Management of Cancer-Related Pain

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- Pain • Malignant • Cancer • Opioids
- Emergency department

Patients and families struggling with cancer fear pain more than any other physical symptom. With the treatment of malignant pain remaining a challenge in the practice of oncology, the emergency department (ED) is often a place of refuge.\textsuperscript{3} There are significant barriers to optimal pain management in the emergency setting, including lack of knowledge, inexperienced clinicians, myths about addiction, and fears of complications after discharge. These factors contribute to unnecessary suffering not only for the patient but also for family and caregivers. Malignant pain is highly responsive to medication. Adequate malignant pain control is possible in more than 90\% of patients if established therapeutic approaches are applied systematically in any practice setting, including the ED.\textsuperscript{2–7} It has been suggested that management of an acute pain crisis in a patient with advanced cancer “is as much a crisis as a code,” and emergency clinicians should, and can, become comfortable caring for patients with cancer in acute pain.\textsuperscript{8}

Patients with cancer often present to the ED because their pain is unmanageable. Although there are multiple physiologic possibilities for inadequate pain control, the emergency clinician should also be aware of the many psychosocial factors contributing to oligoanalgesia in the cancer patient. Depression, unresolved spiritual or social concerns, and misconceptions of prescribed medications may interfere with adequate treatment. With a properly focused evaluation, the treatment of unresolved pain in the cancer patient can be performed rapidly and effectively in the ED.

ASSESSMENT OF MALIGNANT PAIN

General principles of good pain assessment are particularly important in the patient presenting to the ED with malignancy. A rapid assessment of severity, character, likely etiology, timing and location, exacerbating and relieving factors, and associated symptoms provides essential information for proper management. In addition, the
details of the history may reveal particular cancer pain syndromes, some of which require urgent diagnosis and intervention to prevent permanent functional impairment. With an adequate assessment, effective therapy can be quickly implemented in the ED.

The assessment of pain severity in cancer is the same as that of nonmalignant pain. There are several validated measures of a patient’s pain experience. Although any scale is useful for a given patient as long as it is applied consistently, the preferred scale for most patients is the numerical rating scale (NRS). Most commonly, this is an 11-point scale from 0 = “no pain” to 10 = “worst possible pain.” For small children or patients with limited literacy, a picture scale is more successful, with the Faces Pain Scale being a well-accepted choice. In the cognitively impaired patient, the 5-time observational Pain Assessment in Advanced Dementia Scale may be used. All of these scales have been validated and have utility in the ED for the assessment of pain. It should be emphasized that pain scales are intended to provide objectivity to the experience of the patient’s pain. Skepticism has no place in the assessment of suffering and may directly impair proper diagnosis and treatment. Pain can be complex, and these scales provide an objective method of evaluation to gauge treatment success. This is particularly true in acute pain.

The character and etiology of pain are described physiologically as either nociceptive or neuropathic. Cancer pain can be either or both. Nociceptive pain is a response to damaged tissue and can further be classified as either somatic (musculoskeletal/cutaneous) or visceral. Somatic pain is often described as sharp or aching and localized to the area of tissue damage. Pain secondary to bone metastasis is a classic example of somatic pain. Visceral pain is more poorly localized and can be intermittent, sometimes described as dull or cramping. Abdominal pain associated with ovarian or pancreatic cancers is characteristic. Neuropathic pain is primarily caused by nerve injury. The injury may be mechanical (e.g., amputation), metabolic (e.g., diabetes), inflammatory (e.g., radiation), or toxic (e.g., chemotherapy). Neuropathic pain is typically persistent and sometimes paroxysmal and shock-like. Normal stimulus may elicit abnormal pain responses (allodynia). A light touch, for example, may elicit searing pain. There can also be autonomic instability in the affected area, including edema or localized sweating such as that which occurs with complex reflex sympathetic dystrophy. An important treatment distinction between these types of pain is that patients with nociceptive pain are generally more responsive to opioids than are patients with neuropathic pain. Neuropathic pain often requires adjunctive non-opioid therapies for successful treatment.

Pain may rapidly change either in quality or location or may be chronic and slowly progressive. Although the alleviation of the pain crisis should always be the first priority, a search for the cause of the underlying pain ensures the most definitive treatment. Specific types of acute pain may require particular therapies for effective treatment, such as radiation therapy for bone metastasis. Likewise, a new location of pain may be the first sign of a dangerous progression of disease requiring diagnostic evaluation, such as new back pain preceding functional deficit in malignant epidural spinal cord compression. In addition to tumor progression, the aggressive treatments for malignancy may also be a cause for the patient’s pain presentation. Surgical tumor resection may have predictable and self-limited associated pain, whereas chemotherapy-induced neuropathy may be less predictable and more persistent. The approach to treatment of these distinct types of pain will be quite different.

The assessment and management of chronic cancer pain (generally regarded as >3 months) can be challenging. Although similar to acute cancer pain in that either disease progression or treatment is typically responsible for the pain, these patients
often carry a heavier global burden of suffering. The approach to treatment is more complex and must consider existing medications as well as other factors that may influence the approach to treatment.

Prior to diagnostic and therapeutic efforts in the ED, treatment must be guided by a clear understanding of the patient’s goals of care. Some patients may not wish detailed investigations but may simply require pain treatment. Both acute and chronic cancer pain may be caused by disease progression (62%–78%), treatment (19%–25%), or unrelated (3%–10%) causes.13 Patients who develop new pain are, therefore, reasonably anxious about disease progression. Communication should be sensitive to these concerns. The highly functional patient might have a goal of aggressively preserving function and longevity through early and aggressive diagnosis and management, whereas comfort alone may be the goal in an imminently dying patient.

The inescapable physical symptoms and the relentless awareness of the progression of the cancer contribute to physical, spiritual, social, and psychological strife. These factors all have the capacity to exacerbate the underlying pain. In addition, patients with pre-existing nonmalignant pain may come to the diagnosis of cancer already experiencing a sense of overwhelming suffering.14 Cancer patients with pain are twice as likely to develop a psychiatric disorder, and as the disease progresses, the risk increases. The causes are multifactorial, and like pain, may be related to disease progression or treatment. Many of these disorders are amenable to treatment, which should be implemented as early as possible through proper referral and follow-up.15 An interdisciplinary palliative care team, potentially hospice, should be involved as early as possible. Early palliative care intervention improves patient outcomes16 and should be initiated by the emergency clinician when the need is identified. Depending on the institution and the urgency of the situation, palliative care consultation may occur in the ED, during hospitalization, or in the outpatient setting.

TREATMENT STRATEGIES

The WHO Stepladder

With a clear assessment of the details of the patient’s pain, effective treatment can be rapidly implemented in the ED. In 1986 the WHO developed a 3-step ladder to guide the management of cancer pain. It was originally developed to address nociceptive pain (both somatic and visceral) but has proved useful to some degree for neuropathic pain as well. This simple and well-tested approach provides the clinician with a rational guide for the use of selected analgesics. Today, there is general consensus favoring the use of this model for all pain associated with serious illness. Management is based on the initial assessment of pain and should start at the step that corresponds to the patient’s reported severity based on an NRS (0–10). Mild pain is defined as NRS 1 to 3 (step 1), moderate pain as NRS 4 to 6 (step 2), and severe pain as NRS 7 to 10 (step 3).

Step 1 analgesics

All of the nonopioid analgesics that characterize step 1 of the WHO ladder have a ceiling effect to their analgesia (a maximum dose that, if exceeded, yields no further analgesia). Acetaminophen is an effective step 1 analgesic and may be a useful coanalgesic in many situations, including headache. Its site and mechanism of action are not entirely known. It does not have significant anti-inflammatory effects and is presumed to have a central cyclo-oxygenase (COX) related mechanism. Chronic doses more than 4.0 g/24 h or acute doses more than 6.0 g/24 h are not recommended because they may cause hepatotoxicity. Hepatic disease or heavy alcohol use increases the risk further, and the maximum daily dosage may be reduced to 3.0 g/24 h.
Nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin) are also effective step 1 analgesics and may be useful coanalgesics. They work, at least in part, by inhibiting COX, the enzyme that converts arachidonic acid to prostaglandins. There are several classes of NSAIDs. Some patients respond better to one class of NSAIDs than to another, and serial “n of 1” trials may be needed to find one that is efficacious for a given patient. NSAIDs with longer half-lives are likely to enhance compliance. NSAIDs can have significant adverse effects. Gastropathy, renal failure, and inhibition of platelet aggregation can occur with any of the nonselective medications, irrespective of the route of administration. The likelihood of these adverse effects will vary among NSAID classes and may be due, in part, to their relative COX-2 selectivity. It is important to ensure adequate hydration and good urine output in patients on NSAIDs to minimize the risk of renal vasoconstrictive injury, including papillary necrosis. Nonselective medications are relatively contraindicated in the setting of significant pre-existing renal insufficiency. NSAIDs may be contraindicated if bleeding is a problem or coagulation or platelet function is impaired. Gastric cytoprotection with misoprostol or omeprazole may be needed in patients with significant risk of gastrointestinal (GI) problems. Significant risk factors include a history of gastric ulcers or bleeding, current nausea/vomiting, protein wasting, cachexia, and advanced age.

There are parenteral forms of NSAIDs now available for use. A new transdermal form of diclofenac is now available in the United States. Its efficacy has been demonstrated in osteoarthritis but has not yet been studied in localized somatic cancer pain. Ketorolac is available in intravenous (IV) or intramuscular formulations. Short-term (<5 days is considered safe in healthy patients) parenteral use of this potent agent provides excellent analgesia, particularly with visceral pain, and avoids the common central nervous system (CNS) side effects of the opioid analgesics. These advantages must be carefully weighed against the GI, renal, cardiovascular, and bleeding risks for each patient before use.

**Step 2 and step 3 analgesics**

Step 2 and 3 analgesics involve opioid use. The clinician must have an excellent command of opioid pharmacology when using these analgesics. Step 2 agents all have aspirin or acetaminophen present in amounts that limit their dosages to 10 to 12 tablets a day. These agents have a role in moderate pain (4–7/10), but each also has side effects. Codeine derivatives tend to be constipating, and nausea is not infrequent. There are patients who lack the necessary enzyme to convert codeine to its active (morphine) moiety. Therefore, be aware of the need to change to morphine or a step 3 agent if no analgesia is seen. Effective treatment in the ED requires a clear understanding of the pharmacology, clinical setting, and adverse effects of the analgesics prescribed and knowledge of how these may vary from patient to patient.

**PRINCIPLES OF OPIOID THERAPY**

**Opioid Pharmacology**

Opioid analgesic effect correlates with maximal plasma concentration (Cmax) (Table 1). Once Cmax is reached, both the maximum analgesic effect and the maximum side-effect profile have been attained. All pure opioids (except methadone) follow first-order kinetics and act in a very similar pharmacologic manner. They reach their time to peak plasma concentration (Tmax) approximately 60 to 90 minutes after oral (including enteral feeding tube) administration, 30 minutes after subcutaneous or intramuscular injection or rectal administration, and 6 to 10 minutes after intravenous injection. They are eliminated from the body in a linear and predictable way, proportional to the dose. They are first conjugated in the liver, and then the kidneys excrete
90% to 95% of the metabolites. Their metabolic pathways do not become saturated. Because of its complicated cytochrome metabolism, methadone does not follow the first-order kinetics and should not be initiated or titrated in the ED without the consultation of the patient’s primary care physician or a specialist in pain or palliative medicine. Each opioid metabolite has a half-life (t$_1/2$) that depends on its rate of renal clearance. When renal function is normal, codeine, hydrocodone, hydromorphone, morphine, oxycodone, and their metabolites all have effective half-lives of approximately 3 to 4 hours. When dosed repeatedly, their plasma concentrations approach a steady state after 4 to 5 half-lives. Thus, steady-state plasma concentrations are usually attained within a day.

Opioids and their metabolites are primarily excreted renally (90%–95%). Care should be taken when dosing these agents in patients with renal impairment. The clinician should take care in selecting appropriate agents in patients with renal impairment and be prepared to reduce the dose (Tables 2 and 3). Morphine has 2 principal metabolites: morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide is active and has a longer half-life than that of the parent drug morphine. Consequently, when dehydration or acute or chronic renal failure impairs renal clearance, the dosing interval for morphine must be increased or the dosage size decreased to avoid excessive accumulation of active drug and metabolites.$^{18–20}$ If urine output is minimal (oliguria) or none (anuria), routine dosing should be stopped, and morphine should be administered only as needed. This is particularly important when patients are dying. Renal excretion is somewhat less of a concern with hydromorphone, but fentanyl and methadone are considered the safest choices in renal failure. Opioid metabolism is not as sensitive to hepatic compromise. However, if hepatic function becomes severely impaired, the dosing interval should be increased or the dose decreased.

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Renal Failure</th>
<th>Parent Drug</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>Appears safe</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Appears safe</td>
<td>+/-</td>
<td>none</td>
</tr>
<tr>
<td>Morphine</td>
<td>Use with caution/dose adjust</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>+</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>+</td>
<td>+/−</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Inadequate data</td>
<td>Inadequate data</td>
<td>Inadequate data</td>
</tr>
<tr>
<td>Codeine</td>
<td>Do not use</td>
<td>Inadequate data</td>
<td>Inadequate data</td>
</tr>
<tr>
<td>Meperidine</td>
<td></td>
<td>Inadequate data</td>
<td>Inadequate data</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td></td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

Table 2
Opioid selection in renal failure

<table>
<thead>
<tr>
<th>Route</th>
<th>Time to Maximal Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>6–10 min</td>
</tr>
<tr>
<td>Rectal/subcutaneous</td>
<td>30 min</td>
</tr>
<tr>
<td>Oral</td>
<td>60–90 min</td>
</tr>
</tbody>
</table>
Opioid-Naïve Patients

Patients with severe pain who have never been on opioids will need a trial of short-acting opioids to establish their opioid needs and any possible respiratory depressive effect. Oral agonist opioids are appropriate for severe pain if time and circumstance allow. On an outpatient basis, severe pain may be treated with WHO step 3 analgesics as a reasonable first choice. If an immediate-release oral opioid is selected, and the pain is persistent or nearly so, the medication should be given every 4 hours. Once steady state has been reached, the best possible pain control for the dose will be achieved within a day (4–5 half-lives). The patient should see his or her primary physician within the next 24 to 48 hours, and he or she should be started on long-acting, continuous-release medications with breakthrough doses as needed.

Opioid-Tolerant Patients

Opioid-tolerant patients may come to the ED experiencing oligoanalgesia. They often say that their medications are no longer effective. This can be a function of physiologic tolerance, disease progression, or ineffective use of the medications (for example, taking continuous-release opioids only once per day when they were intended for 12-hour use). Opioid-tolerant patients presenting to the ED with severe pain will often need to have increases made in their baseline opioid dosing to achieve pain control.

RESPIRATORY DEPRESSION, NALOXONE, AND DOUBLE EFFECT

Emergency clinicians have a variety of concerns that make providing appropriate dosing of opioids challenging. Emergency staff, patients, and families often have concerns of addiction, misuse of the drug, and unintended outcomes, such as respiratory depression. The actual risk of respiratory depression is likely exaggerated due to the inappropriate application of animal and human models from acute pain research in opioid-naïve subjects. Respiratory depression is very unlikely in the treatment of cancer pain for patients with stable organ function.21 The risks for respiratory depression include patients with advanced age, obesity, sleep apnea, impaired liver or renal function, side effect of sedation, and patients who achieve good pain control after long periods of poor pain control (Box 1).

Pain is a potent stimulus to breathe, and pharmacologic tolerance to respiratory depression develops quickly.22 In similar doses, opioid effects are quite different in patients who are in pain and those who are not in pain. As doses increase, respiratory depression does not occur suddenly in the absence of other signs of overdose, such as lethargy and somnolence. In addition, somnolence always precedes respiratory depression. The presence of unusual somnolence provides an objective guide for safe downward adjustments (or the rare need for intervention) before the onset of respiratory depression. In addition, tolerance to the respiratory depressant effects of opioids occurs rapidly (a few days in most cases). Therefore, opioid-tolerant patients are much less susceptible to these effects.

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dose Reduction of Normal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 mL/min; normal dosing</td>
<td>Normal</td>
</tr>
<tr>
<td>10–50 mL/min</td>
<td>75% dosing</td>
</tr>
<tr>
<td>&lt;10 mL/min</td>
<td>50% dosing</td>
</tr>
</tbody>
</table>

Table 3
Opioid dose reduction in renal failure

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Adequate ongoing assessment and appropriate titration of opioids based on pharmacologic principles will prevent misadventures. As physiologic conditions change, opioid tolerance may change. Opioid-related respiratory depression may be an indication of a physiologic change in the patient, such as worsening renal or hepatic function, ileus, or bowel obstruction. In addition, patients who develop fever or apply heat to a transdermal patch can rapidly and dangerously elevate the drug levels. In such a situation, the removal of the transdermal patch is analogous to decontamination in an acute poisoning and should be done as quickly as possible.

Naloxone may be necessary if the cause of serious respiratory depression (rate <6/min) is an opioid. If Emergency Medical Service is called to the home of a patient for unexpected respiratory depression, an important immediate goal is to avoid an acute withdrawal state. A safe method of intervening while avoiding acute withdrawal is to dilute 0.4 mg naloxone into 10 mL of normal saline (0.04 mg/mL). Administer 0.5 mL IV every 1 to 2 minutes until respirations increase but generally not to the point of alertness. Because the effective plasma half-life is short (10–15 minutes) and because of naloxone’s high affinity for lipids, the patient should be closely monitored every few minutes for recurrent drowsiness. If drowsiness recurs, dosing should be repeated (occasionally a continuous infusion is needed) as required until the patient is no longer compromised.

If the primary goal of care is comfort in a patient whose only conscious experience is excruciating pain, then permissive somnolence might be acceptable. In an actively dying patient, while treating the patient’s suffering with appropriate dosing of medications, the patient may finally stop breathing. With the severely impaired physiology of the actively dying patient, the addition of medications to alleviate suffering consistent with the patient’s goals of care might contribute to his or her death in an unknowable way. This is the principle of “double effect,” which depends entirely on the intention and actions of the treating clinician. If the clinician is using accepted medical practice to treat suffering appropriately and the patient dies, the clinician’s intention has been only to alleviate symptoms. If the intention were to induce death with a dose of medication that will likely result in the patient’s death, then the practice would be referred to as “physician-assisted suicide.” Physician-assisted suicide is illegal in the United States except in Oregon, where its practice is carefully monitored.

**OPIOID DOSING STRATEGIES**

In order to provide rapid, adequate, and safe pain relief with opioids in the ED, it is important to know a patient’s current medication regime. Increasing dosages by
25% to 50% per day when moderate pain persists or by 50% to 100% per day for patients with continued severe pain is considered safe practice. Understanding the pharmacokinetics of opioids, it is nevertheless prudent for patients to be observed at home during the next 24 hours (until steady state is achieved) for signs of dose-limiting toxicity. The emergency clinician should always speak with the primary care outpatient provider to ensure that the opioids can be effectively titrated and the patient receives follow-up care.

Equianalgesic dosing tables help to convert a sometimes complex array of multiple medications into a single opioid equivalent (Table 4). From there, a safe and effective dose for initial treatment can be implemented. When converting from one opioid to another, a helpful first step is to calculate the “oral morphine equivalent” of the patient’s current opioid. The oral morphine equivalent is the dose of morphine that is of equivalent strength to the dose of the current opioid. It is usually calculated for the preceding 24-hour time period. For example, a patient who is taking 4 mg of oral hydromorphone every 4 hours is receiving 24 mg of oral hydromorphone in a 24-hour period. The oral morphine equivalent of 24 mg of oral hydromorphone is approximately 90 mg of oral morphine (24 \[\frac{30}{7.5}\] = 96, rounded down to 90). This is equivalent to 30 mg IV/subcutaneous (SQ) morphine. Accepted guidelines for the conversion of transdermal fentanyl to oral morphine are unusual in that the hourly dose of the transdermal form is equated to the daily (24 h) dose of oral morphine. For example, a 25 mcg/h transdermal fentanyl patch (which is typically maintained for 3 days) is roughly equivalent to 50 mg of oral morphine a day.24

**OPIOID CROSS-TOLERANCE**

Although patients may develop pharmacologic tolerance (a higher dose to achieve the same effect) to the opioid being used, tolerance may not be as marked relative to other opioids. Incomplete cross-tolerance is likely due to subtle differences in the molecular structure of each opioid and the way each interacts with the patient’s opioid receptors. Consequently, when switching opioids, there may be differences between published equianalgesic doses of different opioids and the effective dose for a given patient. It is prudent to start with 50% to 75% of the published equianalgesic dose of the new opioid to compensate for incomplete cross-tolerance and individual variation, especially if the patient’s pain is controlled. If the patient has moderate to severe pain, the dose should not be reduced as much. If the patient has had adverse effects such as sedation, the dose should be reduced even more. However, in the case of a known time-limited side effect such as nausea, the dose may be continued with a trial of treatment of the side effect.

<table>
<thead>
<tr>
<th>Oral/Rectal Dose (mg)</th>
<th>Analgesic</th>
<th>Parenteral Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Codeine</td>
<td>60</td>
</tr>
<tr>
<td>15</td>
<td>Hydrocodone</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Hydromorphone</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>Morphine</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>Oxycodone</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 4

**Equianalgesic opioid dosing table**

**Equianalgesic Doses of OPIOID Analgesics**
An important exception is methadone. Methadone is the only opioid shown to have a nonlinear relationship to standard opioids. For patients receiving morphine doses less than 100 mg/d, the ratio is 4:1 (morphine:methadone). However, if the morphine is >1000 mg/day, the ratio is 20:1 (morphine:methadone). Conversion to methadone is complex and requires expertise in the use of the drug. Expertise with administering methadone as well as close follow-up is essential for safety. Emergency clinicians should discuss any methadone dosing with a pain or palliative care consultant before adjustments to assist as well as ensure safe use.

BREAKTHROUGH DOSING

Treatment in cancer pain is guided by knowledge of the patient’s current medications and dosing for baseline and breakthrough pain. Baseline pain refers to the patient’s pain experience for more than 12 hours in a 24-hour period. Breakthrough pain is a moderate to severe transient increase over baseline pain. Breakthrough dosing is typically 5% to 15% of the total daily dose in oral morphine equivalents every hour (Cmax). Any immediate-release opioid can be used, but care must be taken to avoid acetaminophen toxicity when combination medications are used for breakthrough dosing. Extended-release opioids should not be used for breakthrough pain, as their onset of action is too slow, and risk for cumulative toxicity is high.

BOLUS EFFECT

As the level of opioid in the bloodstream increases due to use of immediate-release preparations, some patients may experience drowsiness 1/2 to 1 hour after ingestion, when the plasma level peaks. This may be followed by pain just before the next dose is due, when the plasma level falls. The name of this syndrome is the “bolus effect,” and it can best be resolved by switching to an extended-release formulation (oral, rectal, or transdermal) or a continuous parenteral infusion. This should reduce swings in the plasma concentration after each dose.

ADJUVANT ANALGESICS

Adjuvant analgesics (or coanalgesics) are medications that, when added to primary analgesics, further improve pain control. They may themselves also be primary analgesics (eg, tricyclic antidepressant medications for postherpetic neuralgia). They can be added into the pain management plan at any step in the WHO ladder and are often used. Common adjuvants include the WHO step 1 medications as well as other medications used in the treatment of neuropathic pain.

Corticosteroids are potent anti-inflammatory agents that are useful in both nociceptive and neuropathic pain. Reducing inflammation and peritumor edema can be important in relieving pressure on a nerve or the spinal cord, decreasing intracranial pressure from a brain tumor, or decreasing obstruction of a hollow viscus. Corticosteroids may also be useful for bone pain, visceral pain (obstruction and/or capsular distention), anorexia, nausea, and depressed mood. At the end of life, dexamethasone is considered the corticosteroid of choice because of its minimal mineralocorticoid effects and thus its decreased tendency for salt and fluid retention. Corticosteroids may also enhance pain control through the creation of a sense of euphoria. Dexamethasone has a long half-life (>36 hours). It can be administered once a day in doses of 2 to 20 mg oral or up to 100 mg IV for acute spinal cord compression. If an agitated delirium ensues, steroid psychosis should be considered. Although proximal
myopathy, oral candidiasis, bone loss, and other toxicities may occur with long-term use, this is seldom a major problem in the setting of advanced disease.

**ROUTES OF ADMINISTRATION**

The oral route is generally the least invasive and most convenient for administering opioids on a routine basis. However, some patients may benefit from other routes of administration if oral intake is either not possible (due to vomiting, dysphagia, or esophageal obstruction) or if it causes uncontrollable adverse effects (nausea, drowsiness, or confusion).

Enteral feeding tubes provide alternatives for bypassing gastroesophageal obstructions. They deliver the medications to the stomach or upper intestine where the medications function pharmacologically as though they had been ingested orally. Immediate-release medications or liquid medications are easily administered through feeding tubes. Long-acting preparations, however, cannot be crushed for administration. One long-acting morphine preparation Kadian has multiple time-release granules that may be removed from the capsule and administered through the feeding tube as a 24-hour, long-acting opioid. Transmucosal (buccal mucosal) administration of more concentrated, immediate-release, liquid preparations provides a similar alternative, particularly in the patient who is unable to swallow. Oral transmucosal fentanyl citrate is a formulation of fentanyl in a candy matrix on a stick that is approved for the treatment of breakthrough pain. To date, experience with this formulation and the recently released fentanyl dissolvable tablet show some usefulness for breakthrough pain, although dosing and cost are problematic. Topical anesthetic creams are currently used most commonly in pediatrics in the ED and are effective. They should be considered as well for cancer patients. Venipuncture may be intolerably painful to a patient in severe discomfort. If it is acceptable in a given situation to wait for a necessary venipuncture, topical analgesia with agents such as eutectic mixture of local anesthetics (lidocaine 2.5%/prilocaine 2.5%) or ELA-Max (4% lidocaine) should be considered.

Open wounds may also be a source of considerable pain, particularly during dressing changes or debridement. If incident pain is significant, the patient should be given medication before performing activities that cause pain. Based on Cmax for opioids, this could be 60 minutes for oral medications, 30 minutes for SQ or rectal, and 15 minutes for IV (see Table 1). It should be noted that these are the most conservative figures and that the Tmax of IV morphine is often quoted at 6 to 8 minutes.

In addition, topical analgesics should be considered. It is known that there are mu opioid receptors throughout the body, and there is some experience with the successful use of the IV form of morphine applied topically. This may be placed topically into the wound during a dressing change. Depending on the size of the wound and opioid tolerance of the patient, 4 to 20 mg of injectable morphine can be placed into an inert cream and applied directly to the wound and covered with gauze dressings. Transdermal patches present an effective alternative route of administration for patients who are receiving stable routine opioid dosing. These patches are currently manufactured only with fentanyl, and they perform quite differently from other extended-release formulations. Steady-state equilibrium is established between the medication in the patch, a subdermal pool that develops, and the patient’s circulation. On average, best possible pain control is achieved within 1 dosing interval (ie, 3 days), with peak effect at about 24 hours. The effect usually lasts for 48 to 72 hours before the patch needs to be changed. Care must be taken to ensure that the patches are placed in an appropriate location so they absorb properly and adhere to the patient’s skin. Fentanyl is highly lipophilic, so an area with adequate subcutaneous fat and no hair
is the best choice. It is also important to understand that if the patch needs to be removed, the drug will continue to exert an effect for up to 12 hours after removal.

Rectal administration of prepackaged suppositories or extended-release oral morphine tablets inserted rectally behave pharmacologically like related oral preparations. This route may be very effective if oral intake is suddenly not possible, although many patients do not like this route for continuous administration.

Parenteral (IV or subcutaneous) administration using injection or infusion can be very useful in some patients. If bolus dosing is required, and IV access is either not present or difficult, the subcutaneous route is an appropriate route. The intramuscular route is not recommended. Intermittent subcutaneous injections are much less painful and just as effective. When renal function is normal, routine parenteral bolus (IV or SQ) doses should be provided every 3 hours and the dose adjusted every 12 to 24 hours once steady state is reached. If a parenteral route will be used for some time, continuous infusions may produce a more constant plasma level, reduce the risk of adverse effects, be better tolerated by the patient, and require less intervention by professional staff. Patient-controlled analgesia has been shown to be both effective and well tolerated by patients. Although intravenous infusions may be preferable when intravenous access is already established and in use for other medications, all opioids available for parenteral use may be administered subcutaneously without the discomfort associated with searching for an IV site or the risk of serious infection. Either 25- or 27-gauge needles can be used for both bolus dosing and infusions. The needles can be left in place for 7 days or more as long as there is no sign of infection or local irritation. Family members can be taught to change the needles.

Pain from tumor infiltration can cause excruciating pain, which is sometimes resistant to medications. In addition, the side effects of systemic medications used to treat pain are sometimes intolerable, even with significant supportive treatment. Anesthetic techniques such as neuraxial (epidural or intrathecal) catheter delivery of pain medication or anesthetic blocks of the involved area can sometimes help dramatically. These approaches are available through specialists in interventional pain management. This is an excellent consideration for patients with pain that is unresponsive to standard aggressive medical therapy or as an adjunct to pain management when side effects are unmanageable.

NONRECOMMENDED OPIOIDS

Not all analgesics available today are recommended. Meperidine has 2 major problems that make it undesirable, and, thus, it has been removed from many hospital formularies. Its principal metabolite, normeperidine, has no analgesic properties of its own, has a longer half-life of about 6 hours, is renally excreted, and produces significant adverse effects when it accumulates, such as tremulousness, dysphoria, myoclonus, and seizures. Additionally, meperidine is poorly absorbed orally and has a short half-life of approximately 3 hours. The routine dosing of meperidine every 3 hours for analgesia leads to unavoidable accumulation of normeperidine and exposes the patient to unnecessary risk of adverse effects, particularly if renal clearance is impaired. Consequently, meperidine is not recommended for routine dosing.

Propoxyphene is also not recommended. It has a narrow therapeutic window, standard dosing is below analgesic threshold, and dose escalation is associated with accumulation of toxic metabolites.

The mixed opioid agonist-antagonists (pentazocine, butorphanol, nalbuphine, and dezocine) cannot be used in patients who might require other opioids. If used together, competition for the opioid receptors may cause a withdrawal reaction. Furthermore,
agonist-antagonists are not recommended as routine analgesics, because their dosing is limited by a ceiling effect, which precludes dose escalation, and some carry a high risk of psychotomimetic adverse effects.

**OPIOID-INDUCED SIDE EFFECTS**

Many people confuse opioid side effects, such as urticaria/pruritis, nausea/vomiting, constipation, drowsiness, or confusion, with allergic reactions. Although 1 or more adverse effect may present on initial dosing, they can be easily managed, and in a relatively brief period of time, patients generally develop pharmacologic tolerance to all of them (except constipation). Urticaria, pruritis, and bronchospasm could be direct opioid effects or signs of allergy. These effects are usually the result of mast cell destabilization by the opioid and subsequent histamine release. Usually, the rash and pruritus can be managed by routine administration of long-acting, nonsedating oral antihistamines while opioid dosing continues (eg, fexofenadine, 60 mg twice a day; diphenhydramine, 25 mg every 6 hours, or loratadine, 10 mg daily). True anaphylaxis, although rare with opioids, should certainly be taken very seriously, and the offending opioid should be replaced with another from a different class.

Many patients who start opioids experience nausea, with or without vomiting. It is easily anticipated and treated with antiemetics and usually disappears within a few days as tolerance develops. Young women seem to be most at risk. Dopamine-blocking agents are most often effective (eg, prochlorperazine, 10 mg before opioid and every 6 hours; haloperidol, 1 mg before opioid and every 6 hours; metoclopramide, 10 mg before opioid and every 6 hours).

**PROPHYLAXIS AGAINST CONSTIPATION**

Constipation secondary to opioid administration is almost universal. It is primarily the result of opioid effects on the CNS, spinal cord, and myenteric plexus of gut, which, in turn, reduce gut motor activity and increase stool transit time. The colon has more time to desiccate its contents, leaving large hard stools that are difficult to pass. Other factors, such as dehydration, poor food intake, and other medications, may make the problem worse. Tolerance to constipation may develop very slowly, if at all. It requires anticipatory and ongoing management. Dietary interventions alone (eg, increase fluid and fiber) are often insufficient. Bulk-forming agents (eg, psyllium) require substantial fluid intake and are not recommended for those with advanced disease and poor mobility.

To counteract the slowing effect of opioids, the clinician should prescribe a routine stimulant laxative (eg, senna, bisacodyl, glycerine, casanthranol, etc) and escalate the dose to effect. Although detergent laxatives or “stool softeners” (eg, docusate sodium) are usually not effective by themselves, combination stimulant/softeners (eg, senna + docusate sodium) can be useful. Prokinetic agents (eg, metoclopramide) may also counteract the opioid effect. If constipation persists, some patients will benefit from the addition of an osmotic agent, such as milk of magnesia, lactulose, or sorbitol, to increase the moisture content of the stool. Many patients have difficulty tolerating the discomfort associated with osmotic agents, so they should be considered second-line therapy when prokinetics and detergent/softener laxatives are inadequate.

When standard therapies for constipation are either inadequate or the route of administration is untenable, methylnaltrexone bromide (Relistor) may be tried. Methylnaltrexone bromide was approved in 2008 by the FDA for use in adult patients with opioid-induced constipation in advanced illness. The mechanism of action is at the
gut mu receptors, where it inhibits opioid uptake. Laxation (without diminished opioid analgesia) is expected for the majority of patients within 4 hours but as early as 30 minutes, with a single dose of 0.15 mg/kg. The drug may be administered as a single subcutaneous injection every other day as needed.\textsuperscript{30,31}

**RAPID OPIOID TITRATION IN THE ED**

The administration of parenteral medication in the ED, as a time-limited therapeutic trial, allows the clinician to discover what medication level a patient can safely and effectively tolerate while the patient is still in the ED. Opioid pain management in the ED can be done rapidly, safely, and effectively if analgesic principles are used. Treating the patient in the ED to establish opioid tolerance of dosing over a period of time is an important safety guard. Because maximal side effects of sleepiness, drowsiness, and respiratory depression occur at Cmax, the emergency clinician can give the patient a test dose, observe this effect, and expect a similar state in the home setting.

Oligoanalgesia in the home environment is often a reason for a patient with malignancy to seek help in the ED. The severity of pain (assessed by an appropriate pain scale) determines the approach. If the pain is assessed as severe, a rapid titration of pain medication in the ED is indicated. Adequate pain control can be achieved rapidly and safely in the ED. There are limited studies looking at rapid titration of opioids, but safety and efficacy are consistently demonstrated using standard dosing guidelines.\textsuperscript{32–34}

If the pain is assessed as mild to moderate (<6/10), a standard history and physical examination should help determine the best intervention in the ED. The reason for oligoanalgesia may be as simple as a misunderstanding of medication dosage or interval. Communication with the primary care physician or oncologist may provide additional information to guide further interventions as well as appropriate disposition. It may make sense to provide a medication or particular dosage in the ED, by an acceptable route to the patient, to determine efficacy. By Cmax (under 90 minutes for enteral routes), if the home situation is acceptable and simple medication or dose adjustments are likely to achieve comfort, then the patient can be safely discharged with appropriate follow-up.

The following approach to the rapid treatment of cancer pain is derived from the Educating Physicians on End of Life Care-Emergency Medicine\textsuperscript{35} curriculum:

**Step 1: Assess**

- Is this pain, despite its intensity, familiar in character to the patient, or is this a new pain?
- Is this likely related to the cancer or something unrelated?
- Is this progressive baseline pain (>12/24 h) or breakthrough pain?
- What medication and dosage has the patient taken for pain control in the past 24 to 48 hours? What is the response (degree of pain relief and duration of effect) to a given dose of each medication? When was the last dose?
- If severe (>7/10), initiate treatment (step 2):
  - If mild to moderate pain (and when severe pain is better controlled):
    - Is the patient taking home medications appropriately?
    - Is the pain expected to be more opioid responsive (nociceptive) or less opioid responsive (neuropathic)?
    - Are appropriate adjuvant therapies being used?
    - Are there serious diagnostic concerns to be addressed emergently within the patient’s goals of care?
**Step 2: Treat**

- Severe pain (>7/10): The optimal route for rapid titration of severe pain is IV (if a port or first-attempt peripheral vein is accessible) or SQ.
  - Opioid naïve: Administer parenteral morphine equivalent to 0.1 mg/kg (less if in a high-risk group).
  - Opioid tolerant: Administer 5% of the patient’s total previous 24-hour parenteral morphine equivalents, minimum 0.1 mg/kg (less if patient is in a high-risk group).
- Mild to moderate pain: Consider best route and choice of medication based on assessment and goals of care.

**Step 3: Reassess**

- Perform pain severity assessment at Cmax (15 minutes after completion of intravenous pyelogram or intravenous piggyback dose, 30 minutes after SQ injection, 60–90 minutes after enteral route).
- Are there unwanted side effects (somnolence, confusion)?

**Step 4: Achieve Adequate Pain Control**

- Persistent severe pain (>7/10) without unmanageable side effects: Double the opioid dose.
- Some response but inadequate relief of pain (<50% improvement): Repeat same opioid dose.

Repeat steps 3 and 4 until pain is controlled or unwanted side effects occur, or limit further escalation.

**Step 5: Determine Plan for Disposition, Discharge Instructions, and Follow-up**

- Patients who cannot be reasonably controlled over a period of dose escalation and observation in the ED should be considered for hospital admission.
- The choice of a long-acting regimen depends on the patient’s previous opioid use, the ability to swallow, the allergy profile, and what has been tolerated in the past. With the exception of methadone (which may have some activity in neuropathic pain), there is no commonly accepted advantage of any particular long-acting opioid. Because of its complicated dosing, methadone should not be initiated or titrated from the ED without consultation from the patient’s primary care physician or a specialist in pain or palliative medicine.
- After achieving adequate pain control with the increase in long-acting opioids accompanied by appropriate breakthrough dosing, discharge instructions and follow-up with the oncologist or primary physician should be arranged.

**SUMMARY**

Patients and families struggling with cancer fear pain more than any other physical symptom. A basic understanding of pain assessment, opioid pharmacology, equianalgesic conversions, rationale for opioid dose escalations, and management of side effects can enhance a clinician’s ability not only to effectively manage pain but also to enhance patient safety.
REFERENCES