Pharmacology of Analgesics: Clinical Considerations

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Continuing Education Units: 3 hours


Disclaimer: Participants must always be aware of the hazards of using limited knowledge in integrating new techniques or procedures into their practice. Only sound evidence-based dentistry should be used in patient therapy.

Participants in this course will be introduced to evidence-based information related to the basic mechanisms of pain, the pharmacology of analgesics, and the rationale for the selection of an analgesic for the treatment of acute odontogenic pain.

Conflict of Interest Disclosure Statement
• Dr. Aminoshariae reports no conflicts of interest associated with this work.
• Dr. Terézhalmy has done consulting work for Procter & Gamble and is a member of the dentalcare.com Advisory Board.

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Overview
Participants in this course will be introduced to evidence-based information related to the basic mechanisms of pain, the pharmacology of analgesics, and the rationale for the selection of an analgesic for the treatment of acute odontogenic pain.

Learning Objectives
Upon completion of this course, the dental professional should be able to:
• Discuss the physiology of pain
• Discuss the pharmacology of analgesics
• Given a patient with pain, prescribe the most appropriate analgesic
• Discuss potential adverse drug events associated with the use of analgesics

Course Contents
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Introduction
The most common complaint causing a person to seek the services of an oral healthcare provider is pain. Pain is a sensory and emotional experience associated with actual or potential tissue damage and underlies most quality of life issues. It is estimated that in the United States approximately 12% of the population suffers from odontalgia. It is also a matter of record that in 2006 the primary diagnostic codes for 403,149 emergency department visits to U.S. hospitals were for pulpal and periapical diseases. The average age of patients was 32.9 years, the mean hospital charge per emergency visits was $480, and total charges for all emergency visits were $163,692,957.

Pain is the consequence of a complex series of neuronal, inflammatory, immunologic, vascular, and morphologic responses to tissue injury. Since tissue damage, associated with trauma and inflammation, is the quintessential stimulus for odontogenic pain, the primary obligation and ultimate responsibility of every oral healthcare provider is to exercise a degree of skill, care, and judgment that will promote optimal healing of diseased tissues and relieve pain. This requires an understanding of the complexity of pain, an appreciation for the factors that determine its expression in the clinical setting, the initiation of disease-modifying procedures, and the implementation of sound pharmacological strategies.

Physiology of Pain
Stimulatory Regulation of Nociceptive Pain
Nociception is the sensory detection, transduction, and neural transmission of noxious stimuli, which affect “high-threshold” primary afferent sensory neurons called nociceptors located in superficial soma (skin, mucosa), deep soma (muscles, bone) and viscera (organs). Nociceptors require intense, actually or potentially tissue damaging stimuli to depolarize their terminals. Intense mechanical stimuli activate mechanoreceptors. Some thermal nociceptors may be activated by cold, while others respond to heat. However, chemical activators (e.g., protons, ATP, bradykinin), which directly excite primary afferent sensory neurons, are the most important stimuli.
Other chemicals, known as sensitizing agents (e.g., prostaglandin E2), increase the sensitivity of nociceptors to chemical activators.\textsuperscript{15}

Protons, from low extracellular pH associated with ischemia and inflammation, activate acid sensitive ions channels (ASICs) and transient receptor potential vanilloid ion channels (TRPV1, TRPV2), which may also be activated by noxious heat. High extracellular ATP levels associated with cell injury activate P2X ligand-gated channels and P2Y Gs-protein-coupled receptors. Bradykinins, associated with tissue damage and inflammation, activate Gs-protein-coupled bradykinin B1 and B2 receptors.\textsuperscript{16} B1 receptors are expressed in response to bacterial lipopolysaccharides and inflammatory cytokines.\textsuperscript{17,18} B2 receptors are expressed constitutionally in neurons and their activation promotes the synthesis of prostaglandin E2 (PGE2), the prototypical sensitizing agent.

Activation of peripheral sensory terminals by noxious stimuli leads to intracellular sodium and calcium ion influx and neuronal depolarization (Figure 1). The generator potential or membrane depolarization induced by noiceptive signals leads to action potential production if the threshold for activation of voltage-sensitive sodium channels is reached. There are six types of voltage-gated sodium channels, of which four are expressed uniquely in primary afferent sensory fibers and two of these only respond to high-threshold peripheral stimuli.

In the trigeminal-spinal complex, incoming action potentials activate pre-synaptic voltage-sensitive calcium channels, which lead to calcium influx, synaptic release of glutamate, and subsequent action potential generation in secondary neurons (Figure 2). Secondary afferent neurons travel in the lateral areas of the spinal cord and project to the thalamus where they synapse with tertiary afferent neurons. Tertiary afferent neurons project to various regions of the brain including the somatosensory cortex, responsible for the localization of pain; and the limbic system, responsible for the emotional aspects of pain.\textsuperscript{19,20}

Afferent sensory neurons can be classified into three principal categories: group A, B, and C. Group A is further subdivided into A-alpha (α), A-beta (β), A-gamma (γ), and A-delta (δ) fibers. Group A and B fibers are myelinated. Group C fibers are nonmyelinated. Nociceptive information is conducted by A-δ and C fibers. Information via A-δ fibers arrives rapidly; it is perceived as sharp, bright, well-localized pain, which is not particularly persistent, but it is immediately associated with tissue injury (first pain). Information via C fibers arrives slowly; it is perceived as dull, throbbing, burning, diffusely localizable pain, which has a persistent quality (second pain).

**Inhibitory Regulation of Nociceptive Pain**

Depolarization of primary afferent sensory neurons of sufficient intensity leads to action potential production and signal generation in secondary

\begin{figure}
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\includegraphics[width=\textwidth]{figure1.png}
\caption{Activation of peripheral sensory terminals.}
\end{figure}
and, ultimately, tertiary neurons. Synaptic transmission is regulated by the actions of both local inhibitory interneurons and efferent projections from the brainstem. The major inhibitory neurotransmitters relevant to this discussion are opioid peptides, norepinephrine, serotonin (5-HT), and endogenous cannabinoids.

**Opioid Peptides**
In painful inflammatory conditions opioid receptors on peripheral sensory fibers are up-regulated and resident immune cells express their endogenous opioid peptides.\(^{21-23}\) Opioid receptor activation on peripheral terminals inhibits activation of primary afferent neurons. In the trigeminal ganglion, opioid peptides inhibit the release of presynaptic vesicles from primary afferent neurons. In the mid-brain, they increase descending inhibitory activity to the trigeminal nucleus and spinal cord; and, in the brain, opioid peptides alter mood, produce sedation, and reduce the emotional reaction to pain.

**Norepinephrine and Serotonin 5-HT**
Norepinephrine is released by descending projections from the brainstem to the spinal cord. Activation of α2-adrenergic Gi-protein-coupled receptors, which are expressed both presynaptically and postsynaptically, reduces presynaptic vesicle release and decreases postsynaptic neuronal excitation. Serotonin is also released by projections that descend from the brainstem to the spinal cord. Serotonergic Gi-protein-coupled receptors, which are also expressed both presynaptically and postsynaptically, appear to mediate the inhibitory actions of serotonin.

**Endogenous Cannabinoids**
There are two cannabinoid G-protein-coupled receptors: CB1 and CB2. CB1 is expressed in sensory neurons, the spinal cord, and the brain. CB2 receptors are expressed predominantly in immune cells; but in pathological pain states, they may be upregulated in the central nervous system (CNS) and the trigeminal or dorsal root ganglia.\(^{24}\) Anandamide and 2-arachidonylglycerol, two endogenous cannabinoids, appear to modulate pain at peripheral afferent sensory fibers and in the spinal cord; and in the periaqueductal grey they appear to modulate efferent inhibitory projections.\(^{25,26}\)

**Role of the Higher Central Nervous System in Nociceptive Pain**
The term perception (attention and cognition), when applied to pain, refers to the awareness of a noxious sensation, appreciation of negative emotions, interpretation, and attribution of meaning to the experience. While patients are surprisingly uniform in their perception of pain, they differ greatly in their reaction to it. Attention and cognition, along with cultural, emotional, and motivational differences, will alter or modulate the intensity of a patient’s response to noxious stimuli.

**Attention**
Attention is largely under conscious control. The patient experiencing pain has a choice: attend to the noxious sensations or attend to signals that can exclude pain perception from conscious awareness. Manipulation of attention for pain control has been used with varying degrees of success. For example, most hypnotic procedures involve the redirection of attention away from
pain; breathing exercises use attentional control to suppress the pain of natural childbirth; and music used during dental procedures requires that the patient concentrate on the music.

Cognition
Cognitive processes include memory, discrimination, and judgment; the matching of present circumstances against expectations; and the attribution of meaning to the experience. Nociceptive afferent activity may affect cognition differently from patient-to-patient and, at different times, even within the same patient if the thought processes associated with the experience are different. Patients in pain also tend to behave in ways congruent with their cultural heritage. Clearly, the expression or display of pain is modulated by its social consequences.

Pharmacology of Analgesic Agents
Analgesics are specific inhibitors of pain pathways. They activate specific receptors in primary afferent sensory neurons and the CNS. Since odontogenic pain predictably is associated with tissue trauma and inflammation, pharmacological treatment with a disease-modifying analgesic, i.e., an agent that not just suppresses the symptom of pain but also reduces inflammation, should be considered as the drug of choice.

Aniline Analgesics
Acetaminophen has analgesic and antipyretic properties, but it has no clinically significant anti-inflammatory activity. Its antipyretic activity appears to be related to N-arachidonoylphenolamine (AM404), a metabolite of acetaminophen and a member of a group of bioactive N-acylamines that includes the endogenous cannabinoid 2-arachidonoylglycerol, which inhibits cyclooxygenase activity in the CNS. The likely mechanism of its analgesic effect is also related to the activity of AM404. It appears to inhibit the cellular uptake of anandamide leading to increased cannabinoid receptor activity.

The absorption of acetaminophen following oral administration is rapid and complete. Onset of analgesia is about 30 minutes. Its plasma protein binding is low (<25%), consequently, it is readily distributed throughout the body. Acetaminophen is metabolized primarily by hepatic conjugation; but about 10-15% is metabolized by the CYP450 isoenzyme 2E1 forming a highly reactive metabolite, which if not detoxified by glutathione conjugation is responsible for acetaminophen's hepatotoxic potential. Inactive metabolites of acetaminophen are eliminated in the kidney.

Nonsteroidal Anti-inflammatory Agents
Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the activity of cyclooxygenase isoenzymes COX-1 and COX-2; and, consequently, the synthesis of prostaglandins. COX-1 is expressed constitutively in virtually all healthy tissues, including platelets, and it is associated primarily with homeostatic or “housekeeping” mechanisms. COX-2 is expressed primarily in the brain, kidneys, female reproductive systems, and bone; and it can be induced by inflammatory cytokines in other tissues. COX-2 is not found in platelets. Inhibition of COX-2 is primarily responsible for the anti-inflammatory effect of NSAIDs.

Prostaglandin PGE₂ affects vascular tone and permeability, modulates inflammation, and influences pain perception. By reducing peripheral prostaglandin synthesis, NSAIDs decrease the recruitment of leukocytes and the synthesis of leukocyte-derived mediators of inflammation, and increase the activation threshold of primary afferent sensory neurons by chemical activators. In the trigeminal nucleus or dorsal horn of the spinal cord, PGE₂ acts as a pain-producing substance. NSAIDs, which cross the blood-brain barrier, also prevent the synthesis of PGE₂ in the CNS. Consequently, NSAIDs are considered disease modifying analgesics.

Acetylsalicylic acid (aspirin) is effective in the treatment of most types of mild-to-moderate pain. However, a single dose of aspirin can irreversibly inhibit platelet function, interfere with hemostasis and cause prolonged bleeding; and precipitate asthma-like symptoms in susceptible patients. High doses and chronic use of aspirin can cause GI ulceration. Furthermore, aspirin increases the risk of Reye’s syndrome in children and adolescents during viral syndromes. Because of the availability of more effective and less toxic alternatives, now aspirin (in low dose) is used primarily for cardio-protection and stroke prevention.

Ibuprofen is the gold standard against which new analgesics are evaluated. Naproxen (and naproxen sodium), like ibuprofen, has analgesic,
anti-inflammatory and antipyretic activity. Other available oral formulations of NSAIDs offer no apparent advantage over ibuprofen or naproxen.

**Ketorolac** is available in both oral and parenteral formulations. The use of the oral formulation is restricted to those patients who have received the drug parenterally during the perioperative period. **Celecoxib**, the only available selective COX-2 inhibitor in the U.S., offers no advantage over nonselective NSAIDs in treating odontogenic pain.

NSAIDs are rapidly absorbed from the stomach and the upper small intestine. They reach appreciable plasma concentrations in 30 to 60 minutes and peak values at about 2 to 3 hours. NSAIDs are distributed throughout the body and cross the placenta. Depending on the agent and dosing, their duration of action is between 4 to 12 hours. NSAIDs are metabolized in the liver by first-order kinetics; however, after larger doses, the enzymes become saturated, which leads to zero-order kinetics and increased half-lives. Metabolites are excreted primarily by the kidneys.

**Opioid-receptor Agonists**
There are three types of opioid receptors: mu (μ), delta (δ), and kappa (K). Opioid-receptor agonists produce analgesia by acting primarily at μ-receptors found in the brain, brainstem, spinal cord, and primary afferent sensory neurons. Presynaptic μ-receptor activation inhibits calcium influx into sensory neurons, which decreases neurotransmitter release. Postsynaptic μ-receptor activation increases K+ conductance, which decreases postsynaptic response to excitatory neurotransmission.

**Morphine** is the archetypical opioid analgesic. It is a naturally occurring strong, full μ-receptor agonist, i.e., it fully activates the μ-receptor displaying maximum efficacy. However, after oral administration, morphine is rapidly metabolized by hepatic glucuronidation and its bioavailability is low. Oxycodone is a semi-synthetic strong full μ-receptor agonist. After oral administration its bioavailability is high. Oxycodone is metabolized by glucuronidation to noroxycodone and by the CYP450 isoenzyme 2D6 to oxymorphone. However, it is oxycodone, and not its metabolites, that is primarily responsible for analgesia.

**Codeine** is a naturally occurring weak, full μ-receptor agonist, i.e., its efficacy is less than that produced by a strong full agonist even when all the available receptors are activated. Its analgesic action is largely dependent on its hepatic demethylation to morphine, which is responsible for its analgesic activity. Demethylation by the CYP450 isoenzyme 2D6 is subject to genetic polymorphism. Up to 10% of patients are poor metabolizers and do not experience analgesia in response to treatment with codeine. Another 10% of the patients rapidly convert codeine to high levels of morphine, leading to severe toxicity (including death), even with therapeutic doses.

**Hydrocodone** is a synthetic weak full μ-receptor agonist. It is similar in structure to codeine, but hydrocodone is a more effective analgesic. Its bioavailability after oral administration is high. Hydrocodone is demethylated by the CYP450 isoenzyme 2D6 into hydromorphone. Because hydromorphone has a much stronger affinity for the μ-receptor than hydrocodone, it has been proposed that hydrocodone is a prodrug. Patients who are CYP450 isoenzyme 2D6 deficient and those on CYP450 isoenzyme 2D6 inhibitors may not achieve adequate analgesia.

**Tramadol** is a weak, centrally acting μ-receptor agonist/norepinephrine reuptake inhibitor. A weak, centrally acting μ-receptor agonist is less effective than a strong full μ-receptor agonist and its activity appears to be limited to the CNS. After oral administration, tramadol is readily absorbed from the gastrointestinal tract. It reaches appreciable plasma concentrations in 60 minutes and peak values at about 2 hours. Tramadol's bioavailability is high and it is readily distributed from the vascular compartment to all tissues. Tramadol is extensively metabolized in the liver. The unchanged fraction of the drug and its metabolites are excreted in the kidneys.

**Tapentadol** is a weak, centrally acting μ-receptor agonist/norepinephrine reuptake inhibitor. It is rapidly absorbed after oral administration, although the bioavailability of the drug is low, due to extensive first-pass metabolism. Tapentadol is readily distributed from the vascular compartment (plasma protein binding ≈20%) to all tissues. The primary metabolic pathway of tapentadol is hepatic glucuronidation. Tapentadol and its metabolites are rapidly and completely excreted in the kidneys.
Therapeutic Considerations
Satisfactory relief of odontogenic pain can be attained through an approach that incorporates disease-modifying procedures, i.e., primary dental care, in conjunction with intraoperative local anesthesia and the postoperative administration of disease-modifying analgesics. Consequently, NSAIDs are the first line of treatment for superficial somatic odontogenic pain, e.g., postsurgical pain from an incision (skin, mucosa). Deep somatic odontogenic pain, e.g., pain following injury or extensive surgical procedures (muscle, bone), is best treated with combination analgesics, i.e., NSAIDs with acetaminophen or NSAIDs and/or acetaminophen with an opioid.

Adjuvant drugs may enhance the efficacy of analgesics or have analgesic activity of their own. Caffeine in doses greater than 100 mg enhances the analgesic effect of commonly used analgesics, i.e., NSAIDs and acetaminophen. Hydroxyzine (an antihistamine) in doses of 25 to 50 mg enhances the analgesic effect of opioids in postoperative pain, and significantly reduces the incidence of opioid-induced nausea and vomiting. Corticosteroids, through their anti-inflammatory and phospholipase-inhibitory effects, can enhance analgesia in patients with pain of inflammatory origin.

The placebo effect of analgesics and its magnitude can be modulated by psychological factors such as conditioning and expectancy. Investigators have found that the placebo response can be blocked pharmacologically by naloxone, an opioid-receptor antagonist, and psychologically by hidden injections. Consequently, the placebo effect can be harnessed to the patient’s advantage. The clinician’s words (attitude) relative to the therapeutic agent affect the patient’s expectations and associated neurobiological changes can result in enhanced analgesia and, ultimately, can lead to a reduction in drug intake with maintenance of clinical effect.

The optimal dose of an analgesic that will provide adequate pain relief must be established by titration and the drug should be administered on schedule. “By-the-clock” administration of analgesics is much more effective than waiting for pain to return before giving the next dose and may actually reduce the total dosage required for the management of a painful episode. The dosage interval is predicated on the elimination half-life of the drug. Metabolism and adverse drug effects can vary widely among individuals and some patients may respond better to one NSAID or combination opioid analgesics than to another.

Currently available analgesic formulations are not optimal, further emphasizing the importance of individualized approach to pain control. At times, clinicians may have to prescribe more than one type of analgesic concurrently to achieve maximal results. For example, the co-administration of ibuprofen with acetaminophen in full doses; or ibuprofen and/or acetaminophen in full doses with an opioid will result in enhanced analgesia. The concurrent administration of drugs with different mechanisms of action is good medicine; the concurrent administration of drugs with similar mechanisms of action has no rational pharmacological basis.

Mild Odontogenic Pain
In patients with mild odontogenic pain, an over-the-counter NSAID is the drug of choice (Table 1). Ibuprofen, 200 mg, is more effective than aspirin, 650 mg; or acetaminophen, 650 mg; or naproxen 200 to 220 mg. Ibuprofen, 400 mg, is more effective than ibuprofen, 200 mg; and it is equianalgesic to naproxen, 400 to 440 mg. A full dose of ibuprofen, and presumably naproxen, in combination with a full dose of acetaminophen is more effective than either of the two components alone. A meta-analysis has also shown that this combination can also reduce postoperative opioid requirements. Acetaminophen, in doses between 650 to 1000 mg, has been shown to be safe and effective for treating pain after mandibular third-molar extractions. However, acetaminophen has no clinically significant anti-inflammatory effect and ibuprofen, 200 mg, is more effective than acetaminophen, 1000 mg. Therefore, with notable exceptions, acetaminophen should be considered an alternative analgesic when NSAIDs are contraindicated (see NSAID-related prescription precautions).

Acetaminophen-related Prescribing Precautions
In healthy people, therapeutic doses of acetaminophen have virtually no adverse effects. In general, the occasional use of acetaminophen
Meta-analysis has shown that full doses of ibuprofen, and presumably naproxen, in combination with a full dose of acetaminophen can also reduce postoperative opioid requirements. However, if moderate pain is not controlled adequately with full doses of a NSAID/acetaminophen combination, a weak full μ-receptor agonist, e.g., codeine or hydrocodone (Table 3), with “add-on” doses of ibuprofen or acetaminophen to augment fixed-dose formulations may be considered.

Meta-analysis has also shown that NSAIDs have a pre-emptive effect and reduce postoperative analgesic requirements. This pre-emptive effect has been shown in association with periodontal surgical procedures, reducing both postoperative surgical pain and the need for postoperative use of opioids. Another study suggests that there may be a window-period, and timely administration, i.e., within an hour of the surgical procedure, will provide a similar benefit. It has also been reported that the preoperative administration of ibuprofen, 1 hour before the administration of local anesthesia, is an effective method for achieving deep anesthesia during RCT of teeth with irreversible pulpitis.

**NSAID-related Prescribing Precautions**

There are no “absolutely” safe biologically active therapeutic agents, i.e., drugs seldom exert their beneficial effects without also causing adverse drug events (ADEs). It is axiomatic that NSAIDs during pregnancy is also considered safe. It is also the preferred analgesic in patients with liver disease because of the absence of platelet impairment associated with NSAIDs. However, hepatotoxicity may occur with overdose and in patients with liver disease, alcohol and malnutrition (even with therapeutic doses of acetaminophen) may enhance this toxicity. It is also of note that the long-term use of acetaminophen may increase the anticoagulant effect of warfarin.

At therapeutic doses, the half-life of acetaminophen may be prolonged in patients with chronic liver disease; but CYP450 isoenzyme 2E1 activity is not increased, glutathione stores are not depleted to critical levels, and there is no evidence of increased risk of hepatotoxicity. The minimum hepatotoxic single dose in healthy adults is between 15 to 20 extra-strength (500 mg) doses; for children it is 150 mg/kg. Nausea, vomiting, anorexia, diarrhea, and abdominal pain occur during the first 24 hours. Clinical evidence of hepatic damage may be noted in 2 to 6 days. When the drug’s half-life exceeds 12 hours, hepatic coma and death are likely.

**Moderate Odontogenic Pain**

In patients with moderate odontogenic pain, full doses of ibuprofen or naproxen are the drugs of choice (Table 2). Ibuprofen, 400 mg, is more effective than codeine with aspirin, 60/650 mg; or codeine with acetaminophen, 60/600 mg. Ibuprofen, 400 mg, is equianalgesic to naproxen, 400 to 440 mg, and naproxen 500 to 550 mg; but ibuprofen, 600 to 800 mg, is more effective. Full doses of ibuprofen, and presumably naproxen, in combination with a full dose of acetaminophen is more effective than either of the two components alone.

### Table 1. Over-the-counter analgesics for mild odontogenic pain

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Usual oral dose</th>
<th>Dosing</th>
<th>Maximum daily dose</th>
<th>Pregnancy risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen (generic, Motrin)</td>
<td>200-400 mg</td>
<td>q4-6h</td>
<td>1200 mg</td>
<td>B* D** (3rd trimester)</td>
</tr>
<tr>
<td>Naproxen sodium (generic, Aleve)</td>
<td>220 mg</td>
<td>q8-12h</td>
<td>1100 mg</td>
<td>B* D** (3rd trimester)</td>
</tr>
<tr>
<td>Acetaminophen (generic, Tylenol)</td>
<td>650 mg</td>
<td>q6h</td>
<td>3000 mg</td>
<td>B*</td>
</tr>
</tbody>
</table>

FDA Pregnancy Categories: *B – no evidence of risk in humans; **D – evidence of risk in humans
like other therapeutic agents, even after the administration of a single dose, may produce ADEs. However, there is also supporting evidence that NSAID-related ADEs are more likely to be associated with prolonged use, high doses, the presence of comorbidities, and polypharmacy.

**Intolerance**

Intolerance to NSAIDs is most likely to occur in individuals with a history of asthma, nasal polyps, and chronic urticaria. A history of rhinorrhea, urticaria, angioedema, or bronchospasm occurring within 3 hours after exposure is an acceptable method of determining intolerance. Even a single dose of these agents can precipitate asthma in susceptible patients. Intolerance is not an immune phenomenon; rather it is related to the ability of NSAIDs to inhibit the enzyme cyclooxygenase and the consequent shunting of arachidonic acid down the lipoxygenase pathway, which results in increased levels of leukotrienes.

**Gastropathy**

Therapeutic doses of NSAIDs may cause nausea and vomiting; and have been associated with abdominal pain, diarrhea, and dyspepsia. They can exacerbate the symptoms of peptic ulcer disease; and with chronic use, ulceration,
perforation, and bleeding can occur. The prolonged use of high doses of NSAIDs, the concomitant use of anticoagulants, aspirin, and corticosteroids, excessive alcohol intake, and advanced age increase the risk of these complications. Mucosal injury is primarily related to blockade of gastro-protective prostaglandin synthesis. Ibuprofen, in general, appears to have the lowest risk of NSAID-associated gastrointestinal toxicity.

**Antithrombotic Effect**
NSAIDs impair platelet adhesion to tissue components and platelet aggregation primarily through the inhibition of thromboxane A2 (TXA2) synthesis. In contrast to aspirin, platelet inhibition is reversible and short-lived with therapeutic doses of NSAIDs. Platelet function returns to normal when most of the drug has been eliminated from the body. However, in the presence of bleeding diatheses, either hereditary, acquired, or drug induced, the antiplatelet effect of these agents may contribute to serious bleeding. NSAIDs in combination with anticoagulants can increase the International Normalized Ration (INR) by as much as 15%.

**Hepatic Toxicity**
Adverse hepatic reactions have been reported in association with NSAIDs, but they appear to be idiosyncratic and often dose-related. Predisposing factors for toxic reactions include advanced age, decreased renal function, and collagen vascular diseases. Hepatotoxicity, like most adverse drug reactions, occurs within 6-12 weeks of initiation of long-term therapy. Patients with cirrhosis of the liver also have impaired hemostasis and the administration of NSAIDs may further increase the risk of bleeding.

**Renal Toxicity**
NSAIDs decrease the synthesis of renal prostaglandins; consequently, decrease renal blood flow, cause fluid retention and increase blood pressure, and may precipitate renal failure in susceptible patients. Risk factors include old age, chronic renal insufficiency, congestive heart failure, hepatic cirrhosis, and the concurrent use of β-adrenergic receptor antagonists and angiotensin-converting enzyme inhibitors. Nephrotic syndrome, acute interstitial nephritis, and an increased incidence of end-stage renal disease have been reported in patients treated chronically with NSAIDs. NSAIDs should be avoided in persons with preexisting renal disease.

**Cardiovascular Toxicity**
Selective COX-2 inhibitors are associated with a small but absolute cardiovascular risk. COX-2 inhibition leads to less prostacyclin (PGI2) and more TXA2 synthesis. PGI2 is a vasodilator and blocks platelet aggregation; TXA2 is vasoconstrictive and promotes platelet aggregation. COX-2 inhibition allows TXA2 to function unopposed. Although NSAIDs block both COX-1 and COX-2, the FDA considers cardiovascular risk a class effect. The risk appears to be related to dose and duration of treatment. In general, NSAIDs should be used with caution in patients with a history of hypertension, ischemic heart disease, stroke, or congestive heart failure.

**Central Nervous System Effects**
Rarely, NSAIDs may cause tinnitus, dizziness, anxiety, drowsiness, confusion, disorientation, depression, and severe headaches. These adverse effects are seen more commonly in older persons. Tinnitus is reversible and appears to be a sign of high blood levels of NSAIDs. Aseptic meningitis has been reported in persons with systemic lupus erythematosus who were taking ibuprofen or naproxen.

**Effects on Pregnancy and Lactation**
NSAIDs at the time of conception may increase the risk of miscarriage. During pregnancy, low dose intermittent administration of NSAIDs, in general, is considered to be safe. However, NSAIDs should not be prescribed during the third trimester of pregnancy. Potential maternal effects include prolonged gestation and labor, and increased peripartum bleeding. Potential fetal effects include premature closure of ductus arteriosus; pulmonary hypertension; renal dysfunction; reduced amniotic fluid volume; and increased cutaneous and intracranial bleeding. In breastfeeding women, ibuprofen and naproxen are considered safe.

**Effects on Children**
The primary concern when children are taking NSAIDs is dosage errors resulting in overdose, which may result in significant morbidity and
even death. Educating the caregivers (parents, guardians, others) about the importance of correct dosing and dosage intervals, avoiding the concurrent use of other medications that may contain NSAIDs (combination cold remedies), and proper storage of analgesics (as other medications) in childproof containers can minimize the risk.

**Drug-drug Interactions**

Drug-drug interactions all seem to have either a pharmacodynamic or a pharmacokinetic basis. NSAIDs may decrease the antihypertensive effects (decreased prostaglandin synthesis) of β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, and diuretics; increase the toxicity of lithium and methotrexate (decreased renal excretion); increase the risk of peptic ulcer disease (additive) with corticosteroids; and increase the risk of bleeding (platelet inhibition) and increase the INR (mechanism unknown) with warfarin sodium.

NSAIDs can also interfere with the anti-platelet effect of low dose aspirin (81 mg per day) by blocking the access of aspirin to its active site, potentially rendering aspirin less effective when used for cardio-protection and stroke prevention. To avoid significant interference, oral healthcare providers should advise patients regarding the appropriate concomitant use of NSAIDs and aspirin, i.e., at least 2 hours should elapse after aspirin dosing before taking a NSAID and at least 8 hours should elapse after NSAID dosing before taking an aspirin.

**Severe Odontogenic Pain**

In patients with severe odontogenic pain, a strong full µ-receptor agonist, i.e., oxycodone, in combination with ibuprofen or acetaminophen (Table 4), with “add-on” doses of ibuprofen or acetaminophen to augment fixed-dose formulations, should be considered. Opioid dose requirements vary widely from one patient to another; but the equivalent of oral morphine, 10 mg per 70 kg of body weight, is a reasonable starting dose. The dose equivalent of codeine is about 60 mg; of hydrocodone it is about 10 mg; and of oxycodone it is about 5 mg.

Hydrocodone with ibuprofen, 15/400 mg, is superior to ibuprofen, 400 mg. Oxycodone with ibuprofen, 5/400 mg, is more effective than oxycodone with acetaminophen, 5/650 mg; or hydrocodone with acetaminophen, 7.5/500 mg. Oxycodeone with acetaminophen, 5/500 mg, is as effective as codeine with acetaminophen, 60/1000 mg; however, ibuprofen, 600 to 800 mg, is more effective than either of the above formulations. Codeine, hydrocodone, and oxycodone formulations with acetaminophen are alternative drugs when NSAIDs are contraindicated.

Tramadol with acetaminophen, 75/650 mg, is as effective for the management of postsurgical dental pain as hydrocodone with acetaminophen, 10/650 mg. However, tramadol with acetaminophen, 112/650 mg, is less effective than ibuprofen, 200 mg. Tapentadol, 200 mg, is less effective for the management of postsurgical dental pain than ibuprofen, 400 mg. Clearly, neither tramadol nor tapentadol should be considered preferred analgesics for postsurgical odontogenic pain. Tapentadol also has a high potential for abuse.

**Opioid-receptor Agonist-related Prescribing Precautions**

As noted before, there are no “absolutely” safe biologically active therapeutic agents and drugs seldom exert their beneficial effects without also causing ADEs. Opioid analgesics like other therapeutic agents, even after the administration of a single dose, may produce ADEs. However, there is also supporting evidence that opioid-related ADEs are more likely to be associated with prolonged use, high doses, the presence of comorbidities, and polypharmacy.

**Intolerance**

Opioid analgesic-related allergic reactions are rare. However, µ-receptor agonists are able to induce histamine release and produce pruritus and cutaneous blood vessels tend to dilate around the “blush areas”, such as the face, neck, and upper thorax. Histamine release can also lead to peripheral vasodilatation and orthostatic hypotension. Opioid-receptor agonists appear to directly activate mast cells and the release of vasoactive substances does not appear to have an immunologic basis. Antihistamines, e.g., diphenhydramine, are effective to manage symptoms.

**Gastropathy**

Nausea and vomiting, as a result of µ-receptor activation in the medullary chemoreceptor trigger...
in the oculomotor nerve causes pupillary constriction (miosis).\(^{85}\)

**Tolerance**

Repeated use of a constant dose of an opioid-receptor agonist can lead to tolerance or decreased therapeutic efficacy.\(^{87}\) Tolerance appears to be either innate, i.e., genetically determined; or acquired, which appears to have a pharmacokinetic or pharmacodynamic basis.\(^{88,89}\) Tolerance may develop with both acute and chronic opioid use. To maintain adequate analgesia, the development of tolerance requires either an increase in the dosage or frequency of drug administration. There does not appear to be any evidence that tolerance leads to dependence.

**Dependence**

Dependence is a potential hazard of opioid use. However, patients who take opioids for acute pain rarely experience euphoria and even more rarely do they develop psychological dependence or addiction. Clinically significant physical dependence is more likely to develop after several weeks of treatment with relatively large doses of an opioid.\(^{80,81}\) In these patients abrupt cessation of treatment results in withdrawal syndrome characterized by dilated pupils, rapid pulse, goose flesh, muscle jerks, flu-like symptoms, vomiting, diarrhea, tremors, yawning, and sleep.\(^{88}\)

**Overdose**

Opioid overdose is a life-threatening condition. The sine qua non of opioid intoxication is respiratory depression.\(^{92}\) A respiratory rate of ≤12 breaths per minute in a patient who is not in physiologic sleep strongly suggests opioid intoxication, particularly when accompanied by

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**Table 4. Strong full μ-receptor agonists for severe odontogenic pain**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Fixed-dose oral formulations</th>
<th>Opioid staring Dose</th>
<th>Controlled substance schedule</th>
<th>Pregnancy risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone w/acetaminophen (generic, Percocet, others)</td>
<td>5/300 mg</td>
<td>5-10 mg, q4-6h</td>
<td>II</td>
<td>C*</td>
</tr>
<tr>
<td>Oxycodone w/ibuprofen (Combunox)</td>
<td>5/400 mg</td>
<td>5-10 mg, q4-6h</td>
<td>II</td>
<td>C*</td>
</tr>
</tbody>
</table>

FDA Pregnancy Categories: *C - risk cannot be ruled out; **D – evidence of risk in humans
miosis and stupor. Patients with respiratory rates ≤12 breaths per minute and stupor should be ventilated with a bag-valve mask; and administered naloxone, a competitive μ-receptor antagonist, which reverses all signs of opioid intoxication. Once the respiratory rate improves, the patient should be observed for 4 to 6 hours.

**Pregnant and Nursing Women**
The use of opioids in the pregnant or nursing patient is discouraged because of their general CNS depressant effects on the fetus and infant. The short-term use of therapeutic doses of codeine in combination with acetaminophen is appropriate for the management of moderate-to-severe odontogenic pain. However, if the mother is a rapid metabolizer, she may produce much more morphine than those with normal metabolic activity. This, in 2 to 3 days, can lead to symptoms compatible with morphine overdose.

**Drug-drug Interactions**
Drug-drug interactions all seem to have either a pharmacodynamic or a pharmacokinetic basis. The most serious adverse effect of opioids is respiratory depression. Consequently, the risk of respiratory depression is increased (additive) with sedative-hypnotic agents such as benzodiazepines or barbiturates; tricyclic antidepressants; and other CNS depressants.

**Conclusion**
Analgesic efficacy in a given patient is determined by the degree of analgesia produced following dose escalation limited by the development of adverse effects. Start with a specific drug for a specific type of pain. Drug metabolism can differ widely among patients and effects reported should not be viewed as psychological since they generally have a pharmacological basis. Know the pharmacology of the medications prescribed. Onset, peak, and duration of analgesic action and maximum safe dosages vary with drugs. When using fixed-dose opioid formulations, to enhance analgesia, add a NSAID and/or acetaminophen. Administer analgesics regularly. “Around-the-clock” administration of analgesics has positive pharmacological and psychological effects on the patient. Side effects such as sedation, nausea, and vomiting should be carefully watched for and the dosage adjusted or symptomatic therapy initiated. Although rare in oral healthcare settings, watch for development of tolerance. Increasing dosage and frequency of administration or switching to an alternate medication may be necessary to maintain analgesic effect. Finally, when prescribing an analgesic: prescribe dose enough, soon enough, often enough, long enough - prescribe as you would receive.
Course Test Preview
To receive Continuing Education credit for this course, you must complete the online test. Please go to:

1. Pain is ________________.
   a. an unpleasant sensory and emotional experience
   b. associated with actual tissue damage
   c. associated with potential tissue damage
   d. All of the above.

2. Nociception or pain perception is ________________.
   a. the sensory detection of noxious events in the CNS
   b. transduction of noxious events to the CNS
   c. neuronal transmission of noxious events to the CNS
   d. All of the above.

3. Which of the following are noxious stimuli that affect “high-threshold” primary afferent sensory neurons or nociceptors?
   a. Intense mechanical stimuli
   b. Intense thermal stimuli
   c. Chemical activators
   d. All of the above.

4. Which of the following are chemical activators of nociceptors?
   a. Ischemia- and inflammation-associated protons.
   b. Cellular injury-associated extracellular ATP.
   c. Tissue damage- and inflammation-associated kinins.
   d. All of the above.

5. Which of the following statements associated with the kinins (bradykinin) is correct?
   a. Kinins directly excite primary afferent fibers.
   c. PGE2 increases the sensitivity of primary afferent sensory neurons to chemical activators.
   d. All of the above.

6. Which of the following statements is correct with reference to the activation of peripheral sensory neurons?
   a. Activation of peripheral sensory terminals by noxious stimuli leads to intracellular sodium and calcium ion influx and neuronal depolarization.
   b. Membrane depolarization leads to action potential generation if the activation threshold of voltage-sensitive sodium channels is reached.
   c. Four types of voltage-sensitive sodium channels are expressed in primary afferent sensory fibers and two of these only respond to high-threshold peripheral stimuli.
   d. All of the above.

7. Which of the following statements is correct with reference to neuronal transmission in the trigeminal nucleus?
   a. Incoming action potentials activate pre-synaptic voltage-sensitive calcium channels.
   b. Calcium ion influx into the primary sensory neuron terminal leads to synaptic release of glutamate.
   c. Glutamate receptor activation leads to action potential generation in secondary relay neurons.
   d. All of the above.
8. Which of the following statement is correct with respect to secondary or tertiary afferent neurons?
   a. Secondary afferent neurons travel in the lateral aspects of the spinal cord and project to the thalamus where they synapse with tertiary afferent neurons.
   b. Tertiary afferent neurons project to the somatosensory cortex, which is responsible for the localization of pain.
   c. Tertiary afferent neurons project to the limbic system, which is responsible for the emotional aspects of pain.
   d. All of the above.

9. Pain arising slowly after injury, which is perceived as burning, aching, dull, poorly localized, and persistent, i.e., second pain, is most likely due to the activation of ___________.
   a. A-delta fibers
   b. C fibers
   c. B fibers
   d. A-gamma fibers

10. Pain arising rapidly after tissue injury, which is perceived as sharp, bright, well-localized, but not particularly persistent, i.e., first pain, is most likely due to the activation of ___________.
    a. A-delta fibers
    b. C fibers
    c. B fibers
    d. A-gamma fibers

11. Which of the following endogenous ligands are major inhibitory neurotransmitters?
    a. Opioid peptides
    b. Norepinephrine and serotonin (-5HT)
    c. Endogenous cannabinoid, e.g., anandamide and 2-arachidonylethanolamide
    d. All of the above.

12. The term perception (attention and cognition), when applied to pain refers to the ___________.
    a. awareness of a noxious sensation
    b. interpretation and appreciation of negative emotions
    c. attribution of meaning to the experience
    d. All of the above.

13. Which of the following pharmacological considerations is correct with respect to analgesics?
    a. Analgesics are specific inhibitors of pain pathways.
    b. Analgesics activate receptors in primary afferent sensory neurons and the central nervous system.
    c. Pharmacological treatment with a disease-modifying analgesic should target specific mechanisms of pain rather than just suppress the symptom.
    d. All of the above.

14. All of the following statements are correct with respect to acetaminophen except which one?
    a. Acetaminophen has clinically significant analgesic, anti-inflammatory, and antipyretic activity.
    b. The antipyretic activity of acetaminophen appears to be related to one of its metabolites, which inhibits cyclooxygenase activity in the CNS.
    c. The likely mechanism of acetaminophen’s analgesic effect is also related to a metabolite, which appears to indirectly increase cannabinoid receptor activity.
    d. Acetaminophen is metabolized primarily by hepatic conjugation, but a small amount is metabolized by a CYP450 isoenzyme into a potentially toxic metabolite.
15. Cyclooxygenase inhibitors block the synthesis of prostaglandin PGE₂, which is known to produce all of the following physiological effects except which one? Prostaglandin PGE₂
__________________.
   a. produces vasodilatation and increase vascular permeability
   b. modulates the inflammatory response and body temperature
   c. decreases the pain threshold, i.e., increases nociception
   d. activates platelets

16. All of the following statements are correct with respect to acetylsalicylic acid (aspirin) except which one?
   a. A single dose of aspirin can irreversibly inhibit platelet function.
   b. High doses and chronic use of aspirin can cause GI ulceration.
   c. Aspirin decreases the risk of Reye’s syndrome in children and adolescents during viral syndromes.
   d. Today, aspirin (in low dose) is used primarily for cardio-protection and stroke prevention.

17. All of the following statements are correct with respect to COX-inhibitors except which one?
   a. Ibuprofen and naproxen formulations have analgesic, anti-inflammatory, but no antipyretic activity.
   b. The oral formulation of ketorolac is restricted to those patients who have received the drug parenterally during the perioperative period.
   c. Oral formulations of NSAIDs, other than ibuprofen or naproxen, offer no apparent advantage over ibuprofen or naproxen.
   d. Celecoxib, a selective COX-2 inhibitor, offers no advantage over NSAIDs in treating odontogenic pain.

18. Which of the following statements is correct with respect to NSAIDs? NSAIDs are
__________________.
   a. rapidly absorbed from the stomach and upper small intestine
   b. distributed throughout the body and cross the placenta
   c. metabolized in the liver by first-order kinetics; however, after large dose, the enzymes become saturated, which leads to zero-order kinetics and increased half-lives
   d. All of the above.

19. Which of the following statements is correct with respect to opioid-receptor agonists?
   a. Opioid-receptor agonists produce analgesia by acting primarily at μ-receptors, which are found in the brain, brain stem, spinal cord, and primary afferent sensory neurons.
   b. Presynaptic μ-receptor activation inhibits calcium influx into primary sensory neurons, which decreases neurotransmitter release.
   c. Post-synaptic μ-receptor activation increases K+ conductance, which decreases post-synaptic response to excitatory neurotransmission.
   d. All of the above.

20. All of the following statements are correct with respect to morphine or oxycodone except which one?
   a. Morphine is a naturally occurring strong full μ-receptor agonist, which after oral administration has very high bioavailability.
   b. Oxycodone is a semi-synthetic full μ-receptor agonist, which after oral administration has high bioavailability.
   c. Oxycodone is metabolized by glucuronidation to noroxycodone and by the CYP450 isoenzyme 2D6 into oxymorphone.
   d. Oxycodone is primarily responsible for its analgesic effect.
21. Which of the following statement are correct with respect to codeine?
   a. Codeine is a naturally occurring weak full μ-receptor agonist and its analgesic action is largely dependent on its hepatic demethylation to morphine.
   b. The metabolism of codeine is subject to genetic polymorphism, up to 10% of the patients are poor metabolizers and do not experience analgesia.
   c. About 10% of patients rapidly convert codeine to morphine, which can lead to severe toxicity (including death), even with therapeutic doses.
   d. All of the above.

22. All of the following statements are correct with respect to hydrocodone except which one?
   a. Hydrocodone is a synthetic weak full μ-receptor agonist with good bioavailability after oral administration.
   b. Hydrocodone is demethylated by the CYP450 isoenzyme 2D6 into hydromorphone.
   c. Hydromorphone has a much weaker affinity for μ-receptors than hydrocodone.
   d. It has been proposed that hydrocodone is a prodrug.

23. Which of the following statements are correct with respect to tramadol or tapentadol?
   a. Tramadol is a weak-centrally acting μ-receptor agonist/norepinephrine and serotonin reuptake inhibitor.
   b. Tapentadol is a weak-centrally acting μ-receptor agonist/norepinephrine reuptake inhibitor.
   c. Tapentadol has low bioavailability after oral administration due to extensive hepatic first-pass metabolism.
   d. All of the above.

24. Which of the following segments are correct with respect to the use of adjuvant drugs in pain management?
   a. Caffeine in doses greater than 100 mg. enhances the analgesic effect of NSAIDs and acetaminophen.
   b. Hydroxyzine (an antihistamine) in dose of 25 to 50 mg. enhances the analgesic effect of opioids and significantly reduces the incidence of opioid-induced nausea and vomiting.
   c. Corticosteroids can enhance analgesia in patients with pain of inflammatory origin.
   d. All of the above.

25. All of the following statements are correct with respect to the placebo effect of analgesics except which one?
   a. The placebo effect of analgesics and its magnitude can be modulated by psychological factors such as conditioning and expectancy.
   b. The placebo response of analgesics cannot be blocked pharmacologically by naloxone (an opioid receptor antagonist).
   c. The clinician’s words (attitude) affect the patient’s expectations and associated neurobiological changes can result in enhanced analgesia.
   d. The placebo effect of analgesics can lead to a reduction in drug intake with maintenance of clinical effect.
26. Based on available evidence, all of the following statements are correct with respect to the treatment of mild odontogenic pain except which one?
   a. Ibuprofen, 200 mg, is more effective than aspirin, 650 mg; or acetaminophen, 650 mg; or naproxen, 200 to 220 mg.
   b. Ibuprofen, 400 mg, is more effective than ibuprofen, 200 mg; and it is equianalgesic to naproxen, 400 to 440 mg.
   c. A full dose of ibuprofen, and presumably naproxen, in combination with a full dose of acetaminophen is more effective than either of the components alone.
   d. In patients with mild odontogenic pain, acetaminophen should be considered the analgesic of choice.

27. Which of the following statements is correct with respect to acetaminophen?
   a. In healthy people, acetaminophen at usual doses has virtually no adverse effects.
   b. Generally, the occasional use of acetaminophen during pregnancy is considered safe.
   c. Acetaminophen is the preferred analgesic in patients with liver disease.
   d. All of the above.

28. Based on available evidence, all of the following statements are correct with respect to the treatment of moderate odontogenic pain except which one?
   a. Ibuprofen, 400 mg, is more effective than codeine with aspirin, 60/650 mg; or codeine with acetaminophen, 600/600 mg.
   b. Ibuprofen, 400 mg, is equianalgesic to naproxen, 400 to 440 mg, and naproxen 500 to 550 mg.
   c. Ibuprofen, 600 to 800 mg, is no more effective than either ibuprofen, 400 mg, or naproxen 400 to 440 mg, and naproxen 500 to 550 mg.
   d. If pain is not controlled adequately with full doses of a NSAID/acetaminophen combination, fixed-dose formulation of a weak full μ-receptor agonist with “add-on” doses of a NSAID or acetaminophen may be considered.

29. Based on available evidence, which of the following statements is correct with respect to the preemptive effect of NSAIDs?
   a. Meta-analysis has shown that NSAIDs have a preemptive effect and reduce postoperative analgesic requirements.
   b. The preemptive effect of NSAIDs has been shown in association with periodontal surgical procedures.
   c. Deep anesthesia during RCT of teeth with irreversible pulpitis has been attributed to ibuprofen administered 1 hour before the administration of local anesthesia.
   d. All of the above.

30. All of the following statements with respect to NSAID-related prescribing precautions are correct except which one?
   a. Intolerance to NSAIDs is most likely to occur in individuals with a history of asthma, nasal polyps, and chronic urticaria.
   b. Therapeutic doses of NSAIDs may cause nausea and vomiting; and have been associated with abdominal pain, diarrhea, and dyspepsia.
   c. NSAIDs impair platelet adhesion to tissue components and platelet aggregation primarily through the inhibition of thromboxane A2.
   d. The antiplatelet effect of NSAIDs is transient and is not likely to contribute to serious bleeding in patients with bleeding diatheses.
31. Which of the following statements with respect to NSAID-related prescribing precautions is correct?
   a. Adverse hepatic effect have been reported in association with NSAIDs, but they appear to be idiosyncratic and often dose related.
   b. Decreased synthesis of renal prostaglandins can result in decrease renal blood flow, fluid retention and increase blood pressure, and renal failure.
   c. According to the FDA, NSAIDs, like selective COX-2, should be used with caution in patients with HTN, ischemic heart disease, heart failure, and stroke.
   d. All of the above.

32. All of the following statements with respect to NSAID-related prescribing precautions are correct except which one?
   a. NSAIDs at the time of conception may increase the risk of miscarriage.
   b. NSAIDs should not be prescribed during the third trimester of pregnancy.
   c. In breastfeeding women, ibuprofen and naproxen are contraindicated.
   d. The primary concern when children are administered NSAIDs is dosage errors resulting in overdose.

33. Based on available evidence, which of the following statements is correct with respect to the treatment of severe odontogenic pain?
   a. Oxycodone with acetaminophen, 5/500 mg, is as effective as codeine with acetaminophen, 60/1000 mg.
   b. Oxycodone with ibuprofen, 5/400 mg, is more effective than oxycodone with acetaminophen, 5/650 mg.
   c. Oxycodone with ibuprofen, 5/400 mg, is more effective than hydrocodone with acetaminophen, 7.5/500 mg.
   d. All of the above.

34. Based on available evidence, which of the following statements is correct with respect to the use of tramadol or tapentadol in the treatment of odontogenic pain?
   a. Tramadol with acetaminophen, 75/650 mg, is as effective as hydrocodone with acetaminophen, 10/650 mg.
   b. Tramadol with acetaminophen, 112/650 mg, is less effective than ibuprofen, 200 mg.
   c. Tapentadol, 200 mg, is less effective than ibuprofen, 400 mg.
   d. All of the above.

35. Which of the following statements with respect to opioid-receptor agonist-related prescribing precautions is correct except?
   a. Allergic reactions to opioid analgesics are rare.
   b. Opioid analgesics may induce histamine release, which does not appear to have an immunological basis.
   c. Histamine release may produce pruritis, dilation of cutaneous blood vessels around “blush areas”, and peripheral vasoconstriction-induced orthostatic hypotension.
   d. All of the above.
36. Which of the following statements with respect to opioid-receptor agonist-related prescribing precautions is correct?
   a. Nausea and vomiting are common adverse effect associated with the initiation of opioid analgesic therapy.
   b. With chronic use of opioid analgesics, constipation is the most common adverse gastrointestinal effect.
   c. Opioid-induced constipation is dose related and patients do not develop tolerance to this effect.
   d. All of the above.

37. Which of the following statements with respect to opioid-receptor agonist-related prescribing precautions is correct?
   a. Mu-receptor activation in the brain stem depresses respiratory chemoreceptor sensitivity to carbon dioxide.
   b. The concurrent administration of an opioid analgesic and oxygen may cause apnea.
   c. Opioids should be used with great caution in the elderly, the debilitated, and those with pulmonary disease, particularly severe asthma.
   d. All of the above.

38. Which of the following statements with respect to opioid-receptor agonist-related prescribing precautions is correct?
   a. Patients who take opioids for acute pain rarely experience euphoria and even more rarely do they develop psychological dependence or addiction.
   b. Clinically significant physical dependence is more likely to develop after several weeks of treatment with relatively large doses of an opioid.
   c. In patients with physical dependence abrupt cessation of treatment results in withdrawal syndrome.
   d. All of the above.

39. Which of the following statements with respect to opioid-receptor agonist-related prescribing precautions is correct?
   a. The sine qua non of opioid intoxication is respiratory depression.
   b. A respiratory rate of ≤12 breaths per minute in a patient who is not in physiologic sleep strongly suggests opioid intoxication.
   c. Patients with respiratory rates ≤12 breaths per minute and stupor should be ventilated with a bag-valve mask and administered naloxone.
   d. All of the above.

40. Which of the following statements with respect to opioid-receptor agonist-related prescribing precautions is correct?
   a. In general, the use of opioids in the pregnant or nursing patient is discouraged because of their general CNS depressant effects on the fetus and infant.
   b. In pregnant patients, the short-term use of codeine with acetaminophen is appropriate for the management of moderate-to-severe odontogenic pain.
   c. If a pregnant or nursing patient is a rapid metabolizer of codeine, she may produce more morphine than those with normal metabolism; this, in 2 to 3 days, can lead to morphine overdose in the fetus or neonate.
   d. All of the above.
References


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Dr. Aminoshariae is a full-time assistant professor and director of predoctoral endodontics at Case Western Reserve University. She also works in an endodontic private practice. Her dental career began when she was accepted to the Pre-Professional Scholars Program, Six-Year Dentistry at Case School of Dental Medicine which was followed by working as a contract dentist for the United States Navy. Dr. Aminoshariae obtained her endodontic training, certificate and masters degree from Virginia Commonwealth University in 2001. She became a Diplomate of the American Board of Endodotics in 2005.

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