Pharmacology of Analgesics: Clinical Considerations

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Introduction
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 course.
• Dr. Terézhalmy has done consulting work for Procter & Gamble and has served on 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 a disease-modifying analgesic regimen 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 odontogenic pain, prescribe the most appropriate analgesic regimen.
• Discuss potential adverse drug reactions associated with the use of analgesics.

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. Pain is the consequence of a complex series of neuronal, inflammatory, immunological, vascular, and morphological responses to tissue injury.

Since tissue injury 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 and the factors that determine its expression, the initiation of disease-modifying procedures, and the implementation of sound pharmacological strategies.

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, while intense heat or cold activate thermal nociceptors.

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. 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).

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

In the trigeminal-dorsal root 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 afferent neurons (Figure 2). Secondary neurons travel to the thalamus and synapse with tertiary afferent neurons, which project to the somatosensory cortex and limbic system responsible for the localization and emotional aspects of pain, respectively.

There are three groups of sensory fibers: groups A (A-α, A-β, A-γ, and A-δ), B, and C. Fibers in groups A and B are myelinated. C fibers are nonmyelinated. Nociceptive information is conducted by A-δ and C fibers. A-δ fibers conduct information rapidly, i.e., first pain, which is perceived as sharp, bright, well-localized pain, but not particularly persistent. C fibers conduct information slowly, i.e., second pain, which is perceived as dull, throbbing, burning, diffuse, and persistent.
Inhibitory Regulation of Nociceptive Pain
Depolarization of primary afferent sensory neurons of sufficient intensity leads to action potential production and signal generation in secondary 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.

In response to tissue damage and inflammation resident immune cells release endogenous opioids and opioid receptors are up-regulated on peripheral sensory fibers. Opioid receptor activation in primary afferent neurons inhibits depolarization; in the trigeminal-dorsal root complex it inhibits the release of glutamate; in the mid-brain it increases descending inhibitory activity; and in the brain it alters mood, produces sedation, and modulates the emotional response to pain.

Efferent projections from the brainstem to the spinal cord release norepinephrine and serotonin 5-HT. Activation of α₂-adrenergic G-protein-coupled receptors by norepinephrine, which are expressed both presynaptically and postsynaptically, reduces both presynaptic and postsynaptic neuronal excitation. Similarly, activation of serotonergic G-protein-coupled receptors, which are also expressed both presynaptically and postsynaptically, exerts an inhibitory neuronal effect.

Nociceptive activity in sensory neurons, the spinal cord, and the periaqueductal grey can be inhibited by endogenous cannabinoids (2-arachidonoylglycerol and anandamide). There are two G-protein-coupled cannabinoid (CB) receptors. CB1 receptors are expressed in sensory neurons, the spinal cord, and the brain. CB2 receptors are primarily expressed in immune cells; but in association with pain they may be upregulated in the trigeminal-dorsal root complex and in the central nervous system (CNS).

Role of the Higher Central Nervous System in Nociceptive Pain
The term perception, 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 patient's response to pain.

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. 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 involves memory, discrimination, and judgment, i.e., matching the present situation against past experiences and attributing meaning to the current problem. Cognition differs from patient-to-patient and even within the same patient at different times if the thought processes associated with the experience are different. Ultimately, patients will respond to pain congruent with their cultural heritage and its social consequences.

Pharmacology of Analgesics
Analgesics are specific inhibitors of pain pathways and include N-acetyl-p-aminophenol (APAP) or acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), opioid-receptor agonists, and opioid-receptor agonist/norepinephrine and serotonin reuptake inhibitors. Since the quintessential requisite for odontogenic pain is tissue trauma and inflammation, the optimal analgesic regimen should include an agent that suppresses pain and reduces inflammation, i.e., a disease-modifying analgesic.

N-acetyl-p-aminophenol
APAP or acetaminophen has analgesic and antipyretic properties, but it has no clinically significant anti-inflammatory activity. The likely mechanism of its analgesic action is related to N-arachidonoyl-phenolamine (AM404), a
metabolite of APAP, which appears to inhibit the cellular uptake of anandamide leading to increased cannabinoid receptor activity. Its antipyretic effect also appears to be related to AM404, which inhibits cyclooxygenase activity in the CNS.

The absorption of APAP following oral administration is rapid and complete. The onset of analgesia is about 30 minutes. Plasma protein binding is low (<25%); consequently, APAP is readily distributed throughout the body. APAP is metabolized primarily by hepatic conjugation. About 10-15% of APAP is metabolized by the CYP450 isoenzyme 2E1 into a hepatotoxic intermediate metabolite, which must be detoxified by glutathione conjugation. Inactive metabolites of APAP are eliminated in the kidney.

Nonsteroidal Anti-inflammatory Drugs
NSAIDs have analgesic, anti-inflammatory and antipyretic activity. They variably inhibit the activities of cyclooxygenase isoenzymes (COX-1 and COX-2); consequently, the synthesis of PGE₂ is in all healthy tissues, including platelets, and has primary homeostatic or “housekeeping” responsibilities. COX-2 is expressed primarily in the brain, kidneys, female reproductive system, and bone; and it is induced by inflammatory cytokines in other tissues. COX-2 is not found in platelets.

By reducing the synthesis of PGE₂, the prototypical sensitizing agent, NSAIDs increase the response threshold of primary afferent sensory neurons by chemical activators such as protons, ATP, and bradykinin. By reducing PGE synthesis, NSAIDs also increase vascular tone; and decrease vascular permeability, the recruitment of leukocytes, and the synthesis of leukocyte-derived mediators of inflammation. Consequently, **NSAIDs are disease-modifying analgesics.**

Acetylsalicylic acid (ASA) is effective in the treatment of most types of mild-to-moderate pain. However, ASA irreversibly inhibits platelet function, precipitates asthma-like symptoms in susceptible patients, and increases the risk of Reye’s syndrome in children and adolescents during viral syndromes. High doses and chronic use can also cause GI ulceration. Since more effective and less toxic analgesics are available, ASA is used primarily for cardio-protection and stroke prevention.

**Ibuprofen** is the gold standard against which new analgesics are evaluated. Other oral NSAIDs such as **naproxen** and **naproxen sodium** offer no apparent advantage over ibuprofen. 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, a selective COX-2 inhibitor, offers no advantage over other NSAIDs in treating odontogenic pain.

NSAIDs are rapidly absorbed from the stomach and the upper small intestine. The onset of analgesia is 30 to 60 minutes. 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 (κ). Opioid-receptor agonists produce analgesia primarily by acting at μ-receptors found in primary afferent sensory neurons, the spinal cord, the brainstem, and the brain. Presynaptic μ-receptor activation inhibits calcium influx into sensory neurons, which decreases neurotransmitter release. Postsynaptic μ-receptor activation increases K⁺ conductance, which decreases postsynaptic neurotransmission.

**Morphine** is a naturally occurring strong, full μ-receptor agonist. 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, oxycodone and not oxymorphone is primarily responsible for analgesia.
**Codeine** is a naturally occurring weak, full μ-receptor agonist. Its analgesic action is largely dependent on its hepatic demethylation to morphine. Demethylation by the CYP450 isoenzyme 2D6 is subject to genetic polymorphism. Up to 10% of the general population are poor metabolizers of codeine and do not experience analgesia in response to treatment; while another 10% rapidly convert codeine to morphine, which can lead 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. Hydrocodone is demethylated by the CYP450 isoenzyme 2D6 to hydromorphone, which has a much stronger affinity for the μ-receptor than hydrocodone and is primarily responsible for hydrocodone’s analgesic effect. Patients who are CYP450 isoenzyme 2D6 deficient and those on CYP450 isoenzyme 2D6 inhibitors may not achieve adequate analgesia.

**Opioid-receptor Agonist/Norepinephrine and Serotonin Reuptake Inhibitors**

**Tramadol** is a weak, centrally acting μ-receptor agonist/norepinephrine and serotonin reuptake inhibitor. After oral administration, tramadol is readily absorbed from the gastrointestinal tract. It reaches appreciable plasma concentrations in 60 minutes. Tramadol's bioavailability is high and it is readily distributed from the vascular compartment to all tissues. Tramadol is metabolized in the liver. The unchanged fraction of the drug and its metabolites are excreted in the kidneys.

**Tapentadol** is also a weak, centrally acting μ-receptor agonist/norepinephrine and serotonin reuptake inhibitor. It is rapidly absorbed after oral administration, although the bioavailability of the drug due to first-pass metabolism is low. Tapentadol is readily distributed from the vascular compartment 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 primary dental care in conjunction with intraoperative local anesthesia and the administration of a postoperative analgesic regimen based on a disease-modifying agent. Therefore, unless otherwise contraindicated, NSAIDs are first-line drugs for the treatment of all odontogenic pain. It is of note that response to an analgesic can vary widely; i.e., some individuals respond better to one analgesic than to another.

Consider the efficacy of NSAIDs vis-à-vis other available options when prescribing analgesics. Since direct head-to-head trials of the various analgesics are not always available, an alternative is to consider the numbers needed to treat (NNT), i.e., the number of patients who need to receive the active drug for one to achieve at least 50% pain relief over 4 to 6 hours compared with a placebo in randomized, double-blind, single-dose studies in patients with moderate-to-severe pain (Table 1). Analgesics should be administered on schedule. The “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 optimal dose of an analgesic that will provide adequate pain relief must be established by titration. The dosage interval is predicated on the drug’s elimination half-life.

**Mild-to-moderate Odontogenic Pain**

Ibuprofen, 200 mg, is somewhat more effective than naproxen sodium, 220 mg, and both are more effective than APAP, 650 mg (Table 2). Consequently, over-the-counter NSAIDs are the drugs of choice for the treatment of mild-to-moderate odontogenic pain. Since APAP has no significant anti-inflammatory activity, in the treatment of odontogenic pain APAP should only be considered as an alternative analgesic, i.e., when NSAIDs are contraindicated.

**Moderate-to-severe Odontogenic Pain**

Prescription strength ibuprofen, naproxen,
Table 1. The Oxford League Table for Analgesic Efficacy.\textsuperscript{36}

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Dosages in milligrams</th>
<th>Number of people in comparison</th>
<th>% with a 50% pain relief</th>
<th>IRR</th>
<th>Lower confidence level</th>
<th>Upper confidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>600</td>
<td>203</td>
<td>79</td>
<td>2.4</td>
<td>2.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400</td>
<td>5,456</td>
<td>55</td>
<td>2.5</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>APAP w/oxycodeone</td>
<td>650/10</td>
<td>315</td>
<td>66</td>
<td>2.6</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>APAP w/tramadol</td>
<td>650/75</td>
<td>679</td>
<td>43</td>
<td>2.6</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>400-440</td>
<td>197</td>
<td>51</td>
<td>2.7</td>
<td>2.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Naproxen</td>
<td>500-550</td>
<td>784</td>
<td>52</td>
<td>2.7</td>
<td>2.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200</td>
<td>3,248</td>
<td>48</td>
<td>2.7</td>
<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Morphine (IM)</td>
<td>10</td>
<td>946</td>
<td>50</td>
<td>2.9</td>
<td>2.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>200-220</td>
<td>202</td>
<td>45</td>
<td>3.4</td>
<td>2.4</td>
<td>5.8</td>
</tr>
<tr>
<td>APAP w/codeine</td>
<td>650/60</td>
<td>1,123</td>
<td>42</td>
<td>4.2</td>
<td>3.4</td>
<td>5.3</td>
</tr>
<tr>
<td>ASA</td>
<td>600-650</td>
<td>5,061</td>
<td>38</td>
<td>4.4</td>
<td>4.0</td>
<td>4.9</td>
</tr>
<tr>
<td>APAP</td>
<td>600-650</td>
<td>1,886</td>
<td>38</td>
<td>4.6</td>
<td>3.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Codeine</td>
<td>60</td>
<td>1,305</td>
<td>15</td>
<td>15.7</td>
<td>11.0</td>
<td>48.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>&gt;10,000</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
and naproxen sodium are more effective than codeine with APAP, 60/650 mg (Table 3). Consequently, full doses of NSAIDs are the drugs of choice for the treatment of moderate-to-severe odontogenic pain. It is also of note that full doses of NSAIDs administered concurrently with APAP (325 to 650 mg) are more effective for the treatment of odontogenic pain than full dose of a NSAID or APAP (650 mg) alone.

If moderate-to-severe odontogenic pain is not relieved with full doses of ibuprofen with "add-on" doses of APAP, a weak, full μ-receptor agonist such as fixed-dose hydrocodone w/ ibuprofen, 5/200 mg, with "add-on" doses of ibuprofen (and APAP) should be considered (Table 4). When NSAIDs are contraindicated alternative options include fixed-doses of hydrocodone w/APAP, 5/325 mg, or codeine w/APAP, 30/325 mg, up to a maximum of two tablets per dose and no "add-on" doses of APAP.

**Severe Odontogenic Pain**

For the treatment of severe odontogenic pain...
pain, a strong, full μ-receptor agonist such as fixed-dose oxycodone w/ibuprofen with “add-on” doses of ibuprofen (and APAP) may be considered (Table 5). Oxycodone w/ibuprofen, 5/400 mg, is more effective than oxycodone w/APAP, 5/650 mg; or hydrocodone w/APAP, 7.5/500 mg. Fixed-dose oxycodone w/APAP, 5/325 mg, up to a maximum of two tablet per dose and no “add-on” APAP is an alternative, i.e., when NSAIDs are contraindicated. Tramadol w/APAP, 75/650 mg, is as effective for the management of postsurgical dental pain as hydrocodone w/APAP, 10/650 mg. However, ibuprofen, 200 mg, is more effective than tramadol w/APAP, 112/650 mg. Ibuprofen, 400 mg, is more effective for the management of postsurgical dental pain than tapentadol, 200 mg. Clearly, neither tramadol nor tapentadol should be considered preferred analgesics for postsurgical odontogenic pain.

Table 4. Weak, Full μ-receptor Agonists for Moderate-to-severe Odontogenic Pain.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fixed-dose oral formulations in milligrams</th>
<th>“Add-on” options</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone w/ibuprofen (Vicoprofen, Reprexain)</td>
<td>5/200</td>
<td>ibupront, 400 mg + APAP, 325 to 650 mg</td>
<td>q4-h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ibupront, 600 mg + APAP, 325 to 650 mg</td>
<td>q8-h</td>
</tr>
<tr>
<td>Hydrocodone w/APAP (generic, vicodin, others)</td>
<td>5/325</td>
<td>N/A</td>
<td>q4-6h</td>
</tr>
<tr>
<td>Codeine w/APAP (generic, Tylenol w/codeine)</td>
<td>30/325</td>
<td>N/A</td>
<td>q4-6h</td>
</tr>
</tbody>
</table>

Table 5. Strong Full μ-receptor Agonists for Severe Odontogenic Pain.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fixed-dose oral formulations in milligrams</th>
<th>“Add-on” options</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone w/ibuprofen (Combunox)</td>
<td>5/400</td>
<td>ibupront, 200 mg + APAP, 325 to 650 mg</td>
<td>q4-h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ibupront, 400 mg + APAP, 325 to 650 mg</td>
<td>q8-h</td>
</tr>
<tr>
<td>Oxycodone w/APAP (generic, Percocet, others)</td>
<td>5/325</td>
<td>N/A</td>
<td>q4-6h</td>
</tr>
</tbody>
</table>
Preemptive Analgesia
Preoperative doses of NSAIDs reduce postoperative pain and the need for postoperative opioids analgesics.\(^{51,52}\) It also appears that there may be a window-period, and the timely administration NSAID, i.e., within an hour of a procedure, will provide a similar benefit.\(^{53}\) It has also been reported that when treating irreversible pulpitis, the administration of ibuprofen one hour before administering a local anesthetic agent is an effective strategy for achieving deep anesthesia.\(^{54}\)

Adjuvant Drugs to Enhance the Efficacy of Analgesics
Adjuvant drugs enhance the efficacy of analgesics or have analgesic activity of their own.\(^{55}\) Caffeine in doses greater than 100 mg enhances the analgesic effect of NSAIDs and APAP. Hydroxyzine, a first generation antihistamine, in doses of 25 to 50 mg enhances the analgesic effect of opioids and reduces the incidence of opioid-induced nausea and vomiting. Corticosteroids, through their phospholipase-inhibitory effects, enhance analgesia in patients with pain of inflammatory origin.

Placebo Effect of Analgesics
The placebo effect of analgesics and its magnitude can be modulated pharmacologically by naloxone (an opioid-receptor antagonist) and psychologically by hidden injections.\(^{56}\) The clinician's positive attitude toward an analgesic also affects the patient's expectations and associated neurobiological changes can result in enhanced analgesia and lead to a reduction in drug intake with maintenance of clinical effect.\(^{56}\) Consequently, the placebo effect can be harnessed to the patient's advantage.

Prescription Precautions Associated with the Use of Analgesics
There are no “absolutely” safe biologically active therapeutic agents, i.e., drugs seldom exert their beneficial effects without also causing adverse drug reactions (ADRs). It is axiomatic that analgesics, like other therapeutic agents, even after the administration of a single dose, may produce ADRs. However, there is also supporting evidence that analgesic-related ADRs are more likely to be associated with prolonged use, high doses, the presence of comorbidities, and polypharmacy.

APAP-related Prescribing Precautions
A Food and Drug Administration (FDA) Drug Safety Communication published on January 13, 2014 states that “acetaminophen-containing prescription products are safe and effective when used as directed, though all medications carry some risks”.\(^{57}\) Indeed, during the past decade, APAP has been identified as the leading cause of acute liver failure (ALF) in the United States and up to 50% of the cases are due to unintentional overdose.\(^{58-61}\)

Concerns about the incidence of ALF prompted the FDA to require a Boxed Warning highlighting the potential for severe liver toxicity with APAP. The FDA also mandated that the Boxed Warning highlight the potential for allergic reactions and for severe liver injury in patients who drank alcohol while taking APAP containing products.\(^{57}\) Manufacturers were also instructed to revise their labeling (package insert) to include a warning about potential increased bleeding in patients taking warfarin.\(^{52}\)

The FDA also set a limit of 325 mg of APAP per tablet, capsule, or other dosage units in prescription drug products, e.g., opioid analgesics w/APAP. The FDA also called upon healthcare professionals to discontinue prescribing combination drug products containing more than 325 mg of APAP (may still prescribe 650 mg per dose).\(^{57,63}\) On March 26, 2014 the FDA formally mandated the withdrawal of all prescription combination drug products from the market containing more than 325 mg of APAP.\(^{64}\)

Recent evidence also suggests that APAP is a hormone disrupter, e.g., it interferes with reproductive and thyroid hormone functions essential for normal brain development. APAP taken during pregnancy has been associated with an increased risk of attention-deficit/hyperactivity disorder (ADHD)-like behavioral problems or hyperkinetic disorders (HKDs) in children.\(^{65}\) A summary of potential ADRs associated with the use of APAP is presented in Table 6.

NSAID-related Prescribing Precautions
Intolerance to NSAIDs is most likely in individuals with a history of asthma, nasal polyps, and chronic urticaria.\(^{66}\) A history of rhinorrhea, urticaria, angioedema, or bronchospasm
### Table 6. Potential APAP-associated Adverse Drug Reactions.

<table>
<thead>
<tr>
<th>Potential ADRs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy</td>
<td>Swelling of the face, mouth, and throat; difficulty breathing; and itching and/or a rash; rare cases of anaphylaxis.</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome and toxic epidermal necrolysis</td>
<td>Reddening of the skin, a rash, blisters, and detachment of the upper surface of the skin.</td>
</tr>
<tr>
<td>Asthma</td>
<td>Increased risk of asthma and wheezing in both children and adults.</td>
</tr>
<tr>
<td>Possible causal relationship between wheezing or asthma in offspring and maternal use of APAP during pregnancy.</td>
<td></td>
</tr>
<tr>
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<tr>
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<td>Acute liver failure (ALF)</td>
<td>In patients with liver disease, alcohol and malnutrition (even with therapeutic doses of APAP) may enhance this toxicity.</td>
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<tr>
<td>Hematologic malignancies</td>
<td>Chronic users of APAP (≥ 4 days/week for ≥ 4 years) have a two-fold increased risk of developing lymphomas and myelodysplastic syndrome.</td>
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<tr>
<td>Cryptorchidism</td>
<td>Increased risk with APAP use for more than 4 weeks during pregnancy, especially during the first and second trimesters.</td>
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<tr>
<td>Attention-deficit/hyperactivity disorders and hyperkinetic disorders in children</td>
<td>Increases the risk with increased frequency of maternal APAP use during pregnancy.</td>
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<td>Drug-drug interactions</td>
<td>Potential interaction between APAP and warfarin sodium.</td>
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<tr>
<td>Drug-drug interactions</td>
<td>Long-term concurrent use of APAP (i.e., 2 to 4 g daily for 4 weeks) and warfarin sodium increases the International Normalized Ratio and the risk of bleeding.</td>
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occurring within 3 hours after exposure to a NSAID is an acceptable method of confirming intolerance. Even a single dose of a NSAID can precipitate asthma in susceptible patients.\textsuperscript{67} Intolerance is related to the inhibition of cyclooxygenase and the consequent shunting of arachidonic acid down the lipooxygenase pathway resulting in increased levels of leukotrienes, a family of inflammatory mediators.\textsuperscript{41}

NSAIDs may cause nausea, vomiting, abdominal pain, diarrhea, dyspepsia. Mucosal injury related to the blockade of prostaglandin synthesis can exacerbate peptic ulcer disease (PUD).\textsuperscript{66,68} Ibuprofen appears to have the lowest risk of NSAID-associated gastrointestinal toxicity.\textsuperscript{39} NSAIDs also impair platelet function through the inhibition of thromboxane A\textsubscript{2} (TXA\textsubscript{2}) synthesis.\textsuperscript{66}

The risk of bleeding with PUD is increased with the concomitant use of aspirin, clopedigrel, and corticosteroids; with anticoagulants, NSAIDs increase the International Normalized Ration (INR) by as much as 15%.\textsuperscript{62,70}

**Hepatotoxicity** has been reported in association with the use of NSAIDs, but it appears to be idiosyncratic and often dose-related.\textsuperscript{66,71}

Predisposing factors for toxic reactions include advanced age, concomitant liver disease, decreased renal function, and collagen vascular diseases. Hepatotoxicity, like most ADRs, occurs within 6-12 weeks of initiation of long-term therapy.\textsuperscript{72} Patients with the liver disease also have impaired hemostasis associated with reduced synthesis of coagulation factors and the administration of NSAIDs may further increase the risk of bleeding.

NSAIDs decrease the synthesis of renal prostaglandins. Consequently, NSAIDs decrease renal blood flow causing fluid retention and increase blood pressure, and may precipitate renal failure in susceptible patients.\textsuperscript{66} 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.\textsuperscript{73} Nephrotic syndrome, acute interstitial nephritis, and an increased incidence of end-stage renal disease have been reported in patients treated chronically with NSAIDs.\textsuperscript{74}

COX-2 inhibition leads to less prostacyclin (PGI\textsubscript{2}) and more TXA\textsubscript{2} synthesis. PGI\textsubscript{2} is a vasodilator and blocks platelet aggregation; TXA\textsubscript{2} is vasoconstrictive and promotes platelet aggregation. COX-2 inhibition allows TXA\textsubscript{2} to function unopposed. Although NSAIDs block both COX-1 and COX-2 variably, the FDA considers cardiovascular risk a class effect.\textsuperscript{39}

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.\textsuperscript{75}

Rarely, NSAIDs may cause dizziness, anxiety, drowsiness, confusion, disorientation, depression, and severe headaches. These central nervous system-related adverse drug reactions may be seen with therapeutic doses of NSAIDs most commonly in older persons. Tinnitus appears to be a sign of high blood levels of NSAIDs.\textsuperscript{66} Aseptic meningitis has been reported in persons with systemic lupus erythematosus who were taking ibuprofen or naproxen.\textsuperscript{76,77}

NSAIDs at the time of conception may increase the risk of miscarriage.\textsuperscript{66,78} During pregnancy, low dose intermittent administration of NSAIDs, in general, is considered to be safe. NSAIDs during the third trimester may prolong gestation and labor and increase peripartum bleeding.\textsuperscript{79,80} 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.

In children, the primary concern when prescribing NSAIDs is dosing errors resulting in overdose, which may lead to significant morbidity and even death.\textsuperscript{66} Educating the caregivers (parents, guardians, others) about the importance of correct dosing and dosage intervals, avoiding concurrent use of other medications that may contain NSAIDs (e.g., combination cold remedies), and proper storage of analgesics (as other medications) in childproof containers can minimize the risk.

**Drug-drug interactions** all seem to have 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 also interfere with the anti-platelet effect of low dose ASA (i.e., 81 mg per day) by blocking the access of ASA to its active site, potentially rendering ASA 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 ASA, i.e., at least 2 hours should elapse after ASA dosing before taking a NSAID and at least 8 hours should elapse after NSAID dosing before taking an ASA.

Opioid-receptor Agonist-related Prescribing Precautions
The United States is in the midst of an opioid overdose epidemic. Opioid analgesics and heroin killed more than 33,000 people in 2015, more than during any other year on record. Nearly half of all opioid overdose deaths were related to prescription opioid analgesics. The hallmark of opioid overdose is the presence of the “opioid overdose triad,” i.e., (1) pinpoint pupils (miosis), (2) unconsciousness, and (3) respiratory depression. Respiratory depression is related to mu-receptor activation in the brainstem, which decreases the sensitivity of respiratory chemoreceptors to carbon dioxide.

The sine qua non of opioid intoxication in a patient who is not in physiologic sleep, particularly when accompanied by miosis and lethargy, is respiratory depression defined as less than 12 breaths/min. Patients with respiratory rates less than 12 breath/min 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 remain under observation for 4 to 6 hours.

Mu-receptor activation in the brain causes dizziness, drowsiness, sedation, and cognitive changes. Cognitive changes present primarily in patients who already have cognitive dysfunction. Paradoxical CNS effects in the elderly are not uncommon. To avoid toxic and paradoxical effects in the elderly, dosages may have to be reduced by as much as one-half to one-fourth. Opioid analgesics also modulate mood and behavior, causing euphoria in some; and anxiety or dysphoria in others. Mu-receptor activation in the oculomotor nerve causes pupillary constriction.

Repeated use of a constant dose opioid-receptor agonist can lead to tolerance or decreased therapeutic efficacy. Tolerance appears to be either innate, i.e., genetically determined; or acquired, which appears to have a pharmacokinetic or pharmacodynamic basis. 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 is a potential hazard of opioid use. However, patients who take opioids for acute pain rarely experience euphoria and even less likely to develop psychological or physical dependence. Clinically significant physical dependence is more likely to develop after several weeks of treatment with relatively large doses of an opioid. 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.

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

**Nausea** and **vomiting**, as a result of μ-receptor activation in the medullary chemoreceptor trigger zone, are common adverse effect associated with the initiation of opioid analgesic therapy. With chronic use, **constipation** is the most ADRs. Opioid analgesics in the gastrointestinal tract bind μ-receptors, which leads to an increase in the tone of the anterior portion of the stomach and decreases gastric motility. Constipation is dose related and patients do not develop tolerance to this effect. The risk may be minimized by increasing fluid and dietary fiber intake.¹⁰⁰

As mentioned earlier, mu-receptor activation in the brainstem depresses respiratory chemoreceptor sensitivity to carbon dioxide.⁹⁰ Concurrent administration of oxygen may cause apnea. Carbon dioxide retention produces intracranial vasodilatation leading to **increased intracranial pressure**; consequently, opioids should be used with extreme caution in patients with head injury. In patients with pulmonary disease, e.g., severe asthma or chronic obstructive pulmonary disease, opioids **suppress the cough reflex**, **impair of ciliary activity**, and **aggravate bronchospasm**.

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 w/APAP is appropriate for the management of moderate-to-severe odontogenic pain. However, if the mother is a rapid metabolizer, i.e., genetic polymorphism related to CTP450 isoenzyme 2D6, she may produce much more morphine than those with normal metabolic activity.¹⁰¹ This, in 2 to 3 days, can lead to symptoms compatible with morphine overdose.¹⁰¹

**Drug-drug interactions** all seem to have either a pharmacodynamic or a pharmacokinetic basis. The most serious ADR to opioid analgesics therapy is respiratory depression.⁹⁰ Consequently, the risk of respiratory depression is increased with concurrent prescriptions of other central nervous system depressants such as benzodiazepines, other sedative-hypnotic agents, and alcohol. Drug-drug interactions between opioid analgesics, alcohol, and sedatives are often present in fatal drug overdoses.

**Summary**

Analgesic efficacy in a given patient is determined by the degree of analgesia produced following dose escalation limited by the development of ADRs. Start with a disease-modifying analgesic when treating odontogenic 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 analgesic, i.e., onset and duration of action and maximum safe dosages.

Currently available analgesic formulations are not optimal. Emphasizing the importance of individualized approach to pain control; at times, clinicians may have to prescribe more than one class of analgesic concurrently to achieve maximal results. The concurrent administration of drugs with different mechanisms of action is good medicine; for example, ibuprofen w/APAP in full doses or fixed-dose opioids with “add-on” doses of ibuprofen and/or APAP will result in enhanced analgesia.

Administer analgesics regularly, i.e., “around-the-clock.” ADRs should be carefully watched for and the dosage adjusted or symptomatic therapy initiated. Although rare in oral healthcare settings, watch for signs of opioid tolerance. Increasing dosage or frequency of administration or switching to an alternate regimen may be necessary to maintain analgesic effect. Finally, when prescribing analgesics: prescribe dose enough, soon enough, often enough, long enough - prescribe as you would receive.
Course Test Preview
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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 stimuli
   b. transduction of noxious stimuli
   c. neuronal transmission of noxious stimuli
   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 bradykinin is correct?
   a. Bradykinins 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 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

10. 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

11. Which of the following endogenous ligands are major inhibitory neurotransmitters?
    a. Opioid peptides.
    b. Norepinephrine and serotonin (-5HT).
    c. Endogenous cannabinoid.
    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. The optimal analgesic regimen should include an agent that suppresses pain and reduces inflammation, i.e., a disease-modifying analgesic.
    d. All of the above.
14. All of the following statements are correct with respect to APAP except which one?
   a. APAP has clinically significant analgesic, anti-inflammatory, and antipyretic activity.
   b. The antipyretic activity of APAP appears to be related to one of its metabolites, which inhibits cyclooxygenase activity in the CNS.
   c. The likely mechanism of APAP’s analgesic effect is also related to a metabolite, which appears to indirectly increase cannabinoid receptor activity.
   d. APAP 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? 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 ASA except which one?
   a. A single dose of ASA can irreversibly inhibit platelet function.
   b. High doses and chronic use of ASA can cause GI ulceration.
   c. ASA decreases the risk of Reye's syndrome in children and adolescents during viral syndromes.
   d. Today, ASA (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 \( \mu \)-receptor agonist, which after oral administration has very high bioavailability.
   b. Oxycodone is a semi-synthetic full \( \mu \)-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 \( \mu \)-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 \( \mu \)-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 \( \mu \)-receptors than hydrocodone.
   d. 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 \( \mu \)-receptor agonist/norepinephrine and serotonin reuptake inhibitor.
   b. Tapentadol is a weak centrally acting \( \mu \)-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. **Based on available evidence, which of the following statement is correct with respect to the treatment of mild odontogenic pain?**
   a. Ibuprofen, 200 mg, is somewhat more effective than naproxen sodium, 220 mg, and both are more effective than APAP, 650 mg.
   b. Over-the-counter NSAIDs are the drugs of choice for the treatment of mild-to-moderate odontogenic pain.
   c. Since APAP has no significant anti-inflammatory activity; it should only be considered an alternative analgesic, i.e., when NSAIDs are contraindicated.
   d. All of the above.
25. Based on available evidence, which of the following statements is correct with respect to the treatment of moderate odontogenic pain?
   a. Prescription strength ibuprofen, naproxen, and naproxen sodium are more effective than codeine with APAP, 60/650 mg.
   b. Full doses of NSAIDs are the drugs of choice for the treatment of moderate-to-severe odontogenic pain.
   c. Full doses of NSAIDs administered concurrently with APAP (325 to 650 mg) are more effective pain than full dose of a NSAID or APAP (650 mg) alone.
   d. All of the above.

26. Based on available evidence, which of the following statements is correct with respect to the treatment of moderate odontogenic pain?
   a. If moderate-to-severe odontogenic pain is not relieved with full doses of ibuprofen with “add-on” doses of APAP, a weak, full μ-receptor agonist such as fixed-dose hydrocodone w/ibuprofen, 5/200 mg, with “add-on” doses of ibuprofen (and APAP) should be considered.
   b. When NSAIDs are contraindicated the therapeutic options include fixed-doses of hydrocodone w/APAP, 5/325 mg, up to a maximum of two tablets per dose and no “add-on” APAP.
   c. All of the above.

27. Based on available evidence, which of the following statements is correct with respect to the treatment of severe odontogenic pain?
   a. For the treatment of severe odontogenic pain, a strong, full μ-receptor agonist such as fixed-dose oxycodone w/ibuprofen with “add-on” doses of ibuprofen (and APAP) should be considered.
   b. Oxycodone w/ibuprofen, 5/400 mg, is more effective than oxycodone w/APAP, 5/650 mg.
   c. Fixed-dose oxycodone w/APAP, 5/325 mg, up to a maximum of two tablet per dose and no “add-on” APAP is an alternative, i.e., when NSAID is contraindicated.
   d. All of the above.

28. 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 w/APAP, 75/650 mg, is as effective for the management of postsurgical dental pain as hydrocodone w/APAP, 10/650 mg.
   b. Ibuprofen, 200 mg, is more effective than tramadol w/APAP, 112/650 mg.
   c. Ibuprofen, 400 mg, is more effective for the management of postsurgical dental pain than tapentadol, 200 mg.
   d. All of the above.

29. Based on available evidence, which of the following statements is correct with respect to the preemptive effect of NSAIDs?
   a. It has shown that NSAIDs have a preemptive effect and reduce postoperative analgesic requirements.
   b. It also appears that there may be a window-period, and timely administration NSAID, i.e., within an hour of a procedure, will provide a similar benefit.
   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. **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 APAP.
   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.

31. **Which of the following statements is correct with respect to the placebo effect of analgesics?**
   a. The placebo response of analgesics cannot be blocked pharmacologically by naloxone (an opioid receptor antagonist).
   b. The clinician's attitude toward an analgesic affects the patient's expectations and associated neurobiological changes can result in enhanced analgesia, and lead to a reduction in drug intake with maintenance of clinical effect.
   c. The placebo effect can lead to a reduction in drug intake with maintenance of clinical effect.
   d. All of the above.

32. **Which of the following statements is correct with respect to APAP?**
   a. According to a Food and Drug Administration (FDA) Drug Safety Communication “acetaminophen-containing prescription products are safe and effective when used as directed”.
   b. During the past decade, APAP has been identified as the leading cause of acute liver failure (ALF) in the United States and up to 50% of acetaminophen-related cases of ALF are due to unintentional overdose.
   c. The FDA and the pharmaceutical industry have taken action to protect consumers from the risk of severe liver damage by formally withdrawing from the market all prescription combination drug products with more than 325 mg of APAP.
   d. All of the above.

33. **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 in combination with anticoagulants they are not likely to increase the International Normalized Ration (INR).

34. **Which of the following statements with respect to NSAID-related prescribing precautions is correct?**
   a. Hepatotoxicity has 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. In general, NSAIDs should be used with caution in patients with a history of hypertension, ischemic heart disease, stroke, or congestive heart failure.
   d. All of the above.
35. **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.

36. **Which of the following statements related to opioid overdose is correct?**
   a. Nearly half of all opioid overdose deaths are related to prescription opioid analgesics.
   b. The hallmark of opioid overdose is the presence (1) pinpoint pupils, (2) unconsciousness, and (3) respiratory depression, i.e. the “opioid overdose triad.”
   c. Respiratory depression is related to mu-receptor activation in the brain stem, which decreases the sensitivity of respiratory chemoreceptors to carbon dioxide.
   d. All of the above.

37. **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.

38. **Which of the following statements with respect to opioid-receptor agonist-related prescribing precautions is correct?**
   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 vasodilation-induced orthostatic hypotension.
   d. All of the above.

39. **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.
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.
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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 Endodontics in 2005.

Dr. Aminoshariae was elected to the American Association of Endodontists Board of Directors during the organization’s recent Annual Session in Boston. Dr. Aminoshariae represents AAE District IV, comprised of Illinois, Indiana, Kentucky, Michigan, Ohio, West Virginia and Wisconsin.

Dr. Aminoshariae is a member of the American Dental Association, Ohio Dental Association and Ohio Association of Endodontists. She is the treasurer and secretary of the Greater Cleveland Dental Society and Alternate Delegate of the Ohio Dental Association. She is also a member of the National Board Endodontics Test Construction Committee for Joint Commission on National Dental Examinations, chair of the American Dental Education Association Endodontic Section, and a member of the Scientific Advisory Boards for the Journal of Endodontics and Journal of the American Dental Association. Dr. Aminoshariae previously served on the AAE Evidence-Based Endodontics Committee.

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Dr. Terézhalmy is Professor and Dean Emeritus, School of Dental Medicine, Case Western Reserve University. In addition, he is a Consultant, Naval Postgraduate Dental School, National Naval Medical Center. Dr. Terézhalmy earned a BS degree from John Carroll University; a DDS degree from Case Western Reserve University; an MA in Higher Education and Human Development from The George Washington University; and a Certificate in Oral Medicine from the National Naval Dental Center.

Dr. Terézhalmy has many professional affiliations and over the past 40+ years, has held more than 30 positions in professional societies. He has served as editor or contributing editor for several publications, co-authored or contributed chapters for several books and has had over 225 papers and abstracts published. Dr. Terézhalmy has accepted invitations to lecture before many local, state, national, and international professional societies.

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