Analgesics in Dentistry

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Faculty

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Faculty Disclosure

Contributing faculty, Richard L. Wynn, BSPharm, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner Disclosure

The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

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Course Objective

The purpose of this course is to describe new reports and new information on analgesics for the dental professional to use in determining the best pharmacotherapeutic approach in those situations requiring oral analgesics.

Learning Objectives

Upon completion of this course, you should be able to:

1. Compare and contrast the analgesic effectiveness of the nonprescription pain relievers in treating dental pain.
2. Compare and contrast the analgesic effectiveness of the nonselective NSAIDs in dental pain.
3. Describe the cardiovascular effects of ibuprofen.
4. Discuss the role of ibuprofen/narcotic combinations in the treatment of dental pain.
5. Describe the dosage and efficacy of COX-2 inhibitors.
6. List the hydrocodone and oxycodone products for dental pain.
7. Describe the unique mechanisms of action and uses of nontraditional analgesics.

INTRODUCTION

In order for a drug product to achieve nonprescription status, the U.S. Food and Drug Administration (FDA) requires it to be safe and effective. Safe is defined as (1) a low incidence of adverse reactions or low incidence of significant side effects under adequate directions for use, and (2) low potential for harm, which may result from abuse under conditions of widespread availability. The requirement for effectiveness means that there is a reasonable expectation that, in a significant proportion of the target population, the drug will provide clinically significant relief of the type of pain claimed when used appropriately [1].

The nonsteroidal anti-inflammatory drugs (NSAIDs) that were originally approved only as prescription drugs and are now also sold over-the-counter include ibuprofen and naproxen sodium. These two have joined aspirin, which has always had a status of over-the-counter availability. Thus, almost all nonprescription pain-relieving products contain either aspirin, acetaminophen, ibuprofen, or naproxen sodium. Also common is a combination of aspirin and acetaminophen or aspirin and acetaminophen in combination with other ingredients, such as caffeine [2].

Acetaminophen, ibuprofen, and naproxen sodium have established a niche over the years as over-the-counter products for the relief of dental pain, while prescription opioids are used for more severe dental pain. Information on their use and effectiveness follows.

ACETAMINOPHEN

Acetaminophen is known chemically as N-acetyl-p-aminophenol. The acronym for the chemical name is APAP, and many products use this acronym to identify the acetaminophen component. The common U.S. brand name is Tylenol. Acetaminophen is known as paracetamol in the United Kingdom [2].

Acetaminophen was first used in medicine in 1893; however, it has gained popularity only since 1949, after it was discovered to be the active metabolite of the pain reliever phenacetin. Indications for use, as stated on the package, are temporary relief of pain from headache, colds, flu, muscle aches, backache, toothache, menstrual cramps, minor arthritic pain, and reduction of fever. The adult dosage is 325–1,000 mg three to four times daily, not to exceed 4 grams over a 24-hour period [2]. Acetaminophen is considered free of any side effects at these doses [3]. There are several warnings of use of acetaminophen imprinted on the package, including not to take the medication for more than 10 days, or for fever no more than 3 days, unless directed by a physician. Patients who are pregnant or nursing should seek the advice of a health professional before using the product, and if individuals consume three or more alcoholic drinks every day, a physician should be consulted before acetaminophen or other pain relievers/fever reducers are taken [4].

EFFICACY STUDIES IN DENTAL PAIN

Studies cited on the evaluation of analgesic efficacy, for the most part, use the third-molar extraction model of acute dental pain developed by Cooper and Beaver [5]. This model provides a snapshot of the levels of pain intensity over time with various available analgesics based on patients who have undergone third-molar extraction. Extraction of an impacted third molar is a model that has been recognized by the FDA as an accepted paradigm for evaluation of analgesic and anti-inflammatory therapies [6; 7]. The extraction of third molars generally produces pain that is reproducible and consistent in severity. The model tests moderate-to-severe postoperative pain that usually occurs within the first three hours postoperatively and that may last for three to five days.

Initial studies of the analgesic efficacy of acetaminophen evaluated acetaminophen alone (1,000 mg) and an acetaminophen-caffeine combination (1,000 mg/100 mg) compared to placebo. The relative potency of the combination was significantly greater than either acetaminophen alone or placebo [8]. In a similar study, acetaminophen-caffeine (1,000 mg/130 mg) was more effective than either acetaminophen alone (1,000 mg) or placebo after third-molar extraction [9]. The intent of adding caffeine to acetaminophen products is to improve analgesic effectiveness while reducing the total amount of analgesic present. One study has shown that the addition of caffeine 65 mg to acetaminophen 500 mg appeared to enhance the analgesic effectiveness of acetaminophen in treating post-extraction pain [10]. It is important to note that the analgesic adjuvant effects of caffeine have not been seriously investigated since this study was published. Clinical trials have suggested that caffeine in doses of more than 65 mg may be useful for enhancement of analgesia; however, doses that are either too low or too high may lead to no analgesic enhancement [11]. When evaluated alone in a post-third-molar extraction pain model, it was reported that caffeine 65 mg was no more effective than placebo [12]. A 2012 systematic review of 19 studies of common pain conditions in adults, including postoperative dental pain, found a small but statistically significant benefit with doses of 100 mg or greater of caffeine as an analgesic adjuvant [13]. A 2014 update to this review reported similar findings [14].

ACETAMINOPHEN AS MONOTHERAPY

When used as a single agent for pain relief, acetaminophen is effective in relieving mild dental pain but appears to have limitations in reducing moderate-to-severe postoperative dental pain. For example, acetaminophen 1,000 mg has been shown to be more effective than placebo in reducing pain after extraction of third molars [15; 16]. However, it is suggested that because of its ceiling-dose effect, acetaminophen is a limited analgesic against postoperative dental pain [17; 18]. Limited analgesic effect has also been shown against postoperative pain resulting from other oral surgeries, including difficult extractions, alveolectomy, multiple extractions, apicoectomy, biopsy, and deep gingival curettage [17]. There is no question that acetaminophen provides better pain relief than placebo. A large meta-analysis examining the efficacy of acetaminophen 500 mg, 600–650 mg, and 975–1,000 mg as monotherapy showed it to be superior to placebo as a postoperative analgesic [18].

In terms of duration of pain relief after acetaminophen administration, peak effect appears to occur within one to two hours. In one study, acetaminophen 500 mg was superior to placebo for treatment of dental pain associated with third-molar extraction, although pain relief was brief and peaked at one hour [19]. In another study, acetaminophen 1,000 mg provided significant pain relief compared to placebo as determined by pain intensity and pain relief scores for up to four hours after oral surgery, and pain relief was maximal at one to two hours after administration [20].

ADDITIVE ANALGESIA: ACETAMINOPHEN/NSAID COMBINATIONS

The rationale for combining acetaminophen with an NSAID has been described in the literature. Theoretically, this approach can lead to greater efficacy and fewer adverse events [21]. A review of randomized controlled trials that compared combinations of acetaminophen with various NSAIDs (i.e., ibuprofen, diclofenac, ketoprofen, ketorolac, aspirin, tenoxicam, rofecoxib) found that the combination of acetaminophen and an NSAID was more effective than either acetaminophen or NSAID alone in 85% and 64% of relevant studies, respectively [22]. Using this idea of an NSAID/acetaminophen combination, it has been suggested that the combination of acetaminophen and ibuprofen should be a useful analgesic regimen against dental pain [23].

The demonstration that additive analgesia results from the combination of an over-the-counter NSAID and acetaminophen without an increase in side effects may provide an alternate strategy for increasing pain relief when an NSAID alone is inadequate. Novel analgesics containing both paracetamol (acetaminophen) and ibuprofen are available in the United Kingdom, but no over-the-counter marketed drug combination in the United States contains an NSAID and acetaminophen [24; 25]. The proposed usual analgesic dose of ibuprofen is 400–600 mg (two to three 200 mg tablets) administered every four to six hours, not to exceed 2,400 mg over a 24-hour period [23; 26]. Acetaminophen is administered in a range of 650–1,000 mg (two to three 325 mg tablets) every four to six hours, not to exceed 4,000 mg (4 grams) in 24 hours [26]. Thus, a combination of ibuprofen 400 mg with acetaminophen 650 mg may be administered every four to six hours without exceeding the maximum recommended doses for either drug. For more intense pain, ibuprofen 600 mg (three 200 mg tablets) plus acetaminophen 1,000 mg (three 325 mg tablets) may be administered every six hours without exceeding the maximum 24-hour dose of either drug [26].

Several studies have evaluated the analgesic effectiveness of ibuprofen plus acetaminophen following oral surgery. In one systematic review, the authors identified three studies that examined several dose combinations [27]. The three studies provided data from 508 participants for the comparison of ibuprofen/paracetamol combination (200 mg/500 mg) with placebo; 543 participants for the comparison of ibuprofen/paracetamol combination (400 mg/1,000 mg) with placebo; and 359 participants for the comparison of ibuprofen/paracetamol combination (400 mg/1,000 mg) with ibuprofen 400 mg alone. The proportion of participants achieving at least 50% maximum pain relief over six hours was 69% with ibuprofen 200 mg/paracetamol 500 mg combination; 73% with ibuprofen 400 mg/paracetamol 1,000 mg combination, and 7% with placebo. For the ibuprofen 400 mg alone group, the proportion was 52%.

In another systematic review, the authors found high-quality evidence that ibuprofen alone is superior to paracetamol for pain relief following third molar removal. Most of the evidence reviewed compared ibuprofen 400 mg with paracetamol 1,000 mg, but the authors found ibuprofen to be superior to paracetamol at doses of 200–512 mg and 600–1,000 mg respectively, based on pain relief measures and use of rescue medication data collected six hours postoperatively [28].

The aim of a third study was to define the analgesic dose-response relationship of different fixed dose combinations of paracetamol/ibuprofen following third molar extraction [29]. Patients 16 to 60 years of age with moderate-to-severe pain were randomized to receive one of the following: a two-tablet combination full dose (paracetamol 100 mg/ibuprofen 300 mg); one tablet combination half dose (paracetamol 500 mg/ibuprofen 150 mg); half a tablet combination quarter dose (paracetamol 250 mg/ibuprofen 75 mg); or placebo. The medications were administered every six hours for 24 hours and the primary outcome measure was the pain intensity over 24 hours. The authors found that all combination dose groups were superior to placebo [29].

ADDITIVE ANALGESIA: ACETAMINOPHEN/ASPIRIN COMBINATION

On the assumption that a combination of acetaminophen and aspirin provides more effective pain relief than either agent alone, some over-the-counter products offer both analgesics in the same preparation, usually along with caffeine. Goody's Headache Powders, Excedrin Extra-Strength Tablets, Excedrin Migraine Tablets, and Vanquish Tablets are examples of some of these combination products. These products, in general, usually contain 250 mg of each agent along with 65 mg of caffeine [4]. Clinical studies are lacking in the evaluation of the pain relief properties of a combination of acetaminophen with aspirin compared to each individual agent against postoperative dental pain.

ACETAMINOPHEN HEPATOTOXICITY

Self-medication with acetaminophen carries the risk of taking large quantities over a long period of time. The population and the dental profession should be aware that doses of greater than 4 grams daily for several weeks may produce severe, often fatal liver damage [2]. Additionally, toxicity has been associated with a single acute ingestion of 7–10 grams in adults [30]. Acetaminophen hepatotoxicity is potentiated by chronic alcohol consumption [2; 31]. One report described 67 patients (all regular users of alcohol) who developed hepatic injury after ingestion of acetaminophen at therapeutic doses [32]. In 1998, the FDA began requiring warning labels on acetaminophen products based on evidence that thousands of Americans may mistakenly take toxic doses that could harm their livers [31; 33]. An FDA review found more than 56,000 emergency room visits a year due to acetaminophen overdoses, with about one-fourth of them unintentional. Chronic and unintentional overdoses account for more than 50% of cases of acetaminophen-related acute liver failure. Labeling of over-the-counter acetaminophen products warns not to use the medication if more than three alcoholic drinks have been or will be consumed because the combination may harm the liver [4; 31; 34].

One prospective study followed a case series of consecutive patients 12 years of age or older with acetaminophen dosage greater than 4 grams per 24 hours who were referred to a poison center [35]. Of 249 individuals, serum aspartate aminotransferase levels less than 50 IU/L were found in 126 patients, aspartate aminotransferase levels of 50–1,000 IU/L were present in 47 patients, and levels were greater than 1,000 IU/L in 47 patients. No one with aspartate aminotransferase levels less than 50 IU/L developed hepatotoxicity. This study concluded that injury caused by supratherapeutic ingestion of acetaminophen is apparent at presentation and related to the dose and duration. All the individuals who developed hepatotoxicity had aspartate aminotransferase levels greater than 50 IU/L [35].

A 2007 review of the literature found that drug-induced liver injury remains an important concern for many existing drugs, including acetaminophen [36]. When given in therapeutic doses over 14 days, acetaminophen produced significant asymptomatic elevations in alanine transferase among healthy volunteers, suggesting that subclinical injury may be more common than previously thought [36]. In the United States, acetaminophen is the most common cause of acute hepatic failure [30; 34; 37; 38].

IS COX-3 ENZYME INHIBITION THE MECHANISM OF ACETAMINOPHEN?

Two cyclooxygenase enzymes, COX-1 and COX-2, are known to produce prostaglandins responsible for pain and inflammation. Both of these enzymes are blocked by aspirin. They are also inhibited by the standard group of NSAIDs. The mechanism of how acetaminophen reduces pain and fever has been uncertain, but it is now generally accepted that it inhibits COX-1 and COX-2 through metabolism by the peroxidase function of these isoenzymes [39]. A third distinct COX enzyme, identified as COX-3, has been isolated from the cerebral cortex and, in lesser amounts, other tissues [39; 40]. This COX-3 enzyme is selectively inhibited by acetaminophen. It has been proposed that the COX-3 enzyme plays a role in central prostaglandin production, which in turn produces pain and fever. Its inhibition by acetaminophen would represent a primary central mechanism by which acetaminophen and possibly other types of analgesics can decrease pain and fever.

It has been suggested that although COX-3 enzyme might have cyclooxygenase activity in dogs, and this activity might be inhibited by acetaminophen, its low expression levels in humans indicate unlikely clinical relevance [39; 41]. In humans, COX-3 encodes proteins with completely different amino acid sequences than COX-1 or COX-2 and without COX activity. Thus, it is improbable that COX-3 in humans plays any role in prostaglandin-mediated fever and pain. The actions of acetaminophen at the molecular level are still unclear [39; 41; 42].

REPORTS ON THE ACETAMINOPHEN/ WARFARIN INTERACTION

A case-control study suggested that the combination of acetaminophen with warfarin (Coumadin) may cause enhanced anticoagulation [43]. For patients who reported taking the equivalent of at least four regular-strength (325 mg) tablets for longer than one week in combination with average therapeutic doses of warfarin, the odds of having an International Normalized Ratio (INR) greater than 6.0 were increased tenfold compared to those not taking acetaminophen. The risk decreased with lower intakes of acetaminophen, reaching a background level of risk at a dose of six or fewer tablets per week. The mechanism for this interaction is unknown [44; 45; 46]. In patients taking acetaminophen along with warfarin, the dose and duration of acetaminophen should be as low as possible, individualized, and monitored.

A study evaluated this acetaminophen-warfarin interaction [47]. It was shown that individuals receiving acetaminophen 2 grams daily had a significantly higher mean INR versus a matched placebo group at week 2 after taking the drugs. At weeks 1, 2, and 3, the acetaminophen 4 grams per day group had significantly higher mean INRs compared with those in the placebo group. These findings supported the existence of a clinically significant interaction between warfarin and daily use of acetaminophen 2–4 grams daily [44; 46; 48]. Patients receiving warfarin should be counseled to have their INR monitored more frequently when starting acetaminophen at dosages exceeding 2 grams daily [44; 46].

NONPRESCRIPTION IBUPROFEN PRODUCTS

Nonprescription ibuprofen is available in a single strength of 200 mg tablets. It is sold under the generic name and a variety of brand names, such as Advil, Motrin IB, and Nuprin [26].

Ibuprofen was originally approved for prescription status in 1974 as the brand name Motrin. In 1984, the FDA approved it for sale without a prescription with a lower daily recommended dosage compared to the prescription product [49]. The dosing instructions imprinted on the package are for adults to take one tablet (200 mg) every four to six hours while symptoms persist. Also imprinted on the package is the statement that if pain or fever does not respond to one tablet, two tablets may be used, but that use should not exceed six tablets in 24 hours unless directed by a physician [2]. It is interesting to note that the recommended dose of prescription ibuprofen to treat mild-to-moderate dental pain is 400–600 mg every four to six hours [26].

The FDA-approved indications for nonprescription ibuprofen include temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, arthritis, menstrual cramps, and the reduction of fever [26].

FDA-required boxed (label) warnings for the use of nonprescription ibuprofen include that it [26]:

- Not be taken longer than 10 days unless directed by a physician.
- May cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include: hives, wheezing, skin reddening, facial swelling, shock, rash, or blisters.

- Contains an NSAID, which may cause stomach bleeding. The risk of stomach bleeding is higher if the individual is 60 years of age or older, has had stomach ulcers or bleeding problems, takes other drugs containing an NSAID (e.g., aspirin, ibuprofen, naproxen, or others), takes blood thinning (i.e., anticoagulant) or steroid drugs, has three or more alcoholic drinks every day while taking this product, or takes more than directed or for a longer period of time than directed.
- Not be used right before or after heart surgery.
- May increase the risk of heart attack or stroke if used on a long-term continuous basis.
- A healthcare professional should be consulted if the individual is pregnant or breastfeeding. It is especially important not to use ibuprofen during the last three months of pregnancy unless definitely directed to do so by a physician because it may cause problems in the unborn child or complications during delivery.

EFFICACY STUDIES IN DENTAL PAIN

A review of 72 studies that compared ibuprofen and placebo found that ibuprofen at 200 mg and 400 mg produced a high level of pain relief in approximately 50% of participants who reported moderate-to-severe acute postoperative pain. Within six hours postoperatively, 48% of participants required remedication with 200 mg ibuprofen and 42% required remedication with 400 mg. Adverse events were uncommon and not reportedly different from placebo [50].

The analgesic effects of a new immediate-release/extended-release (IR/ER) (formulation A or B) 600-mg tablet preparation of ibuprofen were evaluated in two randomized, double-blind, placebo-controlled dental pain studies [51]. The participants were 16 to 40 years of age with moderate-to-severe pain following third molar extraction. The primary outcome measure was a 12-hour summed pain intensity difference. The first study included 196 participants who received either a single dose of ibuprofen 600 mg IR/ER (A or B), naproxen sodium 200 mg, or placebo. Pain scores at 12 hours were most improved with ibuprofen IR/ER A (16.87) and ibuprofen IR/ER B (17.34). The second study included 106 participants who received four doses of ibuprofen 600 mg IR/ER or placebo. Pain scores at 12 hours were significantly better with ibuprofen IR/ER compared with placebo [51]. Ibuprofen 600 mg IR/ER provided safe and effective analgesia after single and multiple doses.

The efficacy of ibuprofen compared to aspirin in dental pain has been well studied. Ibuprofen 400 mg (two nonprescription tablets) has been shown to be as effective as aspirin 600 mg or 900 mg daily in models of moderate pain, but superior to aspirin or acetaminophen in models of dental pain [52]. Anecdotal reports, however, have indicated that many patients seem to have better pain relief and inflammatory reduction with ibuprofen compared to aspirin [12].

Finally, it has been reported that monotherapy with ibuprofen is as or more efficacious than acetaminophen for the management of dental pain [53].

ADVIL LIQUI-GELS COMPARED TO CELECOXIB IN DENTAL PAIN

Ibuprofen is commercially available in a liquid form encapsulated within gelatin capsules under the brand name Advil Liqui-Gels. Each capsule contains 200 mg of liquid ibuprofen [2; 49]. Absorption from the gastrointestinal tract into the bloodstream is faster with this preparation compared to ibuprofen tablets. The gelatin capsule breaks down immediately within the gastrointestinal tract with the quick release and absorption of the liquid ibuprofen contents. The tablet formulation takes longer to breakdown and dissolve prior to release of the ibuprofen for gastrointestinal tract uptake into the bloodstream.

A published study has compared the maximum approved over-the-counter dosing regimen (i.e., three 400 mg capsules every four to six hours) of Advil Liqui-Gels compared to a single dose (200 mg) of celecoxib or placebo in 174 patients with moderate or severe pain following surgical extraction of impacted third molars. Ibuprofen 400 mg every 6 hours provided superior efficacy to celecoxib 200 mg over a 12-hour time period following surgery. Onset of pain relief was 88 minutes faster for ibuprofen compared to celecoxib (median time: 46 minutes for ibuprofen and 135 minutes for celecoxib). In addition, more than 50% of the patients in the Advil Liqui-Gels group achieved meaningful relief by one hour compared with only 18% in the celecoxib group [54].

NONPRESCRIPTION NAPROXEN SODIUM

In January 1994, the FDA approved the status change for naproxen sodium from prescription only to an over-the-counter product [49]. This product joined ibuprofen, aspirin, and acetaminophen as an over-the-counter analgesic and was the first over-the-counter analgesic to receive approval since ibuprofen. Naproxen sodium is available under the product name Aleve. Indications are for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, arthritis, menstrual cramps, and the reduction of fever. Aleve is supplied as 200 mg tablets, although other brands offer varying doses. The over-the-counter labeling indicates that the adult dose is one tablet every 8 to 12 hours while symptoms persist, not to exceed three tablets in 24 hours unless directed by a physician [2]. FDA-required boxed (label) warnings are similar to those for ibuprofen [26].

EFFICACY IN DENTAL PAIN

The pain-relieving efficacy of naproxen is similar to ibuprofen. An initial dose of naproxen 550 mg followed by 275 mg every six to eight hours is equivalent to ibuprofen 400 mg every four to six hours for mild-to-moderate dental pain. For the over-the-counter product, 200 mg naproxen (equivalent to 220 mg naproxen sodium) every 8 to 12 hours is equivalent to 200 mg of ibuprofen every six hours for minor pain.

COMBINATION WITH ACETAMINOPHEN

As previous studies have established the rationale of achieving enhanced analgesia using a combination of an NSAID with acetaminophen, the combination of over-the-counter naproxen sodium and acetaminophen appears to have the potential for effective pain relief. Although there are no published studies evaluating the effectiveness of this combination, there is no reason why both of these agents could not be used to treat dental pain as long as the maximum daily doses of the naproxen sodium and the acetaminophen, as printed on the packaging, are not exceeded.

NAPROXEN IS CARDIOPROTECTIVE AND SIMILAR TO ASPIRIN

A published review has evaluated the cardioprotective actions of naproxen [55]. Naproxen inhibits thromboxane production by 95% and inhibits platelet aggregation by 88%. This suggests that naproxen may have a cardioprotective effect similar to aspirin. Three studies have presented convincing evidence that naproxen decreases the incidence of myocardial infarction compared to other NSAIDs and control subjects [56; 57; 58]. The average dose to achieve this effect was 275 mg every 8 to 12 hours.

OTHER NONPRESCRIPTION PRODUCTS FOR DENTAL PAIN

Acetaminophen, ibuprofen, and naproxen sodium are commercially available in drugstores and supermarkets as both generic and brand name products. Usually, the generic products are priced at a lower retail cost than the brand name products. Evidence supports the fact that there are no differences in efficacy between the generic and brand name products in terms of pain relief. Two commercial dose forms for pain relief, including acute dental pain, are described below.

ACETAMINOPHEN EXTENDED-RELEASE CAPSULES

Acetaminophen has been marketed by McNeil-PPC, Inc. as an eight-hour extended-release formulation containing 650 mg of acetaminophen in each gelatin-coated tablet. The product brand name is Tylenol 8 Hour. The gelatin-coated tablets are called gelcaps. The uses listed on the package label include the treatment of pain resulting from toothache and headache. The adult dose is two gelcaps every eight hours with water, with no more than six gelcaps to be taken within 24 hours [4; 49].

EXTRA-STRENGTH ACETAMINOPHEN ADULT RAPID BURST CHERRY

This medication is supplied as an 8-ounce bottle containing a flavored liquid consisting of 500 mg acetaminophen in each 15 mL (tablespoon) [4].

NSAIDs: NONSELECTIVE COX-1 AND COX-2 INHIBITORS

The ibuprofen family of NSAIDs inhibits both COX-1 and COX-2 enzymes. These drugs are traditionally referred to as the nonselective NSAIDs as they inhibit both COX enzymes. This group of NSAIDs, useful as dental pain relievers, includes ibuprofen, etodolac, flurbiprofen, ketoprofen, diclofenac, diflunisal, ketorolac, and naproxen sodium. The COX-1 enzyme is distributed throughout the body and produces prostaglandins that have a protective role in preventing gastrointestinal ulcers, regulating platelet action, and are necessary for kidney function. The COX-2 enzyme produces prostaglandins, but only as a result of inflammation, pain, or other noxious-type stimuli. Inhibition of both COX-1 and COX-2 enzymes not only reduces inflammation and pain, but has the potential to inhibit the protective actions of COX-1 resulting in gastrointestinal toxicity [59; 60]. Long-term use of NSAIDs also has been associated with renal toxicity [60].

EFFICACY STUDIES OF NSAIDs IN RELIEVING DENTAL PAIN

NSAIDs have been shown over the years to be very effective in relieving pain and inflammation resulting from dental surgery, and a large body of literature and clinical reports have confirmed their pain relieving effectiveness. They are considered the first-line standard treatment for pain relief in dentistry. Ibuprofen at 200 mg and 400 mg has been shown to be superior to placebo at providing pain relief over four to six hours postoperatively. Remedication within six hours was less frequent at doses of 400 mg [50]. Also, monotherapy with ibuprofen has been reported to be as or more efficacious than acetaminophen for the management of dental pain [53; 61]. Ketoprofen 100 mg has been reported to have analgesic efficacy similar to that of acetaminophen 1,000 mg for pain after third-molar extraction [61; 62]. The combination of ketoprofen 100 mg plus acetaminophen 1,000 mg has been shown to provide a more rapid onset of analgesia than either drug given alone in the management of dental pain [63]. Several studies have demonstrated the greater efficacy of diflunisal, flurbiprofen, ibuprofen, and ketorolac in reducing pain after dental surgery compared to acetaminophen 600 mg with codeine 60 mg and acetaminophen 650 mg with codeine 60 mg [64; 65]. A listing of the NSAIDs useful for reducing dental pain and the usual suggested doses are summarized in ***Table 1***.

NONSELECTIVE NSAIDs APPROVED FOR USE TO RELIEVE ACUTE PAIN IN DENTISTRY	
Drug (Brand Name)	**Usual Adult Dose for Moderate or Moderate/Severe Pain**
Diclofenac (Voltaren)	50 mg tab three times daily
Diflunisal (Dolobid)	Initial: 500–1,000 mg tabs, followed by 250–500 mg every 8 to 12 hours
Etodolac (Lodine)	200–400 mg tab every six to eight hours
Flurbiprofen (Ocufen)	100 mg tab every 12 hours
Ibuprofen (Motrin)	200–400 mg every four to six hours
Ketoprofen (Orudis)	25–50 mg tab every six to eight hours
Ketorolac (Acular)	60 mg IM as single dose or 30 mg every six hours, followed by 10 mg tab every four to six hours. Total oral daily dose not to exceed 40 mg. Limit dosing to no more than five days.
Naproxen sodium (Anaprox)	Initial: 500 mg, followed by 250 mg every six to eight hours
Source: [26]	*Table 1*

All the brand name NSAIDs used in dentistry have a generic equivalent. Unless the prescriber indicates on the prescription to the pharmacist to dispense the brand name product, by law the pharmacy will dispense the generic equivalent. The FDA evaluates the efficacy and other standards of generic brands in comparison to the respective brand name product prior to approval to assure similar efficacy and similar incidence of side effects. The prescriber should feel confident that the generic product is equivalent in actions to the brand name product. In general, generic brands are priced at a lower cost to the consumer because the developmental costs were much lower than the costs of developing the initial brand name product.

CARDIOVASCULAR EFFECTS OF NONSELECTIVE NSAIDs

NSAIDs and Congestive Heart Failure

The use of NSAIDs in the previous week by individuals 65 years of age and older has been associated with a doubling of the odds of a hospital admission with congestive heart failure (CHF) [66]. Also, the use of NSAIDs by patients in the same age group with a history of heart disease had an odds ratio of 10.5 for first admission with heart failure compared to an odds ratio of 1.6 for first admission in those without such a history.

This study was conceived from previous reports that showed that NSAIDs were able to raise systemic vascular resistance and reduce renal perfusion in susceptible individuals [67; 68]. In addition, in some individuals, it was thought that these mechanisms could exacerbate the tendency to develop CHF [68].

However, more recently published studies have found lower relative risk estimates than the initial studies published in 1998–2,000. A case-control study of the relationship between recent use of NSAIDs and hospitalization with CHF found weak and statistically nonsignificant associations between use of NSAIDs and hospitalization with CHF [69].

Use of NSAIDs has also been associated with a small increase in risk of a first hospitalization for heart failure (HF). In patients with prior clinical diagnosis of HF, the use of NSAIDs may lead to a worsening of pre-existing HF that triggers their hospital admission [70; 71]. This increased risk, although small, may result in considerable public health impact, particularly among the elderly [71]. Additionally, because the magnitude of risk may vary with individual agents, physicians should consider patterns of risk and benefit, as well as individual cardiovascular risk profile, when selecting the most appropriate agent [72].

Ibuprofen and Reversal/Block of Aspirin Cardioprotection

In a statement released in 2006, the FDA notified consumers and healthcare professionals that the administration of ibuprofen for pain relief to patients taking aspirin for cardioprotection may interfere with aspirin's cardiovascular benefits. The FDA stated that ibuprofen could interfere with the antiplatelet effect of low-dose aspirin (i.e., 81 mg daily). This could result in diminished effectiveness of aspirin as used for cardioprotection and stroke prevention [73]. Although ibuprofen and aspirin may be taken together, the FDA has recommended that consumers talk with their healthcare providers for additional information [2]. In situations in which these drugs could be used concomitantly, the FDA has provided the following recommendations [26; 73; 74; 75; 76]:

- Patients who use immediate-release aspirin (not enteric-coated aspirin) and take a single dose of ibuprofen 400 mg should dose the ibuprofen at least 30 minutes or longer after aspirin ingestion or more than eight hours before aspirin ingestion to avoid attenuation of aspirin's effect.
- Recommendations about the timing of ibuprofen 400 mg in patients taking enteric-coated, low-dose aspirin cannot be made based upon available data. However, one study has shown that the antiplatelet effect of enteric-coated, low-dose aspirin was attenuated when ibuprofen 400 mg was dosed 2, 7, and 12 hours after aspirin.
- With occasional use of ibuprofen, there is likely to be minimal risk from any attenuation of the antiplatelet effect of low-dose aspirin because of a long-lasting effect of aspirin on platelets.
- There is no clear data regarding the potential effect of chronic ibuprofen dosing greater than 400 mg on the antiplatelet effect of aspirin.
- Other over-the-counter NSAIDs (i.e., naproxen sodium, ketoprofen) should be viewed as having the potential to interfere with the antiplatelet effect of low-dose aspirin until proven otherwise. However, the FDA is unaware of any studies that have looked at the same type of interference by ketoprofen with low-dose aspirin. One study of naproxen and low-dose aspirin has suggested that naproxen may interfere with aspirin's antiplatelet activity when they are co-administered. However, naproxen 500 mg administered two hours before or after aspirin 100 mg did not interfere with aspirin's antiplatelet effect. The FDA has stated that there is no data looking at doses of naproxen less than 500 mg. Naproxen sodium over-the-counter strength is 220 mg tablets.
- Acetaminophen 1,000 mg appears to not interfere with the antiplatelet effect of low-dose aspirin (i.e., 81 mg daily) when taken concomitantly.
- Existing data using platelet function tests have suggested there is a pharmacodynamic interaction between 400 mg ibuprofen and low-dose aspirin when dosed concomitantly. The FDA is unaware of data addressing whether taking less than 400 mg of ibuprofen interferes with the antiplatelet effect of low-dose aspirin.
- It is emphasized that the clinical implication of 400 mg ibuprofen interfering with the effect of aspirin may be important because the cardioprotective effect of aspirin, when used for secondary prevention of myocardial infarction, could be attenuated.

The mechanism of ibuprofen's interference with the antiplatelet effect of low-dose aspirin is probably through competitive inhibition of the acetylation site of cyclooxygenase in the platelet. Ibuprofen is a reversible inhibitor of cyclooxygenase, and aspirin is an irreversible inhibitor of cyclooxygenase. Both occupy nearby sites on cyclooxygenase such that the presence of ibuprofen interferes with aspirin binding. Once the ibuprofen leaves the site, the cyclooxygenase will not be inhibited by aspirin because the aspirin will have been excreted due to its short half-life. Thus, the ibuprofen interference diminishes or attenuates the inhibition in platelet aggregation by aspirin [74].

Ibuprofen as a Dental Pain Reliever in Patients Taking Cardioprotective Aspirin

The use of ibuprofen in dentistry is usually on a very short-term basis, and some evidence indicates that this presents little reason to be concerned. The FDA has stated that with occasional use of ibuprofen, a clinically significant interaction with aspirin is unlikely [73]. If ibuprofen is the preferred pain reliever, patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. Patients who use immediate-release aspirin (not enteric-coated) and take a single dose of ibuprofen 400 mg should dose the ibuprofen at least 30 minutes or longer after aspirin ingestion or more than eight hours before aspirin ingestion to avoid attenuation of aspirin's effect. To avoid interference during chronic ibuprofen dosing, a single dose of ibuprofen should be taken at least 30 minutes or longer after aspirin or at least eight hours should elapse after ibuprofen dosing before taking aspirin [73].

Based on available information, acetaminophen or an acetaminophen-narcotic combination analgesic would be suitable for patients taking cardioprotective aspirin who require analgesics for postoperative pain relief. The FDA has recommended that other nonselective NSAIDs should be viewed as having the potential to interfere with the antiplatelet effect of low-dose aspirin until proven otherwise [73].

IBUPROFEN/NARCOTIC COMBINATIONS

When ibuprofen is combined with a narcotic for pain relief, two different mechanisms of analgesic action are being utilized, which should result in a more effective action than either agent alone. In addition, ibuprofen allows for a significant dose reduction of the narcotic to minimize narcotic side effects. Studies have been published on the evaluation of ibuprofen combined with codeine, hydrocodone, or oxycodone to manage acute dental pain. The combination of ibuprofen 400 mg with codeine 60 mg provided superior analgesia compared to ibuprofen 400 mg alone [77; 78]. A combination of ibuprofen 400 mg with hydrocodone 15 mg was superior to ibuprofen 400 mg alone for all hourly measurements of analgesia after abdominal surgery, and side effects were associated primarily with the gastrointestinal tract and central nervous systems (CNS) [79]. The combination of ibuprofen 400 mg with hydrocodone 15 mg was superior to the combination of acetaminophen 600 mg with codeine 60 mg in providing analgesia after third-molar extraction, as demonstrated by superior total analgesia effect and the duration of analgesia [80]. Ibuprofen 400 mg with oxycodone 10 mg provided a faster onset of pain relief after dental surgery than did ibuprofen 400 mg alone [81]. However, the combination of ibuprofen 400 mg with 2.5 mg or 5 mg of oxycodone was not significantly different from ibuprofen 400 mg alone in providing pain relief [81]. There are two commercial products available that combine ibuprofen and a narcotic in the same tablet. One product, with the brand name Vicoprofen, contains hydrocodone 7.5 mg and ibuprofen 200 mg in each tablet. This preparation is indicated for short-term (i.e., less than 10 days) management of moderate-to-severe acute dental pain. The suggested dose is one to two tablets every four to six hours as needed for pain, not to exceed five tablets over a 24-hour period [26].

A second product combines ibuprofen and the narcotic oxycodone under the brand name Combunox. This product contains 400 mg ibuprofen and 5 mg oxycodone. Like Vicoprofen, Combunox is approved by the FDA for the short-term (i.e., less than seven days) treatment of moderate-to-severe acute dental pain. One tablet should be taken every six hours as needed; the maximum dose is four tablets in 24 hours. Combunox should not be taken for longer than seven days [26].

DRUG INTERACTIONS WITH NSAIDs

The following drugs or drug groups have been documented to interact with the nonselective NSAIDs. Below are brief descriptions of these interactions. Some of the interactions are more significant than others and are categorized accordingly [2; 26].

INTERACTIONS OF GREATER SIGNIFICANCE

Anticoagulants

Nonselective NSAIDs may enhance the anticoagulant effect of warfarin derivatives, such as Coumadin. It is suggested that NSAIDs not be used concomitantly with anticoagulants. Acetaminophen is an acceptable analgesic choice in patients taking oral anticoagulants.

Antiplatelet Agents

Nonselective NSAIDs may enhance the effects of antiplatelet agents (e.g., clopidogrel [Plavix]). An increased risk of bleeding may occur. It is suggested that NSAIDs not be used concomitantly with antiplatelet agents. Acetaminophen is an acceptable analgesic choice in patients taking antiplatelet agents. If you must use NSAIDs in patients on antiplatelet therapy, use the lowest dose possible for the briefest duration.

Bisphosphonate Derivatives

NSAIDs may enhance the adverse effects of bisphosphonate derivatives. There may be an increased risk of developing symptoms of gastrointestinal ulceration [82]. Alternative therapy for the NSAID should be considered.

Methotrexate

NSAIDs may decrease the renal excretion of methotrexate. This could result in methotrexate toxicity, including hematologic effects and renal toxicity [4]. If a patient is receiving antineoplastic doses of methotrexate, an alternative agent other than an NSAID should be considered. There is a lesser risk associated with lower doses of methotrexate, such as when it is used to treat rheumatoid arthritis [4].

Lithium

NSAIDs may increase the serum concentration of lithium. This could result in signs of acute lithium toxicity, including dizziness, restlessness, and confusion. It is suggested that a non-NSAID analgesic be used in patients taking lithium [2].

INTERACTIONS OF LESSER SIGNIFICANCE

ACE Inhibitors

The antihypertensive effects of angiotensin-converting enzyme (ACE) inhibitors may be decreased with concurrent therapy with NSAIDs. Blood pressure increases have been noted with both chronic NSAID therapy and following a single NSAID dose [83]. In patients with a history of CHF, consider alternative therapy to avoid the potential negative consequences of concomitant NSAID therapy (e.g., fluid retention, fluid accumulation, edema).

Aspirin (Salicylates)

Aspirin and other salicylate drugs may decrease the serum concentration of NSAIDs [2]. NSAIDs may not achieve full therapeutic effectiveness in the presence of aspirin.

Antacids

Antacids containing aluminum or magnesium may decrease the absorption of NSAIDs from the gastrointestinal tract into the bloodstream. NSAIDs may not achieve full therapeutic effectiveness when taken with these types of antacids.

Loop Diuretics

NSAIDs may diminish the diuretic effect of loop diuretics. This could result in a decreased effect of the medication.

Beta-Blockers

NSAIDs may diminish the antihypertensive effect of beta-blockers. This interaction could be important if NSAIDs are used long-term.

Calcium Channel Blockers

NSAIDs may diminish the antihypertensive effect of calcium channel blockers.

COX-2 INHIBITORS

Studies involving the COX-2 inhibitors, such as rofecoxib (Vioxx), celecoxib (Celebrex), and valdecoxib (Bextra), have indicated an increased risk of heart attack and stroke associated with long-term use of some of the drugs in this group. Specifically, Vioxx was voluntarily withdrawn from the market by the manufacturer in late 2004.

Bextra was taken off the market in April 2005, at the recommendation of the FDA. The FDA cited a risk of serious skin reactions as a major cause for concern in addition to an increased risk of heart attack and stroke.

The relative risks and benefits of the COX-2 inhibitors are still being studied, and it is recommended that readers of this course keep apprised of the current information on this subject and proper use of these medications.

As discussed, NSAIDs exert their effects through the inhibition of the enzyme cyclooxygenase. In the mid-1990s, literature reports described the discovery of at least two cyclooxygenase isoenzymes, COX-1 and COX-2 [84; 85]. The COX-1 enzyme is expressed in most tissues and is responsible for the physiological production of prostaglandins. The COX-2 enzyme is induced by various endogenous compounds such as cytokines, mitogens, and endotoxins in inflammatory cells and is responsible for the elevated production of prostaglandins during inflammatory processes [86]. Although both COX isoforms contribute to the inflammatory process, only COX-2 is induced to enhance the formation of more prostaglandins during acute, as well as chronic, inflammation.

The discovery of the COX-1 and COX-2 isoenzymes has led to the development of a selected class of drugs that show preference to elicit inhibitory effects on the COX-2 enzyme. These drugs have been labeled as the new "super aspirins" by the mass media. Conventional NSAIDs, such as ibuprofen and naproxen, are nonselective COX inhibitors and inhibit both isoenzymes. These new drugs, with a high selectivity for COX-2, may be better tolerated in the gastrointestinal tract [85; 87]. Celecoxib and rofecoxib are about 100 to 1,000 times more selective on the COX-2 than on the COX-1 [88]. The major interest in these drugs has been related to the lower incidence of gastrointestinal bleeding. With conventional NSAIDs, this has been a reason for failure of drug therapy, disablement, and hospitalization, especially in the elderly.

CELECOXIB (CELEBREX): EFFICACY IN DENTAL PAIN

Celecoxib, a COX-2 inhibitor, was approved by the FDA for two new indications: management of arthritis and acute pain in adults and treatment of primary dysmenorrhea [2]. The FDA approval was based on acute analgesic models of post-oral surgery pain, post-orthopedic surgery pain, and primary dysmenorrhea. The recommended dose for both indications is 400 mg initially, followed by an additional 200 mg dose on the first day if needed.

Thereafter, 200 mg twice daily is recommended as needed [4; 26]. These newer indications are in addition to the previous indications for the relief of the symptoms of osteoarthritis and rheumatoid arthritis in adults. Celecoxib is supplied as the brand name, Celebrex, in 50 mg capsules (opaque white encircled by two red bands), 100 mg capsules (opaque white encircled by two blue bands), 200 mg capsules (opaque white encircled by two gold bands), and 400 mg capsules (opaque white encircled by two green bands) [2; 4]. Celecoxib is not available as a generic formulation. The package label states that the adverse events caused by celecoxib when used to manage acute pain were similar to those in arthritis studies [4].

Celecoxib is contraindicated in patients with a history of allergy to sulfa drugs. Celecoxib is a sulfonamide derivative [4].

CARDIOVASCULAR EFFECTS OF CELECOXIB

The nonselective NSAIDs, such as ibuprofen, are known to reversibly decrease platelet aggregation through mechanisms that differ from those of aspirin. According to the manufacturer, celecoxib at a single dose up to 800 mg and multiple doses of 600 mg twice daily had no effect on platelet aggregation or bleeding time [4; 26]. Comparative NSAIDs (i.e., naproxen 500 mg twice daily, ibuprofen 800 mg three times daily, or diclofenac 75 mg twice daily) significantly reduced platelet aggregation and prolonged bleeding times. Thus, celecoxib does not appear to inhibit platelet aggregation at recommended doses [4].

In addition, reports have shown that celecoxib does not generally affect platelet counts, prothrombin times (PTs), or partial thromboplastin time (PTT). Studies of the effect of celecoxib on the anticoagulant effect of warfarin found no alteration of anticoagulant effect, as determined by PT, in patients taking warfarin 2 mg and 5 mg daily. However, the manufacturer has issued a caution when using celecoxib with warfarin because those patients are at increased risk of bleeding complications [4; 26].

Celecoxib and Risk of Cardiovascular Events

In a report published by the American Medical Association, researchers, using a meta-analysis technique, reanalyzed four previously published trials, assessing cardiovascular events in patients receiving either celecoxib or rofecoxib [89]. They found an association between the use of COX-2 inhibitors and cardiovascular events, including myocardial infarction and ischemic stroke. The annualized myocardial infarction rate was found to be significantly higher in patients receiving celecoxib or rofecoxib compared to the control (placebo) group from a meta-analysis of primary prevention trials. Cause and effect could not be established because the trials were originally designed to assess gastrointestinal effects, not cardiovascular effects. The authors believed, however, that the available data suggested a risk of cardiovascular events with the use of COX-2 inhibitors. In their commentary, the authors stated that COX-2 inhibitors did not affect the prothrombotic thromboxane A2 levels, but rather caused a decreased production of the antithrombotic PGI2 levels. Such an action may tip the balance in favor of prothrombotic thromboxane, leading to an increase in thrombotic cardiovascular events. The reader is reminded that the trials in question only addressed continuous use of COX-2 inhibitors. However, studies published subsequently appear to confirm that a risk of cardiovascular events with the use of COX-2 inhibitors exists, and the FDA-approved labeling for celecoxib includes a boxed warning about the increased risk of serious cardiovascular events [2; 4; 90]. Additionally, a review of 18 clinical studies that evaluated the efficacy of COX-2 inhibitors for the treatment of acute dental pain also found no evidence to demonstrate any therapeutic advantage to using a COX-2 inhibitor to treat acute dental pain compared with ibuprofen [90].

CELECOXIB GIVEN TO PATIENTS ON WARFARIN

Celecoxib has not been shown to alter the anticoagulant effects of warfarin. The manufacturer states, however, that bleeding complications may be increased with concomitant administration of these drugs [4]. The effects of celecoxib on the steady-state pharmacokinetic profile and hypoprothrombinemic effect of racemic warfarin in healthy volunteers were investigated. Twenty-four adults taking 2–5 mg daily maintenance doses of racemic warfarin and stabilized to PTs of 1.2 to 1.7 times pretreatment PT values for three days were given celecoxib 200 mg twice daily or placebo twice daily for seven days. PT values were not significantly different in subjects receiving warfarin-celecoxib compared to warfarin-placebo. In addition, steady-state exposure of S-warfarin and R-warfarin (area under the curve [AUC] and maximum plasma concentrations [Cmax]) in subjects receiving celecoxib was within 2% to 8% of the warfarin AUC and Cmax in subjects receiving placebo. This study concluded that concomitant administration of celecoxib had no significant effect on PT or steady-state pharmacokinetics of S-warfarin or R-warfarin in healthy volunteers [91].

A subsequent study investigated whether celecoxib potentiates the anticoagulant effect of warfarin, as measured by the INR. Fifteen patients who were receiving warfarin therapy and required analgesic treatment were evaluated to assess the effect on INR of celecoxib versus codeine (control treatment). During the first phase of the study, patients were randomly allocated to receive celecoxib 200 mg daily or codeine phosphate 7–15 mg three to four times daily for five weeks. During the second phase, patients stopped the first study medication and started the other study medication, with no drug-free interval between phases. Weekly INR testing was performed during the 10-week study period. Investigators found no significant difference in the mean INR values during each five-week treatment period when patients received either celecoxib or codeine. They concluded that treatment with celecoxib does not potentiate the INR when taken with warfarin and recommended that larger randomized trials be conducted to address the effects of co-administration of warfarin and celecoxib [92].

EFFECTS ON THE GASTROINTESTINAL TRACT

The COX-2 inhibitors have been reported to offer improved gastric tolerance as compared to the conventional, nonselective NSAIDs [93; 94; 95; 96]. While patients, particularly young patients, may benefit from NSAIDs without the risk of serious adverse gastrointestinal events, patients with a previous history of serious gastrointestinal complications as well as the elderly (who could be at risk) require alternatives [97; 98]. It is important to note, however, that there is an ongoing discussion about whether the slightly better gastrointestinal tolerability (which is lost if acetylsalicylic acid is co-administered) of the COX-2 inhibitors is offset by their elevated risks for cardiovascular events [2]. In addition, the higher costs for COX-2 inhibitors, when compared to NSAIDs, should be considered if a COX-2 inhibitor will be selected for certain patients with a high risk for gastrointestinal complications. For such treatment, the lowest effective dose should be used for a limited time. Monitoring of kidney function and blood pressure also is advisable. Further controlled studies are needed to better define the therapeutic place of the COX-2 inhibitors [99].

DRUG INTERACTIONS WITH CELECOXIB

The following interactions with celecoxib and other drugs are ranked according to significance. Of the interactions of greater significance, the lithium interaction with celecoxib is similar to the lithium interaction with the nonselective NSAIDs. All the interactions of less significance are similar to the nonselective NSAIDs.

CELECOXIB SUMMARY	
Brand Name	Celebrex
Manufacturer	Searle (a division Pfizer)
Use	Osteoarthritis Rheumatoid arthritis, juvenile idiopathic arthritis Acute pain
Mechanism	More selective on COX-2 than COX-1
Usual Dose	Osteoarthritis = 200 mg/day Rheumatoid arthritis = 100–200 mg twice a day Pain = 400 mg initially, followed by 200 mg dose, if needed on first day; 200 mg twice a day as needed on subsequent days
Documented Drug Interactions	Aspirin, fluconazole, lithium
Probable Interaction with Warfarin	None apparent, but may have increased risk of bleeding complications
Gastrointestinal Effects	Less than NSAIDs
Effects on Platelets	None at normal doses
Contraindications	Allergy to aspirin, NSAIDs, sulfonamides
How Supplied	Capsules, 50 mg, 100 mg, 200 mg, 400 mg

Source: [26] *Table 2*

Interactions of Greater Significance Involving Celecoxib

Aspirin

Concurrent use with celecoxib could result in higher likelihood of gastrointestinal ulceration. Celecoxib may be used with low-dose aspirin; however, rates of gastrointestinal bleeding may be increased with co-administration [2; 4].

Fluconazole (Diflucan)

Fluconazole will inhibit the metabolism of celecoxib through the inhibition of the hepatic P450 2C9 isoform. Concomitant administration of fluconazole at 200 mg once daily has resulted in a twofold increase in the blood levels of celecoxib after a therapeutic dose [2; 4]. If celecoxib is co-administered with fluconazole, the lowest recommended dose of celecoxib should be used [2; 4].

Lithium

Celecoxib at a dose of 200 mg has been shown to significantly increase lithium blood levels (approximately 17%) in patients receiving therapeutic doses of lithium [4]. It is essential that the blood levels of lithium be monitored when the two drugs are administered concomitantly [4].

Interactions of Less Significance Involving Celecoxib

ACE Inhibitors

Concurrent use with celecoxib may decrease the antihypertensive effects of ACE inhibitors [2; 4].

Antacids Containing Aluminum or Magnesium

Concurrent administration with certain antacids has resulted in a 37% decrease in peak blood levels of celecoxib, presumably by interference in gastrointestinal tract absorption of celecoxib. Celecoxib, at doses up to 200 mg twice daily, may be administered without regard to timing of meals. Higher doses (i.e., 400 mg twice daily) should be administered with food to improve absorption [4].

Diuretics

Celecoxib, and the NSAIDs in general, may decrease the natriuretic effects of diuretics, presumably through the inhibition of renal prostaglandin synthesis [4].

SUMMARY OF CELECOXIB

In summary, the COX-2 inhibitor presently approved for use in treating pain of dental origin is celecoxib. ***Table 2*** presents the significant information on celecoxib as reference for the dental health professional.

NARCOTIC ANALGESICS FOR DENTAL PAIN

Narcotic (opioid) analgesics are extremely effective in reducing acute dental and postoperative pain. The narcotic analgesics have established a niche for the treatment of pain in those situations where the NSAIDs are less effective. Although NSAIDs are the established drugs of first choice for the management of mild-to-moderate dental and postoperative pain, at times the oral narcotic analgesics should be used to treat the more severe intensities of pain. For example, in a survey of prescribing patterns in a group of dentists, the percentage of prescriptions written for the management of pain following extraction of a full bony impacted tooth number 32 in healthy patients 18 years of age was 81% for a narcotic analgesic compared to 19% for an NSAID [100]. Hydrocodone, oxycodone, codeine, and occasionally meperidine are the narcotics used to treat dental pain.

In 2016, the FDA issued a warning about safety issues with the entire class of opioid analgesics. The agency is requiring label changes to all opioid drugs to warn healthcare professionals and consumers about the risks, which include serotonin syndrome, adrenal insufficiency, and androgen deficiency. Specific opioids mentioned in this course and included in the FDA safety communication include codeine, hydrocodone, meperidine, oxycodone, and tramadol [101].

GENERAL INFORMATION

Hydrocodone and oxycodone are semisynthetic opioids with multiple actions qualitatively similar to those of morphine. Codeine is an opioid that occurs naturally as a component of the poppy plant, along with morphine, and may be recovered as such from the opium extract of the plant. Codeine has actions similar to morphine and may also be synthesized in the laboratory. All three opiates are chemically very similar to morphine. Meperidine is chemically dissimilar to morphine and is a synthetic compound having similarities of opiate receptor binding and analgesic effect. Hydrocodone, oxycodone, codeine, and meperidine may all produce drug dependence of the morphine type and have the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration, and all of these agents are subject to the Federal Controlled Substances Act [2; 4]. As stated, these agents are the subject of the FDA safety warning and label change requirement [101]. Codeine combination products are controlled substances within the Drug Enforcement Administration (DEA) schedule III (C-III), and hydrocodone combination products, oxycodone, and meperidine are controlled substances within DEA schedule II (C-II) [26; 102; 103].

Narcotic analgesics block pain perception in the cerebral cortex by binding to specific receptor molecules (opiate receptors) within neuronal membranes of synapses. This binding results in a decreased synaptic chemical transmission throughout the CNS, thus inhibiting the flow of pain sensations into the higher centers. Mu and kappa receptors are the two subtypes of the opiate receptor that narcotics bind to in order to cause analgesia. The narcotics are not anti-inflammatory in nature and do not inhibit cyclooxygenase or block the production of inflammatory factors, such as the prostaglandins [26].

These four narcotic analgesics are recommended only for limited acute dosing (i.e., three days or less). These agents should be given with caution to certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, or prostatic hypertrophy or urethral stricture. Any of these agents may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient taking these drugs should be cautioned accordingly. Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with these narcotic preparations may exhibit an additive CNS depression [4; 26].

The use of monoamine oxidase (MAO) inhibitors or tricyclic antidepressants with narcotic preparations may increase the effect of either the antidepressant or the narcotic. The concurrent use of anticholinergics with opioids may produce paralytic ileus [4; 26].

The most frequently observed adverse reactions with these drugs include lightheadedness, dizziness, sedation, nausea, and vomiting. These effects are more prominent in ambulatory than in nonambulatory patients. Some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, skin rash, and pruritus. At higher doses, any of these agents can depress medullary respiratory centers resulting in decreased rate and depth of respirations [4].

Hydrocodone, oxycodone, and codeine are available in combinations with acetaminophen. There is a variety of strengths of each combination product available to the prescriber, providing numerous pharmacologic options for pain reduction. Some preparations also contain aspirin and other ingredients. Oxycodone and codeine are also available alone. Hydrocodone is only available as a combination product. Hydrocodone and oxycodone are available in combination with ibuprofen [26].

HYDROCODONE PRODUCTS

The available hydrocodone oral products useful in dentistry are listed in ***Table 3***. All the products are scheduled as C-II controlled substances, indicating that prescriptions may not be oral, telephone, email, or fax-transmission, and no refills may be authorized [103; 104; 105; 106]. All written prescriptions for schedule C-II controlled substance drugs must handwritten or typed on tamper-resistant prescription forms [107]. All the formulations are combined with acetaminophen except for one containing ibuprofen. All products are available under the various listed brand names and are also available generically, except for Vicoprofen and Xodol. The pharmacist will dispense the generic equivalent, if available, to any brand name that is prescribed, unless the prescriber indicates not to substitute for the brand name.

The strength of hydrocodone in these products ranges from 5–10 mg. Acetaminophen strength ranges from 325–750 mg. Ibuprofen is available in a single-strength combination of 200 mg each. The varied strengths of hydrocodone and acetaminophen allow for prescribing options on the part of the clinician. Thus, the lower dose of hydrocodone, 5 mg, in combination with 500 mg acetaminophen can be prescribed to the patient who may be sensitive to the adverse effects of the narcotic. On the other end of the spectrum, a maximum strength of hydrocodone, 10 mg, is available in combination with 750 mg of acetaminophen. The combination of 5 mg hydrocodone and 500 mg acetaminophen is

HYDROCODONE ANALGESIC COMBINATION ORAL PRODUCTS					
Hydrocodone Bitartrate	**Acetaminophen (APAP)[a]**	**Other**	**Brand Name**	**Generic Available**	**Form**
2.5 mg	325 mg	–	Verdrocet	Yes	Tab
5 mg	300 mg	–	Xodol 5/300, Vicodin	Yes	Tab
5 mg	325 mg	–	Norco	Yes	Tab
7.5 mg	300 mg	–	Xodol 7.5/300, Vicodin ES	Yes	Tab
7.5 mg	325 mg	–	Norco, Lorcet Plus	Yes	Tab
10 mg	300 mg	–	Xodol 10/300, Vicodin HP	Yes	Tab
10 mg	325 mg	–	Norco	Yes	Tab
7.5 mg	325 mg/15 mL	–	Hycet	Yes	Solution
10 mg	325 mg/15 mL	–	Zamicet	Yes	Solution
2.5 mg	–	Ibuprofen 200 mg	Reprexain	Yes	Tab
5 mg	–	Ibuprofen 200 mg	Ibudone; Reprexain	Yes	Tab
7.5 mg	–	Ibuprofen 200 mg	Vicoprofen	Yes	Tab
10 mg	–	Ibuprofen 200 mg	Reprexain; Ibudone; Xylon	Yes	Tab

[a]APAP is the common acronym for acetaminophen and is the abbreviation of the chemical name *N*-acetyl-para-aminophenol.

Source: [2; 4; 26] *Table 3*

available in either tablet or capsule dose forms. A liquid dose form (elixir) is available for those adults who have difficulty swallowing tablets or capsules. Neither hydrocodone nor acetaminophen elicits anti-inflammatory responses. Anti-inflammatory effects may be achieved by prescribing the ibuprofen combination product, assuming, of course, that the patient is not taking warfarin-type oral anticoagulants. Ibuprofen may enhance the anticoagulant effects of warfarin-type drugs. Because of addiction liability of opiate analgesics, the use of hydrocodone should be limited to two to three days postoperatively for the treatment of dental pain. Nausea is the most common adverse effect seen after use in dental patients; sedation, dizziness, and constipation are collectively the second most common effects. Nausea caused by narcotic analgesics is centrally mediated, and the presence or absence of food will not affect the degree or incidence of nausea [26].

The following are the usual adult doses of the hydrocodone oral products [4]:

- One tablet or capsule containing 5 mg of hydrocodone and 300 mg acetaminophen every four to six hours as needed, with dosage being increased to two tablets or capsules every four to six hours if necessary
- One tablet containing 7.5 mg hydrocodone and 300 mg of acetaminophen every four to six hours as needed, with dosage being increased to two tablets every six hours if necessary
- One tablet containing 10 mg of hydrocodone and 300 mg acetaminophen every four to six hours as needed

OXYCODONE ANALGESIC COMBINATION ORAL PRODUCTS					
Oxycodone HCl	**Acetaminophen (APAP)**	**Other**	**Brand Name**	**Generic Available**	**Form**
2.5 mg	325 mg	–	Percocet, Endocet	Yes	Tablet
5 mg	300 mg	–	Primlev 5/300	Yes	Tablet
5 mg	325 mg	–	Percocet, Endocet, Roxicet	Yes	Tablet
5 mg/5 mL	325 mg/5 mL	–	Roxicet liquid	No	Solution
7.5 mg	300 mg	–	Primlev 7.5/300	Yes	Tablet
7.5 mg	325 mg	–	Endocet, Percocet, Xartemis XR	Yes	Tablet
10 mg	300 mg	–	Primlev 10/300	Yes	Tablet
10 mg	325 mg	–	Endocet, Percocet	Yes	Tablet
4.8355 mg 0.38 mg[a]	–	Aspirin 325 mg	Endodan, Percodan	Yes	Tablet
5 mg	–	Ibuprofen 400 mg	Combunox	Yes	Tablet
[a]Oxycodone terephthalate					
Source: [2; 4; 26]					*Table 4*

For the elixir dose form, the recommended dose is 1 tablespoon every four to six hours when necessary for pain. For the ibuprofen products, the recommended dose is one tablet every four to six hours as needed. The maximum dose of the ibuprofen products should not exceed five tablets in 24 hours [2; 4].

The usual adult prescribing limits for the combination hydrocodone-acetaminophen products is up to 40 mg of hydrocodone and up to 4,000 mg of acetaminophen in a 24-hour period. The maximum dose of hydrocodone may be limited by the acetaminophen content of the specific product [26].

OXYCODONE PRODUCTS

The available oxycodone analgesic combination oral products are listed in ***Table 4***. All the products are scheduled as C-II controlled substance, indicating that oxycodone has a high potential for abuse and that all prescriptions must be written in ink or typewritten and signed by the practitioner. Verbal prescriptions are not allowed under normal circumstances and may be given only in a genuine emergency. The oxycodone combination formulations all contain acetaminophen except for two products, one containing aspirin and one containing ibuprofen. Similar to hydrocodone, all products are available under the various listed brand names and available generically. The pharmacist will dispense the generic equivalent, if available, to any brand name that is prescribed, unless the prescriber indicates not to substitute for the brand name.

The strength of oxycodone in the combination products ranges from 2.5–10 mg. Acetaminophen strength ranges from 325–650 mg. Aspirin and ibuprofen are available in a single-strength combination. The varied strengths of oxycodone and acetaminophen allow for prescribing options on the part of the clinician. Thus, a low dose of oxycodone, 2.5 mg, in combination with 325 mg acetaminophen can be prescribed to the patient who may be sensitive to the adverse effects of the narcotic. On the other end of the spectrum, a high dose of oxycodone, 10 mg, may be given in

combination with 650 mg of acetaminophen. The combination of 5 mg oxycodone and 500 mg acetaminophen is available in either tablet or capsule dose forms [4]. A liquid dose form (solution) is also available for those adults who have difficulty swallowing tablets or capsules. Oxycodone has a recognized addictive liability. It is recommended only for limited acute dosing (i.e., four days or less) [4; 26]. Nausea is the most common adverse effect seen after use of oxycodone in dental patients, and virtually every patient will experience some degree of stomach upset after taking any dose of oxycodone. Sedation, dizziness, and constipation are also frequent complaints of patients taking oxycodone products. If the adverse effects outweigh the beneficial effects of pain reduction, then oxycodone products should be discontinued in favor of a nonnarcotic agent. The nausea caused by oxycodone is centrally mediated, and the presence or absence of food will not affect the degree or incidence of nausea [4; 26].

Oxycodone products are usually reserved for patients experiencing severe intensities of pain because of the high degree to which the adverse effects of nausea, sedation, and dizziness are experienced. Oxycodone is not ordinarily recommended for the management of moderate to moderately severe pain.

According to the manufacturer, the dosage of oxycodone combination products should be adjusted according to the severity of the pain and the response of the patient [2; 4]. It may occasionally be necessary to exceed the usual dosage recommended in cases of more severe pain or in those patients who have become tolerant to the analgesic effects of opioids.

The following are the usual adult doses of the oxycodone oral products [4]:

- One or two tablets containing 2.5 mg of oxycodone and 325 mg of acetaminophen every six hours
- One or two tablets containing 5 mg of oxycodone and 325 mg of acetaminophen every six hours
- One tablet or capsule containing 5 mg of oxycodone and 500 mg of acetaminophen every six hours as needed for pain
- One tablet containing 7.5 mg of oxycodone and 500 mg acetaminophen every six hours as needed for pain with a maximum daily dose of eight tablets
- One tablet containing 10 mg oxycodone and 650 mg acetaminophen every six hours as needed for pain with a maximum daily dose of six tablets

For the liquid dose form (5 mg oxycodone/325 mg acetaminophen/5 mL), the recommended dose is one teaspoonful every four to six hours when necessary for pain [2; 4].

For the aspirin product, the recommended dose is one tablet every six hours as needed for pain. The maximum daily dose of aspirin should not exceed 4 grams [2; 4]. The total daily dose of acetaminophen from any product should not exceed 4 grams [2; 4].

The first pain reliever containing oxycodone and ibuprofen within the same tablet, Combunox (manufactured by Forest Pharmaceuticals, Inc.), was approved by the FDA to treat acute pain. The brand-name product, Combunox, has been discontinued, but generic versions are available [108]. Combunox is formulated as oxycodone 5 mg with ibuprofen 400 mg in a film-coated tablet. It is indicated to treat acute, moderate-to-severe pain. The dosage to treat pain in adults is one tablet every 6 hours as needed with a maximum of four tablets over a 24-hour period. Combunox is indicated for short-term (i.e., no more than seven days) treatment for acute pain. It is scheduled as C-II under the DEA classification of controlled substances [4; 49].

RESULTS OF STUDY COMPARING IBUPROFEN, OXYCODONE, AND COMBUNOX IN DENTAL PAIN MODELS			
Factors	**Ibuprofen 400 mg**	**Oxycodone 5 mg**	**Combunox**
Study Group	186 subjects (101 female, 85 male)	63 subjects (33 female, 30 male)	187 subjects (118 female, 69 male)
Median time to onset of pain relief	29.7 minutes	Not available	21.4 minutes
Global evaluation score (Range: 0-4)	2.26	0.66	2.63
Total pain relief through six hours	Mean score: 12.2	Mean score: 4.3	Mean score: 13.3
Sum of pain intensity difference through six hours	Mean score: 6.54	Mean score: 0.14	Mean score: 6.54
Incidence of nausea	3.8%	9.5%	10.2%
Incidence of vomiting	2.7%	7.9%	7.5%
Incidence of dizziness	1.1%	4.8%	2.7%
Source: [109]			*Table 5*

This combination provides additional options in pain relief and pain control after dental surgery [108]. The two components within this formulation, oxycodone and ibuprofen, both have proven track records and strong evidence as an effective narcotic analgesic (oxycodone) and an effective non-narcotic/anti-inflammatory agent (ibuprofen) in treating postoperative dental pain. Similar type products include Vicoprofen (containing hydrocodone bitartrate 7.5 mg and ibuprofen 200 mg), Reprexain (containing hydrocodone bitartrate 10 mg and 200 mg ibuprofen), and Ibudone (containing hydrocodone bitartrate 10 mg and 200 mg ibuprofen) [4].

There are two studies that have been published comparing Combunox to oxycodone alone, ibuprofen alone, oxycodone with acetaminophen, hydrocodone with acetaminophen, and placebo in dental pain models. The first study compared Combunox to oxycodone 5 mg alone, ibuprofen 400 mg alone, and placebo [109]. Subjects underwent third-molar extraction (two or more ipsilateral partially or completely bony impacted third molars completely removed). To qualify for one of the drugs after surgery, subjects had to have a pain intensity score of over 50 mm on a 100 mm visual analog scale (VAS) and a moderate or severe pain-intensity rating within five hours after surgery using a scale following the statement: "My pain at this time is: 0 = none, 1 = slight, 2 = moderate, 3 = severe."

A single dose of each was evaluated in terms of analgesic efficacy, time to onset of pain relief, and a global score of treatment effectiveness. Analgesic efficacy was measured as both total pain relief through six hours derived from the pain relief scores (defined as the area under the observed pain relief-time curve from zero to six hours, with pain relief = 0 at time zero; range: 0 to 24), and the sum of pain intensity difference over six hours derived from the pain intensity difference from baseline pain intensity and defined as the area under the observed pain intensity difference-time curve from zero to six hours. The incidences of nausea, vomiting, and dizziness were also observed for each group. The authors of this study concluded that a single dose of Combunox was fast-acting, effective, and well-tolerated in subjects with moderate-to-severe pain after dental surgery (***Table 5***).

The second study compared Combunox to oxycodone 5 mg/acetaminophen 325 mg (Percocet), hydrocodone 7.5 mg/acetaminophen 500 mg (Lortab), and placebo [110]. Subjects underwent third-molar extraction. Qualifying conditions were similar as the first study. The drugs were evaluated in terms of analgesic efficacy, time to onset of pain relief, and a global score of treatment effectiveness, as described. Each treatment was given as a single dose. The authors of the second study concluded that Combunox provided significantly better analgesia in patients with moderate-to-severe pain after third-molar extraction compared with the other opioid/nonopioid combination drugs tested and was associated with fewer adverse events.

Given that narcotics have a history of causing nausea, vomiting, and dizziness, it was of interest to compare the differences of these effects observed in the various treatments. In the first study, the protocol did not allow for statistical comparisons. In the second study, the incidences of nausea and vomiting observed after Combunox were significantly lower than the two other active treatments.

A more recent systematic review assessed the analgesic efficacy and adverse effects of a single oral dose of ibuprofen plus oxycodone for moderate-to-severe postoperative pain [111]. Studies that the authors included provided data compared the combination: ibuprofen 400 mg/oxycodone 5 mg with placebo (603 participants); ibuprofen 400 mg/oxycodone 5 mg with ibuprofen 400 mg alone (717 participants); and ibuprofen 400 mg/oxycodone 5 mg with oxycodone 5 mg alone (471 participants). Researchers found that 60% of participants given combination ibuprofen 400 mg/oxycodone 5 mg achieved at least 50% pain relief compared with 50% with ibuprofen 400 mg alone, 23% with oxycodone 5 mg alone, 17% with placebo [111]. The prevalence of adverse events was the same for combination ibuprofen 400mg/oxycodone 5 mg, placebo, and ibuprofen 400 mg alone (25%) but slightly higher (35%) with oxycodone 5 mg alone [111].

OxyContin is a long-acting formulation of oxycodone used for moderate-to-severe operative pain. It is most useful when extended use is required [4; 49].

CODEINE PRODUCTS

Codeine is available alone and in combination with acetaminophen. A codeine/aspirin combination was previously available but has been discontinued [26]. Codeine alone is scheduled as a C-II controlled substance, and a combination of codeine with acetaminophen is scheduled as a C-III controlled substance [26]. Codeine alone is supplied generically as tablets (as the sulfate salt) in 15 mg, 30 mg, and 60 mg strengths; as tablets (as the phosphate salt) in 15 mg, 30 mg, and 60 mg strengths; and as an oral solution at 30 mg/5 mL concentration. In dental practice, codeine alone is not recommended as an analgesic agent because of moderate efficacy along with a relatively high incidence and severity of nausea, sedation, dizziness, and constipation. In addition, codeine alone has some worrisome narcotic addiction liability. If codeine is desired as a dental analgesic, it should be used in combination with acetaminophen [26].

The available codeine combination oral products are listed in ***Table 6***. Codeine, when combined with acetaminophen, may be given at a lower dose than that of codeine alone to achieve similar efficacy with less side effects. In theory, the lower codeine dose should result in less severe nausea and sedation compared to the degree of nausea and sedation seen with codeine alone. The optimal dose of codeine in combination with acetaminophen in most patients seems to be 30 mg every four to six hours as needed. Some patients may require up to 60 mg codeine every four to six hours. In any case, no more than 360 mg of codeine should ever be given within a 24-hour period [26].

CODEINE ANALGESIC COMBINATION ORAL PRODUCTS					
Codeine	Acetaminophen (APAP)	Other	Brand Name	Generic Available	Form
15 mg	300 mg	–	–	Yes	Tablet
30 mg	300 mg	–	Tylenol w/ Codeine #3	Yes	Tablet
60 mg	300 mg	–	Tylenol w/ Codeine #4	Yes	Tablet
12 mg/5 mL	120 mg/5 mL	–	Capital w/ Codeine	Yes	Solution

Source: [4; 26] *Table 6*

MEPERIDINE PRODUCTS

Meperidine (Demerol) is not indicated as a first choice narcotic analgesic for dental pain due to its abuse and addictive liabilities. All meperidine preparations fall under DEA schedule C-II, requiring a written prescription in ink and the signature of the prescriber. Meperidine is recommended to be used in codeine-allergic patients when a narcotic analgesic is indicated [26]. In this regard, meperidine has developed a niche in pain management and should be kept under consideration as an optional narcotic analgesic. It should not be used as the narcotic drug of first choice. Additionally, it is important to note that the American Pain Society and the Institute for Safe Medication Practices do not recommend the use of meperidine as an analgesic [26].

Other narcotic agents, such as hydrocodone and oxycodone, have a similar chemical makeup to codeine, and cross allergy between narcotics may exist. Meperidine is chemically dissimilar to codeine. Meperidine is not an anti-inflammatory agent. Also, it is not available in combination with acetaminophen, aspirin, or other NSAIDs. Meperidine preparations are listed in ***Table 7***. It is supplied as meperidine only in tablet and oral liquid form. Meperidine has a proven and well-recognized efficacy against moderate-to-severe pain. However the unwanted effects of dizziness, nausea, sedation, hypotension, weakness, nervousness, and confusion, which often occur, may outweigh any gain in pain management.

Meperidine is recognized as an alternate oral narcotic in patients allergic to codeine in treatment of moderate or moderate-severe pain. Dose for adults is 50–150 mg every two to four hours as needed for pain. Dose for children is 1–1.5 mg/kg/dose every three to four hours as needed for pain [26].

Meperidine is unique from the other narcotics in that it forms a compound via hepatic metabolism known as normeperidine, an active metabolite and CNS stimulant. In patients with seizure disorders, normeperidine may precipitate twitches, tremors, or seizures. Therefore, caution is warranted in the use of meperidine in patients with a history of seizure disorders [26].

DRUG INTERACTIONS

The number of drugs that have the potential to interact with narcotic analgesics is much fewer than the number with the potential to interact with the NSAIDs. In general, because all narcotics can produce sedation, other sedative drugs and alcohol would have the potential to enhance narcotic-induced sedation.

Interactions with Narcotic Analgesics: Hydrocodone, Oxycodone, Codeine

Antipsychotics (Phenothiazines)

These drugs may enhance the hypotensive effect of narcotic analgesics [26].

MEPERIDINE ANALGESIC ORAL PRODUCTS			
Meperidine hydrochloride	**Brand Name**	**Generic Available**	**Form**
50 mg	Demerol HCl	Yes	Tablet
100 mg	Demerol HCl	Yes	Tablet
50 mg/5 mL	Demerol HCl	Yes	Syrup
Source: [26]			*Table 7*

CYP2D6 Inhibitors

This class of drugs may diminish the therapeutic effect of the narcotic analgesics. CYP2D6 is a specific enzyme system within the P-450 (CYP) drug metabolizing enzyme complex in hepatic cells [72]. Narcotics are CYP2D6 substrates [26]. Part of the therapeutic effects of CYP2D6 substrates is due to active metabolites of the substrates. The active metabolites are produced by CYP2D6 actions. Inhibiting this enzyme will reduce metabolism of the narcotics and thereby diminish their therapeutic effectiveness [26]. Some important CYP2D6 inhibitors include cimetidine, chlorpheniramine, fluoxetine, and quinidine.

Selective Serotonin Re-uptake Inhibitors (SSRIs)

The narcotics may enhance the serotonergic effect of SSRIs. This may result in serotonin syndrome, a complex of neurological symptoms including confusion, agitation, myoclonus, and hyper-reflexia [26]. SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline [112]. As stated, the FDA has issued a safety warning regarding a potential association between opioids and serotonin syndrome. The syndrome can occur during concomitant use of opioids with SSRIs, even within the recommended dosage range. Careful patient monitoring during treatment initiation and dose increases is recommended [101].

Interactions with Narcotic Analgesics: Meperidine

Barbiturates

These sedatives may increase the CNS depressant effect of meperidine [26]. Prolonged CNS depression (including sedation) occurred in a patient who had been receiving phenobarbital for approximately two weeks following the administration of meperidine [113].

MAO Inhibitors

MAO inhibitors may enhance the serotonergic effect of meperidine, which may cause serious serotonergic syndrome [26]. This combination should be avoided.

Phenytoin

This anticonvulsant may increase the metabolism of meperidine. This may reduce its analgesic action and may also increase the rate at which normeperidine, a neuroexcitatory metabolite, is formed [2].

NONTRADITIONAL ANALGESICS

There are several analgesics that are available to treat dental pain that are referred to as nontraditional analgesics. These drugs include tramadol (Ryzolt, Ultram), tramadol with acetaminophen (Ultracet), and gabapentin (Neurontin). These drugs are not NSAIDs nor are they narcotics, and their mechanisms of actions all differ from the traditional analgesics.

TRAMADOL (ULTRAM)

Tramadol (Ultram) was approved by the FDA in 1995. It has been used in more than 39 million patients in 39 countries since 1977 [114]. As stated, tramadol is included in the 2016 FDA safety warning and label change requirement [101]. It is scheduled IV, meaning it has a slight abuse potential.

Tramadol represents a unique class of analgesics. To reduce pain, it acts on opiate-mediated systems and monoaminergic pain-inhibitory pathways. This latter effect predominates over its opiate actions. Monoaminergic neural pathways originate in the medullary regions of the brain and descend the spinal cord to modulate and attenuate ascending pain tracts from the periphery and the dorsal horn of the spinal cord. These pathways use monoaminergic transmitters (serotonin and norepinephrine), which reduce or inhibit propagated pain impulses within ascending tracts. Tramadol blocks neuronal re-uptake of serotonin and norepinephrine to permit excesses of these transmitters. Pain reduction by tramadol through enhancement of serotonin and norepinephrine is consistent with the activity of tricyclic antidepressants in reducing chronic pain [2; 4; 115].

Chemically, tramadol is related vaguely to codeine and has a weak action at opiate receptors. Thus, tramadol is not a controlled substance and does not seem to be addictive [26]. In the clinical literature, tramadol is referred to as an atypical opioid analgesic. It is converted to the M1 active metabolite in the liver. This metabolite has a better affinity for the opiate receptor and contributes to the analgesic actions of the parent tramadol. The narcotic antagonist naloxone partially blocks the analgesic effects of tramadol, which is blocked almost totally by a monoaminergic antagonist yohimbine, thus confirming the dual mechanism of analgesic action [4; 116].

Efficacy Studies in Dental Pain

An early study of the effectiveness of tramadol in relieving dental pain showed that up to 2.5 mg/kg of tramadol taken orally after dental procedures provided good to satisfactory pain relief in cases of chronic periodontitis, pulpitis, and alveolitis [117]. Tramadol inadequately relieved pain from deep caries and acute purulent pulpitis. Ibuprofen enhanced the efficacy of tramadol.

A study of 128 healthy subjects who had undergone surgical extraction of the third molar was conducted to compare the analgesic efficacy of tramadol 75 mg/acetaminophen 650 mg to codeine 20 mg/acetaminophen 500 mg/ibuprofen 400 mg in the management of acute pain after oral surgery. When patients reported at least moderate pain after dental surgery (i.e., score greater than 5 on a 10-point scale), they were randomized to one of two treatment groups, which were similar in terms of baseline pain severity and demographic characteristics. The median times to onset of perceptible pain relief were 21.0 and 24.4 minutes, respectively, and the median times to the onset of meaningful pain relief were 56.4 and 57.3 minutes, respectively. Both the safety profile and the efficacy of the tramadol/acetaminophen combination were comparable to the codeine/acetaminophen/ibuprofen combination. Tramadol/acetaminophen provided rapid and effective analgesia for acute postoperative dental pain in this study group [118].

A controlled study of 200 patients compared the efficacy and safety of tramadol 37.5 mg/acetaminophen 325 mg, hydrocodone bitartrate 10 mg/acetaminophen 650 mg, and placebo in the treatment of postoperative dental pain. Patients were randomized to receive one or two tramadol/acetaminophen tablets, one hydrocodone bitartrate/acetaminophen tablet, or placebo. Scores for hourly pain relief, pain intensity difference, and combined pain relief/pain intensity differ-

ence were based on reported pain at 30 minutes and each successive hour for eight hours. Primary efficacy measures were summary pain intensity and pain relief scores, sum of pain intensity differences, and sum of pain relief/pain intensity differences for zero to four hours, four to eight hours, and zero to eight hours. Tramadol/acetaminophen tablets provided effective, rapid (i.e., less than 34 minutes), and dose-dependent analgesia for the treatment of postoperative dental pain. Two tramadol/acetaminophen tablets provided analgesia comparable to that provided by hydrocodone bitartrate/acetaminophen, but with better tolerability [119].

A meta-analysis of more than 1,000 patients compared the efficacy and time to analgesia of tramadol/acetaminophen combination tablet to tramadol or acetaminophen alone. Patients in each of three studies were evenly randomized to a single dose of tramadol 75 mg/acetaminophen 650 mg, tramadol 75 mg, acetaminophen 650 mg, or placebo. The results demonstrated that the combination tramadol/acetaminophen was superior to either tramadol or acetaminophen alone with respect to pain relief and duration of action [120].

A randomized, placebo-controlled study was conducted to evaluate the efficacy of a submucosal application of tramadol for acute postoperative pain following third molar extraction [121]. Sixty patients were randomly divided to receive either tramadol 1 mg or saline 2 mL, applied submucosally following surgery. There were no significant differences in the difficulty of the procedure or the duration of extraction between the two groups. Pain was evaluated using a visual analog scale postoperatively. The authors found no significant group differences in the visual analog scores both 24 and 48 hours postoperatively. The first analgesic was taken significantly later in the tramadol group compared to the saline group, and total analgesic intake in the saline group was significantly higher. Although further studies are needed to validate the efficacy of submucosal tramadol, it appears to be an effective, safe, and reliable method of reducing facial pain following third molar extraction [121].

Dosage and Side Effects

When taken orally, 75% of tramadol is absorbed into the bloodstream, and the onset of analgesia occurs within one hour. Food does not affect the rate or extent of absorption from the stomach. The time to peak serum concentration is two hours, and the serum half-life elimination is six hours [2; 26].

The most common side effects of tramadol (1% to 10% incidence) are dizziness, constipation, and sleep disorder [4; 26]. The manufacturer emphasizes that these effects may include symptoms of underlying disease or side effects of other medications used concomitantly. These incidence rates of adverse reactions to tramadol were the same for the two active control-group medications: acetaminophen/codeine (300/30 mg) and aspirin/codeine (325/30 mg) [49]. There also were no significant differences in side effects between the two submucosal groups [121].

Concomitant administration of tramadol and carbamazepine (Tegretol) increases tramadol metabolism significantly and is not recommended [49]. Quinidine inhibits liver metabolism of tramadol, thus increasing tramadol blood levels. The results of this interaction are presently unknown [49]. Concomitant administration of tramadol and MAO inhibitors increases the risk of seizures [49]. Tramadol has weak binding affinity to plasma proteins and, therefore, may be administered with protein-bound drugs, such as oral hypoglycemics and warfarin, with no fear of protein displacement of these agents causing toxic levels in the bloodstream [4].

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Seizure risk is increased with doses of tramadol above the recommended range [4]. Administration of tramadol may increase seizure risk in patients with epilepsy, and tramadol should be prescribed with caution to patients who use alcohol, opiates, phenothiazines, tranquilizers, or sedative hypnotics [4].

Suggested doses are 50–100 mg every four to six hours (up to 400 mg daily) as needed for pain. For moderate pain, 50 mg may be an adequate initial dose; for severe pain, 100 mg usually is more effective as an initial dose. Tramadol is supplied in tablets of 50 mg [2].

When to Use Tramadol

Tramadol is an interesting compound and is the first agent in a new class of analgesics that differs from the NSAIDs and traditional narcotics. Although its efficacy in relieving dental pain resembles that of other analgesics, tramadol may be useful in cases in which NSAIDs are contraindicated (e.g., in patients who use anticoagulants, oral hypoglycemics, or lithium). Unlike NSAIDs, however, tramadol is not an anti-inflammatory agent. Tramadol causes nausea, constipation, and dizziness, and it may offer no advantage over narcotic analgesics in terms of side effects. On the other hand, tramadol is neither a controlled substance nor addictive. Development of new analgesics like tramadol, which are more effective and cause fewer side effects than current dental analgesics, should be of therapeutic benefit.

PROPOXYPHENE NAPSYLATE WITH ACETAMINOPHEN

This analgesic is a combination of a weak narcotic agent (propoxyphene napsylate) and acetaminophen and was first approved for use in 1965. In the past, it was supplied as Darvocet-N 50 (50 mg propoxyphene napsylate/325 mg acetaminophen), Darvocet-N 100 (100 mg propoxyphene napsylate/650 mg acetaminophen), and Darvocet A500 (100 mg propoxyphene napsylate/500 mg acetaminophen), though all of these products have been discontinued [4; 26]. Because this is a weak narcotic agent, it was scheduled by the DEA as C-IV. If this drug is given in excessive doses with other CNS depressants, severe respiratory depression may occur. In patients dependent on opiates, this agent should be given with caution, if at all. Dizziness, nausea, and vomiting are the most frequently reported adverse reactions [4; 26]. In 2010, propoxyphene-containing products were voluntarily removed from the market due to data indicating an increased risk for serious toxicity to the heart even at therapeutic doses [122].

TRAMADOL AND ACETAMINOPHEN (ULTRACET)

In 2001, the FDA approved a tablet formulation of the combination tramadol and acetaminophen under the brand name Ultracet [4]. Each tablet contains tramadol hydrochloride 37.5 mg and acetaminophen 325 mg and is indicated for the short-term (i.e., five days or less) management of acute pain [4]. Because it contains tramadol, Ultracet is considered a controlled substance. Its mechanism of analgesic action is based on the tramadol component, inhibition of the re-uptake of norepinephrine and serotonin, which modifies the ascending pain pathways. It also binds to mu opiate receptors within the CNS to cause inhibition of ascending pain pathways, thus altering the perception and response to pain. Based on the acetaminophen component, it inhibits the synthesis of prostaglandins in the CNS and peripherally blocks pain impulse generation; it produces antipyresis from inhibition of the hypothalamic heat-regulating center [4; 26]. The usual dose to treat acute pain, including dental pain, is two tablets every four to six hours as needed for pain relief, with a maximum of eight tablets daily. Treatment with Ultracet should not exceed five days [26].

The efficacy of Ultracet against dental pain has been reported in the literature [120]. Three centers conducted a randomized, double-blind, parallel group, active controlled, single-dose trial with a placebo control. Twelve hundred patients were enrolled, and 400 were randomized equally at each of three sites with five treatment groups per site. Active drugs were Ultracet (tramadol 37.5 mg; acetaminophen 325 mg), tramadol alone (37.5 mg), acetaminophen alone (325 mg), and ibuprofen (200 mg). The pain model was evaluation of pain relief and pain intensity following extraction of third molars. The results showed that all treatments were superior to placebo. Ultracet was superior to tramadol alone and acetaminophen alone with respect to pain relief after eight hours and superior in overall changes in pain intensity. Onset of pain relief was 17 minutes for Ultracet compared to 51 minutes for tramadol alone, 18 minutes for acetaminophen alone, and 34 minutes for ibuprofen. Median time for supplemental analgesia in the Ultracet group was longer than with the individual tramadol and acetaminophen and comparable with that of ibuprofen. Adverse effects were transient, mild-to-moderate in severity, and comparable in incidence between Ultracet and tramadol alone. The adverse effects included nausea, vomiting, and dizziness. The study concluded that Ultracet was a rapidly acting, long-duration analgesic that was effective and well-tolerated for the treatment of acute pain [120]. Other studies have confirmed these findings [123; 124].

The packet label states that seizures may occur when Ultracet is taken at recommended doses. Also, risk of seizures is increased in patients receiving carbamazepine, tricyclic antidepressants, SSRIs, MAO inhibitors, and amphetamines [4]. Carbamazepine decreases the half-life of tramadol by 33% to 50%. Carbamazepine and hydantoin anticonvulsants may increase the hepatotoxic potential of acetaminophen [26].

Ultracet is contraindicated in opioid-dependent patients. It is also contraindicated in patients with hepatic dysfunction. The drug should not be given in combination with any of the traditional narcotics [26].

Although a niche has yet to be achieved for Ultracet in dental practice, it would seem to be useful in those situations where NSAIDs are not indicated. The patient with a history of gastric ulcers may benefit from Ultracet rather than risking gastric effects with an NSAID. Also, there are indications that NSAIDs should not be given to patients taking certain platelet aggregation inhibitors, such as clopidogrel (Plavix) [4; 125]. Ultracet may be a good alternative in these situations.

GABAPENTIN (NEURONTIN)

Neurontin, which is the brand name for gabapentin, is a unique antiepileptic agent approved for use as an add-on treatment for partial epileptic seizures. This GABA-mimetic compound also has been shown to have effect in the treatment of chronic pain syndromes, particularly neuropathic pain [126]. In 2002, the FDA issued approval to Pfizer to allow marketing of Neurontin for the management of postherpetic neuralgia, or pain in the area affected by herpes zoster after the disease has been treated [127]. The suggested dose from the manufacturer for adults older than 18 years of age is to be titrated to a maximum dose of 1,800 mg per day according to the following schedule: 300 mg once a day on day 1; 300 mg twice a day on day 2; and 300 mg three times a day on day 3. Thereafter, the dose may be increased using increments of 300 mg per day given in three divided doses. Neurontin is supplied in capsules containing 100 mg, 300 mg, or 400 mg, or in tablets containing 600 mg or 800 mg. It is also available as an oral solution containing 250 mg/5 mL of gabapentin [4; 26].

A multicenter, eight-week trial of 229 subjects from sixteen outpatient clinical centers was conducted to evaluate gabapentin for the treatment of postherpetic neuralgia [128]. The objective of this early study was to determine the efficacy and safety of gabapentin in reducing postherpetic neuralgia pain. The 229 subjects were randomized with approximately half receiving gabapentin and the other half receiving a placebo. The primary measure of efficacy was change in the average daily pain score based on an 11-point Likert scale (0, no pain; 10, worst possible pain) from baseline week to the final week of therapy. The dosing consisted of following an initial dose of 300 mg daily, increased over the next four weeks in a step-up manner to 900 mg, 1,800 mg, 2,400 mg, and 3,600 mg/day divided in three doses. Treatment was then maintained for another four weeks at the maximum tolerated dose. If any dose was intolerable, the dose was decreased by one level. Of 113 subjects, 83.3% received at least 2,400 mg/day and 65.0% received 3,600 mg/day.

One hundred thirteen subjects received gabapentin, and 89 completed the study; 116 received placebo, and 95 completed the study. Subjects receiving gabapentin had a statistically significant reduction in average daily pain score from 6.3 to 4.2 points compared with a change from 6.5 to 6.0 points in subjects who received placebo. Also, changes in sleep interference showed improvement with gabapentin. Somnolence, dizziness, ataxia, peripheral edema, and infection were all more frequent in the gabapentin group, but withdrawals were comparable in the two groups. The gabapentin group had 15 withdrawals, and the placebo group had 11 withdrawals. The investigators concluded that gabapentin was effective in the treatment of pain and sleep interference associated with postherpetic neuralgia [128].

There have been other reports on the effectiveness of gabapentin in treating neuropathic pain [129; 130; 131; 132]. In addition, gabapentin seems to have a favorable safety profile and a lack of drug interactions compared to other pharmacologic agents used for the treatment of neuropathic pain [131; 132]. Gralise, a once-daily extended-release formulation of gabapentin, has been shown to provide comparable drug exposure with an identical daily dose of the immediate-release formulation when administered three dimes daily. Patients given Gralise 1,800 mg daily showed a significant reduction in average daily pain intensity scores, reduced interference in sleep caused by pain, and a greater reported improvement in patient-reported impression of change [133]. Gralise should be titrated to an 1,800-mg dose taken orally once daily with the evening meal. It is not interchangeable with other gabapentin products due to differing pharmacokinetic profiles that affect the frequency of administration [4].

PREGABALIN (LYRICA)

Pregabalin (Lyrica) is a newer drug within the same family as gabapentin. It gained FDA approval for the management of pain associated with diabetic peripheral neuropathy, management of postherpetic neuralgia, and adjunctive therapy for partial-onset seizure disorder in adults. Pregabalin's mechanism of action is an ability to bind to the alpha2-delta subunit of voltage-gated calcium channels within the CNS, inhibiting excitatory neurotransmitter release. Although structurally related to GABA, it does not bind to GABA or benzodiazepine receptors. It exerts antinociceptive and anticonvulsant activity. It decreases the symptoms of painful peripheral neuropathies and, as adjunctive therapy in partial seizures, decreases the frequency of seizures [26].

The dosing in adults for diabetes-associated neuropathic pain is initially 150 mg/day in divided doses (50 mg three times/day); this may be increased within one week based on tolerability and effect. The maximum dose is 300 mg/day. Dosages of up to 600 mg/day were evaluated with no significant additional benefit and an increase in adverse effects. For postherpetic neuralgia, the initial dose is 150 mg/day in divided doses (75 mg two times/day or 50 mg three times/day), which may be increased to 300 mg/day within one week based on tolerability and effect. Further titration (to 600 mg/day) after two to four weeks may be considered in patients who do not experience sufficient relief of pain provided they are able to tolerate pregabalin. The maximum dose for postherpetic neuralgia is 600 mg/day [26].

Adverse effects reported in more than 10% of users are [26]:

- Peripheral edema (up to 16%)
- Dizziness (8% to 45%)
- Somnolence (4% to 36%)
- Ataxia (1% to 20%)
- Weight gain (up to 16%)
- Xerostomia (1% to 15%)
- Tremor (up to 11%)
- Blurred vision (1% to 12%)
- Diplopia (up to 12%)

CONCLUSION

There are a myriad of analgesic products sold over the counter in drug stores and supermarkets as nonprescription pain relievers. People experiencing dental pain are likely to self-medicate with these nonprescription pain relievers before seeing the dentist. Therefore, it is important for dental professionals to have a clear understanding of the available agents for the control of dental pain.

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