# Medical Management of Odontogenic Pain

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INTRODUCTION
The most common complaint causing a person to seek the services of an oral health care provider is pain. Consequently, the primary obligation and ultimate responsibility of every clinician is not only to restore function but also to relieve pain. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Proper management of pain requires an understanding of its complexity, an appreciation for the factors that determine its expression in the clinical setting, and the implementation of sound clinical and pharmacological strategies.

ETIOLOGY AND EPIDEMIOLOGY

Activation of Nociceptive Pain Pathways

Nociception is the activation of primary sensory nerve fibers (nociceptors) by noxious stimuli (i.e., mechanical perturbations, intense temperatures, and chemicals) that are transduced into electrical potential. Nociceptors have free nerve endings in skin, mucosa, deep soma, and viscera. Nociceptor cell bodies are located in the trigeminal ganglion for innervation of the face. Nociceptors transmit electrical impulses from the periphery to the trigeminal ganglion where the information is processed through synaptic circuitry and transmitted to various parts of the brain. Because nociceptors transmit information toward the brain, they are called afferent neurons.

Tissue damage is the primary stimulus for nociceptor activation. Chemical agents released by injured cells (e.g., serotonin, histamine, bradykinin, prostaglandins, and other neuroactive substances) lead to nociceptor activation. Activated nociceptors release substance P and calcitonin gene-related peptide (CGRP) which initiate the inflammatory response to promote healing. Blood vessel dilation promotes the recruitment of immunocompetent cells. Mast cell degranulation releases histamine and serotonin, further increasing nociceptor sensitization and the generation of action potentials in afferent neurons.

Based on the degree of myelination, neurons are classified as A-fibers (alpha, beta, gamma, and delta subgroups), B-fibers, and C-fibers. A- and B-fibers are myelinated, whereas C-fibers are unmyelinated. Information generated by nociceptors are carried in afferent A delta– and C-fibers. Information delivered via A delta–fibers is transmitted rapidly to the central nervous system (CNS) and permits the perception of sharp, bright, well-localized (first) pain that is not particularly persistent but is immediately associated with tissue injury. Information delivered via C-fibers is transmitted to the CNS slowly and permits the perception of burning, aching, dull, and poorly localized, but persistent (second) pain.

Primary afferent nociceptors have cell bodies in the trigeminal nucleus or medullary dorsal horn (MDH) where they synapse with secondary afferent neurons. The neurotransmitter for primary afferent neurons is glutamate. The secondary afferent neurons travel to the thalamus, where they synapse with tertiary afferent neurons that have projections to the somatosensory cortex (localization of pain) and the limbic system (emotional aspects of pain).

Intrinsic Modulation of Nociception

Amplification

After tissue injury, as macrophages and other cells of the immune system invade the damaged area in an attempt to remove cell debris and to prevent...
or combat infection, the inflammatory process promotes the formation of prostaglandins, which enhance the effects of other algogenic substances on pain receptors. Tissue injury may also provoke an efferent sympathetic reflex, which decreases microcirculation in the area, producing ischemia and amplifying nociception at peripheral afferent terminals.

**Inhibition**

Inhibition of nociception can also occur at peripheral terminals of afferent nerves. Such effects are particularly prominent in painful inflammatory conditions, as resident immune cells in inflamed tissue express their endogenous ligands, opioid peptides. Corticotropin-releasing hormone and cytokines stimulate the release of these opioid peptides, resulting in local analgesia. Similarly, simultaneous activity in large myelinated fibers can modulate small-fiber transmission by activating inhibitory cells in the MDH.

Central control systems, by means of **efferent fibers**, can further inhibit signal transmission. A pain modulation pathway extends from the periaqueductal gray to the raphe magnus. High-density projections from the raphe magnus to the trigeminal nucleus contain substance P terminals and opiate receptors. Within this same region, there are small interneurons, which contain and, on activation, release endogenously produced opioid peptides (enkephalins, endorphins, and dynorphins).

**Perception of Pain**

The term **perception** when applied to pain refers to the awareness of a noxious sensation and the interpretation and attribution of meaning to the experience. While patients are surprisingly uniform in their perception of pain, they differ greatly in their reactions 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.

**Odontogenic Pain**

Complaints of anguish, postural displays, groaning, wincing, and grimacing are all equated with pain, along with limitation of normal activity (function), excessive rest, social withdrawal, and demand for medication. Most patients can attain satisfactory relief of odontogenic pain through an approach that incorporates primary dental care in conjunction with local anesthetics and the administration of analgesics.

**Local Anesthetic Agents**

Local anesthetic agents (LAs) are nonspecific inhibitors of peripheral sensory, motor, and autonomic pathways. They inhibit the conduction of action potentials in all afferent and efferent neurons such that sensory information is not transmitted effectively to the brain and motor impulses are not transmitted effectively to muscles. Consequently, the sequential loss of pain and temperature, proprioception, touch and pressure, and ultimately motor functions is typical. The ideal LA should provide profound reversible local anesthesia with rapid onset, satisfactory duration of action, and minimal adverse local or systemic effects.

Cocaine, a plant alkaloid found in the leaves of *Erythroxylon coca*, was the first LA to be discovered. However, cocaine’s untoward properties of CNS excitation and mood alteration, profound cardiac stimulation, intense vasocon-
strictive properties, and the development of psychological and physical dependence, preclude its use in routine clinical practice.

Currently available LAs have three structural domains: an aromatic nucleus, an amide group, and an ester or amide linkage connecting these two groups. Those agents connected by an ester (e.g., procaine, benzocaine) are referred to as **ester-linked LAs**, and those linked by an amide (e.g., lidocaine, mepivacaine, prilocaine, bupivacaine, and articaine) are called **amide-linked LAs**. The aromatic group influences the hydrophobicity of the drug; the ester or amide linkage influences the duration of action and side effects of the drug; and the amino group influences the rate of onset of action and potency of the drug.

**Pharmacodynamic Considerations**

Resting nerve fibers are electropositive on the outside and electronegative on the inside. In response to noxious stimuli, a transient reversal of this polarity (depolarization) results from an increase in neuronal permeability to sodium ions (Figure 3-1). Thereafter, the process of repolarization begins and continues until the resting neuronal membrane potential is restored behind the traveling impulse by the efflux of potassium ions.

LAs prevent impulse transmission by blocking sodium channels in neuronal membranes. The pKa (the pH at which a drug is 50% ionized and 50% un-ionized) of LAs is between 7.6 and 8.9. Only a small percentage of an LA will be in the un-ionized (free base) form at a tissue pH of 7.4; yet, it is the free base that crosses biological barriers, including the neuronal membrane, reestablishing equilibrium between the basic and cationic forms. The ionized form of LA binds sodium channels from the inside surface of the neuronal membrane and decreases or prevents a large transient increase in permeability to sodium ions.

**Pharmacokinetic Considerations**

**Absorption**

Following administration (topical or injection), while LAs diffuse to their site of action, they are also taken up by local tissues and are removed from the site of administration by the systemic circulation. The amount of LA absorbed into the systemic circulation and the potency of the LA determine the systemic toxicity of the agent. The rate of systemic absorption of LAs is a
function of their inherent chemical characteristics (i.e., lipid solubility and pKa), vascularity at the site of administration, and the presence or absence of a vasoconstrictor in the formulation.

**Distribution**

Once in the systemic circulation, LAs bind reversibly to albumin and alpha-1 acid glycoprotein. The volume of distribution ($V_d$) for less hydrophobic LA (e.g., procaine) is small. A more hydrophobic LA (e.g., bupivacaine) will have a greater $V_d$ and greater tissue binding (particularly the heart, lungs, liver, kidneys, brain, and cross the placenta).

**Metabolism and excretion**

The metabolism of ester-linked LAs takes place in the vascular compartment by plasma cholinesterases; this process is fast (minutes) and the resulting products are eliminated in the kidney. Amide-linked LAs are metabolized mainly in the liver by the CYP450 enzyme system. The metabolites are returned to the circulation and eliminated by the kidney. Metabolism is slowed in patients with cirrhosis or other liver diseases. Prilocaine and articaine may also be metabolized by plasma cholinesterases and some metabolism of amide-linked LAs can also occur in lung and kidney.

**Pharmacotherapeutic Considerations**

The vehicle for LAs is sterile water. Sodium chloride is added to produce isotonicity; hydrogen chloride is used to adjust the pH. Because LAs are weak bases, they form water-soluble salts with hydrochloric acid. These solutions are stable at a pH of 4.5 to 6.0. At this pH, LAs are primarily in their ionized forms. Once an agent is injected, the buffering capacity and pH of the extracellular fluid (pH 7.4) favor free-base formation, allowing for greater tissue penetration.

Vasoconstrictors (e.g., epinephrine, levonordefrin) are included in some LA formulations to slow the rate of absorption of the local anesthetic agent from the site of administration into the systemic circulation, thus increasing the duration of anesthetic action. Metabisulfite, which is an antioxidizing agent, is included in these formulations to minimize the oxidation of vasoconstrictors.

Currently available LAs (Table 3-1) may conveniently be divided into three categories based on their relative duration of anesthetic action. Procaine has a relatively short duration of action. Lidocaine, mepivacaine, prilocaine, and articaine are agents of intermediate duration. Bupivacaine will produce anesthesia of long duration. The choice of the agent and the technique used for its administration are important determinants of activity.

**Topical anesthesia**

Mucous membranes may be anesthetized by the topical (direct) application of aqueous or viscous formulations of benzocaine or lidocaine. Benzocaine 20% is an effective topical anesthetic agent when used before the injection of LAs. It has a relatively rapid onset and short duration of action and its systemic absorption through mucous membranes is limited. Lidocaine is available in 2% viscous, 5% ointment and liquid, and 10% spray formulations. Toxicity related to these agents has largely been attributed to the use of large doses with excessive systemic absorption. The ability of topical LAs to interfere with the pharyngeal phase of swallowing and thus cause aspiration has been documented.

**Infiltration and nerve block anesthesia**

Infiltration anesthesia comprises the injection of an LA solution directly into or adjacent to the area to be treated. In dentistry, there are several modified
<table>
<thead>
<tr>
<th>DRUGS AND FORMULATIONS</th>
<th>pKa</th>
<th>% FREE BASE AT pH 7.4</th>
<th>FDA RISK STATUS</th>
<th>mg/mL</th>
<th>TOXIC DOSE mg/kg (MAXIMUM RECOMMENDED DOSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine (Novocain)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2% plain (medical formulation)</td>
<td>8.9</td>
<td>3</td>
<td>C</td>
<td>20</td>
<td>6.0 (300)</td>
</tr>
<tr>
<td>Lidocaine (Xylocaine, others)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2% plain</td>
<td>7.9</td>
<td>24</td>
<td>B</td>
<td>20</td>
<td>4.5 (300)</td>
</tr>
<tr>
<td>2% with epinephrine 1:50,000</td>
<td>7.9</td>
<td>24</td>
<td>B</td>
<td>20</td>
<td>7.0 (200)</td>
</tr>
<tr>
<td>2% with epinephrine 1:100,000</td>
<td>7.9</td>
<td>24</td>
<td>B</td>
<td>20</td>
<td>7.0 (500)</td>
</tr>
<tr>
<td>2% with epinephrine 1:200,000</td>
<td>7.9</td>
<td>24</td>
<td>B</td>
<td>20</td>
<td>7.0 (500)</td>
</tr>
<tr>
<td>Mepivacaine (Carbocaine, others)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3% plain</td>
<td>7.6</td>
<td>39</td>
<td>C</td>
<td>30</td>
<td>6.6 (600)</td>
</tr>
<tr>
<td>2% with levonordefrin 1:20,000</td>
<td>7.6</td>
<td>39</td>
<td>C</td>
<td>20</td>
<td>6.6 (550)</td>
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<tr>
<td>Articaine (Septocaine)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4% with epinephrine 1:100,000</td>
<td>7.8</td>
<td>25</td>
<td>C</td>
<td>40</td>
<td>7.0 (500)</td>
</tr>
<tr>
<td>Prilocaine (Citanest)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4% plain</td>
<td>7.9</td>
<td>24</td>
<td>B</td>
<td>40</td>
<td>8.0 (600)</td>
</tr>
<tr>
<td>4% with epinephrine 1:200,000</td>
<td>7.9</td>
<td>24</td>
<td>B</td>
<td>40</td>
<td>8.0 (600)</td>
</tr>
<tr>
<td>Bupivacaine (Marcaine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5% with epinephrine 1:200,000</td>
<td>8.1</td>
<td>17</td>
<td>C</td>
<td>5</td>
<td>2.0 (90)</td>
</tr>
</tbody>
</table>
techniques to conventional infiltration anesthesia (e.g., intrapulpal, intraligamental). Nerve block anesthesia is associated with the injection of an LA around peripheral nerve trunks or nerve plexuses. This technique provides anesthesia to a greater anatomical area.

**Primary line drugs**

- **Lidocaine hydrochloride.** Lidocaine (Xylocaine, others), 2%, is the most commonly used LA. It is an amine-linked drug of moderate hydrophobicity, rapid onset of action, medium duration of action, and moderate potency. Formulations with epinephrine have a longer duration of action. Toxic effects are manifested mainly as CNS depression (drowsiness, tinnitus, twitching, and seizures) and decreased myocardial contractility.

- **Mepivacaine hydrochloride.** Mepivacaine (Carbocaine, others), 3% or 2%, has an onset and duration of action, potency, and toxicity similar to lidocaine. Mepivacaine may be used for short procedures in a 3% concentration without a vasoconstrictor. Mepivacaine, 2% with levarterenol, 1:20,000, is less likely to cause beta1-adrenergic receptor activation and cardiac stimulation than epinephrine.

- **Prilocaine hydrochloride.** Prilocaine (Citanest), 4%, has vasoconstrictive activity and will produce satisfactory anesthesia without a vasoconstrictor or with epinephrine 1:200,000. Common adverse drug effects are similar to those of lidocaine. However, prilocaine has been associated with a statistically significant increase in the incidence of paresthesia when compared with lidocaine or mepivacaine and may produce methemoglobinemia in susceptible patients.

- **Articaine hydrochloride.** Articaine (Septocaine), 4%, with epinephrine 1:100,000 is the newest amide-linked local anesthetic agent. It is unusual in that it has a thiophene nucleus. It also contains an ester group, which means that it can be partially metabolized by plasma cholinesterases. Articaine’s rapid metabolism in plasma may minimize its potential systemic toxicity. Common adverse drug effects are similar to those of lidocaine, but articaine, like prilocaine, is more likely to cause a statistically significant increase in the incidence of paresthesia when compared with lidocaine or mepivacaine and may produce methemoglobinemia in susceptible patients.

**Secondary line drug**

- **Bupivacaine hydrochloride.** Bupivacaine (Marcaine), 0.5% with epinephrine 1:200,000, is a long-acting local anesthetic agent. It is a highly hydrophobic, high-potency agent with long duration of action and should be used with caution in the young and the old. Common adverse drug effects are similar to those of lidocaine; however, its cardiotoxicity at higher concentrations limits its use.

**Tertiary line drug**

- **Procaine hydrochloride.** Procaine (Novocain), available only as a 30-mL medical formulation (2% without epinephrine), is a short-acting (low hydrophobicity), low-potency, ester-linked LA. It is degraded rapidly by plasma cholinesterases and excreted by the kidney. One of the metabolites of procaine is paraaminobenzoic acid (PABA), a highly allergenic compound. Procaine is the LA of choice for that rare patient with true hypersensitivity to amide-linked agents.

**Adverse Drug Events**

Accurate statistics on the frequency of untoward reactions to LAs (i.e., morbidity and mortality) are not readily available because few such cases have been reported. Estimates range from 1 death in 1.4 million local anesthetic administrations to 1 in 45 million. Despite an apparent excellent record of safety
Clinical Medicine and Therapeutics

Table 3-2. Clinical Manifestations of Local Toxic Effects

<table>
<thead>
<tr>
<th>EPITHELIAL TISSUE</th>
<th>NERVE TISSUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue edema</td>
<td>Anesthesia</td>
</tr>
<tr>
<td>Desquamation</td>
<td>Causalgia</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Neuritis</td>
</tr>
<tr>
<td>Decreased wound healing</td>
<td>Paresthesia</td>
</tr>
</tbody>
</table>

with LAs, clinicians must not compromise precautionary measures (e.g., attention to medical history, aspiration, and the use of minimal dose).

Local toxic reactions
Local toxicity primarily manifests as epithelial, vascular, or neural damage when the recommended dose of an LA is exceeded (Table 3-2). Most of these adverse drug effects are transient, but prolonged anesthesia or paresthesia of the lip or tongue may take 2 to 6 months to resolve. In rare instances, the neurological deficit may become permanent. (Refer to Chapter 2: Adverse Drug Events.)

Systemic toxic reactions
Systemic toxic reactions are usually associated with inadvertent intravascular injection, injection into a highly vascular area, altered detoxification, overdose, and injecting without a vasoconstrictor. The signs and symptoms of systemic toxicity predominate in the central nervous, respiratory, and cardiovascular systems, and they account for the majority of the adverse reactions to LAs (Table 3-3). A practical approach to determine the dosage of LAs is based on the patient’s weight (Table 3-1).

Methemoglobinemia. Methemoglobinemia is a relatively uncommon toxic reaction to prilocaine, articaine, or benzocaine in susceptible patients. Metabolites of these drugs bind hemoglobin molecules and interfere with their oxygen-carrying capacity. Cyanosis in the absence of cardiopulmonary symptoms, nausea, sedation, seizures, and coma has been reported in severe overdose.

Sympathetic reactions
LA formulations may contain 1:100,000 (0.01 mg/mL) epinephrine, 1:200,000 (0.005 mg/mL) epinephrine, 1:50,000 (0.02 mg/mL) epinephrine, or 1:20,000 (0.05 mg/mL) levonordefrin, which physiologically is equivalent to 1:100,000 epinephrine. Healthy adults can safely receive up to 0.2 mg of epinephrine and 1.0 mg of levonordefrin per visit.

Table 3-3. Clinical Manifestations of Systemic Toxic Effects

<table>
<thead>
<tr>
<th>Lightheadedness</th>
<th>Lethargy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremors</td>
<td>Coma</td>
</tr>
<tr>
<td>Disorientation</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Altered mood</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Slurred speech</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Visual and auditory disturbances</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Clonic seizures</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
</tr>
</tbody>
</table>
The inadvertent intravascular injection of an LA containing a vasoconstrictor, the use of an LA containing a high concentration of a vasoconstrictor, the potentiation of the injected vasoconstrictor by endogenous catecholamines, and concomitant therapy with other sympathomimetic agents may contribute to adverse sympathetic effects (Table 3-4).

Vasoconstrictors must be avoided in patients under the influence of cocaine. There are also a number of clinical situations where the judicious use of vasoconstrictors is imperative. These include treating patients with blood pressure in excess of 180/110, patients with severe cardiovascular disease (i.e., recent myocardial infarction [more than 7 days but less than 1 month], unstable angina pectoris, decompensated heart failure, severe valvular disease, supraventricular arrhythmias, symptomatic ventricular arrhythmias, supraventricular arrhythmias with uncontrolled ventricular rate, and high-grade AV block), and patients with uncontrolled hyperthyroidism.

Exercise capacity is a simple and reliable index to estimate cardiac function in patients with heart disease. It has been shown that the hemodynamic effects of infiltration anesthesia (72 mg of lidocaine and 0.045 mg of epinephrine) were less than those produced by ergometric stress testing at 25 watts in young patients and at 15 watts in older subjects. The workload of ergometric stress testing at these levels is about four metabolic equivalents (METs).

Four METs are approximately the same as the workload produced by climbing a flight of stairs, walking 4.8 km/hour, doing light yard work (raking leaves, weeding, or pushing a power mover), painting, or doing light carpentry work. Based on this evidence, 0.045 mg of epinephrine can be administered safely to patients who can tolerate the activities noted above with minimal or no symptoms such as shortness of breath, chest pain, or fatigue. Based on U.S. formulations of LAs, 0.045 mg of epinephrine is equivalent to the amount in 4.5 mL of any LA with epinephrine 1:100,000.

It has also been documented that oral surgical procedures (e.g., tooth extraction, alveoplasty, soft tissue biopsy) under LA (lidocaine 2% with epinephrine 1:100,000 or bupivacaine 0.5% with epinephrine 1:200,000) did not affect cardiac rhythm in patients with cardiovascular diseases (i.e., hypertension, coronary artery disease [e.g., angina pectoris, previous myocardial infarction], conduction abnormalities, and heart failure). The epinephrine dose administered ranged from 0.010 to 0.079 mg, or the equivalent of 1.0 to 7.9 mL of any LA with epinephrine 1:100,000.

**Allergic reactions**

In the past, allergic reactions to LAs were accurately attributed to procaine. The antigenicity of procaine and other ester compounds lies in their structural
formula. The breakdown of the ester-linked LAs proceeds via hydrolysis, which is catalyzed by plasma cholinesterase. One of the breakdown products, PABA, a highly antigenic compound, is capable of eliciting the formation of antibodies or sensitized lymphocytes.

True allergy to amide-linked LAs is rare. In the past, many amide-linked LAs contained methylparaben, a germicide with bacteriostatic and fungistatic properties. Methylparaben, an alkyl ester of PABA, is structurally similar to PABA, suggesting the mechanism for hypersensitivity. Sulfites, widely used as antioxidants in food, are also found in local anesthetic solutions containing a vasoconstrictor. Angioedema and urticaria have been reported following the administration of LAs containing antioxidants (metabisulfite), but there appears to be no cross-allergenicity with sulfonamide antibacterial agents. (Refer to Chapter 2: Adverse Drug Events and Chapter 7: Management of Medical Emergencies in the Oral Health Care Setting.)

Psychomotor reactions
Psychomotor reactions are likely to occur in the oral health care setting in response to emotional stress brought on by pain, surgical manipulation, the sight of blood, or heat. Psychomotor reactions are seen most commonly in young adults.

Vasopressor syncope. Patients with vasopressor syncope experience cerebral ischemia as a result of dilation of resistance vessels secondary to a generalized, progressive autonomic discharge with an initial adrenergic and a compensatory cholinergic component (Table 3-5). The adrenergic component produces pallor, tachycardia, hyperventilation, clonic activity, and pupillary dilation. The cholinergic component is characterized by perspiration, nausea, salivation, hypotension, bradycardia, and syncope. (Refer to Chapter 7: Management of Medical Emergencies in the Oral Health Care Setting.)

Hyperventilation. Hyperventilation is a state of decreased systemic carbon dioxide concentration. Affected patients usually have a history of dyspnea often precipitated by anxiety, but it may also be from hypoxia associated with cardiopulmonary disease. Signs and symptoms include paresthesia (burning or prickling feeling) of the extremities and face accompanied by chest tightness, dizziness, and a dry mouth. Occasionally, cerebral vasoconstriction may lead to syncope. Tonic muscle spasms are diagnostic. (Refer to Chapter 7: Management of Medical Emergencies in the Oral Health Care Setting.)

Local anesthetic agents, epinephrine, and pregnancy
There is no evidence that any LA is teratogenic in humans; however, drugs in general should be administered with caution for pregnant women. To assist

<table>
<thead>
<tr>
<th>Table 3-5. Clinical Manifestations of Vasopressor Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenergic Component</strong></td>
</tr>
<tr>
<td>• Pallor</td>
</tr>
<tr>
<td>• Tachycardia</td>
</tr>
<tr>
<td>• Hyperventilation</td>
</tr>
<tr>
<td>• Papillary dilatation</td>
</tr>
<tr>
<td>• Clonic activity</td>
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<td></td>
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</tbody>
</table>
Medical Management of Odontogenic Pain

Medical practitioners, the U.S. Food and Drug Administration (FDA) has established a code for categorizing drugs according to their potential to cause fetal injury (Table 3-1). (Refer to Chapter 1: General Principles of Pharmacology and Chapter 2: Adverse Drug Events.) Lidocaine 2% with epinephrine 1:100,000 (FDA Pregnancy Category rating of B) is the LA of choice in the treatment of pregnant women. While vasoconstrictors can adversely affect uterine blood flow and prolong labor, studies have not documented adverse fetal effects with dosages less than 0.01 mg of epinephrine.

**ANALGESICS**

Three types of analgesics are available for the management of acute odontogenic pain: cyclooxygenase (COX) inhibitors (Table 3-6), opioid analgesics (Table 3-7), and adjuvant drugs. An adjuvant may either enhance the efficacy of an analgesic or it may have an analgesic activity of its own. Caffeine in doses of 65 to 200 mg enhances the analgesic effect of acetylsalicylic acid (ASA), acetaminophen (APAP), and ibuprofen in dental and other acute pain syndromes. 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 produce analgesia in some patients with pain of inflammatory origin.

**Pharmacodynamic Considerations**

**Cyclooxygenase inhibitors**

Prostaglandins are ubiquitous endogenous substances known to modulate inflammation, affect vascular tone and permeability, and influence pain perception. At least three cyclooxygenase isoenzymes are known to catalyze the rate-

<table>
<thead>
<tr>
<th><strong>Table 3-6. Selected Cyclooxygenase Inhibitors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUGS</strong></td>
</tr>
<tr>
<td>Acetylsalicylic acid (Aspirin [OTC], Anacin [OTC], others)</td>
</tr>
<tr>
<td>Acetaminophen (Tylenol [OTC], others)</td>
</tr>
<tr>
<td>Ibuprofen (Advil [OTC], Nuprin [OTC], Motrin, others)</td>
</tr>
<tr>
<td>Naproxen (Naprosyn)</td>
</tr>
<tr>
<td>Naproxen sodium (Aleve [OTC], Anaprox, others)</td>
</tr>
</tbody>
</table>

*Refer to Chapter 1: General Principles of Pharmacology.

OTC, over the counter.
Table 3-7. Selected Opioid-Receptor Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Pregnancy Risk Category*</th>
<th>Restrictions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>With ASA, 30/325 mg (Empirin with codeine)</td>
<td>C</td>
<td>C-III</td>
</tr>
<tr>
<td></td>
<td>With APAP, 30/325 mg (Tylenol with codeine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>With ASA, 5/500 mg (Lortab ASA)</td>
<td>C</td>
<td>C-II</td>
</tr>
<tr>
<td></td>
<td>With ibuprofen, 7.5/200 mg (Vicoprofen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>With APAP, 5/500 mg (Vicodin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg (Ultram) With APAP 37.5/325 mg (Ultracef)</td>
<td>C</td>
<td>Rx</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>With ASA, 5/325 mg (Percodan)</td>
<td>C</td>
<td>C-II</td>
</tr>
<tr>
<td></td>
<td>With APAP, 5/500 mg (Percocet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>With ibuprofen, 5/400 mg (Combunox)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Refer to Chapter 1: General Principles of Pharmacology.

APAP, acetaminophen; ASA, acetylsalicylic acid.

Limiting step of prostaglandin synthesis: COX-1 (acetylsalicylic acid [ASA] and other nonsteroidal anti-inflammatory agents [NSAIDs]), COX-2 (celecoxib), and COX-1 variant (acetaminophen [APAP]). COX-1 is expressed in most tissues, including platelets, and it is also thought to protect the gastric mucosa. COX-2 is expressed primarily in the brain and kidneys and can be induced in other tissues (especially in association with inflammation), but it is not found in abundance in platelets. COX-1 variant is expressed primarily in the CNS. To varying degrees, ASA and other NSAIDs block all three COX isomers. In therapeutic doses, celecoxib selectively inhibits COX-2. APAP, a relatively weak inhibitor of peripheral prostaglandin biosynthesis, is highly effective in inhibiting COX-1 variant in the CNS. COX inhibitors alter sensitivity (i.e., increase the pain threshold) to noxious stimuli, but they all reach a ceiling dose for their maximum analgesic effect.

Opioid-receptor agonists

Opioid-receptor agonists produce analgesia by interacting with opioid receptors, which are also the natural binding sites for a number of endogenous peptides (beta-endorphins, endomorphins, enkephalins, and dynorphins). Opioid receptors are found in the peripheral nervous systems and CNS and their natural ligands appear to inhibit calcium influx into neurons and the release of substance P from neuron terminals. The affinity of a particular opioid-receptor
Table 3-8. Opioid Receptors

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Primary Endogenous Ligands</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>mu (MOP or OP₃)</td>
<td>Endorphins and endomorphins</td>
<td>• Analgesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Euphoria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decreased respiration</td>
</tr>
<tr>
<td>delta (DOP or OP₃)</td>
<td>Enkephalins</td>
<td>• Analgesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decreased respiration</td>
</tr>
<tr>
<td>kappa (KOP or OP₂)</td>
<td>Dynorphins</td>
<td>• Analgesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dysphoria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No respiratory effect</td>
</tr>
<tr>
<td>Opioid-receptor-like</td>
<td>Orphanin FQ or nociceptin</td>
<td>• Analgesia</td>
</tr>
<tr>
<td>(ORL or OP₄)</td>
<td></td>
<td>• No respiratory effect</td>
</tr>
</tbody>
</table>

Agonist to a specific receptor subtype explains the therapeutic and adverse effects of opioid-receptor agonists (Table 3-8). Most pain can be relieved with opioid analgesics if the drugs are given in adequate dosages. Stronger opioid agonists, such as morphine, have no clinically relevant ceiling effect to analgesia. As the dosage is raised, analgesic effect increases in a log-linear function until either analgesia is achieved or somnolence occurs.

Pharmacokinetic Considerations

Cyclooxygenase inhibitors

COX inhibitors 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. The rate of absorption is determined by the formulation and pKa of the drug, the pH at the mucosal surface, vascularity of the absorptive surface, and gastric emptying time. Because absorption occurs primarily by passive diffusion of lipid-soluble molecules across the gastrointestinal mucosal membranes, the rate of absorption is decreased in an alkaline environment. After absorption, COX inhibitors are distributed throughout most body tissues and fluids, and cross the placenta. They are metabolized in many tissues but particularly in liver endoplasmic reticulum and mitochondria. The metabolism of therapeutic doses normally follows first-order kinetics; however, after larger doses, the enzymes that metabolize these drugs become saturated, which leads to increased half-lives. Metabolites are excreted primarily by the kidneys as water-soluble conjugates.

Opioid-receptor agonists

Opioid-receptor agonists are readily absorbed from the gastrointestinal tract but not all are suitable for oral administration because of significant first-pass metabolism in the liver. All opioids are to some degree protein bound in plasma. The free forms readily leave the blood and accumulate in organs with high parenchyma (i.e., kidney, liver, lung, and spleen) and cross the blood-brain barrier. During pregnancy, placental transfer occurs. The decline in opioid plasma levels parallels the decline in opioid analgesia and is coincident with
the appearance of metabolites in the liver. The major pathway for detoxification of opioids is conjugation with glucuronic acid. The major route of elimination of opioids and their metabolites is by glomerular filtration.

**Pharmacotherapeutic Considerations**

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. Some patients may respond better to one COX inhibitor or COX-inhibitor/opioid combination than to another. Currently available formulations may not be optimal in the management of all pain of odontogenic origin, and clinicians may have to prescribe more than one analgesic to be administered concurrently to achieve maximal results. Prescribing two drugs (at therapeutic doses) with similar mechanisms of action has no rational pharmacological basis, but prescribing two drugs (at therapeutic doses) with different mechanisms of action is good medicine. Table 3-9 represents sample prescriptions for the treatment of acute odontogenic pain.

**Primary line drugs (mild pain)**

ASA, the standard for the comparison and evaluation of orally effective analgesics, is effective in the treatment of most types of mild pain. Unlike other NSAIDs, however, a single dose of ASA irreversibly inhibits platelet function for the 8- to 10-day life of the platelet, interfering with hemostasis and prolonging the bleeding time. A single dose of ASA can also precipitate asthma in ASA-sensitive patients. High doses or chronic use of ASA can cause gastropathy.

APAP, 650 mg, is as effective as ASA 650 mg, with similar potency and time-effect curve. Maximum analgesic effect usually occurs with single doses between 650 and 1300 mg; however, it does not have the antiplatelet and adverse gastrointestinal effects, and the frequent renal and possible cardiovascular toxicity associated with NSAIDs. Most healthy patients can take up to 4 g daily with no adverse effects.

APAP, 650 mg, is less effective than 200 mg of ibuprofen; however, 200 mg of ibuprofen in combination with 650 mg of APAP is more effective than 200 mg of ibuprofen or 650 mg of APAP alone. Ibuprofen, 400 mg, is superior to 200 mg of ibuprofen with longer duration. Naproxen sodium, 440 mg, is comparable to 400 mg of ibuprofen with longer duration.

Since ASA’s principal use today is in low doses as a platelet inhibitor and APAP has no clinically useful anti-inflammatory activity, over-the-counter (OTC) formulations of ibuprofen, 200 mg (Advil, Nuprin, others), or naproxen sodium, 220 mg (Aleve, others), are the drugs of choice for the management of mild odontogenic pain.

**Secondary line drugs (moderate pain)**

In single full doses, most NSAIDs are more effective analgesics than full doses of ASA and APAP for moderate pain and some have shown equal or greater analgesic effect than usual doses of an oral opioid combined with ASA or APAP. The adverse effects of NSAIDs are qualitatively similar to those of ASA. They can precipitate asthma and anaphylaxis in ASA-sensitive patients. Unlike ASA, however, NSAIDs cause reversible inhibition of platelet aggrega-
### Table 3-9. Sample Prescriptions (3-Day Regimen) for the Treatment of Acute Odontogenic Pain

#### Primary Line of Treatment

<table>
<thead>
<tr>
<th>OTC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA, 500-mg tabs, 2 tabs QID, max. daily dose 4,000 mg</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (Advil), 200-mg tabs, take 2 tabs QID, max. daily dose 2,400 mg</td>
<td></td>
</tr>
<tr>
<td>Naproxen (Aleve), 200-mg tabs, take 2 tabs QID, max. daily dose 1,375 mg</td>
<td></td>
</tr>
<tr>
<td>APAP, 500-mg tabs, take 2 tabs QID, max. daily dose 4,000 mg</td>
<td></td>
</tr>
</tbody>
</table>

#### Secondary Line of Treatment

<table>
<thead>
<tr>
<th>Rx</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen, 800-mg tabs</td>
<td>Disp. 10 tabs</td>
</tr>
<tr>
<td>Sig. Take 1 tab TID until all tabs are taken</td>
<td></td>
</tr>
<tr>
<td>Naproxen sodium, 275-mg tabs</td>
<td>Disp. 10 tabs</td>
</tr>
<tr>
<td>Sig. Take 2 tabs stat then 1 tab TID until all are taken</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone with ibuprofen, 7.5-mg/200-mg tabs</td>
<td>Disp. 24 tabs</td>
</tr>
<tr>
<td>Sig. Take 2 tabs QID until all are taken</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone with APAP, 5-mg/500-mg tabs</td>
<td>Disp. 24 tabs</td>
</tr>
<tr>
<td>Sig. Take 2 tabs QID until all are taken</td>
<td></td>
</tr>
<tr>
<td>Tramadol with APAP, 37.5-mg/325-mg tabs</td>
<td>Disp. 24 tabs</td>
</tr>
<tr>
<td>Sig. Take 2 tabs QID until all are taken</td>
<td></td>
</tr>
</tbody>
</table>

#### Tertiary Line of Treatment

<table>
<thead>
<tr>
<th>Rx</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone with ibuprofen, 5-mg/400-mg tabs</td>
<td>Disp. 24 tabs</td>
</tr>
<tr>
<td>Sig. Take 2 tabs QID until all are taken</td>
<td></td>
</tr>
<tr>
<td>Oxycodone with APAP, 7.5-mg/500-mg tabs</td>
<td>Disp. 24 tabs</td>
</tr>
<tr>
<td>Sig. Take 2 tabs QID until all are taken</td>
<td></td>
</tr>
</tbody>
</table>

APAP, acetaminophen; ASA, acetylsalicylic acid; OTC, over the counter.

Ibuprofen, 400 mg, has been shown to be more effective than 60 mg of codeine, more effective than 650 mg of ASA with 60 mg of codeine, and more effective than 600 mg of APAP with 60 mg of codeine. Hydrocodone, 15 mg, with 400 mg of ibuprofen has been shown to be superior to 400 mg of ibuprofen alone; but it has also been shown that 800 mg of ibuprofen has a longer duration of action than 400 mg of ibuprofen and has a dose-dependent increase...
in its analgesic and anti-inflammatory efficacy. Consequently, 800 mg of ibuprofen is the drug of choice for the management of moderate odontogenic pain.

**Tramadol.** Tramadol is a nonopioid opioid-receptor agonist, which also blocks the reuptake of norepinephrine and serotonin. It appears to have fewer associated adverse effects than opioid analgesics. In the management of odontogenic pain, 50 mg of tramadol is equianalgesic to 60 mg of codeine. In patients with dental pain, two orally administered fixed combination tablets of tramadol/APAP, 37.5/235 mg, are more effective than one tablet and as effective as hydrocodone/APAP, 10/650 mg. Tramadol in combination with APAP may be an appropriate alternative for the management of odontogenic pain in those situations where NSAIDs or opioid analgesics are contraindicated.

**Tertiary line drugs (severe pain)**

Oxycodone, 5 mg, with 400 mg of ibuprofen has been shown to be superior to oxycodone, 5 mg, with 325 mg of APAP, which was still superior to hydrocodone 7.5 mg with 500 mg of APAP. Clearly, oxycodone in combination with ibuprofen is the drug of choice for the management of severe odontogenic pain.

**Adverse Drug Events**

**Cyclooxygenase inhibitors**

**Intolerance.** Uncommonly, COX inhibitors can cause IgE-dependent hypersensitivity reactions leading to vasomotor collapse. Intolerance to NSAIDs is most likely to occur in patients with a history of asthma, nasal polyps, and chronic urticaria. A single dose of these agents can precipitate asthma in susceptible patients, probably related to COX-1 inhibition, which results in increased levels of leukotrienes. A history of rhinorrhea, urticaria, angioedema, or bronchospasm occurring within 3 hours after exposure is an acceptable method of determining intolerance. APAP is usually well tolerated in recommended therapeutic dosages. However, an erythematous or urticarial rash may occur occasionally, accompanied at times by fever and mucosal lesions. The mechanism of intolerance to APAP is unknown.

**Gastropathy.** Therapeutic doses of NSAIDs may cause epigastric distress, nausea, and vomiting. They can also exacerbate the symptoms of peptic ulcer disease and, with long-term use, bleeding, ulceration, and perforation can occur. Gastric bleeding induced by NSAIDs is painless and may lead to iron-deficiency anemia. COX-2 inhibitors have been associated with abdominal pain, diarrhea, and dyspepsia.

**Antithrombotic effects.** NSAIDs impair platelet adhesion to tissue components and platelet aggregation primarily through the inhibition of thromboxane A2 synthesis. ASA irreversibly inhibits platelet function for the lifetime of the platelet, or about 8 to 10 days. In contrast to ASA, platelet inhibition is reversible and short-lived with therapeutic doses of other NSAIDs. Platelet function returns to normal when most of the drug has been eliminated from the body. However, in the presence of bleeding diatheses (hereditary, acquired, or drug induced), the antiplatelet effect of these agents may also contribute to serious bleeding. APAP appears to be a suitable substitute in patients with peptic ulcer disease, hemorrhia, or other bleeding disorders, and those taking anticoagulants.

**Pregnancy-related events.** There is no evidence that therapeutic doses of NSAIDs cause fetal abnormalities other than reduced birth weight with ASA.
However, an increased incidence of postpartum bleeding has been observed in patients taking NSAIDs. In pregnant patients, APAP is a suitable substitute for NSAIDs in the management of pain.

**Hepatic toxicity.** Adverse hepatic reactions have been reported in association with most NSAIDs. They appear to be idiosyncratic and often dose-related. Predisposing factors for toxic reactions include advanced age, decreased renal function, and collagen vascular diseases. Lower dosages of these drugs should be used when factors predisposing to liver toxicity are present; monitoring liver function test results in patients with a history of long-term use is reasonable.

APAP is metabolized primarily by hepatic conjugation. In high doses, APAP is converted by the CYP2E1 isoenzyme into a hepatotoxic metabolite. (Refer to Chapter 2: Adverse Drug Events.) Ethanol abuse and malnutrition may enhance such toxicity even at therapeutic doses. 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.

**Renal toxicity.** COX inhibitors decrease the synthesis of renal prostaglandins, decrease renal blood flow, cause fluid retention, and may precipitate renal failure in susceptible patients. Risk factors include old age, chronic renal insufficiency, congestive heart failure, cirrhosis, and concurrent diuretic use.

**Opioid-receptor agonists**

**Gastropathy.** Nausea, vomiting, and constipation are the most common adverse effects of opioid analgesics. Nausea and vomiting are direct results of stimulation of the chemoreceptor trigger zone in the medulla. Depression of the vomiting center occurs late in the course of intoxication. Opioid-induced constipation is a result of decreased mobility associated with an increase in the tone of the anterior portion of the stomach.

**Intolerance.** Allergic reactions to opioid analgesics are rare. However, some opioids are able to induce histamine release from mast cells and cause peripheral vasodilatation and orthostatic hypotension (pseudoallergic reaction). The cutaneous blood vessels tend to dilate around the “blush areas” (e.g., face, neck, upper thorax). (Refer to Chapter 2: Adverse Drug Events.)

**Cardiovascular effects.** Opioids promote the release of histamine. In the supine patient, this may lead to orthostatic hypotension. In patients with coronary artery disease, morphine decreases oxygen consumption, making it the preferred analgesic in patients with ischemic heart disease.

**Respiratory effects.** Opioids depress respiratory chemoreceptor sensitivity to carbon dioxide. Concurrent administration of oxygen may cause apnea. Carbon dioxide retention produces intracranial vasodilatation and may aggravate increased intracranial pressure. Opioids should be used with great caution in cases of head injury, the elderly, those otherwise debilitated, and patients with pulmonary disease, particularly severe asthma, because of cough reflex suppression, impairment of ciliary activity, and aggravation of bronchospasm.

**Effects on the central nervous system.** Opioids modulate mood and behavior, causing drowsiness and euphoria in some, anxiety and dysphoria in others. They produce miosis as a result of an excitatory action on the autonomic segment of the nucleus of the oculomotor nerve. The miosis is marked and pinpoint pupils are pathognomonic of opioid use/abuse.

**Effects on pregnant women and nursing infants.** The use of opioids in the pregnant or nursing patient is discouraged because of their general CNS...
depressant effects on the fetus and infant. However, short-term use of therapeutic doses of codeine in combination with APAP is appropriate for the management of moderate-to-severe odontogenic pain.

**Effects on geriatric patients.** A paradoxical sensitivity to opioids in the elderly is not uncommon. Frequently, the dosages must be reduced by as much as one-half to one-fourth of the usual therapeutic dosage to avoid both toxic and paradoxical effects.

**Tolerance.** Tolerance is influenced by dose, frequency (long-term use), and the specific opioid administered. Cross-tolerance among opioids has been observed. Tolerance develops to most of the adverse effects of opioids, including respiratory and CNS depression, at least as rapidly as tolerance to the analgesic effect. However, no tolerance develops to their gastrointestinal (constipation) and papillary (miosis) actions.

**Dependence.** Patients who take opioids for acute pain rarely experience euphoria and even more rarely develop psychological dependence or addiction to their mood-altering effects. Clinically significant dependence develops only after several weeks of treatment with relatively large doses. Withdrawal symptoms include dilated pupils, rapid pulse, goose flesh, muscle jerks, a flulike syndrome, vomiting, diarrhea, tremors, yawning, and then sleep.

**Overdose.** Constricted pupils (miosis), depressed to absent respiration with cyanosis (depressed respiratory chemoreceptor sensitivity to carbon dioxide), hypotension (sometimes shock), hypothermia, sedation, stupor, coma, and convulsions characterize overdose. The respiratory depressant effects of various opioid analgesics are comparable with equianalgesic doses. Naloxone, a narcotic antagonist, will reverse apnea and coma that results from opioid toxicity. Seizures can be treated with diazepam.

**MEDICAL MANAGEMENT OF NEUROPATHIC PAIN**

Unlike patients with nociceptive pain, patients with neuropathic pain generally do not respond to conventional analgesic therapy. The treatment of neuropathic pain disorders with psychotropic pharmacotherapeutic agents is an evolving area of therapy. Tricyclic antidepressants, such as amitriptyline and imipramine, and anticonvulsants, such as carbamazepine, clonazepam, valproic acid, gabapentin, lamotrigine, topiramate, and phenytoin, are effective in the management of many neuropathic pain syndromes. The use of these medications requires meticulous titration and laboratory screening before and during therapy.

**CONCLUSION**

In practice, the efficacy of any particular local anesthetic agent or analgesic in a specific patient will be determined by the degree of anesthesia or analgesia produced following dosage escalation through a range limited by the development of adverse effects. Clinicians should prescribe medication at high enough dosage, soon enough, often enough, and long enough; they should prescribe as they would wish to receive.

**BIBLIOGRAPHY**
