Analgesics in Dentistry

Focusing in on non-opioid medications

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Analgesics in Dentistry: Focusing in on non-opioid medications

ABSTRACT

Historically, management of acute odontogenic pain in adolescents and adults has typically been accomplished through an approach that incorporated nonparenteral opioid and/or non-opioid analgesics. However, the availability of opioid analgesics has resulted in epidemic levels of opioid abuse and addiction. Alternative treatment strategies utilizing non-opioids are preferable for management of acute pain, where indicated, including moderate to severe pain. Non-opioids include NSAIDs, acetaminophen, and combination medications, and are more, or as, effective as opioids. This article reviews opioid medications before focusing on non-opioid analgesics, as both monotherapy and combination therapy, for the safe and effective management of acute postprocedural pain in dentistry.

EDUCATIONAL OBJECTIVES

The overall goal of this course is to provide information on non-parenteral analgesics used in dentistry. After completing this article, the reader will be able to:

1. Describe opioid medications and aspects of the new ADA policy on opioids.
2. List and describe ingested nonsteroidal anti-inflammatory drugs (NSAIDs) used in dentistry for pain management.
3. Describe an inhaled NSAID that can be used for acute pain management.
4. Review findings from systematic reviews and trials comparing opioid and non-opioid analgesics.

Analgesics are prescribed and/or recommended to dental patients to relieve pain, which may be acute or longer-term chronic in nature. Pain experienced following oral maxillofacial surgery is acute pain, while an example of chronic pain would include patients with long-term temporomandibular joint pain associated with temporomandibular joint disease. Analgesics for postprocedural pain management are mainly used following oral maxillofacial surgery for extractions, implant placement, bone grafting, endodontic therapy, and periodontal surgery. However, they may also be recommended and prescribed preprocedurally for the management of postprocedural pain. The main focus of this article is the use of nonparenteral analgesics that are ingested orally or administered nasally for the relief of acute dental pain in adults. Analgesic medications used in dentistry include opioid and non-opioid medications, typically given orally.
Understanding Pain

Pain has often been defined as an unpleasant experience that results from actual or perceived damage to tissue. It is the result of a variety of physical and psychological responses to tissue injury, most notably inflammation. For dental and other therapies that involve damage and injury to oral tissues, the experience of pain is unfortunately a consequence of that therapy. Acute pain is a protective, physiological response that warns us of the danger of bodily injury and bodily injury that has already occurred. Chronic pain, in contrast, is pain of long duration. Pain may also be categorized as nociceptive or neuropathic pain.

Nociceptive pain

The process of nociception involves the transmission of pain impulses to the brain via nociceptors, and the processing/responses to stimuli that are damaging, or potentially damaging, to tissues. Clinically, this is seen when tissue damage and inflammation occur as a result of trauma, surgery, inflammation, infection, and ischemia. Nociceptors are afferent sensory neurons located in numerous tissues throughout the body, including skin, muscles, and bone. They respond to mechanical stimuli, such as pressure or swelling, thermal stimuli (heat or cold), and chemical stimuli from a variety of inflammatory mediators released from damaged cells, including cytokines, histamines, prostaglandins, and leukotrienes. Nociceptors have a high depolarization threshold. Thus, to become active, nociceptors require mechanical or thermal stimuli of an intensity which would probably damage healthy tissue. Prostaglandins sensitize nociceptors to activate at lower-intensity stimuli.

A complex set of "pathways" is involved in transmitting pain messages from the periphery to the central nervous system. The pain impulse is transmitted from the site of the injury along the ascending peripheral nociceptor fibers to the dorsal horn in the spinal cord. Nociceptive fibers may be classified as either type A or type C nerve fibers. Type A nerve fibers are myelinated and conduct pain rapidly, which is perceived as sharp, bright, “pinprick” pain. Type C nerve fibers are non-myelinated and, thus, conduct pain slowly, which is perceived as a dull, throbbing ache or as a burning pain. Ascending pathways travel up the spinal cord toward the brain carrying sensory information to the brain. Conversely, descending pathways travel down the spinal cord and allow the brain to control body movement. Ultimately, the ascending peripheral nociceptors synapse with central neurons at the dorsal horn of the spinal cord to transmit the message to the brain stem, aided by excitatory neurotransmitters including glutamate, bradykinin, and substance P. The pain impulse is then transmitted from the spinal cord to the brain stem and thalamus, where it is processed by the thalamus and then sent to the somatosensory cortex and limbic system, where perception of pain takes place.

The perception of pain is the result of pain transmission and occurs when pain becomes part of the patient’s conscious awareness. The somatosensory cortex governs the perception and interpretation of pain impulses, including identifying the location and intensity of the pain, and comparing it to past painful experiences. The reticular system governs the autonomic and motor response to pain, such as trying to remove the tissue from the source of injury, as well as the affective-motivational response to pain, such as assessing the tissue for any obvious injury. The limbic system governs the emotional and behavioral responses to pain, including attention, cognition, and mood, also in comparison to past painful experiences.

Transmission of pain to the brain may be down-regulated by inhibitory interneurons and efferent projections from descending nerve fibers. Descending inhibition involves the release of inhibitory neurotransmitters that block, or partially block, the transmission of pain impulses, and therefore produce analgesia. Inhibitory
neurotransmitters involved with the modulation of pain include endogenous opioids, serotonin, gamma-aminobutyric acid, and endogenous cannabinoids.\textsuperscript{5,6} Endogenous pain modulation helps to explain the wide variations in the perception of pain and the emotional response to pain from patient to patient based on the same stimulus/stimuli.

Expression of cyclooxygenase (COX), consisting of COX-1 and COX-2, plays a significant role in acute pain. In one study evaluating COX levels before and after extraction of third molars, COX expression was a significant contributor to the onset of pain.\textsuperscript{7}

**Neuropathic Pain**

Some patients report pain in the absence of actual tissue damage. Neuropathic pain is pain caused by an injury or dysfunction of either the peripheral or the central nervous system. It results from neuronal sensitization by inflammatory mediators, including neuropeptides, and chemicals (chemotherapeutics), and may be a motor, sensory, or autonomic dysfunction. These agents are secreted by A-delta and C neuronal fibers. Pro-inflammatory cytokines such as interleukin-2 (IL-2, IL-6, IL-1β) and tumor necrosis factor alpha (TNFα) also function as neuronal sensitizers.\textsuperscript{4} In general, peripheral nociceptors become sensitized by injury such that patients have a lower threshold for firing and have an increased response to stimuli.\textsuperscript{8} The persistent pain is both distressing for the patient and confusing, since it appears to the patient that pain has become dissociated from actual tissue damage. As a result, these patients avoid any activity which may worsen this pain and immobility becomes an issue. One example is avoidance of swallowing or jaw movement by patients with oral mucositis.\textsuperscript{9} Spontaneous or continuous pain may be experienced with neuropathic pain.

Ultimately, pain is very subjective and difficult to measure or even to quantify. Thus, treating pain requires an understanding of its complexity and the factors that determine its expression.

**Opioid Medications**

Orally administered opioid analgesics include codeine, oxycodone, and hydrocodone, and are formulated as combinations of an opioid and a non-opioid. (Table 1) Vicodin, a combination of hydrocodone and acetaminophen, was reported to be the most commonly prescribed opioid following oral maxillofacial surgery.\textsuperscript{10} Opioid prescribing started to increase, and use of other analgesics to decrease, during the 1990s and after, when widespread promotion of opioids for pain management surged and support for their use increased among healthcare professionals and the general public.\textsuperscript{11,12}

By 2009, the vast majority of hydrocodone and oxycodone used globally was prescribed in the United States. In a review of prescription data from 2010 through 2015 for patients with private health insurance, 17% of all first prescriptions for opioids were for odontogenic pain, and accounted for almost a quarter of first prescriptions among individuals 9 to 25 years of age.\textsuperscript{13} In addition, four-fifths of repeat prescriptions within 30 days of these also involved the dental setting. One review of Medicaid data for 2000 through 2010 revealed that more than half of individuals between 14 and 24 years of age received opioid medication for pain relief following

<table>
<thead>
<tr>
<th>Active Ingredients</th>
<th>Brand Name</th>
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<tbody>
<tr>
<td>Hydrocodone and acetaminophen</td>
<td>Vicodin®</td>
</tr>
<tr>
<td>Hydrocodone and acetaminophen</td>
<td>Norco®</td>
</tr>
<tr>
<td>Hydrocodone and acetaminophen</td>
<td>Lorcet®</td>
</tr>
<tr>
<td>Hydrocodone and acetaminophen</td>
<td>Lortab®</td>
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<tr>
<td>Hydrocodone and ibuprofen</td>
<td>Vicoprofen®</td>
</tr>
<tr>
<td>Hydrocodone and ibuprofen</td>
<td>Reprexain®</td>
</tr>
<tr>
<td>Oxycodone and acetaminophen</td>
<td>Percocet®</td>
</tr>
<tr>
<td>Oxycodone and aspirin</td>
<td>Percodan®</td>
</tr>
<tr>
<td>Codeine and acetaminophen</td>
<td>Tylenol with codeine®</td>
</tr>
</tbody>
</table>
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In another review of prescription patterns for a 2-year period covering 2012 and 2013 in one state, data from a prescription drug monitoring program revealed that dentists wrote more than 650,000 prescriptions for immediate-release opioids. These represented 99.9% of all opioids prescribed by dentists, and 96% of the prescriptions were for initial (index) opioid medication. It was also found that combination opioids were prescribed more often than monotherapy opioids.

From 2010 through 2015, among private patients, 17% of all first prescriptions for opioids were for odontogenic pain.

Side Effects and Adverse Events
Combination formulations containing an opioid analgesic and a non-opioid analgesic have been widely used in dentistry for management of moderate to severe dental pain. The combination of acetaminophen with hydrocodone has demonstrated greater efficacy in providing pain relief than either ingredient used individually. However, when pain is acute and high combination doses of opioid and acetaminophen are used, this carries an added risk of liver toxicity. Since the opioid analgesic ingredient may increase the risk of adverse effects, such as central nervous system depression, respiratory depression and gastrointestinal upset, combination analgesic products that contain only non-opioid ingredients are attractive alternatives. Other side effects of opioid medications include but are not limited to dizziness, sedation, sleep disturbances, nausea and vomiting, and constipation.

The Opioid Epidemic and Addiction
Medications containing opioids combined with acetaminophen were reported to be the most frequently prescribed analgesic in healthcare in 2014. Prescription opioids also resulted in an addiction epidemic. The potential for habituation and euphoria was first reported for one opioid, hydrocodone, as early as 1923, and addiction to it was reported in 1961. In 2010, more than five times the number of deaths occurred due to prescription opioid overdose than were due to heroin overdose, and by 2014 more than 47,000 deaths were attributable to drug overdose involving opioids overall.

Addiction to hydrocodone was first reported in 1961.

Data from 2016 shows that opioid overdoses resulting in death were higher for synthetic opioids, e.g., fentanyl (which is also contained in numerous street drugs), than for prescription opioids. It is reported that 46% of more than 42,000 opioid-related overdose deaths were from synthetic opioids.

<table>
<thead>
<tr>
<th>TABLE 2. Sources of diverted opioids</th>
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<tbody>
<tr>
<td>Bogus call-in prescriptions</td>
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<tr>
<td>Altered and fraudulent prescriptions</td>
</tr>
<tr>
<td>Opioids prescribed to family and friends</td>
</tr>
<tr>
<td>Theft</td>
</tr>
<tr>
<td>Internet distribution</td>
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<tr>
<td>Healthcare professional diversion</td>
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<tr>
<td>Dealers</td>
</tr>
</tbody>
</table>
and over 17,000 from prescription opioids with the remainder associated with heroin. Misuse/illicit use of opioids occurs as a result of diversion due to theft, bogus call-in prescriptions and altered and fraudulent prescriptions, and distribution via the internet, dealers, and acquaintances who have acquired opioids that had been prescribed for family members or friends. (Table 2) The U.S. opioid crisis was declared a public health emergency in 2017.

**Recommendations and Policies**

Since misuse of prescription opioids accounts for the initial event for the majority of individuals with opioid addictions, healthcare prescribing patterns and recommendations for analgesics are a key element in the use of opioid and non-opioid medications. Reducing the number and nature of opioid prescriptions, and instead recommending or prescribing non-opioid analgesics reduces the potential for addiction, misuse, and illicit/diverted use of opioids. Dental professionals licensed to prescribe opioids are responsible for a relatively small percentage of overall opioid prescriptions, and reported to have decreased from 15.5% in 1998 to 8% by 2009 and 6.4% by 2012. (Figure 1)

In March 2018, the American Dental Association announced a new policy to help fight the epidemic of opioid use and addiction and had previously issued a Statement on the Use of Opioids in the Treatment of Dental Pain. This policy states that it supports compulsory continuing education on opioid prescribing as well as other controlled substances, statutory limits on opioid dosage, a statutory maximum duration of 7 days, which is in line with the recommended maximum number of days in a recent CDC report, and the utilization of Prescription Drug Monitoring Programs. The prior statement related to opioid prescribing included but was not limited to the recommendations that “Dentists should consider nonsteroidal anti-inflammatory analgesics as the first-line therapy for acute pain management,” and “… should recognize multimodal pain strategies for management for acute postoperative pain as a means for sparing the need for opioid analgesics.” More detailed full recommendations can be found on the ADA website.

The remainder of this article addresses options for ingested and nasal application of non-opioid analgesics, which includes nonsteroidal anti-inflammatory drugs, acetaminophen, and combination medications.

**Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

NSAIDs have long been considered a first-line therapy in the treatment of dental pain. They include ibuprofen, naproxen, and diflunisal (Table 3). NSAIDs are rapidly absorbed from the gut, with an onset of analgesia in as little as 30 minutes. Duration of action can vary greatly, however, depending on the individual agent. For example, ibuprofen is typically dosed every 4 to 6 hours, while naproxen is often dosed every 12 hours. Duration of action of the NSAIDs may also vary based on the dose administered.

<table>
<thead>
<tr>
<th>TABLE 3. NSAIDs used in dentistry</th>
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<tbody>
<tr>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Ibuprofen sodium</td>
</tr>
<tr>
<td>Naproxen</td>
</tr>
<tr>
<td>Naproxen sodium</td>
</tr>
<tr>
<td>Diflunisal</td>
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metabolism may become saturated, resulting in metabolism according to zero-order kinetics and much longer duration of action. This is most commonly experienced with aspirin. Ibuprofen is considered the standard against which all other analgesics for odontogenic pain are evaluated. There is no definitive evidence to support the conclusion that other NSAIDs, such as naproxen, offer any apparent advantage over ibuprofen in its ability to relieve dental pain. However, naproxen at a dose of 500 mg is more effective than use of oxycodone and as effective as the combination of oxycodone (10 mg) and acetaminophen (650 mg).

Other NSAIDs, such as meloxicam, have a much longer duration of action, up to 24 hours. These are preferred for the treatment of chronic inflammatory pain, such as osteoarthritic pain, since they allow for the convenience of once or twice daily dosing. NSAIDs with shorter durations of action are preferred for the treatment of acute inflammatory pain, such as dental pain, since they allow for more flexible dosing to accommodate episodes of breakthrough pain, i.e., at the point in time when pain surfaces sufficient to require remedication. Naproxen (500 mg) has been found to be more effective than oxycodone and as effective as the combination of oxycodone (10 mg) and acetaminophen (650 mg).

Patients may believe that since NSAIDs are available without a prescription, that they are therefore inferior in their ability to relieve dental pain. There is a substantial amount of evidence, however, that shows that ibuprofen at 200-mg and 400-mg doses is an effective pain reliever in treating postoperative dental pain. Studies comparing ibuprofen to placebo found that ibuprofen provided greater pain relief in patients with moderate to severe postoperative dental pain and with similar adverse effects to placebo. Monotherapy with ibuprofen has been shown to be equal or superior to monotherapy with acetaminophen in the management of dental pain. In a systematic review of 27 randomized, controlled trials it was concluded that there was moderate evidence for nonsteroidal anti-inflammatory drugs (NSAIDs) taken pre- or post-operatively for pain of endodontic origin and for steroids for patients experiencing pain associated with inflammatory pulpitis. It was concluded that NSAIDs should be considered drugs of choice, barring any contraindication, and if necessary could be combined with acetaminophen.

In a systematic review of 27 randomized, controlled trials it was concluded that NSAIDs should be considered drugs of choice, barring any contraindications.

Contraindications, Adverse Events

NSAIDs should be used at the lowest therapeutic dose and for as short a time as possible. NSAIDs may cause GI upset and abdominal pain. This is thought to be related to mucosal injury resulting from inhibition of COX-1. They can also increase the risk of gastrointestinal bleeding, by impairing platelet function and interfering with plasma-protein binding of anticoagulants, and can increase risk for ulceration and perforation. The risk increases as the dose and/or duration of use increases. Patients may also inadvertently overdose when self-medicating with over-the-counter analgesics; therefore, patient education on the appropriate dose to take is essential. Further, some patients are at greater risk and more susceptible to these adverse events than others. The use of NSAIDs is contraindicated in patients with an ulcerative or erosive gastrointestinal condition/disease.

Although NSAIDs block both COX-1 and COX-2 enzymes, NSAIDs can increase risk for serious cardiovascular thrombotic events, including heart attack and stroke. The risk can increase the longer an NSAID is taken. By decreasing the synthesis of prostaglandins, NSAIDs may cause fluid retention, exacerbating cardiovascular disease and decreasing the antihypertensive effects of beta-blockers, ACE inhibitors, and diuretics, as well as interfere with the cardioprotective effect of low-dose aspirin. NSAIDs should be used...
with caution in patients with hypertension, coronary artery disease, and congestive heart failure.\textsuperscript{37} The cardioprotective effect of low-dose aspirin is preserved by administering the aspirin first and then waiting two hours before administering the NSAID.\textsuperscript{38} NSAIDs can also cause high blood pressure, anemia, mild and severe skin reactions and allergic reactions, and in susceptible patients may cause renal failure or precipitate bronchospasm.\textsuperscript{33,39–41} NSAIDs should be avoided during the first and third trimester of pregnancy. They may interfere with fetal circulation during the third trimester and may also prolong gestation and labor.\textsuperscript{42,43}

More information on contraindications, adverse events, and a warning box can be found in the prescribing information for a specific medication.

**NSAIDs should be used at the lowest therapeutic dose and for as short a time as possible.**

**Aspirin**

While patients may self-medicate with aspirin for pain relief, this is indicated for the relief of mild to moderate pain rather than acute moderate to severe pain. It is worth noting that while short-term use of regular-dose aspirin is not associated with serious gastrointestinal adverse events, its use is associated with dyspepsia.\textsuperscript{44}

**Acetaminophen**

Acetaminophen is often referred to as APAP which is an acronym for its chemical name (N-acetyl-para-aminophenol), and outside the United States is known as paracetamol. Within the United States, most individuals refer to acetaminophen as Tylenol, its common brand name. Acetaminophen has analgesic and antipyretic activity that is equivalent to that of aspirin, but very weak anti-inflammatory effects when compared with aspirin or NSAIDs. Although acetaminophen is not a true anti-inflammatory drug, it can be effective in treating pain resulting from inflammation. While its exact mechanism of action is not fully understood, and it may have multiple mechanisms of action, it is thought that acetaminophen, like NSAIDs and aspirin, inhibits prostaglandin synthesis. However, it appears that acetaminophen’s main modality may be its effects on the central nervous system.\textsuperscript{45}

For patients for whom aspirin and NSAIDs are contraindicated, acetaminophen is usually the drug of choice. However, acetaminophen’s analgesic effect is limited in the treatment of moderate to severe postoperative pain resulting from other dental procedures, especially at high doses.\textsuperscript{31} In addition, the U.S. Food and Drug Administration in 2011 requested that manufacturers stop marketing products with more than 325 mg of acetaminophen due to the risk of severe liver damage.\textsuperscript{46} A maximum daily dose of <3,000 mg has been recommended.\textsuperscript{67}

Acetaminophen has long been considered the “safe” analgesic because it produces few side effects at usual adult doses. It is tolerated well by the majority of patients.\textsuperscript{67} Studies have, however, demonstrated some clinically significant drug interactions and adverse drug reactions.\textsuperscript{31} It has been shown that, at high doses, acetaminophen may interact with warfarin, which can result in an abnormally high international normalized ratio and means that the blood takes longer to clot.\textsuperscript{68} The most serious adverse effect associated with acetaminophen is drug-induced hepatotoxicity, due to an acute or chronic overdose with the drug. In addition, while it is well known that acetaminophen may cause acute liver toxicity at overdose levels (supratherapeutic doses), high therapeutic doses of acetaminophen may still result in hepatic injury.\textsuperscript{46,69} A recent warning by the FDA notified healthcare professionals and patients that acetaminophen has been associated with a risk of Stevens-Johnson syndrome and toxic epidermal necrolysis.\textsuperscript{50}

**Combination Non-opioid Analgesics**

Combinations of non-opioid analgesics may provide improved relief from pain compared to monotherapy with one medication. Additionally, since the therapeutic and adverse effects of non-opioid analgesics are dose related, the use of lower doses in a combination analgesic product would be considered advantageous in offering a synergistic approach to pain relief. Historically, the therapeutic superiority of the combination of acetaminophen and
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Ibuprofen over either drug alone remained controversial.

While there is as yet no nonprescription analgesic product available in the U.S. that combines acetaminophen with ibuprofen, studies have compared combinations of acetaminophen with various NSAIDs. In a review of therapy combining ibuprofen and acetaminophen, this combination was found in several randomized controlled trials to result in significantly greater analgesic efficacy compared with ibuprofen or acetaminophen alone for acute postoperative dental pain in adolescents and adults following third molar extractions. The authors concluded that pain relief was superior to opioids using a combination of 315 mg acetaminophen and 200 mg of ibuprofen. In addition, adverse events remained similar to monotherapy with no additive effect.

In another study, the addition of an opioid (codeine) to ibuprofen and acetaminophen did not increase the effectiveness of pain relief following extraction of third molars. Ibuprofen (200 mg)/acetaminophen (500 mg) and ibuprofen (400 mg)/acetaminophen (1000 mg) have been found to be significantly more effective compared with comparable doses of ibuprofen or acetaminophen alone in relieving moderate to severe acute dental pain, and significantly more effective than placebo in providing sustained pain relief. (Table 4) In one review, 77%, 72%, 69% and 69% of patients experienced at least 50% maximum pain relief with 600 mg ibuprofen, 400 mg of ibuprofen plus 1,000 mg of acetaminophen, 200 mg ibuprofen plus 500 mg acetaminophen, and 50 mg flurbiprofen, respectively.

**Contraindications, Adverse Events**

The risks associated with the use of either analgesic are present in combination formulation. In addition, use of the combination of acetaminophen and an NSAID has been reported to increase the risk of GI bleeding in elderly

<table>
<thead>
<tr>
<th>Author, year, and type</th>
<th>Medication</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore and Hersh, 2013 (review)</td>
<td>Ibuprofen + acetaminophen</td>
<td>Greater efficacy than ibuprofen or acetaminophen alone for acute pain following third molar extractions.</td>
</tr>
<tr>
<td>Moore and Hersh, 2013 (review)</td>
<td>Ibuprofen (200 mg) + acetaminophen (315 mg)</td>
<td>Greater analgesic efficacy than opioids.</td>
</tr>
<tr>
<td>Derry et al, 2013 (review)</td>
<td>Ibuprofen (400 mg) + acetaminophen (1000 mg) vs. monotherapy</td>
<td>Combination significantly more effective than either medication alone for relief of moderate to severe pain.</td>
</tr>
<tr>
<td>Alexander et al, 2014 (review)</td>
<td>Ibuprofen (200 mg) + acetaminophen (500 mg) vs. monotherapy</td>
<td>Combination significantly more effective than either medication alone for relief of moderate to severe pain.</td>
</tr>
<tr>
<td>Best et al, 2017 (RCT)</td>
<td>Ibuprofen + acetaminophen vs. ibuprofen + acetaminophen + codeine</td>
<td>Addition of codeine (opioid) to ibuprofen + acetaminophen did not increase the effectiveness of pain relief following removal of impacted third molars.</td>
</tr>
</tbody>
</table>
patients compared with either agent alone. In a review of five randomized, controlled trials the most common adverse events were mild to moderate, and included headache, nausea, vomiting, and dizziness. In one study, there were fewer adverse events for the combination therapy compared to monotherapy with 400-mg ibuprofen.

Caffeine-containing Analgesics

Several nonprescription combination analgesics contain caffeine. Caffeine is not thought to possess any analgesic properties on its own; however, it can be included with traditional analgesics such as acetaminophen, ibuprofen, and aspirin. Studies have demonstrated that the addition of caffeine to these analgesics provides an increase in the number of patients who experienced good pain relief. As a result, a combination analgesic containing acetaminophen and ibuprofen may well contain caffeine as an adjunct. One study found that the addition of caffeine resulted in greater reductions in postoperative swelling than an analgesic alone.

Ketorolac Tromethamine With Nasal Application

Ketorolac tromethamine nasal spray (Sprix), an NSAID, is a novel medication for the management of pain. It is indicated only for adults for the short-term relief of moderate to severe pain. Ketorolac tromethamine was first approved in 1989 as an injectable analgesic, and experimentally an adhesive film containing ketorolac tromethamine was found to be safe and effective for the management of acute pain when applied intraorally following free gingival graft procedures.

As with other NSAIDs, the main mechanisms of action for ketorolac tromethamine is the inhibition of COX-1 and 2, especially for COX-1. At this time, it is the only NSAID pain-relieving medication administered as a nasal spray.

It must not be inhaled. It can be used up to 4 times daily for up to 5 days, every 6 to 8 hours, 1 spray in each nostril for adults under 65 years of age with normal renal function and weighing at least 110 pounds. For adults 65 years of age or older and/or with abnormal renal function and/or weighing <110 pounds, half this dose is recommended, i.e., 1 spray in 1 nostril is administered every 6–8 hours, up to 4 times per day. The spray is delivered in 5 color-coded bottles, each containing 8 metered sprays. (Figure 2)

The bottles have a blue safety clip that is removed prior to priming the bottle for use by pressing down on the finger flange and releasing the pump 5 times. (Figure 3) Since this medication does not contain a preservative, a new bottle must be used each 24 hours, keeping it at room temperature, and the previous day’s bottle discarded along with any remaining medication contained within it.

The instructions for use are to blow the nose first to clear the nostril(s), then to sit up straight or stand while keeping your head tilted in a downward direction towards the toes, then to place the tip of the bottle into the nostril, hold the bottle upright and spray toward the back of the nose. It is essential to hold your breath while spraying to avoid inhalation and afterward to breathe gently through the mouth. Full information on use, storage requirements, contraindications, and warnings are contained in the package insert.

Efficacy

In a phase I randomized trial in 2007, maximum intranasal absorption occurred after 45 minutes, which was similar to the intramuscular injection, and bioavailability was 67% and 75%, respectively.

Figure 2. Color-coded bottles

Source: Patient information on medication
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studies assessed the management of postoperative pain following abdominal surgery, finding it to be effective and to reduce the use of opioids. In a third study, its safety and efficacy in managing postoperative pain following bony-impacted third molar extractions was evaluated in 80 patients. The study was randomized and double-blinded, and included a placebo group. Sixty percent of individuals receiving the intranasal medication reported rapid pain relief. Pain relief was rated as excellent, very good, or good for up to 8 hours following surgery after a single dose of 31.5 mg (one spray in each nostril) vs. 13% in the placebo group. Around half of patients using the nasal spray containing ketorolac tromethamine remedicated after approximately 6 hours while four-fifths of patients using the placebo remedicated after approximately 2 hours. Mild adverse events were found in 8 patients receiving placebo, and in 3 patients receiving the intranasal medication, a mild headache was reported. In a review of studies reported up to 2012 on the safety, efficacy, and pharmacokinetics of intranasal ketorolac tromethamine, it was concluded that this intranasal spray was effective in providing significant pain reduction for moderate to moderately severe pain following a range of procedures, and that it was well tolerated.

Side Effects
The most common side effects associated with use of intranasal ketorolac tromethamine are intranasal stuffiness, discomfort or pain, increased lacrimation (tearing), throat irritation, decreased amounts of urine, skin rash, bradycardia, increased liver enzymes, and high blood pressure. Across two placebo-controlled studies, a small percentage of patients experienced these effects. Nasal discomfort and pain were reported by 15% and 13% of patients using this medication, while the other side effects were experienced by between 2% and 5% of patients using ketorolac tromethamine and by up to 1% of patients using the placebo nasal spray (Table 5).

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Placebo</th>
<th>Ketorolac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal discomfort</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>Nasal pain</td>
<td>&lt;1%</td>
<td>13%</td>
</tr>
<tr>
<td>Increased lacrimation</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>&lt;1%</td>
<td>4%</td>
</tr>
<tr>
<td>Rash</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Urine output decreased</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Source: Prescribing information

Contraindications and Adverse Events
Ketorolac tromethamine should not be used at the same time as ketorolac dimethamine administered intramuscularly, intravenously or orally, nor at the same time as aspirin or other NSAIDs. As with other NSAIDs, ketorolac tromethamine nasal spray must be used exactly as prescribed, at the lowest therapeutic dose and for as short a time as possible. Ketorolac
tromethamine is contraindicated in the setting of coronary artery bypass graft surgery. As discussed earlier in this article, NSAIDs can also increase the risk of gastrointestinal bleeding, ulceration and perforation, with a dose- and duration-response. Other side effects associated with NSAIDs in general, as discussed under the section in NSAIDs, can also occur.

Full information on contraindications, adverse events and drug interactions, can be found in the prescribing information for ketorolac tromethamine.

Preprocedural Analgesics

Preprocedural analgesics have been recommended for an additive effect to the pain relief obtained from postprocedural analgesics. However, evidence is lacking for efficacy of preprocedural use of analgesics for pain management for oral maxillofacial or other oral/dental procedures, and is limited for other procedures. In a 2002 systematic review of preoperative administration of analgesics and their effect on postoperative pain, reductions on postoperative pain were observed only for 2 trials using nitrous oxide preoperatively, neither of which was for pain of odontogenic origin, and no reductions were observed for analgesics including in 20 trials on NSAIDs. Six of the trials had involved the use of analgesics, specifically NSAIDs, preoperatively for dental procedures—3 trials were in patients undergoing third molar extractions, and one trial each was with patients undergoing periodontal, endodontic or periodontal, and oral surgery procedures. None of the trials demonstrated any reduction in pain associated with preoperative administration of NSAIDs.

Similar conclusions were drawn in a systematic review of preoperative pain relief with orally administered analgesics in children and adolescents prior to restorative or extraction treatments that included local anesthesia or prior to orthodontic separator placement without local anesthesia. The review included 5 trials with almost 200 participants. It was found that preprocedural use of ibuprofen may be of benefit for patients undergoing orthodontic separator placement. For other procedures for which local anesthesia was given, no incremental benefit in postoperative pain was observed following use of preoperative acetaminophen (paracetamol) prior to local anesthesia.

Relieving Pain Associated With Oral Mucositis

Oral mucositis presents with painful erythematous ulcerative lesions and occurs as a result of high-dose head and neck radiation and chemotherapy. It affects almost all patients receiving treatment for head and neck cancer, typically presenting 3 weeks after the start of radiation therapy, increasing in severity until week 5 and then subsiding between 2 and 4 weeks of cessation of radiation therapy. It also occurs in up to 40% of patients receiving chemotherapy, is of greater severity in patients receiving both radiation therapy and chemotherapy. In patients receiving stem cell transplants during cancer therapy, oral mucositis dramatically impacts patients’ quality of life by causing severe acute pain of long duration, making it difficult for patients to eat, speak, sleep, or function.

As a result of difficulty eating and swallowing, it also results in nutritional deficiency and in severe cases necessitates the use of feeding tubes and parenteral feeding. In some cases, it results in interruptions in cancer therapy. Oral mucositis pain includes both nociceptive and neuropathic etiologies.

Managing Oral Mucositis Pain

Pain associated with oral mucositis is managed using topical and systemic drugs. Appropriate oral care using an extra soft brush also helps to reduce pain associated with oral mucositis and its severity.

Almost all patients with severe pain have received opioid analgesics. However, while these are effective for nociceptive pain, they may not be effective for
neuropathic pain.\textsuperscript{7} Combinations of medications are used to provide ongoing pain relief. The addition of gabapentin has also demonstrated an additive effect that improves pain control, may enable lower doses of opioids and reduced total doses, and provides relief from neuropathic pain. The mechanisms by which this occurs are believed to include greater inhibition of nociception.\textsuperscript{9}

Topical agents used to temporarily relieve oral mucositis pain include 2\% lidocaine mouthrinse (15 to 30 minutes), topical morphine mouthrinse (4 to 6 hours), magic mouthrinse which is pharmacy-compounded and usually contains viscous lidocaine, diphenhydramine, and an antacid (typically Maalox), salt, and baking soda, and a rinse containing 0.15\% benzydamine rinse which is an NSAID.\textsuperscript{5,65,68,69} 0.15\% benzydamine rinse is a locally acting NSAID for the relief of oropharyngeal pain, including dental pain and oral mucositis. It is administered by rinsing or gargling with 15 ml every 90 to 180 minutes for pain relief as required. It may be used a maximum of 7 days and is contraindicated in children 12 and under. An FDA-cleared medical device (episil) forms a barrier in 1 minute, provides pain relief within 5 minutes that lasted for up to 8 hours in one study. No difference in efficacy was observed when its use was combined with use of an NSAID (benzydamine).\textsuperscript{65} Additional options for topical relief of pain associated with oral mucositis include the use of supersaturated calcium phosphate rinses.\textsuperscript{70} A gel, rinse, and spray (StellaLife) were recently introduced and are reported to result in relief of pain associated with oral mucositis, and following procedures.\textsuperscript{71}

Supplemental medication may be necessary to provide relief from breakthrough pain, which occurs in almost half of all patients receiving treatment for head and neck cancer therapy.\textsuperscript{72} This may occur in association with swallowing or be spontaneous. A transnasal spray containing fentanyl has been recommended for breakthrough pain in patients with oral mucositis, and has been found to be effective in treating pain in general.\textsuperscript{64,73} Transnasal fentanyl pectin spray was more effective in providing pain relief than morphine during swallowing in patients with at least grade 4 mucositis in one study, and with faster onset of relief.\textsuperscript{74} However, fentanyl is a synthetic opioid with a high risk of addiction that is 50 to 100 times more potent than heroin or morphine.\textsuperscript{75} Only very small amounts are sufficient to cause a drug overdose.

Experimentally, regeneration of oral mucosa has been observed using keratinocyte growth factor; amino acids, peptides, and antioxidants are being investigated for their role in preventing oral mucositis; also being studied is the use of epidermal growth factor to reduce the severity of oral mucositis and to decrease the use of opioids.\textsuperscript{4} In other research, the pro-enkephalin gene was introduced into modified herpes simplex virus, which results in the production of endogenous opioids and in preclinical trials demonstrated efficacy for relief of facial pain.\textsuperscript{76}

**Conclusions**

Relief of orodontal/odontogenic pain in adolescents and adults has typically been accomplished through an approach that incorporated nonparenteral opioid and/or non-opioid analgesics. Studies have shown that non-opioid medications and combinations of non-opioid medications are at least as, or more effective, than opioid medications. Non-opioids typically used in dentistry include NSAIDs and acetaminophen. Novel agents are now also available, including non-opioid intranasal analgesic spray. In addition, in situations where opioids are indicated, the addition of non-opioid medications can increase efficacy and reduce the overall dose of opioid required. Given the current opioid epidemic, alternative non-opioid medications are preferable where effective. Pain management must be individualized for patients, and the full prescribing information must be consulted in determining appropriate medications.
References


Analgesics in Dentistry: Focusing in on non-opioid medications


46. U.S. Food & Drug Administration. All manufacturers of prescription combination drug products with more than 325 mg of acetaminophen have discontinued marketing. March 2014. Available at: https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm390509.htm.


52. Alexander L, Hall E, Eriksson L, Rohlin M. The combination of non-selective NSAID 400 mg and paracetamol 1000 mg is more
1. Acute pain is a __________________ response.
   a. protective, psychological
   b. protective, physiological
   c. destructive physiological
   d. a or b

2. Nociceptors __________________.
   a. are afferent sensory neurons
   b. have a high depolarization threshold
   c. are sensitized by prostaglandins
   d. all of the above

3. The ________________ governs the autonomic and motor response to pain.
   a. somatosensory cortex
   b. limbic system
   c. reticular system
   d. hypothalamic cortex

4. Expression of ________________ plays a significant role in acute pain.
   a. chorooxygenase (COX), consisting of COX-2
   b. chorooxygenase (COX), consisting of COX-1 and COX-2
   c. cyclooxygenase (COX), consisting of COX-1
   d. cyclooxygenase (COX), consisting of COX-1 and COX-2

5. In one study, the most commonly prescribed analgesic for relief of pain following third molar extractions was reported to be a combination of ________________.
   a. hydrocodone and ibuprofen
   b. hydrocodone and acetaminophen
   c. oxycodone and naproxen
   d. oxycodone and acetaminophen

6. To help fight the epidemic of opioid use and addiction, the ADA policy supports statutory limits on opioid prescribing.
   a. True
   b. False

7. It is reported that ________________ of more than 42,000 opioid-related overdose deaths were from synthetic opioids, and over ________________ from prescription opioids with the remainder associated with heroin.
   a. 26%; 11,000
   b. 36%; 13,000
   c. 46%; 17,000
   d. 56%; 19,000

8. Duration of action of nonsteroidal anti-inflammatory drugs varies depending on the ________________.
   a. dose administered
   b. individual agent
   c. time of day
   d. a and b

9. Naproxen (500 mg) has been found to be much more effective than use of ________________.
   a. the combination of oxycodone and acetaminophen
   b. oxycodone
   c. the combination of hydrocodone and aspirin
   d. none of the above

10. NSAIDs with shorter durations of action are preferred for the treatment of ________________.
    a. psychosomatic pain
    b. acute profl ammatory pain
    c. chronic pain
    d. acute inflammatory pain
11. There is a substantial amount of evidence that shows that ibuprofen at doses of 200 mg and 400 mg is an effective pain reliever in treating postoperative dental pain.
   a. True
   b. False

12. Nonsteroidal anti-inflammatory drugs can increase the risk of ________________.
   a. gastrointestinal bleeding
   b. cardiovascular thrombotic events
   c. serious allergic reactions
   d. all of the above

13. Acetaminophen’s main mechanism of action may be its effects on ________________.
   a. prostaglandin production
   b. the central nervous system
   c. cyclogenase overexpression
   d. interleukin production

14. The most serious adverse effect associated with acetaminophen is ________________.
   a. drug-induced hepatotoxicity
   b. thrombotic events
   c. severe allergic reactions
   d. gastrointestinal bleeding

15. Combinations of non-opioid analgesics may ________________.
   a. provide improved pain relief compared to monotherapy
   b. increase the risk of adverse events because higher doses are used
   c. reduce the efficacy of either drug alone
   d. result in habituation

16. Ketorolac tromethamine nasal spray ________________.
   a. is indicated for the short-term relief of moderate to severe pain in adults
   b. works primarily by inhibiting COX-1 and COX-2
   c. must not be inhaled and can be used for up to 5 days
   d. all of the above

17. In a randomized double-blinded study on the efficacy of ketorolac tromethamine in relieving postoperative pain following impacted third molar extractions, ________________ percent of individuals receiving the intranasal medication reported rapid pain relief.
   a. Fifteen
   b. Thirty
   c. Sixty
   d. One hundred

18. ________________ is one of the most common side effects associated with use of intranasal ketorolac tromethamine.
   a. Intranasal discomfort or pain
   b. Throat irritation
   c. Increased lacrimation
   d. all of the above

19. ________________ is/are used to provide ongoing pain relief for the management of pain associated with oral mucositis.
   a. Monotherapy
   b. Combinations of medications
   c. Only opioid medications
   d. Only non-opioid medications

20. Non-opioid medications and combinations of non-opioid medications are at least as, or more effective, than opioid medications as shown in studies.
   a. True
   b. False
**Analgesics in Dentistry: Focusing in on non-opioid medications**

CE ANSWER FORM (E-mail address required for processing)

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<tr>
<th>Name</th>
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<td>Contact</td>
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<td>EDUCATIONAL OBJECTIVES</td>
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1. Describe opioid medications and aspects of the new ADA policy on opioids.
2. List and describe ingested nonsteroidal anti-inflammatory drugs (NSAIDs) used in dentistry for pain management.
3. Describe an inhaled NSAID that can be used for acute pain management.
4. Review findings from systematic reviews and trials comparing opioid and non-opioid analgesics.

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Please evaluate this course using a scale of 3 to 1, where 3 is excellent and 1 is poor.

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2. Usefulness of content .................................. 3     2     1
3. Benefit to your clinical practice ....................... 3     2     1
4. Usefulness of the references ................................ 3     2     1
5. Quality of written presentation ......................... 3     2     1
6. Quality of illustrations ................................ 3     2     1
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10. Did this lesson achieve its educational objectives?   ○Yes  ○No
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2. A   B   C   D
3. A   B   C   D
4. A   B   C   D
5. A   B   C   D
6. A   B   C   D
7. A   B   C   D
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10. A   B   C   D
11. A   B   C   D
12. A   B   C   D
13. A   B   C   D
14. A   B   C   D
15. A   B   C   D
16. A   B   C   D
17. A   B   C   D
18. A   B   C   D
19. A   B   C   D
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