CURRENT AND EMERGING TREATMENT STRATEGIES: OPIOID ANALGESICS

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ABSTRACT

Opioids are widely used for the treatment of acute pain in a broad range of settings, yet the risks and benefits of treatment are often poorly understood by patients and clinicians. Pharmacists are often the healthcare professionals to whom patients first turn with questions about pain management, and they are often called upon to recognize and assess patients with acute pain. A wide variety of single-entity and combination products are available for the treatment of acute pain. The specific medication selected must be carefully matched to the type and severity of the patient’s pain, in addition to the patient’s other clinical characteristics. Opioids may be classified in several ways, including their derivation (ie, naturally occurring, semisynthetic, or synthetic), affinity for binding at specific opioid receptor subtypes (ie, μ, κ, or δ receptors), and pharmacokinetic properties. Most of the opioids used in clinical practice are μ opioid receptor agonists. The prototypical member of this group is morphine; more potent or selective alternatives to morphine include oxymorphone and hydromorphone. Several agents (eg, codeine, hydrocodone, and oxycodone) are inactive prodrugs that require hepatic metabolism for the formation of active metabolites. Fentanyl is a highly lipophilic μ agonist that has been developed for transdermal and oral transmucosal administration. Other analgesics act at more than one type of receptor. The opioid agonist-antagonists are a class of analgesics that combine κ receptor agonism with μ receptor antagonism. Tramadol is a weak μ opioid receptor agonist that also acts as an inhibitor of serotonin and norepinephrine reuptake. Fixed-dose combination products that combine an opioid with a nonopioid analgesic, such as acetaminophen or ibuprofen, provide greater pain relief than their individual components and are often more convenient for patients. Patients who use combination products containing acetaminophen must be counseled not to exceed the maximum daily acetaminophen dose. Regular assessment of safety and efficacy outcomes is essential for all patients who are using opioid analgesics. (Adv Stud Pharm. 2008;5(2):41-47)

Opioids are an important part of the standard of care for the treatment of moderate-to-severe acute pain in a wide variety of clinical settings, including surgery, musculoskeletal injuries, infections, headache, and dental procedures. Recent advances in the management of acute pain include a growing number of opioid analgesics, new formulations and combination products, greater understanding of dependence and addiction with acute therapy, increased attention to opioid-related adverse effects, and better patient follow-up and assessment of treatment success. Despite these advances, several obstacles to the effective management of acute pain remain. Misconceptions about the risk of addiction or dependence with acute therapy are common among patients and healthcare professionals, and many patients struggle with poorly controlled pain. Opioid-induced adverse effects are often not recognized or are inadequately prevented or treated. This paper provides pharmacists with an

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overview of the use of opioids in acute pain management, including assessment of patients with pain and the basic prescribing principles of opioid medications. Accompanying articles discuss the risk of addiction or dependence with acute opioid therapy, and the management of opioid-induced adverse effects.

**ASSESSING PAIN**

In general, pain is often classified as either acute or chronic. Acute pain is defined as pain of relatively limited duration (e.g., postsurgical pain), whereas chronic pain persists for an undefined, extended period of time. In addition, pain may be classified as either nociceptive or neuropathic. Nociceptive pain is caused by tissue damage or by stimuli that have the potential to cause tissue damage, and may be further subdivided as either visceral (e.g., abdominal cramps or other poorly localized pain originating in the visceral organs) or somatic (e.g., sprains, burns, or other pain corresponding to a specific site of injury). Neuropathic pain is caused by nervous system lesions or dysfunction, often without any physical findings (e.g., diabetic neuropathy).

Pharmacists are often the first healthcare professionals to identify or assess patients who are experiencing pain. Patients often turn to a pharmacist for help treating acute pain that is caused by an accident, an injury, a medical condition, or another cause. However, many individuals struggle with pain that has not been diagnosed or even recognized by a primary care provider or other healthcare professional. In many cases, pain is a significant underlying problem for patients who are taking medications for sleep or mood disorders. Pain is also common for patients with diabetes or other chronic illnesses. Simply talking with patients is often sufficient to identify pain that is untreated or insufficiently treated. Several other methods are also available for the rapid assessment of pain.

The Brief Pain Inventory is a paper-and-pencil test that includes a simple 4-question scale to assess the patient’s average pain intensity, most intense pain, and least intense pain during the past 7 days, in addition to the patient’s current pain intensity (available online at http://www.mdanderson.org/pdf/bpilong.pdf). The Visual Analog Scale consists of a line (usually 10 cm long, presented horizontally) that is labeled “no pain” at one end and “worst pain imaginable” at the other. The patient makes a mark on the line to indicate the current intensity of pain, and the pain intensity is scored by measuring the distance from the low end of the scale to the patient’s mark. Several variations of this concept are used to assess pain (Figure), including the Faces Scale or a Numerical Rating Scale in which the patient is asked to rate the severity of pain from 0 (no pain) to 10 (severe pain). More complex rating scales are used for research purposes to assess pain intensity and changes in pain over time. In recent years, improving functional impairment has increasingly been recognized as a principal goal of pain therapy. Rating scales that include an assessment of function include the McGill Pain Questionnaire and the Brief Pain Inventory. These tests are designed to assess the degree to which pain limits the ability of patients to carry out their normal daily activities. For example, the Brief Pain Inventory asks patients to rate, on a scale from 1 (least pain) to 10 (most pain), how pain has limited their ability to walk, sleep, work, and perform other activities over the course of the preceding 7 days.

The World Health Organization has described the role of opioid medications in pain treatment using a 3-step “analgesic ladder,” in which analgesia is matched to the intensity of the patient’s pain. Although originally described for cancer pain, this general method is also appropriate for other types of pain. According to this approach, mild pain is initially managed using a nonopioid analgesic, possibly in combination with an adjuvant therapy (i.e., a drug that may not relieve pain...
on its own, but that enhances the efficacy of other pain-relieving medications or that is used to reduce the impact of adverse events.

Patients with moderate pain or persistent, unrelieved mild pain undergo a trial of a mild opioid (eg, codeine, tramadol, or low-dose oxycodone), which may be combined with an adjunctive agent such as a tricyclic antidepressant or an anti-convulsant. Patients with severe or persisting pain are treated with a strong opioid (eg, morphine, oxycodone, hydromorphone, or fentanyl), which may be administered with an adjunctive therapy. In addition, patients with moderate-to-severe pain may also receive combination therapy with a nonopioid pain reliever (eg, aspirin and acetaminophen), which may provide greater pain relief than an opioid alone.

OPIOID PHARMACOLOGY AND DRUG SELECTION

All opioid medications are derivatives of opium alkaloids. Opioids may be classified as either naturally occurring (morphine or codeine), semisynthetic (eg, hydrocodone, oxycodone, and hydromorphone), or synthetic (eg, fentanyl and methadone). All of these agents act by binding to specific endogenous opioid receptors (µ, κ, or δ receptors) within the central nervous system (CNS) or the peripheral tissues. The binding of opioids to their receptors results in hyperpolarization of neurons that transmit pain information, reducing the rate of nerve impulses and interrupting the transmission of pain information to or within the CNS. Most of the opioids used in clinical practice are µ opioid receptor agonists. There are several different chemical classes of µ agonists, including the phenanthrenes (eg, morphine, codeine, hydrocodone, hydromorphone, levorphanol, oxycodone, and oxymorphone), the phenylpiperidines (eg, meperidine, fentanyl, sufentanil, and alfentanil), and the phenylethylamines (eg, methadone and propoxyphene).

Patients who have allergies to opioids from one class are often able to attain pain relief by switching to an agent from another class.

Opioids vary significantly in several important respects, including intensity of analgesic effect, selectivity for particular opioid receptor subtypes, time to onset of analgesia, half-life, and route of elimination (Tables 1 and 2). The selection of a particular therapy depends on several factors, including the type and intensity of pain, the specific clinical setting, the patient’s age, and the presence of comorbid conditions.

Codeine is a relatively weak analgesic that is used primarily for mild-to-moderate pain. The analgesic effect of codeine requires the conversion from codeine (which is an inactive prodrug) to morphine by the CYP 2D6 enzyme. Approximately 4% to 10% of the white population lack this enzyme, and do not derive analgesic efficacy from codeine, although they are still at risk of adverse effects. Products combining codeine with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen are widely used in pain management, and controlled clinical trials have demonstrated that these agents are more effective for acute pain (eg, postoperative pain) than NSAIDs or acetaminophen alone. Hydrocodone and oxycodone are also prodrugs that are metabolized to active forms by the CYP 2D6 enzyme. These agents have greater oral bioavailability than codeine (approximately 60%) and are more potent analgesics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate Time to Onset of Action, min</th>
<th>Approximate Time to Peak Effect, min</th>
<th>Approximate Duration of Effect, hr</th>
<th>Dose Equivalance, mg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>1–2</td>
<td>5</td>
<td>1–2</td>
<td>0.01</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2–3</td>
<td>10–15</td>
<td>~2</td>
<td>0.2</td>
</tr>
<tr>
<td>Meperidine</td>
<td>10</td>
<td>30</td>
<td>3–4</td>
<td>10</td>
</tr>
<tr>
<td>Methadone</td>
<td>2–3</td>
<td>5–6</td>
<td>6–12</td>
<td>1</td>
</tr>
<tr>
<td>Morphine</td>
<td>2–4</td>
<td>15–20</td>
<td>~2</td>
<td>1</td>
</tr>
</tbody>
</table>

*On a milligram-to-milligram basis relative to morphine, fentanyl is approximately 100 times more potent, hydromorphone is approximately 5 times more potent, and meperidine is approximately 1/10 as potent.

greater potency of these agents in comparison with codeine may reduce the proportion of an administered dose that contributes to side effects.\(^{18}\) Randomized controlled clinical trials have demonstrated that hydrocodone and oxycodone are both significantly more effective than ibuprofen or acetaminophen for the treatment of acute pain.\(^{19-22}\)

Morphine, the prototypical selective \(\mu\) receptor agonist analgesic, is a potent and effective analgesic that is available in many formulations for the treatment of moderate-to-severe acute pain.\(^{18}\) Morphine is relatively hydrophilic, and has a slower onset and longer duration of action than the more lipophilic agents, such as fentanyl. Morphine metabolism yields at least 2 active metabolites (morphine-3-glucuronide [M3G] and morphine-6-glucuronide [M6G]) that may contribute to the adverse effects of morphine at high doses (especially neuromotor effects, such as motor excitation or seizures).\(^{23}\) These metabolites are eliminated by renal clearance, and may therefore contribute to an increased risk of adverse events for patients with renal impairment.\(^{24,25}\) Other agents are more potent and selective \(\mu\) agonists than morphine. Oxymorphone is more potent than morphine, is more lipophilic (resulting in more rapid onset of effect), and has a longer duration of action. Hydromorphone is also more potent than morphine that does not yield M3G or M6G as metabolites. Fentanyl is a highly lipophilic \(\mu\) opioid agonist that is available in several transdermal and transmucosal delivery systems.\(^{26}\)

Several analgesics act at more than one type of neurotransmitter receptor. The opioid agonist-antagonists act as \(\kappa\) receptor agonists and \(\mu\) receptor antagonists. This category includes the analgesic agents butorphanol, nalbuphrine, and pentazocine.\(^{1}\) Pentazocine is an opioid agonist-antagonist for oral administration that is formulated with naloxone.\(^{19}\) Naloxone antagonizes the effects of pentazocine if administered parenterally but not orally, as naloxone is not bioavailable with oral administration.\(^{18}\) Unlike the \(\mu\) receptor agonists, which produce greater analgesia with increasing drug dose, the agonist-antagonists may produce a ceiling effect in which higher doses result in diminished pain relief due to \(\mu\) receptor antagonism.\(^{1}\) Tramadol is a weak \(\mu\) opioid agonist and an inhibitor of serotonin and norepinephrine reuptake.\(^{27}\) Tramadol is not a scheduled substance in the United States, and it may be less likely to cause somnolence or constipation than conventional opioids.\(^{18}\) Levorphanol acts at \(\mu\) opioid receptors and at \(N\)-methyl-D-aspartate glutamate receptors, and is sometimes used as a second-line analgesic.\(^{10}\)

Some opioids are not recommended for the routine treatment of acute pain. Propoxyphene possesses analgesic efficacy that is similar to acetaminophen,\(^{28}\) but is associated with the potential for significant adverse effects, including the risk of irreversible cardiac injury.

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**Table 2. Selected Clinical Pharmacokinetics of Commonly Used Oral Opioids**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate Time to Onset of Action, min</th>
<th>Approximate Time to Peak Effect, hr</th>
<th>Approximate Duration of Effect, hr</th>
<th>Approximate Bioavailability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>30–45</td>
<td>1.5–2</td>
<td>3–4</td>
<td>60</td>
</tr>
<tr>
<td>Meperidine</td>
<td>30–45</td>
<td>1.5</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Methadone</td>
<td>30</td>
<td>2–3</td>
<td>6–12</td>
<td>80</td>
</tr>
<tr>
<td>Morphine (immediate release, sublingual)</td>
<td>30–45</td>
<td>1.5–2</td>
<td>3–4</td>
<td>30</td>
</tr>
<tr>
<td>MS Contin*, Oramorph SR(^1), other generics</td>
<td>120</td>
<td>6–8</td>
<td>10–12</td>
<td>30</td>
</tr>
<tr>
<td>Kadian(^2)</td>
<td>120</td>
<td>8–12</td>
<td>18–24</td>
<td>30</td>
</tr>
<tr>
<td>Avinza(^3)</td>
<td>45</td>
<td>4–6</td>
<td>18–24</td>
<td>30</td>
</tr>
<tr>
<td>Oxycodone (immediate release)</td>
<td>20–45</td>
<td>1.5–2</td>
<td>3–4</td>
<td>80</td>
</tr>
<tr>
<td>Oxycodone (controlled release)</td>
<td>30–60</td>
<td>4–6</td>
<td>10–12</td>
<td>80</td>
</tr>
</tbody>
</table>

\(^*\)Morphine sulfate sustained release, Purdue Pharma, Pickering, ON, Canada.

\(^1\)Morphine sulfate sustained release, AAI Pharma, Inc., Wilmington, NC.

\(^2\)Morphine sulfate extended release, Alpharma, Bridgewater, NJ.

\(^3\)Morphine sulfate extended release, King Pharmaceuticals, Inc., Bristol, TN.

and arrhythmias that are caused by the accumulation of a metabolite (norpropoxyphene). Meperidine has a short duration of action, which may result in breakthrough pain, and an active metabolite (normeperidine) that is a CNS stimulant that may cause seizures and other CNS adverse effects. The half-life of normeperidine is much longer (15–20 hours) than the half-life of meperidine (approximately 3 hours), and therefore has the potential for significant accumulation if treatment is continued for more than 1 to 2 days. Meperidine is absolutely contraindicated in patients who are using or who have recently used a monoamine oxidase inhibitor, as this combination has been associated with hypertensive crisis and cardiovascular collapse. Although the use of meperidine is still described in some pain management guidelines, many experts recommend against its use in routine pain management.

**DOSING CONSIDERATIONS: PHARMACOKINETICS AND ROUTE OF ADMINISTRATION**

Short-acting preparations are used primarily for the treatment of acute pain, or for “rescue” dosing to relieve acute pain exacerbations in patients who are being treated for chronic pain. They may also be used during initial dose-finding for patients who are being treated for chronic pain. Long-acting opioids, such as methadone, are generally used for the treatment of chronic pain. In addition, several products are available for opioid-experienced patients in which opioids are delivered using a variety of extended-release or sustained-release formulations, including morphine, oxycodone, oxymorphone, and a fentanyl patch. Although they are not generally recommended for acute pain, extended-release products may be preferred for some patients due to improved treatment adherence and the reduced risk of addiction.

Another important consideration in drug selection is the route of administration. Opioids are available in numerous forms for varying routes of administration. Oral and transdermal agents are usually the most convenient, and are preferred where possible. Several opioids are available in liquid formulations. New opioid medications that are being developed for the treatment of acute pain include novel formulations of currently approved drugs, in addition to investigational opioids that may soon be approved for clinical use. New formulations include a recently developed sublingual sufentanil product (sufentanil nanotabs), which is designed to provide a more rapid onset of effect and more consistent analgesia over time than currently available oral medications. This formulation of sufentanil is being evaluated in clinical studies for analgesia in patients undergoing orthopedic surgery. A novel transdermal hydromorphone 24-hour patch is currently being developed, which achieves steady-state hydromorphone levels within approximately 4 hours (compared to up to 72 hours for transdermal fentanyl). This transdermal product is being evaluated for moderate-to-severe acute pain. Tapentadol is a novel opioid analgesic with a dual mechanism of action—it is a μ opioid receptor agonist and a norepinephrine reuptake inhibitor. This mechanism of action is similar to that of tramadol, which is a μ receptor agonist and a serotonin/norepinephrine reuptake inhibitor. However, the potency of tapentadol is greater than that of tramadol, which may reflect differences in the way the drugs are metabolized. Tramadol is a racemic mixture of positive and negative enantiomers that requires conversion of one enantiomer to an active metabolite in order to activate μ receptors. Tapentadol does not require conversion to an active metabolite to produce analgesia. Preliminary findings from a randomized clinical trial presented at the 2006 annual meeting of the American Pain Society suggested that tapentadol produced significant dose-related pain relief in patients undergoing bunionectomy surgery. Doses of 100 or 200 mg produced analgesia that was similar to that of morphine 60 mg, but with a lower incidence of nausea, dizziness, somnolence, and vomiting. Tapentadol is being evaluated for the treatment of acute pain in patients undergoing abdominal hysterectomy surgery, and for patients with chronic low back pain.

**COMBINATION THERAPY**

Combination therapy, in which opioids are combined with other types of analgesics, is widely used for the treatment of acute pain. Several combination products are available in which an opioid is combined with a nonopioid pain reliever. For example, several products combine acetaminophen, aspirin, or ibuprofen with codeine, hydrocodone, or oxycodone. The terms “multimodal analgesia” or “balanced analgesia” have been used to refer to treatment with more than one analgesic agent or modality that act by different mechanisms of action, with the goals of increasing analgesia efficacy, reducing the risk of adverse effects,
Combination therapy may be administered by individually prescribing 2 or more pharmacologically compatible drugs. Alternatively, several fixed-dose combination products are also available for the treatment of acute pain. These combinations are associated with several potential advantages, including the selection of medications with complementary mechanisms, the use of dosages that are known to produce additive or synergistic analgesia while minimizing adverse effects, evidence from clinical trials supporting the efficacy and safety of the combination, and the convenience of a simplified dosing schedule. Fixed-dose combinations also possess potential limitations, including inflexible dosing and the potential for toxicity associated with high doses of the nonopioid component of the combination product. For example, many combination products are formulated with NSAIDs or acetaminophen, both of which can cause adverse events if taken in large doses. Although doses of opioids may be increased until pain relief occurs or adverse effects become intolerable, the presence of nonopioid pain relievers limits the maximum dose attainable with many combination products. A total daily dose of acetaminophen in patients receiving combination pain relievers should not exceed 4000 mg. Patients should be counseled not to exceed the prescribed dose, and to ensure that they are not using other medications that contain acetaminophen.

Combination products have been evaluated for the treatment of acute pain in a number of settings, including dental pain, postoperative pain, and other types of acute pain. Due to the potential for adverse effects associated with NSAID therapy (eg, gastrointestinal symptoms and increased bleeding risk in surgical patients), most combination products have included an opioid with acetaminophen. Clinical studies have demonstrated significantly better pain control with combination products than with their individual components, including acetaminophen or ibuprofen in combination with codeine, oxycodone, hydrocodone, or tramadol.

**Ensuring Effective and Safe Opioid Therapy**

It is essential to monitor efficacy and safety outcomes for patients who are receiving opioid therapy. A simple approach to the assessment of outcomes is to remember the “4 As” of pain management:

- Analgesia: is the patient experiencing adequate pain relief?
- Adverse effects: what side effects of therapy has the patient experienced?
- Activities of daily living: is the treatment improving with (or interfering with) the patient’s ability to function normally?
- Aberrant behavior: Are there aberrant drug-related behaviors that indicate the presence of a substance use problem (eg, forging prescriptions and repeatedly losing prescriptions)?

Many professional societies have established guidelines for the assessment of treatment of acute pain. The American Pain Society is considered by many to be the definitive source of information about pain management. Important publications from the American Pain Society include:

- Pain Control in the Primary Care Setting (http://www.ampainsoc.org/pub/pdf/ProductBrochure.pdf)
- Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain (http://www.ampainsoc.org/pub/principles.htm)

Other guidelines or resources for healthcare professionals have been developed by several professional organizations. Some of these include:

- Veterans Health Administration and Department of Defense: Clinical Practice Guideline for Management of Postoperative Pain (http://www.oph.med.va.gov/cpg/PAIN/PAIN_GOL.htm)
- Federation of State Medical Boards (www.fsmb.org/pain/resource.html)

**Conclusions**

Opioid analgesics for the treatment of acute pain vary in their pharmacokinetic and pharmacodynamic properties, and are available in several different formulations and fixed-dose combination products. The specific opioid chosen depends on the type and severity of pain, the patient’s response to prior therapy, the clinical setting, patient age, comorbid conditions, and other factors. Pharmacists are often the first to identify or assess patients with pain, and provide ongoing assessment of the efficacy and safety of opioid therapy.
REFERENCES