Cancer remains the second most common cause of death in the United States despite advances in prevention, early detection, and newer treatment protocols. Pain continues to be the most feared complication of this diagnosis. Numerous studies have shown that when the World Health Organization treatment guidelines are followed, 90% of patients are pain-free. Although clinical evidence is convincing that opioids are effective in treating patients for cancer pain, physician reluctance to prescribe them and patient unwillingness to take such medication continue. Barriers to opioid use are multifactorial, but with education and increased surveillance (ie, screening for prostate-specific antigen, colonoscopy, and breast and testicle self-examination). Mortality rates for certain cancers (colon, prostate, female breast) continue to decline as the result of increases in population, as well as longer average life expectancy. Incidence also decreased as the result of increased surveillance (ie, screening for prostate-specific antigen, colonoscopy, and breast and testicle self-examination). Mortality rates for certain cancers (colon, prostate, female breast) continue to decline as the result of screening guidelines that allow early detection and advances in treatment.1

Pain continues to be a major problem in patients with cancer, affecting 25% to 30% of patients with recently diagnosed cancers. The incidence of such discomfort in advanced stages of cancer approaches 70% to 80%.2-6 A major fear of cancer patients is associated pain,5 which can occur as a result of the cancer itself, treatment, or from other causes. Cancer can spread by metastasis or direct invasion, and 90% of patients with prolifeeration to osseous structures report pain.7 Patients with cancer can have neuropathic pain due to direct compression of nerves, a plexus and/or spinal cord. Chemotherapeutic drugs such as vinca alkaloids or radiation therapy can produce neuropathic pain. Steroids used in treatment of patients with cancer have been associated with avascular necrosis of the hip and subsequent fracture. Postsurgical pain commonly occurs in patients who have had thoracotomy, mastectomy, or amputations to manage their neoplastic disease.

Inadequate treatment and undertreatment are associated with increased pain scores, decreased functional ability, and increased depression and anxiety.8,9 The American Pain Society and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) recently placed emphasis on this problem with a movment to have pain become the “fifth vital sign” because this important parameter, like other vital signs such as blood pressure, heart rate, respiratory rate, and body temperature, needs frequent assessment. The Visual Analog Scale and 11-point (0 to 10) numeric scale are used for measurement, a process that allows frequent reassessment and therefore adequate treatment.

The World Health Organization (WHO) in 1986 established a stepladder approach for treatment of patients with cancer pain (Figure).2,4 The goal was to provide treatment guidelines that healthcare practitioners could easily follow. The initial step consisted of acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) with or without adjuvant therapy. If pain is not controlled, medications combining mild to moderate opioids with acetaminophen are added to step one. If pain persists, stronger opioids such as morphine sulfate are added and titrated to pain relief. Around-the-clock dosing schedules are used to minimize the frequent use of medications for breakthrough pain.

Most pain in patients with cancer can be controlled by morphine oral doses of less than 200 mg/d. Greater than 80% of patients with cancer can be pain-free when physicians follow WHO guidelines and use higher doses as needed to obtain relief.4,6

To provide adequate analgesia in patients with cancer, WHO guidelines...
list major classes of pain medications with their respective mechanisms of action and doses, in addition to adjuvant drugs such as ketamine, antidepressants, anticonvulsants, steroids, bisphosphonates, topical analgesics, anxiolytics, laxatives, hormones, antihistamines, and antiemetics.4

**NSAIDs, COX-2 Inhibitors, ASA, and Acetaminophen**

Prostanoids play important roles in many cellular responses and pathophysiologic processes, including modulation of inflammatory reactions, erosion of cartilage and juxta-articular bone, gastrointestinal cytoprotection and ulceration, angiogenesis and cancer, hemostasis and thrombosis, renal hemodynamics and progression of kidney disease.10 Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase type 2 (COX-2) inhibitors, and acetylsalicylic acid (ASA) prevent formation of prostanoids from arachidonic acid. This synthesis of prostaglandins from arachidonic acid is controlled by two separate cyclooxygenase enzymes (COX-1 and COX-2).

Traditional nonselective NSAIDs inhibit both COX-1 and COX-2, a nonselective inhibition that results in not only an anti-inflammatory response but also reduced gastrointestinal cytoprotection; this latter effect causes gastric mucosal ulceration and bleeding. Newer COX-2 inhibitors were designed to selectively inhibit only this enzyme, thus maintaining an anti-inflammatory response with low risk of side effects that occur with nonselective inhibitors of COX enzymes.10,11

Recently, however, COX-2 inhibitors have received attention because of an increased incidence of stroke and myocardial infarction. The entire class of NSAIDs is now under increased scrutiny as these unwanted adverse reactions effects may not be class-specific.10,12 Therefore, new black box warnings have been applied to all NSAIDs, not just celecoxib, the remaining COX-2 inhibitor. Despite these concerns, NSAIDs and COX-2 inhibitors are promising as anticancer drugs because they inhibit tumor angiogenesis and induce tumor cell apoptosis.

NSAIDs play a key role in the first step of WHO guidelines for management of cancer pain. Nearly 90% of patients with bone metastasis present with pain,9 and since prostaglandins appear to play an important role in this condition,7 NSAIDs are the most effective agents. A 2004 systematic review showed NSAIDs are more effective than placebo for controlling cancer pain and that they all are comparable in safety profile and effectiveness.6 Comparisons of opioid combination preparations with NSAIDs alone showed no, or at most, only slight differences that were not statistically significant.6,9,11,13

**Figure.** World Health Organization (WHO) “stepladder” guidelines for pain relief. (Published with permission from the WHO. Available at: http://www.who.int/cancer/palliative/painladder/en/. Accessed November 19, 2007.)

**Opioids**

Management of cancer pain with opioids remains the “gold standard” with which other treatment modalities are compared.2,4,5,14 The second step of WHO guidelines involves use of mild to moderate opioids in combination with acetaminophen or ASA. Administration of medications used in step one is continued because NSAIDs, COX-2 inhibitors, and acetaminophen have been shown to increase analgesia when added to opioids. Adjuvant medications are also indicated here as well as in all steps of the WHO ladder (Figure).

In 1973, several teams of researchers found the presence of an “opioid receptor” in the nervous system.15 It was believed that endogenous substances when released subsequently bound to opioid receptors and provided analgesia; this binding was reversed by naloxone. These endogenous substances were later identified as enkephalins, b-endorphins, and dynorphin. Three separate opioid receptors (as well as new individuals subtypes) were identified and labeled: µ, κ, and δ. The major receptor associated with analgesia is µ, and development of synthetic opioids has centered...
on targeting this site while avoiding complication to other opioid receptors that produce unwanted side effects (e.g., nausea and respiratory depression).

Oral morphine is the primary opioid used in the United States for treatment of patients with severe pain in advanced stages of cancer. In the United Kingdom, diamorphine (heroin) is used secondarily because of its greater solubility, but it has no clinical advantage over morphine. Methadone hydrochloride, a drug commonly prescribed to prevent withdrawal in recovering drug users, is used in hospice programs in the United Kingdom and Canada. It is also employed in the United States for treatment of patients with refractory or neuropathy-associated pain.3,5,14-16

Numerous opioid preparations are now available (Table).

Currently, morphine can be obtained in an immediate-release (IR) form (e.g., oxycodone IR, fentanyl IR, oxymorphone IR) and a sustained-release (SR) form (e.g., oxycodone SR) with dosing of every 8, 12, or 24 hours. Newer extended-release technology allows for sprinkling pellets in applesauce, which was not possible with the previously available preparations. Other long-acting formulations could not be given via gastrotomy tube because of problems with uncontrolled and variable release if pellets were crushed or cut. Additional problems with newer SR preparations have been associated with high and unpredictable serum levels when exposed to ethanol (black box warning).17

Fentanyl, an analgesic commonly used in anesthesia, is widely used via the intravenous route. This strong opioid is also available for transdermal or transmucosal administration with predictable drug concentrations comparable to that achieved via the intravenous route. Recently, the US Food and Drug Administration (FDA) issued a warning that several deaths and other serious adverse events occurred following use of a fentanyl buccal tablet; the actual statement from the FDA MedWatch site is, “These deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients), improper dosing and/or improper product substitution.”18

In terms of efficacy, one opioid formulation offers no advantage over another for pain control. Experience of the healthcare provider and cost seem to be the determining factors in choosing one preparation over another.5,14

Long-term use of opioids is associated with physical dependence and tolerance. These two physiologic processes have nothing to do with addiction, which is psychological. Tolerance is defined as a physiologic phenomenon of progressive decline in the potency of an opioid with continued use, manifested by the requirement of increasing opioid dose to achieve the same therapeutic effect.5 Tolerance may occur in any patient taking narcotics daily for more than 1 or 2 weeks, though the degree to which tolerance occurs in patients with cancer-related pain is uncertain.

Increased doses can continue to provide adequate analgesia as there appears to be no ceiling, but escalating doses can increase side effects (e.g., nausea, vomiting, constipation, sedation, respiratory depression, abdominal pain, pruritus) that may limit their use.8,19 Tolerance occurs due to:

- increased activation and/or upregulation of the N-methyl-D-aspartate (NMDA) receptor because of repeated exposure of μ receptors to opioids; use of an NMDA-receptor antagonist can diminish or reverse tolerance.
- downregulation or possible conformational changes in opioid receptors (or both) that are thought to occur with long-term opioid exposure.8,19,20

N-methyl-D-aspartate receptors are present in the periphery as well as the central nervous system (CNS). Activation of these sites is associated with memory, learning, neural development, plasticity, and acute and chronic pain states. Acute and chronic stimulation of peripheral pain fibers (A-β and C) can result in activation and recruitment of NMDA receptors; when these two events develop, symptoms of both allodynia and hyperalgesia can occur, especially in patients with neuropathic pain.21-23

Rotating opioids reduces tolerance. Rapid switching from one opioid to another can be easily accomplished with minimum periods of inadequate analgesia. A standard equianalgesic table for conversions from one to another is used only as a guide because incomplete or decreased cross-sensitivity may play a part in the conversion process. In switching from one opioid to another, 60% to 70% of the total daily dosage of the current opioid calculated from an equianalgesic conversion table should be used and accompanied by frequent supplementation with as-needed rescue dosing.

Because dosing and conversion of opioids are complex processes requiring knowledge of opioid properties, professional skill, and caution, this article does not include a conversion table. Readers instead should refer to prescribing information and available resources for calculating opioid conversion.

Dependence is a physiologic process that is independent of tolerance and characterized by withdrawal symptoms on abrupt reduction or discontinuation of chronic administration. Addiction is a psychological and behavioral syndrome manifested by drug-seeking behavior, loss of control over drug use, and continued use despite adverse effects. In 1980, Porter and Jack19 reported that addiction is rarely seen in patients with cancer pain when use is appropriate; however, patients with a history of previous addiction may be at an increased risk for this behavior.

Adjuvant Medications for Analgesia

Ketamine

This agent, a derivative of phencyclidine, has been used in anesthesia for more than 40 years. Ketamine provides both amnesia and intense analgesia resulting in “dissociative anesthesia,” a state of catatonia in which the patient appears awake yet is unable to respond or communicate. Use of ketamine has been limited because of emergence delirium,24 which can be partially inhibited by preoperative doses of a benzodiazepine.

The mechanism of action is non-competitive blockade of the NMDA receptor. Ketamine has been shown to attenuate and reverse morphine tolerance by inhibition of NMDA receptors.22 Ketamine has been used in a variety of pain conditions that are refractory to high-dose opioids and other conventional modes of therapy. Low-dose continuous
### Table
Common Opioid Analgesics With Usually Recommended Doses*

<table>
<thead>
<tr>
<th>Name†</th>
<th>Formulation and Strength</th>
<th>Dosing</th>
<th>Indications, Contraindications, and Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Codeine</strong></td>
<td>Tablet: 15 mg, 30 mg, 60 mg</td>
<td>PO: 15 mg-60 mg every 4 h-6 h</td>
<td>Weak analgesic with no effect in 10% of patients</td>
</tr>
<tr>
<td>- With acetaminophen</td>
<td>Injectable: 15 mg/mL, 30 mg/mL</td>
<td>Maximum: See PI for acetaminophen dosing</td>
<td></td>
</tr>
<tr>
<td>— (Tylenol #2)</td>
<td>25 mg/300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— (Tylenol #3)</td>
<td>30 mg/300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— (Tylenol #4)</td>
<td>60 mg/300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Propoxyphene</strong></td>
<td>Tablet: 100 mg propoxyphene/325 mg acetaminophen</td>
<td>1-2 tablets every 4 h</td>
<td>Do not prescribe to patients who are suicidal or addiction prone.</td>
</tr>
<tr>
<td>— (Darvocet N-100)</td>
<td></td>
<td>Do not exceed 6 tablets per day</td>
<td></td>
</tr>
<tr>
<td><strong>Hydrocodone</strong></td>
<td>Tablet: 7.5 mg/200 mg</td>
<td>PO: 5 mg-15 mg every 4 h</td>
<td>Less potent and shorter acting than morphine</td>
</tr>
<tr>
<td>— With ibuprofen</td>
<td>2.5 mg/500 mg, 5 mg/500 mg, 7.5 mg/500 mg, 10 mg/500 mg</td>
<td>Elderly: 2.5 mg-5 mg</td>
<td></td>
</tr>
<tr>
<td>— (Lortab)</td>
<td>Elixer: 2.5 mg hydrocodone/167 mg acetaminophen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— (Vicodin)</td>
<td>5 mg/500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— (Vicodin ER)</td>
<td>7.5 mg/750 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— (Lorcet)</td>
<td>10 mg/650 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fentanyl</strong></td>
<td>Injectable: 50 μg/mL</td>
<td>Initial dosing: 25 μg-50 μg IV 5-15 min.</td>
<td>Not recommended for intermittent use because of short half-life. Consider PCA use for acute postoperative pain.</td>
</tr>
<tr>
<td>— Intravenous</td>
<td>After initial dosing: initial with 10 μg/h to 20 μg/h. Titrate to goal pain control in 10-μg/h increments until 100 μg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— (Sublimaze)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Transdermal</td>
<td>Patch: 12.5 μg, 25 μg, 50 μg, 75 μg, 100 μg</td>
<td>Starting dose: 25 μg every 72 h in opioid-naive patients with dose increases every 3 days</td>
<td>Transdermal patches are contraindicated in the management of acute or postoperative pain, for mild or intermittent pain response to PRN opioids or nonopioids and in doses&gt;25 μg/h at initiation of opioid therapy. Fentanyl patch reaches peak effect in 24 h, maintains constant blood level for 18 h after removal.</td>
</tr>
<tr>
<td>— (Duragesic)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adapted with permission from Schechter L, Meadows S. Adult Pain Management Guidelines. Philadelphia, Pa: Thomas Jefferson University Hospital; 2007. This table is a derivative collection from several sources, including the 2007 manufacturers’ full prescribing information available as package inserts or in the latest edition of the Physicians’ Desk Reference.

† Primary entries of opioids are by generic name; proprietary names appear in parentheses.

Abbreviations: CNS, central nervous system; CR, controlled release; ER, extended release; G-tube, gastrostomy tube; IR, immediate release; IV, intravenous; MAOI, monoamine oxidase inhibitor; PCA, patient-controlled analgesia; PI, manufacturer’s prescribing information; PO, by mouth; PR, per rectum; PRN, as needed.
intravenous administration of ketamine can provide analgesia with a minimum incidence of associated cardiovascular or neurologic side effects. Infusion rates of 0.1 to 5.0 milligrams per kilogram of body weight per hour (mg/kg/h) titrated to sedative effects have been used to treat patients with refractory pain resistant to opioid therapy. During titration, opioid consumption can be slowly reduced by 10% to 90%. Ketamine can provide analgesia without the sedation of high-dose opioid administration. Tachyphylaxis can develop with prolonged use of either intravenous or oral ketamine, and bioavailability from oral administration can also limit long-term effectiveness.

### Antidepressants

Tricyclic antidepressants (TCAs) have efficacy in treatment of patients with neuropathic pain and those presenting with pain syndrome and comorbid depression. Doses effective for neuropathic pain are usually lower than those used for depression. TCAs have no differences in their effectiveness.

<table>
<thead>
<tr>
<th>Name</th>
<th>Formulation and Strength</th>
<th>Dosing</th>
<th>Indications, Contraindications, and Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fentanyl (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Lozenges</td>
<td>Oral lozilite: 200 µg/unit, 400 µg/unit, 600 µg/unit, 800 µg/unit, 1200 µg/unit, 1600 µg/unit</td>
<td>Initial dose 200 µg May use 1 additional unit 15 min after previous unit completed for single breakthrough episode Maximum 4 units/d</td>
<td>Indicated only for the management of breakthrough cancer pain in opioid-tolerant patients. Contraindicated in the management of acute or postoperative pain or opioid naive patient. Only approved for cancer pain in opioid-tolerant patients. Unit should be allowed to dissolve, not chewed or bitten. Caution around children. Must be disposed of properly according to manufacturer’s recommendations.</td>
</tr>
<tr>
<td>□ (Actiq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydromorphone</strong></td>
<td>Liquid: 1 mg/mL Tablet: 1 mg, 2 mg, 3 mg, 4 mg, 8 mg Suppository: 3 mg Injectable: 1 mg/mL, 2 mg/mL, 4 mg/mL</td>
<td>PO: 1 mg-2 mg every 3-4h PR: 3 mg every 6-8h IV: 0.5 mg-1 mg every 3-4h</td>
<td>Slightly shorter duration of action than morphine. PCA use for acute postoperative pain. Less pruritus than with morphine. Short half-life, a good choice for elderly.</td>
</tr>
<tr>
<td>□ (Dilaudid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meperidine</strong></td>
<td>Injectable: 25 mg/mL, 50 mg/mL, 75 mg/mL</td>
<td>Oral use not recommended IV use limited to: treatment of rigors, documented allergy to all other opioids, moderate sedation (patient with normal renal function and no history of seizures) IV: 25-50 mg every 1-2 h Maximum dose: 600 mg/24 h</td>
<td>Toxic metabolite accumulates with repetitive dosing to cause CNS excitation/seizures. Contraindication: renal failure, history of seizures, or MAOI use within 2 weeks. Use with caution in patients receiving St John’s Wort.</td>
</tr>
<tr>
<td>□ (Demerol)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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especially for concurrent neuropathic pain syndrome. The major mechanism of the analgesic effect was believed to be related to inhibition of norepinephrine or serotonin reuptake or both. Common side effects include sedation, confusion, orthostatic hypotension, weight gain, tachycardia, arrhythmia, anticholinergic effects (dry mouth, blurred vision, and urinary retention).

Tricyclic antidepressants should be administered cautiously in elderly patients and in those with angle-closure glaucoma, benign prostatic hypertrophy, urinary retention, constipation, cardiovascular disease, or impaired liver function. These agents should be avoided in patients with severe liver disease, second- or third-degree heart block, arrhythmias, QT prolongation, and those with a history of recent myocardial infarction.

### Table (continued)
**Common Opioid Analgesics With Usually Recommended Doses**

<table>
<thead>
<tr>
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<th>Formulation and Strength</th>
<th>Dosing</th>
<th>Indications, Contraindications, and Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methadone</strong></td>
<td>Tablet: 5 mg, 10 mg</td>
<td>PO: 5 mg-10 mg every 6-8 h Elderly: 2.5 mg every 6-8 h</td>
<td>Cardiac and respiratory deaths have been reported during initiation and conversion of patients to methadone. Respiratory depression is the chief hazard associated with methadone administration. Cases of QT interval prolongation and serious arrhythmia have been observed during methadone treatment. Accumulates with repeated dosing and requires decreases in dose and frequency especially on days 2-5. Long half-life, peak effect in 4-10 days. Dose decreased for renal impairment. Consult a conversion chart for converting from another opioid to methadone.</td>
</tr>
</tbody>
</table>

| **Morphine IR** | Tablet: 10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg | PO: 10 mg-30 mg every 3-4 h IV: 2 mg-5 mg every 2-4 h PR: 5 mg-10 mg every 4-6 h Continuous infusion: Initiate at 1 mg/h to 2 mg/h. Titrate to goal pain control in 1-mg/h increments, until 6 mg/h, then increase in 2-mg/h increments. | Metabolites may accumulate with prolonged use, especially in renal failure leading to sedation, pruritus, confusion, respiratory depression. PCA use for acute postoperative pain. Liquid contains alcohol. |

| **Morphine CR** | Tablet: 15 mg, 30 mg, 60 mg, 100 mg, 200 mg | PO: 30 mg every 12 h Elderly: 15 mg every 12 h Dose should be based on or adjusted to IR requirements. | Tablet not to be cut, crushed, or chewed. |


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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine ER</strong>&lt;br&gt;□ (Avinza)&lt;br&gt;□ (Kadian)</td>
<td>Capsules&lt;br&gt;30 mg, 60 mg, 90 mg, 120 mg&lt;br&gt;20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg</td>
<td>PO: 30 mg daily&lt;br&gt;PO: 50% of other oral morphine dose every 12 h, or 100% daily&lt;br&gt;Dose should be based on or adjusted to IR requirements</td>
<td>Indicated for once-daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. Capsules should be swallowed whole or sprinkled on applesauce. Do not chew or crush because of risk of rapid release and absorption of a potential fatal dose of morphine. Consumption of alcohol while taking Avinza may result in the rapid release and absorption of a potentially fatal dose of morphine. G-tube administration: flush 16 French or larger G-tube with 10 mL of water. Open capsule and sprinkle into 15 mL of apple juice. Using 30-mL catheter tip syringe, draw up juice and medication. Holding the syringe horizontally, slowly administer the solution into the G-tube. Flush with another 10 mL of apple juice.</td>
</tr>
<tr>
<td><strong>Oxycodone (IR)</strong>&lt;br&gt;□ (Roxicodone)&lt;br&gt;□ (OxyIR)&lt;br&gt;□ With acetaminophen — (Percocet, Endocet Roxicet)</td>
<td>Tablet: 5 mg, 15 mg, 30 mg&lt;br&gt;Solution: 5 mg/5 mL&lt;br&gt;Capsule: 5 mg&lt;br&gt;2.5 mg/325 mg, 5 mg/325 mg, 7.5 mg/500 mg, 10 mg/650 mg</td>
<td>PO: 5 mg-10 mg every 3-4 h&lt;br&gt;Elderly: 2.5 mg- 5 mg</td>
<td>Simultaneous use of aspirin, ibuprofen, or acetaminophen limits dose of combination products.</td>
</tr>
<tr>
<td><strong>Oxycodone (CR)</strong>&lt;br&gt;□ (OxyContin)</td>
<td>Tablet: 10 mg, 20 mg, 40 mg, 80 mg</td>
<td>PO: 10 mg-20 mg every 12 h&lt;br&gt;Elderly: 10 mg every 12 h</td>
<td>Indication for the management of moderate to severe pain when continuous, around-the-clock analgesics needed for an extended period of time. Tablet not be crushed or chewed because of rapid release and absorption of potentially fatal oxycodone.</td>
</tr>
</tbody>
</table>


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In general, secondary amines have fewer sedative and anticholinergic effects than tertiary amines; therefore, these former TCAs may be more desirable in elderly patients.26 In this latter population, the starting dose is usually 10 mg at bedtime, then gradually titrated to a therapeutic level. Trazodone hydrochloride is as effective as amitriptyline in cancer-related neuropathic pain syndrome.13 The selective serotonin and norepinephrine reuptake inhibitor duloxetine hydrochloride, an antidepressant, has also been shown to be effective for neuropathic pain.27 It is reported that doxepin oral rinse is effective for debilitating oral mucositis induced by cancer therapy.28

**Anticonvulsants**

Anticonvulsants have been used in treatment of neuropathic pain for many...
years. The mechanism of the analgesic activity of carbamazepine, phenytoin, and valproic acid is thought to be associated with blocking sodium channels and increased membrane stability. Clonazepam increases \( \gamma \)-aminobutyric acid (GABA) levels and also activates the benzodiazepine receptor; this receptor activation causes an increase in chloride ion which inhibits neuronal activity. Gabapentin, initially was designed to be an analog of GABA receptor. Modulation of the \( \alpha 2 \delta \) subunit of the N-type voltage-dependent \( \text{Ca}^{2+} \) channels is the probable reason for its antiepileptic and analgesic properties. Pregabalin, a newer anticonvulsant, also modulates the \( \alpha 2 \delta \) subunit of N-type voltage-gated calcium channels on neural tissue. Activation of this subunit reduces release of neurotransmitters from presynaptic terminals.\(^{29}\) Advantages of pregabalin compared with gabapentin include 90% absorption with predictable serum levels. There is less chance of drug interactions since these two agents are not protein-bound, nor do they cause induction or inhibition of cytochrome systems.

Caution should be taken when administering carbamazepine, phenytoin sodium, or valproic acid because they have known severe adverse effects such as bone marrow depression and liver toxicity. Baseline evaluation of liver function and a complete blood cell count should be done before initiating use of these medications.

Pregabalin, a newer anticonvulsant, also modulates the \( \alpha 2 \delta \) subunit of N-type voltage-gated calcium channels on neural tissue. Activation of this subunit reduces release of neurotransmitters from presynaptic terminals.\(^{29}\) Advantages of pregabalin compared with gabapentin include 90% absorption with predictable serum levels. There is less chance of drug interactions since these two agents are not protein-bound, nor do they cause induction or inhibition of cytochrome systems.

Caution should be taken when administering carbamazepine, phenytoin sodium, or valproic acid because they have known severe adverse effects such as bone marrow depression and liver toxicity. Baseline evaluation of liver function and a complete blood cell count should be done before initiating use of these medications.

At present, gabapentin is the most commonly used adjuvant analgesic for neuropathic pain.\(^{30}\) It has been shown to be efficacious in different neuropathic pain syndromes and to possess a good safety profile. Most of the controlled trials of gabapentin in patients with various neuropathic pain syndromes demonstrate that it reduces both pain and sleep interference and improves the quality of life. It is the only antiepileptic that has been tested to be effective in cancer-related neuropathic pain.\(^{29}\) Gabapentin is not metabolized and has no known drugdrug interactions; most of it is excreted unchanged in the urine, but some elimination (10%-23%) occurs via the feces. Treatment usually starts with 100 mg/d to 300 mg/d. Gradual dose titration continues until benefit occurs, side effect supervenes, or the total daily dose reaches 3600 mg. Occasionally, patients

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**Table (continued)**

**Common Opioid Analgesics With Usually Recommended Doses**

<table>
<thead>
<tr>
<th>Name†</th>
<th>Formulation and Strength</th>
<th>Dosing</th>
<th>Indications, Contraindications, and Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxymorphone (IR)</strong>&lt;br&gt; (Opana)</td>
<td>Tablet: 5 mg, 10 mg PO: 5 mg-10 mg every 4-6 h</td>
<td>Not indicated as first- or second-line therapy for pain management. Patients stabilized on oxymorphone as outpatients may continue therapy when admitted. Must be given on an empty stomach 1 h before or 2 h after a meal.</td>
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<tr>
<td><strong>Oxymorphone ER</strong>&lt;br&gt; (Opana ER)</td>
<td>Tablet: 5 mg, 10 mg, 20 mg, 40 mg PO: 5 mg every 12 h Dose should be based on or adjusted to IR requirements</td>
<td>Indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Not intended for use as a PRN analgesic. Tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved or crushed tablets leads to rapid released and absorption of a potentially fatal dose of oxymorphone. Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol. The co-ingestion of alcohol may result in increased plasma levels and a potentially fatal overdose of oxymorphone.</td>
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</tbody>
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* Adapted with permission from Schechter L, Meadows S. Adult Pain Management Guidelines. Philadelphia, Pa: Thomas Jefferson University Hospital; 2007. This table is a derivative collection from several sources, including the 2007 manufacturers’ full prescribing information available as package inserts or in the latest edition of the Physicians’ Desk Reference.

† Primary entries of opioids are by generic name; proprietary names appear in parentheses.

**Abbreviations:** CNS, central nervous system; CR, controlled release; ER, extended release; G-tube, gastrostomy tube; IR, immediate release; IV, intravenous; MAOI, monoamine oxidase inhibitor; PCA, patient-controlled analgesia; PI, manufacturer’s prescribing information; PO, by mouth; PR, per rectum; PRN, as needed.
receive benefits at even higher doses. An adequate trial should include 1 to 2 weeks at the maximum tolerated level. The most common side effects are dizziness and somnolence; others include confusion, and peripheral edema. Therefore, gabapentin should be titrated slowly in patients who are elderly and those with impaired renal function.

Like gabapentin, pregabalin and levetiracetam have proven efficacy for neuropathic pain. Dunteman reported a 70% reduction of opioid use with the administration of levetiracetam, as well as improved pain relief in patients with neoplastic plexopathies previously resistant to standard analgesic approaches. Tiagabine hydrochloride is a new GABA reuptake inhibitor, and compared with gabapentin, it has similar effectiveness in pain reduction but greater efficacy for sleep improvement.

**Corticosteroids**

Corticosteroids are given as adjunctive therapy for cancer-related neuropathic pain, especially for metastatic spinal compression, pain associated with soft tissue infiltration, and visceral distension.

Mechanisms of action include:
- inhibiting prostaglandin production and reducing inflammation;
- decreasing capillary permeability and reducing peritumor edema; and
- directly affecting membrane stabilization, which decreases neuronal excitability.

Administering these drugs can produce significant adverse effects such as hypertension, hyperglycemia, immunosuppression, gastrointestinal ulceration, and psychiatric disorders. Dexamethasone is the corticosteroid most commonly used for spinal cord compression because of a decreased tendency for salt and fluid retention. The doses range from 10 mg to 20 mg administered intravenously every 6 hours. Corticosteroids are also used to enhance appetite, reduce nausea and malaise, and improve overall quality of life. When given with docetaxel and mitoxantrone to treat patients for metastatic hormone-refractory prostate cancer, these medications increase analgesia and the quality of life.

**Bisphosphonates, Calcitonin and Radionuclides**

Bone pain secondary to tumor expansion and inflammation is a common symptom of some cancers. Radiation therapy with corticosteroids is highly effective for the treatment of patients with focal bone lesions. Some medications useful for managing bone pain by inhibiting osteoclast activity include bisphosphonates, calcitonin, and radionuclide.

The analgesic efficacy of bisphosphonates, particularly the second-generation bisphosphonate pamidronate disodium and ibandronate sodium, have been well established. For tumor-related bone pain, 60 mg to 90 mg of pamidronate disodium or 2 mg to 6 mg of ibandronate sodium injected intravenously is recommended every 3 to 4 weeks. Adverse effects include hypocalcemia, and a flu-like syndrome. Zoledronic acid, a new bisphosphonate, is approximately two to three times more potent than—and as effective as— pamidronate.

Calcitonin is usually administered subcutaneously and intranasally. The initial dose is 200 IU in one nostril a day, alternating nostrils every day. Apart from infrequent hypersensitivity reactions associated with subcutaneous injections, the main side effect is nausea.

Radionuclides that are absorbed at areas of high bone turnover have been assessed as potential therapies for metastatic bone pain. Strontium-89 chloride and samarium-153 are available in the United States. Studies demonstrated that these radiopharmaceuticals are effective in the palliation of metastases whose pain is not controlled with conventional analgesic regimens.

**Local Anesthetics**

Evidence has been presented showing a higher density of Na⁺ channels after nerve damage and subsequent spontaneous firing. By inhibiting sodium channels, local anesthetics are effective in treating patients with nonmalignant and cancer-related neuropathic pain syndrome. These agents should be considered after trials of anticonvulsants or antidepressants have failed. Local anesthetics (eg, lidocaine) are used for diagnostic and therapeutic treatment prior to neurolytic procedures (celiac plexus block) used to treat patients for refractory cancer pain (pancreatic cancer). Common adverse effects are paresthesias (fingers), abnormal taste, tinnitus, blurred vision, drowsiness, dysarthria, or local skin rash secondary to topical application of the anesthetic.

Severe systemic toxicity due to high plasma levels can cause seizure or result in cardiotoxicity with cardiac arrest. For intravenous lidocaine infusion, the dose is 1 mg/kg or 5 mg/kg given over 2 hours. When administered topically, 5% of lidocaine gel or patch is placed directly on skin over painful regions; there is minimal systemic absorption. Mexiletine hydrochloride, an antiarrhythmic with structural similarity to lidocaine, has been used off label to treat patients with neuropathic pain from numerous etiologies and is the preferred oral local anesthetic. Topical capsaicin, a peptide that depletes substance P in small primary afferent neurons, has been shown to significantly decrease cancer-related neuropathic pain. A major side effect, localized irritation that causes a burning sensation, limits use of capsaicin.

**Miscellaneous Adjuvants**

Other medications are sometimes used as adjuvants for pain or symptom management related to cancer treatment.

- Baclofen for spasticity, trigeminal neuralgia, and central pain secondary to spinal cord lesions; its mechanism of action is activation of GABA receptors.
- Benzodiazepines can reduce cancer pain by reducing fear, apprehension, and anxiety related to cancer.
- Psychostimulant drugs (dextroamphetamine, methylphenidate) can reduce opioid-induced somnolence, improve cognition, treat patients for depression, and alleviate fatigue.
- Antihistamines, anticholinergic drugs, antipsychotics, and laxatives are sometimes used to treat patients for cancer-related symptoms or complications of cancer treatment, such as dizziness, vertigo, nausea and vomiting, confusion and delirium, and constipation. This group of medications should be used cautiously, with precautions taken to reduce side effects and drug-drug interactions.
Hormonal therapy for breast or prostate cancer pain (eg, tamoxifen or leuprolide, respectively) can provide beneficial effects.

The following case presentation describes a patient whose name and other possible identifiers have been changed to maintain privacy. This case vignette illustrates the issue and complexity involved in treating patients for cancer-related pain.

Illustrative Vignette Case Presentation

Jeff, a 32-year-old man, was evaluated in consultation for intractable leg pain. Past history included metastatic colon cancer with both liver, pelvic, and bone involvement. Initial presentation of illness was bowel obstruction with abdominal pain and emesis. Surgical exploration revealed colon cancer with localized lymph node involvement. Treatment included bowel resection and several rounds of chemotherapy. Jeff had remained symptom free with serial computed tomography (CT) scans showing no other regions of involvement of lymph nodes or liver.

Two years after his initial presentation, Jeff sought evaluation for dyspnea, tachycardia, and tachypnea. Spiral CT scan showed significant pulmonary embolism to the right pulmonary artery as well as liver metastasis. Further workup including CT scanning of the abdomen and pelvis and bone scan. Metastases were present in the sacrum and femur bilaterally. After insertion of a vena cava filter, prophylactic intramedullary rods were inserted. Treatment for recurrence included additional chemotherapy and external beam radiation.

After 6 months, Jeff had recurrent pulmonary embolism and was treated with low-molecular-weight heparin and warfarin sodium. Jeff complained of pain involving his right leg in the distribution of L5 and S1. Repeated CT studies showed epidural metastasis as well as infiltration with tumor in the body of L5. Jeff continued to complain of burning, searing, stabbing pain despite high doses of oral morphine sulfate in immediate- and sustained-release preparations and gabapentin. He remained hospitalized for pain control. Despite, parenteral morphine with continuous infusion of 50 mg/h and intermittent bolus of 10 mg per every 15-minute demand, Jeff’s pain was still uncontrolled and side effects were unsatisfactory. Jeff complained of severe drowsiness, but with his medications at lower doses, his pain on the 11-point numeric scale was 10.

Jeff’s oncologist requested a pain management consultation. Recommendations included intravenous ketamine with dose titration to effect and low-dose amitriptyline (10 mg/d). Because of the neuraxial metastasis and anticoagulation, intrathecal catheter implantation was not considered. Neurolytic blocks were also not considered secondary to Jeff’s ambulatory status.

An infusion of ketamine was started at 0.1 mg/kg/h (1000 mg ketamine in 1000 mL of 0.9% saline solution). Hourly titration with increases of 0.1 mg/kg/h was continued. During this time, morphine infusion was also slowly reduced. After 5 hours, Jeff’s pain score was 2/10 with a ketamine infusion of 0.5 mg/kg/h and morphine at 20 mg/h. Morphine infusion was slowly reduced to 5 mg/h with the same dosage of ketamine. Jeff rated his pain at a score of 2/10 and reported no central nervous system effects. After 5 days, the decision was made to send Jeff home with infusion therapy of both ketamine and morphine. Visiting nurses assessed Jeff’s pain daily and consulted with a board-certified anesthesiologist specialist in pain management for recommendations for dosage adjustments. The patient remained on this therapy for 28 days.

Salvage chemotherapy was planned, but because of limited intravenous access, the ketamine infusion was stopped. The hope was that after prolonged infusion, NMDA receptors had been reset and benefits of pain relief would continue. Jeff did well for 5 days with pain controlled with escalating dosage of morphine. Salvage chemotherapy was instituted. On day 6, visiting nurses reported that Jeff had intractable pain despite administration of additional boluses and elevations in infusions.

The family decided to place Jeff in hospice care and to discontinue any further interventional therapies. Ketamine infusion was restarted with rapid escalation of dosage to 0.8 mg/kg/h and morphine to 120 mg/h. Pain was well controlled on this dosage; Jeff died 4 days later.

Discussion

This case illustrates the complexity of dealing with patients with metastatic disease and its associated complications. The management of the pain suffered by patients with cancer presents a unique problem. Management is affected not only by the system disease, but also by the need to provide pain relief, yet also allow for quality-of-life issues in a terminally ill patient. This patient’s concern was primarily pain relief, but without the systemic effects associated with high doses of opioids. The quality-of-life issues involved family interaction including his 7- and 5-year-old sons. Jeff wished to be able to spend quality time with his family without the excessive sedation and lethargy that he had experienced. Ketamine allowed him to have this quality of life without the CNS effects, but with satisfactory pain relief.

The other issue was the institution of hospice at the last few days of life. Unfortunately, institution of hospice care occurs too late when the usefulness of the hospice team’s services cannot be used to the fullest extent. Hospice care not only includes control of pain, but it also provides support for both the family and the patient’s medical, physical, and emotional needs.

Comment

Pain management is an important goal in holistic care of patients with cancer. Studies have shown that effective pain control can be achieved in 90% of patients by following the WHO step-ladder system. Major obstacles still exist that prevent reduction of pain in patients with cancer. Education of patients, families, healthcare providers, legislators, and law enforcement agencies is needed to improve the treatment of patients with cancer-related pain with all the pharmacologic therapeutic modalities availability.

References


