Pharmacologic pain management at the end of life

Abstract: Escalating pain is common in the final weeks of life, requiring skilled management to assist patients with a life-limiting illness. Using a cancer model, pharmacologic approaches to treat pain in the final weeks of life are reviewed.

By Pamela Stitzlein Davies, MS, ARNP-BC, ACHPN

Pain is common in advanced disease, especially in the last months of life. Skilled symptom management is a vital proficiency for NPs caring for patients with life-limiting illnesses. Knowledgeable use of pharmacologic and nonpharmacologic therapies in advanced illness is essential and was identified as a core competency in the American Association of Colleges of Nursing publication Peaceful Death: Recommended Competencies and Curricular Guidelines for End-of-Life Nursing Care, as well as in a position statement by the American Society for Pain Management Nursing. The purpose is to improve care of the dying and contribute toward the ultimate goal of a “good death.”

The term “end of life” (EOL) refers to a variety of phases in a terminal illness, such as the last few years of life, the last 6 months of life when the patient becomes eligible for hospice, and the final days of life when someone is “actively dying.” This article focuses on pharmacologic management of pain in adults in the final days and weeks of life using a cancer model, and the setting of outpatient palliative care, home management, and home hospice.

Case study
Mr. R, 67, is a White male with metastatic renal cell carcinoma, diagnosed 3 years ago. He was referred to palliative care for management of complex

Keywords: cancer pain, cancer pain management, end of life, pharmacologic management
Pain and symptoms related to progression of the disease. His prognosis is “months.” Mr. R has a large metastatic lesion in the left pelvis that is pressing on the sciatic nerve, eroding the iliac crest, and creating tissue pressure from tumor bulk. His primary complaint is severe left-sided burning pain deep in the left gluteal area with radiation down the left posterior thigh. He also reports moderate aching and sharp pain in the left buttocks and pelvis, and mild-to-moderate aching pain at various sites of bony metastatic disease in the left iliac crest, left femur, and ribs. His pain is nociceptive and somatic (tumor bulk in pelvis, and bony metastasis) and neuropathic (sciatica).

Pain significantly impacts Mr. R’s quality of life and sleep, and is creating significant distress for him and his caregiver daughter. He is taking an extended-release (ER) opioid (fentanyl, 100 mcg per hour, transdermal patch every 72 hours) and an immediate-release (IR) opioid (oxycodone 10 mg, 1 to 2 tablets every 4 hours as needed), totaling 80 to 100 mg of oxycodone per day. Mr. R has declined radiation therapy and pharmacologic therapy for neuropathic pain. Other symptoms include fatigue, anorexia and cachexia, sleep problems, anxiety, and depression.

Prevalence of pain at EOL
Pain is the most feared symptom at EOL. End-stage illness is associated with worsening pain for both cancer and noncancer diagnoses. A study of opioid prescriptions in a cohort of nearly 30,000 patients with 5 common cancers found that pain was a prominent symptom in the last 3 months of life, with a requirement for increasing opioid doses in all groups, as death approached. In addition to pain, other common symptoms encountered at EOL include fatigue, breathlessness, weakness, weight loss, anorexia, constipation, anxiety, depression, and delirium.

Approach to pain management
Several factors impact the approach to symptom management in advanced disease:
- Prognosis (days versus months)
- Individual goals of care (comfort versus aggressive care)
- Comorbid conditions (kidney dysfunction, heart failure)
- Setting of care (home, inpatient hospice, adult family home)
- Access to specialized treatment (interventional blocks, radiation therapy)
- Cost considerations (including restrictions on certain drugs by hospice or insurance policies)
- Patient and caregiver wishes

Existential distress will significantly impact the degree of suffering from pain and symptoms at EOL. Existential suffering derives from a sense of hopelessness, feeling a burden to others, loss of a sense of dignity, and loss of the will to live. The concept of total pain explains the importance of not only the physical domain of suffering but also the psychological, social, and spiritual domains. It is essential to appreciate the complex and multifactorial experience represented by reports of pain at EOL and include screening for existential suffering. In some cases, intense suffering may be best treated with strategies such as spiritual counseling rather than increasing the opioid dose.

Pain assessment
Thorough pain assessment is essential in establishing the source of the pain and to create the proper management strategy. A detailed history of the pain experience includes:
- Location and radiation of pain
- Word descriptors of pain quality (aching, throbbing, burning)
- Intensity (mild, moderate, severe)
- Duration (constant, intermittent)
- Pain-relieving factors (medication, distraction)
- Pain-aggravating factors (standing, coughing)
- Associated symptoms (nausea, anxiety, insomnia)

Additional questions include the impact of pain on quality of life, mood, sleep, activity, and concentration. A detailed physical exam should include evaluation of the affected area and nearby structures. Specifically assess for myofascial pain and trigger points, which can cause severe pain but are not particularly responsive to opioids. Review of scans will further assist in determining the source of nociceptive or neuropathic pain. A bulky tumor from melanoma that is noted to erode the iliac crest and compress the sciatic nerve creates pain of both nociceptive somatic origin (tissue compression, bone metastasis) and neuropathic origin (sciatica). This understanding will prompt the NP to add an adjuvant agent for managing neuropathic pain to the opioid regimen.

Assessing pain in the patient who cannot self-report is a special concern, as inability to communicate is common in the final days of life. NPs should attempt to obtain a self-report from the patient, as those with mild-to-moderate dementia are able to provide an accurate report of pain; identify conditions likely to cause pain; observe for common pain behaviors, such as facial grimace, moaning, guarding; solicit input from caregivers; and initiate an analgesic trial and observe for changes in pain behaviors. Given the high incidence of pain at EOL, assume that pain is present in the patient with far advanced disease who cannot self-report and treat the patient presumptively with opioids, titrating upward until observed pain behaviors are reduced.
### General approach to EOL pain management

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
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<tr>
<td>Provide reassurance of pain control</td>
<td>Recognize that anxiety about uncontrolled pain at EOL is a nearly universal fear. Provide reassurance that the team will work together to keep pain under adequate control. (However, do not make promises that the patient will experience “no pain.”) Advise the patient/caregiver to notify the team if pain is not acceptably controlled.</td>
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<tr>
<td>Schedule “around-the-clock” dosing for ongoing chronic pain</td>
<td>Provide immediate-release medications on a scheduled basis around-the-clock. Then transition to extended-release for convenience and better pain control.</td>
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<td>Prescribe medications for breakthrough pain (BTP)</td>
<td>To determine the dose for breakthrough pain, calculate 10% of the total daily opioid intake. Give every 1-4 hours orally, or every 30-60 min subQ or I.V.</td>
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<td>Simplify the medication regimen</td>
<td>Discontinue unnecessary medications. In general, limit opioids to one IR opioid and one ER opioid medication.</td>
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<td>Use the oral route if the patient is able to swallow and pain is adequately controlled</td>
<td>The oral route is simple, convenient, and the lowest-cost route.</td>
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<td>Convert medications to other routes if the patient is unable to swallow</td>
<td>Sublingual is the most common alternate route, although its efficacy is in question. Other routes include I.V. and subQ. Rectal route is an option, but many drugs do not come in a rectal formulation, there is variable absorption of medications, and some patients and caregivers will find it objectionable.</td>
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<tr>
<td>Evaluate for kidney impairment</td>
<td>Kidney impairment is common at EOL. For estimated glomerular filtration rate less than 60, it is advisable to avoid drugs with toxic active metabolites, such as morphine, which can trigger or exacerbate delirium.</td>
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<tr>
<td>Evaluate for hepatic impairment</td>
<td>Use lower doses and longer intervals of opioids and other drugs. In severe liver failure, consider using IR opioids only, not ER, to prevent excess accumulation of drug.</td>
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<td>Investigate all reports of an opioid “allergy”</td>
<td>Most reported “allergies” are expected adverse reactions, such as nausea, vomiting, sedation, or constipation. True immune-mediated allergic reactions to opioids are rare.</td>
</tr>
<tr>
<td>Maximize the use of neuromodulators and nonopioid analgesics</td>
<td>Use antiepileptic drugs (Gabapentin, pregabalin) off-label use, and antidepressants (duloxetine, nortriptylne) off-label use, for managing neuropathic pain. Use non-opioid analgesics, including corticosteroids (dexamethasone), acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and topical agents, to improve pain control and provide an “opioid-sparing” effect.</td>
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<tr>
<td>Prescribe a hospice “Comfort Kit” when the patient enrolls in home hospice care</td>
<td>Standard hospice order sets include a “Comfort Kit” kept in the home refrigerator. The kit contains several medications for urgent management of severe pain, anxiety, shortness of breath (SOB), or seizures. Concentrated opioid solution, such as morphine or oxycodone, can be utilized for management of a pain crisis, at the direction of the hospice team.</td>
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<tr>
<td>Evaluate for delirium</td>
<td>Delirium occurs in 80% to 90% of patients in the final days of life. Hyperactive delirium may appear to be pain behaviors, yet does not improve with increasing doses of opioids. A trial of haloperidol will improve delirium symptoms and help to distinguish delirium from pain.</td>
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<tr>
<td>Address existential distress</td>
<td>Existential distress significantly impacts the pain experience. Assess psychological, social, and spiritual domains of suffering. Utilize social work, chaplaincy, and psychology services for management.</td>
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Pharmacologic pain management at EOL
Progressively worsening pain is expected as life comes to an end. Opioids are the foundation for treating pain at EOL.22 However, it is also important to maximize the use of adjuvant agents, nonopioid analgesics, and nonpharmacologic therapies to achieve the best results.5 Refractory pain that does not respond as expected to standard therapies occurs in 10% to 20% of patients.22 In such cases, the NP may benefit from consultation with specialists in pain management or palliative care.

Opioids
The primary agents to treat pain from cancer at EOL are the pure \( \mu \)-agonist opioids, with morphine considered the gold standard.20 Unlike most pharmaceuticals, these opioids have no ceiling effect, indicating that the drug can be titrated upward without a maximum or ceiling dose.20,23 Oral opioids are available as IR, or short-acting agents, which provide a rapid onset of analgesia within 30 to 60 minutes.20 IR drugs are the initial formulation prescribed for pain, taken as needed, or scheduled every 4 to 6 hours. IR medications are also used for breakthrough pain (also called episodic pain or pain flares) given in conjunction with an ER opioid. Oral ER drugs are formulated to release the opioid in a slow and steady fashion and are dosed every 8 to 12 hours, creating steady serum drug levels and more consistent analgesia.20

Considerations in opioid selection
The pure \( \mu \)-agonist opioids are similarly efficacious with similar adverse effects when given at equianalgesic doses.5,20,24 However, significant interindividual variability exists in response, due to genetic polymorphisms that affect opioid binding and efficacy.10,23,24 Morphine is commonly the first choice for pain management in hospice settings because it is low-cost, available in multiple forms, and readily accessible. Yet the literature indicates that morphine should be avoided (due to accumulation of toxic metabolites) in patients with kidney and hepatic impairment that are commonly encountered at EOL.5,10,11 Instead, fentanyl or methadone is advised, as these drugs have inactive metabolites.5 However, methadone requires specialized knowledge for use, and transdermal fentanyl has limited use in severely cachectic patients.

Morphine
Morphine is the gold standard by which all other pure \( \mu \)-agonist opioids are compared. It comes in numerous formulations and can be given by multiple routes. It is metabolized by the liver and excreted by the kidneys. In

<table>
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<th>Determining the source of pain(^{5,20})</th>
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<tr>
<td><strong>Type of pain</strong></td>
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<td><strong>Tissue involved</strong></td>
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<td><strong>Example of disease</strong></td>
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<tr>
<td><strong>Mechanism</strong></td>
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<td>(using a cancer model)</td>
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<td><strong>Pain description</strong></td>
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<tr>
<td><strong>Example of medication therapy</strong></td>
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Kidney dysfunction, the active metabolites of morphine-3-glucuronide and morphine-6-glucuronide may lead to neurotoxicity, including myoclonus (involuntary muscle jerking) and seizures.5,11,20

Opioid-induced hyperalgesia occurs more commonly from morphine compared with other opioids. Occasionally, it will be used in patients with kidney or hepatic impairment. In such cases, the NP should prescribe or request a rotation to another opioid to avoid neurotoxicity.20

**Oxycodone**

Oxycodone is a good choice for late-stage disease for oral, sublingual (SL), and rectal administration. I.V. and rectal routes are not available in the United States, but oral IR tablets may be inserted rectally if other routes are not immediately available.20 It is formulated as a highly concentrated solution of 20 mg per mL and is particularly useful in hospice settings for SL administration in patients who cannot swallow.5 Oxycodone is metabolized by the liver and excreted by the kidneys but may be used with caution in hepatic or kidney impairment if given with lower doses and longer dosing intervals.20 It is available as a combination product with various drugs, including acetaminophen. Care must be used to avoid accidental acetaminophen overdose.20

**Hydromorphone**

Hydromorphone is a potent analgesic available in oral solution and can be administered orally or SL, rectal suppository, or a high-potency injectable solution that can be administered as a subcutaneous (subQ) infusion in the hospice setting.3,12,15 The equianalgesic potency of hydromorphone compared with morphine is unclear, and current equianalgesic tables may underestimate the potency, especially with prolonged dosing; therefore, care should be used when rotating to this drug.20 A lower dose and longer dosing intervals should be used in moderate-to-severe kidney impairment or in severe hepatic insufficiency.5,25

**Hydrocodone**

Hydrocodone IR is available in combination with acetaminophen, ibuprofen, or other drugs. Such combination products limit the use in advanced disease to those with moderate pain that will not require significant dose escalations.

**Oxymorphone**

Although the semi-synthetic drug has been available for decades in parenteral and rectal forms, it has not been commonly used. Oxymorphone IR and ER oral formulations were introduced in 2006, but high cost has limited its use.

**Methadone**

Methadone is a pure mu-agonist with unique properties and a naturally long half-life, taking 5 or more days to reach steady state.6,23 It has additional unique effects, including N-methyl-d-aspartate receptor blockade, which is theorized to improve neuropathic pain through nonopioid mechanisms.22 Methadone is metabolized in the liver and has no active metabolites. It is available in a liquid solution formulation and can be administered via a feeding tube or SL.20 Methadone is frequently used by hospice clinicians to treat advanced disease pain but requires expert knowledge to prescribe safely.5,22,23,27

Methadone has multiple complex drug interactions that may significantly alter the bioavailability of both the inducer and inhibitor.

Unlike most opioids, which have linear pharmacokinetics, methadone has curvilinear pharmacokinetics.28 This means the higher the dose of methadone, the more potent it is, with an exponential effect at the highest doses, creating a risk for accidental opioid overdose.27 Therefore, methadone dose titration is more conservative than with standard opioids (due to the long and variable half-life) with lower initial doses and dose increases limited to every 5 to 7 days and longer for kidney or hepatic impairment or older adults.5 Methadone has multiple complex drug interactions that may significantly alter the bioavailability of both the inducer and inhibitor. Consultation with an experienced pharmacist or provider familiar with methadone is strongly recommended.

Methadone may cause QT interval prolongation, necessitating a screening ECG at the initiation of therapy, with a recheck in a few months, and after any dose increase. A corrected QT interval (QTC) greater than 450 milliseconds is borderline high, and methadone should be initiated with caution. If the QTC is greater than 500 milliseconds, methadone should be stopped and another opioid chosen.29 An ECG may be omitted if it is determined with the patient or caregiver that the benefit outweighs the risks in the setting of far advanced disease (when death is anticipated within weeks).

**Fentanyl transdermal (TD) patch**

Fentanyl TD patch is useful for controlling pain in advanced disease, especially in patients who have trouble...
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remembering to take their oral ER medications regularly. The patch is applied to hairless skin on the upper torso, with a fresh patch applied to a new site every 72 hours (or every 48 hours if end-of-dose failure occurs). To avoid accidental overdose, instruct the patient or caregiver to remove the used patch at the time the new patch is applied. At first application, it takes 12 to 24 hours for fentanyl TD to take effect, and similarly, 12 to 24 hours to washout of the system when removed. The drug is stored in adipose tissue and has unreliable absorption in cachectic patients, but is an option to consider in patients with cachexia when use of other drugs is not feasible. However, higher-than-expected doses may be required to obtain adequate analgesia, and caution is needed when rotating from fentanyl TD to a different opioid, as the conversion dose may be much lower than anticipated in a cachectic patient. Fever, heating pads, and immersion in hot water will increase drug absorption; diaphoresis will impact adhesion to the skin, resulting in decreased absorption. Advise patients to avoid exposing the patch to heat sources such as heating pads or hot tubs.

Transmucosal immediate-release fentanyl (TIRF)
TIRF is FDA approved for managing breakthrough cancer pain in opioid-tolerant patients. It provides rapid onset of opioid analgesia for transient pain flares and is available in a variety of formulations, including SL tablet, oral lozenge, buccal tablet, and nasal or SL spray. TIRF formulations are not interchangeable and similar doses are not equianalgesic. A mandatory FDA Risk Evaluation Mitigation Strategy (REMS) program exists for TIRF, requiring prescriber enrollment and knowledge testing every 2 years.

Each patient must be individually registered with the TIRF-REMS program and acknowledge receipt of instructions of the risk and benefits of the TIRF. These drugs provide rapid and effective analgesia, but are quite costly, and typically are not covered by the hospice benefit. TIRF is not intended to take the place of standard IR medications and should only be used for severe pain episodes.

Tramadol and tapentadol
Tramadol and tapentadol are unique dual-action drugs that bind to the mu-opioid receptor and also have weak binding as a serotonin-norepinephrine reuptake inhibitor (SNRI). These drugs are approved for moderate to moderately severe pain (tramadol) and moderate-to-severe (tapentadol) acute pain. Both are available in IR and ER formulations, and may be considered for use in advanced disease settings. However, they have a maximum dose ceiling, limiting the ability to titrate upward in severe and uncontrolled pain. Additionally, they must be dose-reduced in older patients, those with kidney or hepatic impairment, or for drug interactions, due to the SNRI component of the molecule. They are not typically utilized for pain from advanced disease or in the hospice setting and are best limited to conditions with mild-to-moderate pain, in patients with normal kidney and hepatic function, that are not anticipated to develop severe and rapidly worsening pain.

Other opioid agents
The partial agonist buprenorphine and mixed agonist-antagonist agents, such as nalbuphine, which are not typically utilized for cancer pain in the United States but are gaining popularity in other countries. Starting an agonist-antagonist agent may precipitate opioid withdrawal in an opioid-tolerant patient, especially if taking higher doses of a pure mu-agonist. Therefore, caution and consultation is advised when considering use of these drugs.

Opioids not recommended
Meperidine is not recommended due to neurotoxicity from active metabolites, especially in patients with kidney and hepatic impairment and older adults. Codeine may be considered, but it is not a first choice in advanced disease, as some experts believe it has a ceiling effect and creates more constipation than other opioids. In addition, approximately 10% of the population lack the enzyme needed to convert the prodrug codeine to morphine, resulting in inadequate analgesia; some ultra-rapid metabolizers may develop an exaggerated response to codeine.

Route of opioid administration
The oral route is preferred for opioid administration if a patient can swallow, as it is simple, convenient, and cost-effective. However, when swallowing becomes difficult, I.V., subQ, SL, or rectal routes of administration are used. Patients with a permanent venous access through a port or indwelling central line can be easily converted to I.V. administration when needed. SubQ infusions
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or intermittent injections are good options for parenteral administration when the patient can no longer swallow opioid medication. SubQ administration of opioids should be avoided in severely immunocompromised patients and those with a bleeding disorder.33

SL administration of small amounts of highly concentrated opioid solutions of morphine, oxycodone, or methadone is an option for patients with minimal ability to swallow.12 However, except for the highly lipophilic drugs fentanyl and methadone, hydrophilic drugs such as morphine and hydrocodone are poorly absorbed by the SL route and likely absorbed primarily by being swallowed.33 Thus, no compelling evidence exists for the use of SL administration of hydrophilic drugs in the hospice setting.33

The evidence for delivering opioids via rectal route is mixed.33 The rectal route cannot be used if fecal impaction, diarrhea, anal fissure, inflamed hemorrhoids, or tumors of the rectum or pelvis are seen.

Dosing of opioids for initial use and worsening pain
In general, ER formulations are initiated only in opioid-tolerant patients as defined by the FDA.25

The National Cancer Comprehensive Network Guidelines on Cancer Pain provides a practical guide to initiation and titration of opioids in the opioid-naïve and

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<tr>
<th>Class</th>
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<th>Comments</th>
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<tr>
<td>Acetaminophen</td>
<td>Pain</td>
<td>• Maximum 3,000–4,000 mg per day, less in older adults.</td>
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<td></td>
<td></td>
<td>• Calculate intake from combination and over-the-counter acetaminophen-containing products to prevent accidental overdose.</td>
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<td>• Reduce to less than 2,000 mg per day in alcohol abuse and liver impairment. Avoid in hepatic insufficiency.</td>
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<tr>
<td>Corticosteroid (dexamethasone)</td>
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<td>• Reduce pain, improve appetite, mood, and energy</td>
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<td></td>
<td>• Spinal cord compression from metastasis, to reduce swelling and pressure on nerves, and reduce pain and paralysis</td>
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<td>• Avoid or use great caution in concurrent use with anticoagulants or NSAIDs due to increased risk of bleeding.</td>
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<td></td>
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<td>• May cause gastroduodenal bleeding, kidney impairment or failure, lower extremity edema, thrush, hyperglycemia, anxiety, agitation, or mania.</td>
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<td>• Causes insomnia, take second dose by early afternoon.</td>
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<td>• Use lowest effective dose for shortest period possible.</td>
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<td>• Recommend a limited trial with clear end-points, as prolonged use (over 2 weeks) may cause proximal muscle weakness, osteoporosis, or avascular necrosis.</td>
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<tr>
<td>Anticonvulsants ( gabapentin or pregabalin, FDA approved for neuropathic pain; off-label use for bone metastasis)</td>
<td></td>
<td>• Neuropathic pain</td>
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<td></td>
<td></td>
<td>• Insomnia</td>
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<td></td>
<td></td>
<td>• Metastatic bone pain</td>
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<td>• Pregabalin may provide analgesia as early as 2–3 days. Gabapentin takes longer for analgesic effect.</td>
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<td>• Reduce dose in kidney impairment.</td>
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<td></td>
<td></td>
<td>• May improve pain from bone metastasis (off-label use).</td>
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<td>Antidepressants ( duloxetine, nortriptyline, or desipramine)</td>
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<td>• Neuropathic pain</td>
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<td></td>
<td></td>
<td>• Depression</td>
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<td></td>
<td></td>
<td>• Takes days to weeks for analgesic effect.</td>
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<td></td>
<td>• Antidepressant effect takes weeks.</td>
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<td></td>
<td></td>
<td>• Causes sedation, anticholinergic effects.</td>
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<td></td>
<td></td>
<td>• Multiple drug interactions.</td>
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<td>• Reduce dose and use with caution in kidney or hepatic impairment.</td>
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<tr>
<td>Nonsteroidal anti-inflammatory drugs (NSAIDs) (naproxen or ibuprofen)</td>
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<td>• Metastatic bone pain</td>
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<td></td>
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<td>• Avoid or use great caution in concurrent use with anticoagulation therapies or steroids due to increased risk of bleeding.</td>
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<td>• NSAIDs may cause gastroduodenal bleeding, kidney impairment or failure, and lower extremity edema. May cause fatal cardiovascular thrombotic events.</td>
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<tr>
<td>Topical analgesics (lidocaine topical patch)</td>
<td></td>
<td>• Pain</td>
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<td>• Minimal systemic absorption of lidocaine, no drug interactions.</td>
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<td>• May cause skin reaction otherwise few adverse reactions.</td>
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<td>• Expensive.</td>
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Adjuvant and nonopioid analgesic medications for pain at the EOL5,11,20,37

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Opioid-tolerant patient. For episodes of worsening pain, explore the source of the pain, whether from tumor progression, myofascial spasm, or the patient simply forgetting to take analgesic medicine.

Opioid rotation
Rotation to another opioid may provide more effective analgesia (as there is significant genetic variability from opioid polymorphisms) or may be used to improve refractory adverse reactions or address opioid tolerance. Equianalgesic tables are available for conversion from one opioid to another. However, incomplete cross-tolerance of opioids exists, requiring dose reduction of the new opioid to prevent accidental overdose. To avoid accidental overdose, conversions involving methadone and fentanyl require additional expertise.

Adverse reactions
Respiratory depression and sleep apnea. Respiratory depression is the most serious adverse reaction of opioids, especially in opioid-naive patients who receive rapidly escalating doses of opioids for severe pain. Opioids may cause worsening of sleep apnea, both obstructive and central. The addition of a benzodiazepine or another sedative significantly magnifies the respiratory depressant effect. Nonetheless, patients often receive a benzodiazepine along with escalating doses of opioids for multisymptom management in the last days and weeks of life.

Constipation. Start patients on a stimulant (senna or bisacodyl) and an osmotic laxative (polyethylene glycol) or stool softener (docusate) when opioid therapy is initiated to help prevent constipation. Standard strategies to promote peristalsis, such as walking, increased fluid intake, and dietary fiber, are difficult for the patient with advanced disease due to anorexia and generalized weakness. Supplemental fiber intake (psyllium) is not advised for patients with advanced cancer affecting the gastrointestinal tract and peritoneum, such as bulky abdominal tumors, ascites, or peritoneal carcinomatosis. These conditions create a functional bowel syndrome that can be worsened by fiber intake, especially with inadequate fluid intake.

Tolerance does not develop to the constipating effects of opioids, and patients will need to remain on the laxatives long-term. Because obstipation is uncomfortable and may progress to a dangerous bowel obstruction, a bowel management program remains a priority, even in the final days and weeks of life. Lactulose syrup can usually be ingested even in the final days of life.

There are newer drugs (methylnaltrexone, naloxegol, lubiprostone) available for opioid-induced constipation, however these drugs are FDA-approved for chronic noncancer pain. Methylnaltrexone, given by subcutaneous injection, is an excellent option for patients with chronic noncancer pain but it is costly and may not be covered by insurance or hospice.

Nausea. Nausea management may include deep breaths, a fan directed toward the face, or antiemetics, such as prochlorperazine or ondansetron. If nausea continues, opioid dose reduction or rotation to another drug may be considered.

Pruritus. Itching may respond to cool compresses, medicated lotions, or gabapentin (off-label use) or ondansetron (off-label use). Although antihistamines (diphenhydramine, hydroxyzine) are commonly used for opioid-induced pruritus, however evidence to support this is lacking, and these drugs may cause dangerous oversedation. If pruritus continues, opioid dose reduction or rotation to another drug may be considered.

Fatigue and drowsiness. Fatigue and drowsiness that do not improve over time may require the use of a stimulant such as caffeine or methylphenidate (off-label use). If symptoms continue, consider reducing the opioid dose or rotation to another drug.

Myoclonus. Myoclonus is involuntary jerking, usually of the arms or legs, caused by opioid use. It occurs most commonly from morphine due to buildup of toxic metabolites, but may occur with any opioid. High opioid doses, kidney impairment, dehydration, and a terminal state increases the incidence. Severity can range from mildly bothersome to severe enough that the patient is inadvertently hitting himself or kicking the bed partner. Medication management includes addition of a benzodiazepine or baclofen (off-label use) to diminish the myoclonus, or rotation to another opioid, such as methadone.

Opioid-induced hyperalgesia (OIH). OIH is an uncommon adverse reaction of high-dose opioids that is challenging to diagnose with certainty in advancing illness in the dying patient. Observation of progressively worsening pain despite multiple opioid dose increases that would typically be expected to relieve pain, along with curious skin sensitivity to all touch (alldynia), should raise the suspicion of OIH. Initial management includes rotating to another...
opioid while maximizing adjuvant agents and nonpharmacologic therapies. If needed, specialist consultation with pain management or palliative care is needed for consideration of the off-label use of the anesthetic agent ketamine or the local anesthetic lidocaine for management.5,11,12,20

Adjuvant and nonopioid analgesics
Adjuvant agents, or coanalgesics, relieve pain through mechanisms other than the opioid receptor and may provide enough improvement (up to 30% reduction in pain) to create an opioid-sparing effect, allowing for opioid dose reduction.11 Neuromodulators refer to adjuvant agents that specifically aid neuropathic pain.20 Many adjuvant agents do not have FDA indication for use in pain management. (See Adjuvant and nonopioid analgesic medications for pain at the EOL.)

Antiepileptic drugs
Gabapentin and pregabalin (off-label use) can be particularly helpful for treating neuropathic pain and may improve pain from bony metastasis.20,25 Pregabalin needs minimal titration and can have a pain-relieving effect within a few days due to high oral bioavailability.20 Gabapentin may take a few weeks to notice an effect. The sedating adverse reaction may prove beneficial for insomnia.12 Gabapentin and pregabalin require dose reductions based on creatinine clearance for patients with kidney impairment.

Antidepressants
Off-label use of antidepressants with analgesic properties include the SNRIs such as duloxetine and venlafaxine or tricyclic antidepressants (TCA), such as nortriptyline and amitriptyline. They improve pain via the descending inhibitory modulating system and usually take several weeks to show an effect.12 These drugs, especially the TCAs, can have bothersome adverse reactions, including sedation, dizziness, postural hypotension, cardiac rhythm disturbances, and delirium. Multiple drug interactions exist, so caution is advised in their use, especially in older adults.24 Start antidepressants at low doses and titrate to the target dose over a few weeks.

Corticosteroids
Dexamethasone, prednisone, and methylprednisolone, are useful to reduce pain, presumably by reducing inflammation.4 They also improve appetite, mood, and feelings of well-being; and they may be added to the treatment regimens late in advanced disease. Dexamethasone is commonly used in the palliative and hospice setting. Many adverse reactions are seen, and the burden-to-benefit ratio must be carefully considered, even with a shorter prognosis.4,5,11,24

Psychiatric adverse reactions include insomnia, agitation, anxiety, and mania. Corticosteroids increase risk of gastroduodenal bleeding, especially when used concurrently with anticoagulants or nonsteroidal anti-inflammatory drugs (NSAIDs); combinations that are not recommended. They increase water retention and may precipitate exacerbation of heart failure or raise BP. Proximal muscle wasting may occur in the quadriceps, creating weakness and inability to arise from a chair or walk.12 For these reasons, the corticosteroid should be stopped or dose-reduced as soon as possible (preferably within 14 days of initiation) unless the benefit clearly outweighs the burdens.12

NSAIDs
Naproxen and ibuprofen are useful for treating nociceptive pain, especially from bony metastasis. They should not be given concurrently with anticoagulants due to increased risk of gastroduodenal bleeding. They may also exacerbate heart failure and hypertension and increase the risk of cardiovascular events.20 NSAIDs can cause kidney failure, especially in the older adult and dehydrated patient.5,23,37 Because kidney impairment and dehydration are common in the dying patient, significant consideration must be given to the burden-to-benefit ratio when utilizing NSAIDs. Query patients and caregivers to confirm that they are not double-medicating with over-the-counter (OTC) and prescribed NSAIDs.

Acetaminophen
Acetaminophen is a useful adjuvant drug for mild-to-moderate somatic pain and fever reduction. The FDA recently reduced the maximum tablet strength of acetaminophen to 325 mg both alone or combined with other medications. The recommended maximum daily dose of acetaminophen remains at 4,000 mg.38 However, patients with hepatic impairment or alcohol abuse should reduce to 2 g/day or avoid acetaminophen altogether.17 Assess for “hidden” OTC acetaminophen use, as this could lead to inadvertent acetaminophen overdose, causing liver failure.

Other adjuvant drugs
A variety of oncologic therapies for pain control may be considered if prognosis is anticipated to be more than 3 to 6 months. These include chemotherapy or biological

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agents to impede tumor progression; and bisphosphonates (pamidronate or zoledronic acid), or radiopharmaceuticals (strontium-89) to reduce pain from bony metastasis.\textsuperscript{11,12} In addition to opioids, pain from malignant bowel obstruction may be improved with use of corticosteroids or octreotide injection.\textsuperscript{20}

### Palliative sedation

This option of last resort is used for intractable and distressing pain or symptoms that cannot be controlled in the imminently dying patient. The purpose is to relieve intolerable symptoms and suffering, not hasten a patient’s death. Progressively higher doses of sedative are administered until intractable symptoms (pain, delirium, status epilepticus) are controlled. Drugs used include benzodiazepines (lorazepam, midazolam), barbiturates (phenobarbital, pentobarbital), or the anesthetic agent propofol.\textsuperscript{3,9}

### Case study summary

Mr. R was followed for 7 months until his death. At the initial visit, the NP titrated the ER opioid fentanyl patch to 200 mcg/hr (apply two 100 mcg/hr transdermal patches) every 72 hours. A corticosteroid was added for rapid pain relief, as well as to improve fatigue and appetite: dexamethasone 4 mg twice day for 14 days, then discontinued. The patient was encouraged to reconsider radiation therapy to the massive pelvic tumor to relieve pain. He completed 14 fractions with subsequent improvement in sciatica. Also recommended was the sequential addition of gabapentin and duloxetine for neuropathic pain, which were subsequently started and titrated to effective doses.

As the disease progressed, Mr. R required further titration of opioids for pain, necessitating a rotation to methadone and hydromorphone IR. He developed a pain crisis and was admitted to inpatient hospice center for rapid pain control with an I.V. opioid and ketamine infusion. The hospice chaplain helped him address significant existential distress, which helped his anxiety and fear of death significantly. He was discharged to home on oral methadone and ketamine, and appeared much more at peace.

Mr. R experienced a pathologic fracture of the left femur after a fall. He was admitted to an acute care hospital for fracture stabilization. The acute inpatient pain service started him on both I.V. patient-controlled analgesia with fentanyl and intrathecal bupivacaine infusion. He was discharged home and continued oral ketamine therapy, all of which provided good pain control. A caregiver was hired because he was no longer able to walk. For other symptoms, Mr. R received dexamethasone 2 mg each morning for the last few weeks of life for pain, mood, and general sense of well-being; haloperidol 0.5 to 1 mg every 8 hours for delirium and nausea; and treatment for ongoing constipation. Mr. R died at home surrounded by family, with his pain and other symptoms relatively well controlled.

### Moving forward

Pain management in the final days and weeks of life is challenging due to progression of disease, multisystem failure, and existential distress. Yet strategies exist to provide adequate analgesia, allowing the patient to die in relative comfort and without undue suffering. By addressing all domains of suffering and utilizing pharmacologic and nonpharmacologic therapies, the NP provides a key role in pain management at EOL. 

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