging treatments are prohibited), or philosophy (to hasten death) are common and may limit referrals to palliative specialists. Explaining the rationale for consultation, the distinction from hospice, and the goals of a specialist PC evaluation with patients may increase receptiveness to these interventions.

When is the best time to discuss PC?

Trigger tools have been created to standardize engagement of subspecialty PC, including in specific disease states, such as heart failure, or locations, such as the intensive care unit (77–79). Patient education is a fundamental component of PC. Simple tools (80) that allow patients to initiate the communication with their care team and family and enable them to complete the important task of life review can be helpful. Advance care planning and surrogate identification give patients the opportunity to provide anticipatory guidance about their care. When situations evolve, it is important to keep patients and surrogates informed about clinical changes, prognosis, and treatment options.

In the Clinic
Tool Kit

Best Practices in Caring for Seriously Ill Patients

Patient Information

https://medlineplus.gov/palliativecare.html
https://medlineplus.gov/languages/palliativecare.html
Information on palliative care in English and other languages from the National Institutes of Health's MedlinePlus.

www.cancer.gov/about-cancer/advanced-cancer/care-choices/palliative-care-fact-sheet
Fact sheet on palliative care in cancer for patients and their families from the National Cancer Institute.

https://medlineplus.gov/endoflifeissues.html
Information on end-of-life issues from the National Institutes of Health's MedlinePlus.

https://getpalliativecare.org/handouts-for-patients-and-families
Handout for patients and families on what to know about palliative care from the Center to Advance Palliative Care.

Information for Health Professionals

https://ascopubs.org/doi/10.1200/JCO.2016.70.1474
American Society of Clinical Oncology clinical practice guideline update on the integration of palliative care into standard oncology care.

www.acpjournals.org/doi/10.7326/M17-0938
American College of Physicians position paper on ethics and the legalization of physician-assisted suicide.

https://jnccn.org/view/journals/jnccn/15/7/article-p883.xml
National Comprehensive Cancer Network clinical practice guidelines on oncology for antiemesis.

www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm
Clinical practice guideline for prescribing opioids for pain from the Centers for Disease Control and Prevention.

WHAT YOU SHOULD KNOW ABOUT PALLIATIVE CARE

What Is Palliative Care?

When you have a serious health condition, you need special care and attention. A serious health condition is chronic and cannot be cured. Living with a serious health condition can be hard in many ways. It can affect how your body feels, your emotional health, and your family's and friends' emotional health.

Palliative care is a way to give you the special care you need while living with a serious health condition. You can get palliative care while you are in a hospital or at your doctor's office. You do not need a specialist to receive palliative care, and many physicians can provide this treatment. When you get palliative care, you can expect to receive:

- Help in learning how to manage your health condition
- Relief from your symptoms
- Help in feeling better day-to-day
- Support for yourself and your loved ones
- Answers to your questions about care planning or the future
- Support in having conversations about your wants, needs, and wishes with your doctor and loved ones
- Help in making plans for the future

Who Will Be on My Care Team?

Your care team includes the people who take care of you. They will help teach you about treatments and support you in making decisions about your health. They can also help educate and give support to you and your loved ones. Your care team will usually include a doctor, a nurse, a chaplain, and a social worker.

What Is the Difference Between Palliative Care and Hospice Care?

Hospice is also a special type of care for someone who has a serious health condition. However, hospice care is for a person who is expected to die within the next 6 months. Palliative care is for all patients in all stages of a serious health condition. This can mean right after you are diagnosed and any time after that.

How Will Palliative Care Help My Symptoms?

It can be very hard to live with a serious health condition. Many people have:

- Pain that won't go away
- Trouble breathing
- Nausea
- Confusion, anger, sadness, or depression
- Less appetite
- Weight loss

There are treatments, medicines, and therapies that can help you feel better. These can include getting relief from:

- Pain. For mild or moderate pain, your doctor may suggest over-the-counter pain medicines like acetaminophen or NSAIDs. For more severe pain, you may be prescribed strong pain medicines like opioids. Be sure to follow your doctor's instructions on how to take them.
- Breathing trouble. Your doctor may prescribe medicines to help with your breathing. Your doctor might also suggest pulmonary rehab, which will help you learn how to breathe better and live well with breathing problems.
- Depression or anxiety. There are medicines that might help you feel better day-to-day. It might also help to talk to the other members of your palliative care team about how you feel. In addition, it might help to receive care from a licensed mental health provider.
- Nausea or vomiting. There are medicines that can help you feel less nauseous and prevent vomiting. Some medicines might even help you feel hungry again.

Your treatment will depend on your symptoms. Ask your care team about what treatment options are right for you and your symptoms.

Questions for My Doctor

- What is the best way to plan for my future?
- Where can I find support for myself and my loved ones?
- Can we discuss what I want for my future?
- How will I feel as my health condition progresses?
- Whom can I talk to about my wants and needs?
- What is the best way to manage my symptoms now?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

MedlinePlus
https://medlineplus.gov/palliativecare.html

National Institute of Nursing Research
www.ninr.nih.gov/sites/default/files/docs/palliative-care-brochure.pdf

Patient Information