Opioid-Mediated Analgesia

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Introduction

Opioids are a class of central-acting analgesics that provide powerful dose-dependent pain relief. They have and still remain the therapeutic foundation for the management of moderate to severe postoperative pain.\(^1\,2\,3\) Opioids include compounds:

- With variable pharmacokinetics
- With no cardiac or hepato-renal toxic effects
- With no ceiling effect for achievable pain relief
- Which are available for oral, parenteral, and neuraxial administration.

Opioid Pharmacology

Opioids interact with specific transmembrane G protein-coupled binding sites termed opioid receptors. These receptors are located primarily in spinal dorsal horn, central grey, limbic cortex, and other regions of the CNS that process the suffering and emotional aspects of pain perception.\(^1\,3\) Naturally occurring opiates (eg, morphine) and synthetic opioids (eg, oxycodone, hydrocodone) have structural or chemical characteristics that permit binding and activation of opioid receptors, resulting in powerful analgesia (Figure 6.1). Four opioid receptor subtypes, designated as \(\mu\), \(\kappa\), \(\delta\), and sigma have been characterized.\(^1\,4\)

- \(\mu\) receptors mediate supraspinal analgesia and euphoria, as well as respiratory depression, nausea and vomiting, bowel hypomotility, and physical and psychological dependence.\(^1\,2\) \(\kappa\) receptors are responsible for spinal analgesia, visceral analgesia, and sedation, but have minimal effect on respiration.\(^1\,3\) Sigma receptors are believed to be responsible for opioid-related dysphoria, hallucinations, and confusion.

Based on binding specificity, opioids are classified as either\(^1\,4\):

- Agonists
- Partial agonists
- Mixed agonist-antagonists
- Complete antagonists.

Opioid agonists include compounds such as morphine, hydromorphone, or fentanyl that bind receptors with moderate to high affinity, and are capable of producing a maximal analgesic response. Partial agonists, such as buprenorphine, have high affinity at mu receptors but activate them incompletely. The analgesic efficacy curve of partial agonists is bell shaped, such that low doses provide increasing levels of analgesia to a point after which additional doses either do not increase pain relief or slightly diminish it.\(^1\,3\) This “analgesic ceiling effect” restricts their use to patients with mild to moderate pain (Figure 6.2). Antagonists such as naloxone and naltrexone bind to all receptor subtypes with high affinity but do not activate the receptor. Antagonists competitively block the activity of agonists by preventing or displacing their binding to the receptor.

Opioid analgesic onset is determined by the ability of an agonist to enter the CNS and distribute into grey matter where receptors are primarily localized.\(^1\,3\,5\) Opioid potency, or the amount of drug required to achieve an analgesic effect, is closely related to the lipophilicity and intrinsic efficacy of the agonist. As a rule, highly lipophilic opioids, such as fentanyl, have significantly greater potency than hydrophilic agents such as morphine.\(^1\,3\,5\,6\) Analgesic duration is related to several factors, including receptor dissociation kinetics, and both plasma and CSF elimination kinetics. Pharmacological correlates of opioid effects are presented in Table 6.1.

Tolerance and Hyperalgesia

Continued patient exposure to opioid analgesics leads to tolerance development and clinical manifestations, such as physical dependence. Tolerance is defined as the progressive increases in dose required to maintain a desired pharmacologic effect, and is characterized by a shift to the right in the classic dose-response curve.\(^1\,3\,7\,8\) This physiologic adaptation is observed in patients prescribed opioids for pain relief, as well as those abusing this class of drug. Physical dependence is a normal and commonly observed phenomenon in opioid-tolerant patients. Upon abrupt discontinuation of opioids, parasympathetic tone is markedly increased,\(^1\,2\,7\,8\) and patients experience unpleasant withdrawal symptoms including sweating, shaking, cramping, and diarrhea.

Psychological dependence includes drug-seeking behavior and use for purposes other than pain control. Addiction is a term describing an extreme form of psychological dependence where patients demonstrate craving, compulsive drug seeking, and continued use despite harm. Surgeons and their patients should recognize that unlike physical dependence, opioid addiction is rarely observed in patients suffering moderate to severe postsurgical pain.

A second clinical alteration observed in patients treated with opioids is termed “opioid-induced hyperalgesia” (OIH).\(^9\) This phenomenon is characterized by paradoxical increases in pain intensity and the development of new pain complaints in response to increasing administration of opioid analgesics. OIH is most often observed in tolerant patients but has also been observed in naive individuals. Excitatory effects of opioid metabolites (eg, morphine-3-glucoronide, hydromorphone-3-glucoronide) may also play a
role in the development and progression of OIH. Treatment of OIH includes discontinuation or dose reduction of the offending opioid, switching to a different agonist (opioid rotation) such as methadone, and use of adjuvants such as ketamine.9

**Parenteral Opioid Therapy**

Since oral analgesics are poorly tolerated during the immediate postoperative period, parenteral (IV, IM, and SC) opioids are commonly prescribed for surgical pain management. There are several situations where parenteral opioids may be employed:

- IV-PCA
- Nurse-administered IV bolus
- IV/IM opioids administered by the clock or PRN.

**Administration Using IV-PCA**

IV-PCA allows patients to titrate opioids in amounts necessary to reduce pain intensity to a tolerable level.10 Opioids commonly employed for IV-PCA include morphine and hydromorphone, with fentanyl reserved for highly tolerant or allergic patients. A loading dose of opioid is usually administered for immediate pain control prior to initiation of patient-initiated bolus doses. Bolus doses generally range from 1 mg to 1.5 mg for morphine or 0.2 mg to 0.3 mg for hydromorphone. A bolus lockout interval or minimum delay between doses is usually 6 to 8 minutes. A basal infusion equivalent to 1 bolus dose administered over a 1-hour interval may be provided to opioid-tolerant patients and others with very severe pain. Patients prefer PCA to parenteral analgesic techniques as it offers greater control for their pain management and that they do not have to worry about receiving too much or too little drug.11

PCA systems work under a number of assumptions, the first being that opioid side effects occur at higher CNS concentrations than those needed to produce analgesia.10 While extremely high opioid doses could theoretically eliminate all pain (but with unacceptable levels of respiratory depression), an adequate level of analgesia usually represents a compromise between tolerable pain and troublesome side effects. A second assumption is that pain intensity is rarely constant. Postoperative pain is intensified by movement and physical therapy, and seems to have a circadian rhythm with increasing pain at night.10,11 Night time pain is especially problematic as that is when adequate staffing may be limited and physicians are least available.

Two common reasons why patients become dissatisfied and fail with PCA include:

- Inadequate analgesia
- Excessive nausea/vomiting.

Patients must be trained to treat pain before the stimulus becomes overwhelming. For example, incremental boluses should be administered prior to physical therapy or any form of movement that might increase discomfort. They must also understand that PCA may never completely eliminate their pain, and that if side effects are experienced, they should ask for medication or call the nurse or pain service to reduce their dose. They should not stop using the PCA device and suffer in silence. Finally, concerned relatives should never push the PCA button for the patient!13

The safety and efficacy of IV-PCA requires motivated, alert, and well-informed patients, trained clinical and pharmacy staff, and specific order sets. Problems associated with IV-PCA include patient overuse of drug, and the fact that the infusion pump, IV lines, and power cables often interfere with patient mobility.10 To reduce these potential drawbacks, IV-PCA is generally reserved for patients who are NPO and restricted to the first 24 to 36 hours following surgery. Reduced-dose IV-PCA morphine (0.5 mg bolus dose) or hydromorphone (0.1 mg bolus dose) may be effective when employed with multimodal analgesic adjuvants or as a supplement for continuous regional nerve block or longer acting local anesthetic infiltration techniques.

**Nurse-Administered IV Bolus**

Nurse-administered IV bolus doses per patient request (PRN) are useful for individuals advancing from IV-PCA or epidural opioid-based analgesia who have moderate to severe discomfort but have yet to tolerate oral diets. Parenteral dosing is of particular importance in patients who are nauseous or vomiting, who might not absorb oral agents.

**IV/IM Opioids Administered by the Clock or PRN**

Several subsets of patients including the elderly, the cognitively impaired, and overly dependent individuals are poor candidates for IV-PCA and may achieve better pain control with IV/IM opioids administered by the clock or PRN.10,14 These patients might also benefit from non-opioid adjuvants. In these individuals, PRN requests and total parenteral dose administered during early postoperative intervals may be used to calculate follow-up oral analgesic dosing. Opioid-dependent patients with significant tolerance development may require both baseline chronic opioid therapy (eg, methadone, controlled-release oxycodone), as well as IV-PCA or parenteral opioid infusions for acute surgical pain.8

**Oral Analgesic Dosing**

Oral administration offers a convenient, noninvasive, and cost-effective method of controlling acute pain that should always be considered in patients who continue to experience moderate to severe discomfort. Oral opioids including morphine, hydrocodone, and
oxycodeone and compounded preparations containing acetaminophen, aspirin, and ibuprofen can provide effective relief, depending upon pain intensity levels and drug tolerability. Orally administered morphine and meperidine are poorly absorbed and undergo significant enterohepatic metabolism.\textsuperscript{1,2} When compared to parenteral dosing, onset is delayed, duration is less predictable and dose requirements are increased.

Short-acting oral opioids agents, such as morphine immediate release (IR), hydrocodone IR, hydromorphone IR, oxycodone IR, and oxymorphone IR may be favored initially because they are better tolerated and easier to titrate.\textsuperscript{2,14,15} Oxycodone and hydrocodeone are more reliably absorbed than morphine.\textsuperscript{14} These agents are best employed in opioid-naive patients recovering from uncomplicated procedures that require relatively limited durations of treatment.

Short-acting opioids are characterized by a rapid rise and fall in serum opioid levels, whereas serum levels of sustained-release opioids increase slowly to therapeutic levels, remain there for an extended period, then decline slowly.\textsuperscript{16} Opioid toxicity and adverse events are most likely to occur at these peak serum levels. Sustained-release opioid preparations, including morphine (MS-Contin), oxycodone (Oxycontin), and oxymorphone (Opana ER ), while not primarily indicated for surgical pain management offer several advantages, including less frequent administration intervals, avoidance of peak and trough plasma levels and greater analgesic uniformity.\textsuperscript{16,17} These preparations provide 8 to 12 hours of pain relief and are best suited for patients suffering chronic pain or prolonged postoperative pain.

An additional opioid preparation that may be considered for patients who cannot tolerate oral analgesics but continue to experience brief episodes of severe pain is the fentanyl oralet (Actiq and other generic equivalents). Fentanyl oralet releases between 100 mcg to 400 mcg of fentanyl within 15 minutes, with high bioavailability.\textsuperscript{18}

Less potent opioid analgesics, such as tramadol and codeine, may be prescribed to patients recovering from procedures associated with mild to moderate pain. A compounded form of tramadol (Ultracet) provides greater effectiveness than tramadol alone. Ultracet is an oral multimodal analgesic containing tramadol plus acetaminophen, approved for the short-term management of acute pain.\textsuperscript{19} A newer and more powerful “dual-acting” analgesic tapentadol (Nucynta) activates mu opioid receptors and also inhibits norepinephrine reuptake. Its analgesic efficacy is equivalent to oxycodone, however, it has a better tolerability profile, causing less nausea, vomiting, constipation and pruritus.\textsuperscript{20,21} Oral and parenteral opioids employed for surgical pain management are detailed in Chapter 14.

Neuraxial Opioids

Neuraxial administration of opioid analgesics into the spinal (intrathecal) or epidural space can provide powerful pain control in patients recovering from a variety of surgical procedures. Following spinal or epidural administration, opioid molecules traverse the CSF and bind to receptors in dorsal horn, effectively blocking pain transmission at the first synapse in the CNS. Epidural and spinaly administered opioids provide greater analgesic potency than similar doses administered parenterally.\textsuperscript{22,23} Morphine (Astamorph, Duramorph) was first to receive FDA approval for spinal use and remains the most widely used opioid for spinal analgesia.\textsuperscript{22} A single spinal dose (0.2 mg to 0.75 mg) is commonly utilized for control of pain following thoracic, abdominal, pelvic, and lower extremity surgery.\textsuperscript{22} In general, analgesic onset is appreciated after 30 to 60 minutes, peak effect at 90 to 120 minutes, and duration of effect is prolonged, ranging from 12 to 24 hours. Surgeons should understand that spinal morphine doses are only 1/10 to 1/20th of the 24-hour parenteral morphine dose while providing superior pain relief. In addition, spinal morphine is basically a single-dose technique and cannot match the duration and analgesic uniformity of continuous epidural opioid infusions.

Continuous epidural infusions and patient-controlled epidural analgesia (PCEA) offer high analgesic efficacy and patient satisfaction, with lower dose requirements than IV-PCA or IV boluses of parenteral opioids. Analgesic effects can be maintained for a prolonged period of time (24 to 96 hours) depending upon the site and invasiveness of the surgical procedure. Epidural doses of morphine are associated with a high incidence of pruritus and delayed-onset respiratory depression.\textsuperscript{22} Hydromorphone and fentanyl have become the epidural opioids of choice as they:

- Have rapid onset
- Can easily be titrated to analgesic effect
- Have greater tolerability and safety.\textsuperscript{23,26,27}

Epidural solutions of hydromorphone (10-20 mcg/mL) and fentanyl (5 mcg/mL) are generally infused at 6-16 mL/hour, depending upon the location of the epidural catheter and the number of dermatomes involved in the surgery.\textsuperscript{23,24,25,26} Infusions via thoracic epidural catheters are recommended for chest and upper abdominal procedure, while lumbar catheters may be used for pelvic and lower extremity surgeries. Patient controlled bolus doses of 2-4 mL every 6 to 10 minutes may be added to continuous epidural infusions to better control pain with procedures and movement. Finally, the effectiveness of epidural opioids may be further improved by the addition of dilute solutions of bupivacaine or ropivacaine.\textsuperscript{26,27} It should be recognized that the addition of local anesthetics often results in sensory/motor and sympathetic blockade and hypotension in volume-depleted patients. Agents and doses recommended for continuous epidural infusions and epidural PCA are outlined in Table 6.2.

Epidural- and spinal-administered opioids are associated with a number of annoying and occasionally serious adverse effects, including pruritus, nausea, urinary retention, somnolence, and respiratory depression.\textsuperscript{23,27} Pruritus and nausea are the most common
side effects associated with epidural or spinal opioids, however, respiratory depression is the most feared complication.\textsuperscript{23,27} Mild elevations in PaCO\textsubscript{2} are commonly observed with effective epidural analgesia; however, the incidence of clinically significant respiratory depression or arrest ranges between 0.1\% and 0.4\%.\textsuperscript{23} Morbidly obese patients and those with obstructive sleep apnea and chronic obstructive pulmonary disease are at highest risk for severe respiratory compromise.\textsuperscript{23,27} In addition to pulse oximetry, vigilant nursing observation and documentation of inadequate respiratory effort, slow respiratory rate, or unusual somnolence represent the best form of monitoring.\textsuperscript{23,27} Prophylactic naloxone infusions (400 ug/L) at 100-125 mL/hour have been advocated to reduce the risk of opioid-induced respiratory depression in elderly or debilitated patients while maintaining effective analgesia.\textsuperscript{23,27} Naloxone infusions effectively reduce the incidence and severity of other adverse effects, including pruritus, nausea, and urinary retention.

Contraindications to spinal opioid analgesia include spinal fracture, infection at the insertion site, sepsis, coagulopathy, and treatment with low-molecular weight heparinoids. Concern has been raised about the safety of using anticoagulant-based prophylaxis of deep venous thrombosis (DVT) with regional anesthesia in patients undergoing surgery.\textsuperscript{28} In December 1997, the FDA issued an advisory letter about the potential risk of epidural hematoma in patients receiving regional (spinal or epidural) anesthesia and low molecular weight heparin (LMWH). The American Society of Regional Anesthesia (ASRA) issued guidelines with respect to the safe use of anticoagulants in patients to be treated with neuraxial analgesia.\textsuperscript{29} The use of LMWH with spinal and epidural analgesia is safe as long as published guidelines and recommendations from experienced clinical authorities are observed.

Opioid-Related Adverse Events

In settings of acute pain, most opioid-related adverse events (AEs) are transient and tend to resolve with ongoing treatment.\textsuperscript{1,3} Common AEs associated with parenteral and orally administered opioids and their active metabolites include nausea, vomiting, sedation, pruritus, and constipation.\textsuperscript{30} In sensitive individuals, the incidence and severity of these AEs may be so annoying and distressing that patients self-limit or discontinue opioid dosing and suffer poor pain control.\textsuperscript{30,31} Patients recovering from colorectal and gynecologic surgery are generally at risk for opioid-induced bowel dysfunction and ileus, mandating that such therapy be supplemented with stool softeners, bulk laxatives, and occasional enemas.

Most opioid-related AEs are dose dependent, which is why it is important to initiate therapy with the lowest effective dose and to utilize a multimodal analgesic approach. Some opioid-related AEs are often treated symptomatically, eg, prescribing an antiemetic for nausea or laxatives and/or a peripheral mu antagonist for constipation.\textsuperscript{1,3,31} Other side effects, such as sedation and pruritus, are typically addressed by decreasing the opioid dose rather than by treating the symptom. In addition to dose reductions, other strategies that can be employed to minimize opioid-related AEs include changing the route of administration, switching to a different opioid, or providing adjuvant analgesic therapy.\textsuperscript{31}

Variability in Opioid Response

Opioids tend to have a highly variable response in individual patients. A therapeutic failure with one opioid agonist does not necessarily mean that the patient will fail to respond to others. Pharmacokinetic and pharmacodynamic variables and other interindividual genetic variations can result in clinically measurable differences in analgesic efficacy and adverse effect profile between opioid agonists.\textsuperscript{32,33} (Table 6.3). The concept of incomplete cross tolerance describes the unexpectedly improved effectiveness or tolerability of a newly prescribed agonist when compared with equivalent doses of others that the patient has found unacceptable. In recent years, over 20 polymorphisms of the \textmu opioid receptor gene (OPRM1) have been identified.\textsuperscript{34} In a clinical trial that evaluated patients with opioid receptor polymorphisms of gene 118, those homozygous for allele GG self-administered significantly more morphine and incurred more AEs during the first 48 hours following knee surgery than those homozygous for the AA allele (homozygous AA 25 mg, heterozygous AG 26 mg, homozygous GG 40 mg).\textsuperscript{35}

Conclusion

Opioids will continue to play a major role in postsurgical pain management for the considerable future. Existing parenteral and oral analgesics offer effective pain relief, however, no agonist can provide the optimal combination of high efficacy and low side effect profile for all patients. For the near term, novel delivery systems for existing opioids and the ongoing development of dual-acting compounds will provide new tools to help facilitate surgeon- and anesthesiologist-based pain management. Increasing knowledge regarding opioid receptor polymorphisms may permit patients to be screened and treatment plans developed preoperatively, thereby insuring that the optimal agonist can be administered perioperatively.

REFERENCES


Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology.* 2006;104(3):570-587.


**TABLE 6.1 — Pharmacological Correlates of Opioid Activity**

**Potency**
- High lipid solubility

**Onset**
- Low degree of ionization
- High CNS penetration
High receptor affinity

Duration
- High water solubility (CSF trapping)
- High receptor binding kinetics
- Low hepatic/renal clearance
- Active metabolites
- Large volume of distribution

Safety
- Mu receptor specificity
- Lack of active or toxic metabolites

Efficacy
- Multiple receptor specificity
- High receptor affinity
- High intrinsic efficacy

### TABLE 6.2 — Dosing Guidelines for Epidural Opioid Infusions and PCEA

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Site of Administration</th>
<th>Continuous Infusion Technique</th>
<th>PCA Technique</th>
<th>Adjunctive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Lumbar catheters:</td>
<td>2-4 mg bolus followed by infusion (40 mcg/mL);</td>
<td>Lumbar catheters:</td>
<td>IV ketorolac or ibuprofen, oral celecoxib, IV-</td>
</tr>
<tr>
<td></td>
<td>incisions below T8</td>
<td>Lumbar catheters: 6-12 mL/h</td>
<td>6-8 mL/h</td>
<td>APAP; add epidural bupivacaine (0.05%-0.1%)</td>
</tr>
<tr>
<td></td>
<td>Thoracic catheters:</td>
<td>Thoracic catheters: 4-8 mL/h</td>
<td>Thoracic catheters:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>upper abdominal and</td>
<td></td>
<td>2-6 mL/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>thoracic surgery</td>
<td></td>
<td>PCEA bolus dose 1-2 mL q15min</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Hydromorphone</td>
<td>Lumbar catheters:</td>
<td>0.5-1.5 mg bolus followed by infusion (10-20 mcg/mL);</td>
<td>Lumbar catheters:</td>
<td>IV ketorolac or ibuprofen, oral celecoxib, IV-</td>
</tr>
<tr>
<td></td>
<td>incisions below T10</td>
<td>Lumbar catheters: 8-14 mL/h</td>
<td>6-10 mL/h</td>
<td>APAP; add epidural bupivacaine (0.05%-0.1%)</td>
</tr>
<tr>
<td></td>
<td>Thoracic catheters:</td>
<td>Thoracic catheters: 4-8 mL/h</td>
<td>Thoracic catheters:</td>
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<td></td>
<td>upper abdominal and</td>
<td></td>
<td>4-6 mL/h</td>
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<tr>
<td></td>
<td>thoracic surgery</td>
<td></td>
<td>PCEA bolus dose 1-2 mL q65min</td>
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<tr>
<td>Fentanyl</td>
<td>Lumbar catheters:</td>
<td>50-100 mcg bolus followed by infusion (4 mcg/mL);</td>
<td>Lumbar catheters:</td>
<td>IV ketorolac or ibuprofen, oral celecoxib, IV-</td>
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<td></td>
<td>incisions below T12</td>
<td>Lumbar catheters: 8-14 mL/h</td>
<td>6-10 mL/h</td>
<td>APAP; add epidural bupivacaine (0.05%-0.1%)</td>
</tr>
<tr>
<td></td>
<td>Thoracic catheters:</td>
<td>Thoracic catheters: 4-8 mL/h</td>
<td>Thoracic catheters:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>almost everything else</td>
<td></td>
<td>4-6 mL/h</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>PCEA bolus dose 1-3 mL q6min</td>
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</tr>
</tbody>
</table>

- Dependent on age, physique status, height, extent of surgical dissection, degree of opioid tolerance, and so on.
- Unless contraindicated.

### TABLE 6.3 — Patient Variability in Opioid Response

- Mu-opioid receptor polymorphisms
- Opioid tolerance
- Genetic alterations in opioid metabolism (CYP450)
- Incomplete cross-tolerance
- Extremes in patient age
- Exposure to drugs that compete for metabolic enzymes
- Exposure to drugs that increase CNS depression
- Patient comorbidity (hepatic failure, CNS lesions, renal failure)

### FIGURE 6.1 — Classification of Naturally Occurring, Semisynthetic, and True Synthetic Opioid Families
FIGURE 6.2 — Opioid Dose-Response Curves

These curves illustrate the potency and efficacy of various opioid analgesics. Potent agonists, such as fentanyl, require the lowest dose to achieve the maximal analgesic effect. Morphine achieves the maximal effect but requires a considerably greater number of molecules to be administered. Mixed agonist antagonists and partial agonists such as buprenorphine are either more or less potent than morphine; however, they cannot achieve the maximal effect despite increases in dose. This ceiling effect in analgesic efficacy limits their ability to control moderate to severe pain. The antagonist naloxone has no analgesic efficacy.