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Evidence-Based Use of Nonopioid Analgesics

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Analgesia is a necessary component of any anesthetic technique, and can be achieved with local anesthetics, opioid and nonopioid analgesics, and inhaled anesthetic agents. Risks and benefits are associated with each of the agents and techniques described here, including local anesthetic systemic toxicity, respiratory depression, nausea, and urinary retention. Implementation of Enhanced Recovery After Surgery (ERAS) protocols, use of preemptive analgesia techniques, and the national opioid crisis are fostering increased utilization of nonopioid analgesics, including local anesthetics, nonsteroidal anti-inflammatory medications, intravenous acetaminophen, neuromodulatory agents such as gabapentin, corticosteroids, centrally acting α2 agonists, and ketamine. Certified Registered Nurse Anesthetists optimize the safety and quality of care they provide through use of evidence-based practice, including the drugs they select, order, and administer, such as opioid and nonopioid analgesics, when providing anesthesia care.

Keywords: Analgesia, nonopioids, opioids.

Objectives
At the completion of this course the reader should be able to:
1. Describe the risks and benefits of opioid analgesics.
2. Review nonopioid analgesics in terms of mechanisms of action, doses, risks, and benefits.
3. Discuss the impact of Enhanced Recovery After Surgery protocols on pain management.
4. Identify the impact of the opioid crisis on selecting, ordering, and administering opioid agonists.
5. List the mechanisms of action for psychotropic and anticonvulsant agents used as analgesic adjuncts.

Introduction
Opioids suppress pain through their actions in the brain, spinal cord, and peripheral nervous system. Appropriate titration and monitoring of opioids attenuate many of the adverse effects of these drugs. Opioids are central to the analgesic aspect of anesthesia, notably when total intravenous (IV) anesthesia is used. The common acute clinical effects of opioid agonists are discussed in this section and in Table 1. Common chronic effects of opioids include tolerance, physical dependence, and constipation.

Opioids have effects on the major body systems, including the central nervous system (CNS), where varying degrees of analgesia, sedation, and euphoria are associated with these drugs. Opioids produce analgesia through direct inhibition of ascending transmission of nociception from the dorsal horn of the spinal cord and activation of descending pain control pathways from the midbrain via the rostral ventromedial medulla to the spinal cord and dorsal horn. Opioids can have sedative and euphoric effects that vary according to the involved agent, with µ agonists such as morphine producing greater sedation and euphoria and κ agonists like butorphanol producing dysphoria.

In healthy patients, when opioids are included in an anesthetic regimen, bradycardia resulting from medullary vagal stimulation occurs, with little effect on blood pressure. Dose-dependent peripheral vasodilation is associated with opioids, but myocardial contractility, baroreceptor function, and autonomic responsiveness are not affected. Cough suppression results from the depressant effects of opiates on the cough center in the medulla. In the context of anesthesia and critical care, opioids help patients tolerate breathing devices and mechanical ventilation.

Benefits of Opioid Analgesics
The term balanced anesthesia was first used in 1926, meaning that a combination of anesthetic agents and techniques could be used to produce the components of anesthesia, including analgesia, amnesia, muscle relaxation, and ablation of autonomic reflexes. Use of an opioid as a component of balanced anesthesia attenuates...
pain and anxiety, decreases hemodynamic responses to airway instrumentation, lowers minimal alveolar concentration requirements for inhaled anesthetics, and provides postoperative analgesia. The synergy between opioids and induction agents reduces the dose requirement for induction agents.\textsuperscript{4,6}

Lowenstein et al\textsuperscript{7} demonstrated in 1969 that opioid-based anesthesia using morphine, 0.5 to 3 mg/kg, could be used safely in patients with minimal cardiac reserve undergoing open heart surgery. Hemodynamic stability can now be achieved with myriad drugs and anesthetic regimens, with opioids, including fentanyl and its analogs, remaining key components of anesthesia care.\textsuperscript{4} Alfentanil and remifentanil allow rapid titration because of the 1- to 2-minute onset to peak effect times, and narcotic antagonists are seldom needed after remifentanil administration.\textsuperscript{1}

Opioids are associated with prevention of myocardial ischemia through $\delta$ and $\kappa$ receptor agonism, enhancing myocardial resistance to oxidative and ischemic stressors. Mitochondrial adenosine triphosphate (ATP)-regulated potassium channels ($K_{\text{ATP}}$) may be pivotal in this signaling pathway.\textsuperscript{8}

### Drawbacks of Opioid Analgesics

Morphine, even in the large doses described earlier, is unlikely to cause direct myocardial depression. However, changing from a supine to a standing position in a patient medicated with morphine can result in orthostatic hypotension and syncope related to altered sympathetic nervous system compensatory responses due to venous pooling.\textsuperscript{9} Decreased blood pressure due to bradycardia and histamine release are known morphine side effects than can be attenuated by not administering greater than 5 mg/min of morphine, having the patient maintain the supine position, and providing adequate hydration.\textsuperscript{10}

Opioid agonists produce respiratory depression that is dose-related through $\mu_2$ receptor agonism resulting in depression of brainstem ventilation centers.\textsuperscript{11} Respiratory depression related to opioids is rapid and persists for several hours, as evidenced by decreased ventilatory responses to carbon dioxide. Death due to opioid overdose typically results from ventilatory depression.\textsuperscript{12}

Sedation typically precedes analgesia with morphine. A suggested interval of 5 to 7 minutes between morphine doses permits evaluation of the clinical effects of this drug. The sedation associated with morphine should not be construed as adequate analgesia.\textsuperscript{12}

Opioids provoke nausea and vomiting through stimulation of the chemoreceptor trigger zone in the medullary area postrema. Vestibular components may also contribute to postoperative nausea and vomiting, since this occurs more frequently in ambulatory surgical patients. Postoperative nausea and vomiting are more frequent when opioids are included in anesthetic management.\textsuperscript{13}

<table>
<thead>
<tr>
<th>Acute effect</th>
<th>Chronic effect</th>
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<td>Tolerance</td>
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<td>Respiratory depression</td>
<td>Physical dependence</td>
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<td>Sedation</td>
<td>Constipation</td>
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<td>Euphoria</td>
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<td>Dysphoria</td>
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<td>Vasodilation</td>
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<td>Cough suppression</td>
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<td>Miosis</td>
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<td>Pruritis, rash</td>
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<td>Antishivering (meperidine)</td>
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<td>Histamine release</td>
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<td>Hormonal effects</td>
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Table 1. Common Clinical Effects of Opioid Agonists

When large doses of fentanyl and its analogs are administered rapidly, generalized skeletal muscle rigidity that interferes with ventilation can result. This increased skeletal muscle tone is likely related to decreased striatal $\gamma$-aminobutyric acid (GABA) release and increased dopamine release and can be offset by muscle relaxants or opioid antagonists.\textsuperscript{14} This phenomenon is described as being uncommon in one article, with the authors noting that “this complication is better described in pediatric patients” with anesthetic doses of fentanyl and other opiates. Chest wall rigidity can occur with analgesic doses of fentanyl and its analogs. Management includes ventilatory support and reversal with naloxone or administration of a neuromuscular blocking agent.\textsuperscript{15}

Opioids can result in itching, rash, and a feeling of warmth in the face, arms, and upper aspect of the chest. This occurs with histamine as well as nonhistamine-releasing drugs and occurs more frequently with neuraxial opioids, likely because of activation of central $\mu$ receptors.\textsuperscript{16} Narcotic antagonists like naloxone and naltrexone may be used to treat pruritis at the expense of decreased analgesia. Nalbuphine, droperidol, antihistamines, and ondansetron can also be used to treat pruritis associated with opioids.\textsuperscript{17}

Opioids decrease gastric motility and peristalsis, prolonging gastric emptying time and reducing secretions throughout the gastrointestinal (GI) tract. This produces opioid-induced constipation and postoperative ileus. Opioid-induced constipation does not lessen over the
course of long-term opioid treatment. Peripherally acting μ opioid receptor antagonists, including methylnaltrexone, naloxegol, and alvimopan improve bowel symptoms without compromising opioid analgesic effects. The potential side effects of these drugs include abdominal pain.\textsuperscript{18}

Dose-dependent increases in biliary duct pressure and sphincter of Oddi tone are produced by opioid receptor-mediated mechanisms. Opioids also increase urinary sphincter tone.\textsuperscript{2}

Although opioids blunt the surgical stress response, these drugs also have immunosuppressant effects. Opioids inhibit natural killer cell function and stimulate cancer cell proliferation because of their effects on angiogenesis and tumor cell signaling pathways.\textsuperscript{19} Use of nonopioid analgesics may help offset these risks in scenarios involving immunocompromise or cancer.

Nonopioid Mechanisms of Analgesia

The Certified Registered Nurse Anesthetist (CRNA) has a robust arsenal of nonopioid analgesic drugs from which to choose, depending on the individual patient's history and needs (Table 2). Acetaminophen is a well-characterized nonopioid analgesic drug, often chosen because of its benign effect on gastric mucosa and platelet function, although it is known to have no ameliorating effect on inflammation.\textsuperscript{20} The exact mechanism of action of acetaminophen remains unclear, although some investigations have suggested the drug has a weak effect on cyclooxygenase 1 (COX-1) and COX-2 gene expression. The IV form of acetaminophen, marketed as Ofirmev, is given over 30 minutes at a dose of 1,000 mg every 6 hours for children and adults weighing more than 50 kg, and 15 mg/kg every 6 hours for children 2 to 12 years of age and adults and adolescents weighing less than 50 kg.\textsuperscript{21} Clinical investigation has shown the parenteral form of acetaminophen to have a powerful analgesic opioid-sparing effect, presumably due, at least in part, to the lack of a first-pass liver effect.\textsuperscript{22} The side effects of acetaminophen can include allergic reaction and liver toxicity. Indeed, it is important to inform the patient and postoperative care team members of acetaminophen administration, to prevent overdose.

Ketamine is a dissociative anesthetic agent with profound analgesic effects due to noncompetitive inhibition of N-methyl-d-aspartate receptors in the CNS.\textsuperscript{23} Ketamine use for nonopioid analgesia has been revived in recent years because of the drug's efficacy and lack of opioid-related side effects, and its utility when used for opioid-dependent chronic pain patients.\textsuperscript{24} Ketamine doses for analgesia vary depending on the patient and clinical situation, and in one clinical investigation of opioid-dependent patients undergoing back surgery, patients received 0.5 mg/kg of ketamine on induction, followed by an infusion of 10 μg/kg/min started before incision and terminated on skin closure.\textsuperscript{24} Patients who received ketamine required 37% less morphine and reported less pain at 6-week postoperative follow-up. Side effects include increased oral secretions, tachycardia and hypertension, vivid and unpleasant dreams, and increases in intracranial pressure.

Dexamethasone is a glucocorticoid steroid drug, which is a fluorinated derivative of prednisolone.\textsuperscript{25} Used traditionally for its anti-inflammatory effects on such conditions as airway inflammation and cerebral edema, this glucocorticoid drug is being increasingly used for its systemic analgesic effect\textsuperscript{23,25} and for its ability to prolong peripheral neural blockade when administered parenterally or as a component of the local anesthetic solution.\textsuperscript{26} Doses vary widely depending on the intended effect, route of administration, and clinical situation, with 8 mg intravenously having been reported to have a systemic analgesic effect, and a similar dose combined with local

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<th>Drug classification</th>
<th>Mechanism</th>
<th>Example</th>
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<tr>
<td>MOR agonists</td>
<td>Stimulate central and peripheral MOR, produce analgesia</td>
<td>Morphine, hydromorphone, fentanyl</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>Block sodium channels peripherally; depress CNS</td>
<td>Lidocaine, bupivacaine, ropivacaine</td>
</tr>
<tr>
<td>Anticonvulsants (adjuvant drug)</td>
<td>Block spinal cord voltage-dependent calcium channels</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Antianxiety (adjuvant drug)</td>
<td>Inhibit reuptake of norepinephrine and serotonin at descending inhibitory fiber synapses</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>NMDA antagonists</td>
<td>Block NMDA receptors</td>
<td>Ketamine</td>
</tr>
<tr>
<td>Alpha-2 agonists</td>
<td>Block nerve cord α\textsubscript{2} receptors</td>
<td>Dexametomidine, clonidine</td>
</tr>
<tr>
<td>COX inhibitors/NSAIDs</td>
<td>Block COX-1 and/or COX-2 enzymes, inhibiting PGE production</td>
<td>Ibuprofen, ketorolac, naproxen</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Block phospholipase A\textsubscript{2}</td>
<td>Dexamethasone</td>
</tr>
</tbody>
</table>

Table 2. Analgesic Drug Classes and Mechanisms of Effect

Abbreviations: CNS, central nervous system; COX, cyclooxygenase; MOR, μ (mu) opioid receptors; NMDA, N-methyl-d-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs; PGE, prostaglandin E.
Topical 5% lidocaine has been used to successfully treat postherpetic neuralgia and painful neuropathies as well as postsurgical pain. Some formulations of topical diclofenac and ketoprofen provide effective analgesia for sprains and strains but are less effective than topical lidocaine in treating chronic pain such as that associated with osteoarthritis. Adverse effects observed with topical lidocaine in treating chronic pain such as that associated with osteoarthritis, myalgias, arthralgias, and neuralgias. This compound is a transient receptor potential vanilloid (TRPV1) cation channel agonist. In inflammatory conditions, TRPV1 receptor sensitivity is increased; TRPV1 receptors are found on unmyelinated peripheral C-fiber endings. Activation of the TRPV receptor results in the release of high-intensity impulses and substance P, which causes burning. Ongoing release of substance P as a result of capsaicin exposure results in decreased C-fiber activation. Topical capsaicin lacks efficacy with treatment of musculoskeletal and neuropathic pain.

Capsaicin, a major component of chili peppers, is sold over the counter for temporary relief of pain related to arthritis, myalgias, arthralgias, and neuralgias. This compound is a transient receptor potential vanilloid (TRPV1) cation channel agonist. In inflammatory conditions, TRPV1 receptor sensitivity is increased; TRPV1 receptors are found on unmyelinated peripheral C-fiber endings. Activation of the TRPV receptor results in the release of high-intensity impulses and substance P, which causes burning. Ongoing release of substance P as a result of capsaicin exposure results in decreased C-fiber activation.
The NSAIDs may enhance bleeding when given with anticoagulants or antiplatelet drugs, may decrease the efficacy of angiotensin-converting enzyme inhibitor antihypertensive drugs, may decrease diuretic effects, and increase serum digoxin concentrations.43,44

A wide variety of psychotropic medications are used in managing chronic pain, and increasingly acute pain with limited evidence of efficacy, and a brief review of selected examples follows. These medications include antidepressants such as amitriptyline, desipramine, imipramine, and nortriptyline. The suggested mechanism of effect is decreased reuptake of the neurotransmitters norepinephrine and serotonin in descending inhibitory pain-modulating pathways. Major side effects include sedation; altered cardiac conduction; and anticholinergic phenomena, such as dry mouth and difficulty urinating. Anticonvulsant drugs such as carbamazepine are also used in chronic pain management, blocking pain impulses by sodium channel blockade, but use is limited by side effects including sedation, ataxia, blood dyscrasias, nausea, and vomiting. Newer anticonvulsants such as gabapentin are also used, with a less severe side effect profile. Onset of effect is slow and variable (may take weeks), and dosing varies widely depending on patient and clinical factors.45

The Opioid Crisis and Opioid Prescriptions
The Centers for Disease Control and Prevention notes that the United States “is in the midst of an opioid overdose epidemic.”46 Prescription opioids as well as heroin killed more than 33,000 people in 2015, the highest recorded number of such fatalities. Prescription opioids are involved in almost half of opioid overdose deaths.46

Suggested steps to improve opioid prescription patterns, enhance addiction treatment, and limit access to illegal opioids include the following:

- Improve opioid prescribing to limit opioid exposure, prevent abuse, and stop addiction.
- Expand access to medication-assisted treatment, an evidence-based treatment program, for people dealing with opioid addiction.
- Increase access to and use of naloxone for first responders and family members.
- Use of state prescription drug monitoring programs, to provide information needed for safe prescribing practices.46

The judicious use of opioids in anesthesia care, combined with the integration of nonopioid adjunctive drugs, may help ameliorate concerns related to the amount of perioperative opioids administered. Enhanced Recovery After Surgery protocols judiciously balance the use of anesthetic agents and techniques to achieve optimal patient outcomes.

Enhanced Recovery After Surgery protocols are lists of multimodal, multidisciplinary actions recommended to anesthesia and surgery teams with the goal of decreasing time spent as an inpatient following major surgery. Such approaches are growing swiftly in popularity since being introduced in recent years because of their cost-effectiveness in reducing the economic burden on patients and institutions, and are supported through research, program development, and institutional implementation by such nonprofit national organizations as the American Society of Enhanced Recovery (ASER) and the ERAS Society, an international professional organization. Typically, ERAS perioperative approaches contain some combination of the following elements: minimally invasive surgical approaches that avoid large incisions; carbohydrate drinks 2 hours before incision; careful fluid titration to avoid overhydration; avoidance of nasogastric tubes, wound drains, and early removal if indicated; and early mobilization. From its inception, ERAS has incorporated anesthetic technique and pain management approaches as central to achieving the goal of early ambulation and discharge.47

Regional anesthesia is employed, which may involve neuraxial approaches such as combined spinal and epidural, or epidural anesthesia with catheter placement for postoperative analgesia. In general, the thoracic spine level of epidural catheter insertion depends on the location of the planned surgery, with an upper T-spine placement (approximately T6-T7) for thoracic surgery; midthoracic placement for thoraco-abdominal and upper abdominal procedures (approximately T7-T9); and lower T-spine placement for lower abdominal surgeries. Typically, postoperative analgesia is maintained for approximately 48 hours with infusions of dilute local anesthetics (usually bupivacaine or ropivacaine) in combination with a low concentration of a hydrophilic or lipophilic opioid at several milliliters per hour, with boluses for breakthrough pain, and titrated to patient comfort. Benefits include early ambulation and effective pulmonary hygiene, and reduced incidence of postoperative ileus. Side effects, although rare, can be bothersome and require an educated staff to prevent, treat, and deal. Local anesthetics can cause sympathetic, sensory, and motor block, and epidural opioids can cause urinary retention, pruritis, nausea, and vomiting.46 In general, epidural analgesia is used effectively in ERAS protocols for major urologic, orthopedic, and other surgeries.

Conclusion
In the past, opioids were regarded as the first-line and most effective and safest treatment of painful injuries, syndromes, and surgeries. Now that the limitations and side effects of opioid drug therapy have been recognized and with the onset of the devastating opioid overdose epidemic, it is clear that a paradigm shift in the treatment of pain is imperative. Clinical scientists have begun making progress in presenting anesthesia providers with an ever-
increasing range of pain treatment options, including nonopioid analgesic drugs and neural block procedures. As the treatment of pain continues to evolve and increasingly includes nonopioid approaches, it is essential that CRNAs remain abreast of these developments so that we may continue to offer the safest and most efficacious treatment modalities to our patients.

REFERENCES
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DISCLOSURES
The authors have declared no financial relationships with any commercial entity related to the content of this article. The authors did discuss off-label use within the article.