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Appropriate analgesic prescribing for the general dentist

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This article reviews dental and medical literature pertaining to the safety, efficacy, and mechanisms of action of common analgesic treatments for acute postoperative pain. MEDLINE searches were conducted for 2005 through 2009 using the terms "dental analgesia," "postoperative pain," "pain medication," "pathophysiology," "treatment," and "dentistry." Reports selected for further review included those published in peer-reviewed journals. The authors gave preference to articles reporting randomized controlled trials.

Acetaminophen and NSAIDs continue to be the most appropriate choices for the treatment of mild to moderate acute dental pain. The use of selective cyclo-oxygenase (COX)-2 inhibitor NSAIDs may be considered for patients at risk of gastrointestinal sequelae or those taking blood thinners such as warfarin. Whether analgesic medications are used alone or in combination, prescribers must be aware of the potential safety concerns associated with them, especially in light of new information promoting lower doses, shorter treatment durations, and decreased maximum recommended doses.

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Pain has both physiological and psychological components, and an experience of poorly managed pain related to dentistry can cause patients to avoid or postpone treatment, as well as make them more difficult to treat and less likely to comply with prescribed regimens.[1,2] Oral medications administered postoperatively that reduce pain improve clinical outcomes, making them an integral part of dental practice.[3-9] Analgesic medications in dentistry are indicated for the relief of acute pain, postoperative pain, and chronic pain and for controlling adjunctive intraoperative pain.[5] In addition, these medications can be given preoperatively to mitigate both postoperative pain and postoperative pain medication requirements.[10-12]

The majority of postoperative dental pain is acute in nature and typically is accompanied by tissue injury or inflammation.[13] While this pain can resolve spontaneously once the underlying cause (for example, inflamed pulp, a carious lesion, or abcessed gingiva) is definitively treated, a pharmacological approach to pain management may be considered the standard of care. The drugs of choice for postoperative dental pain are acetaminophen and NSAIDs, which act by inhibiting cyclo-oxygenase (COX) enzymes that are are responsible for the formation of prostaglandins that promote pain and inflammation.[14] Since opioid-based medications are not anti-inflammatory agents, medications such as morphine, hydromorphone, and oxycodone are not considered the drugs of choice for treating the majority of postoperative dental pain. Rather, these medications should be reserved for the small percentage of dental patients with severe, uncontrolled orodental and postoperative pain, and even then they are best prescribed as combination products that contain an NSAID as well as the narcotic moiety.

In 2005, the FDA began asking manufacturers of all marketed prescription NSAIDs, including COX-2 selective NSAIDs (Celebrex, Pfizer Inc.), to include a boxed warning and a medication guide with the package inserts for their products. The boxed warning highlights the drugs' potential to increase the risk of cardiovascular (CV) events and the well-described and potentially life-threatening gastrointestinal (GI) bleeding associated with their use. The medication guide accompanies every prescription NSAID at the time it is dispensed to better inform patients about the CV and GI risks. At the same time, the FDA asked manufacturers of non-prescription OTC NSAIDs to revise their labeling to include more specific information about the potential GI and CV risks and more information to assist consumers in the safe use of these drugs.[15]

Acetaminophen is found as a single agent and in combination with other ingredients in OTC products; it commonly is combined with narcotic agents in prescription products. In 2005, U.S. consumers purchased more than 28 billion doses of products containing acetaminophen.[16] In

general, acetaminophen is considered a safe medication, especially because it is not associated with the GI, renal, and bleeding adverse effects seen with the NSAIDs; however, hepatic injury resulting from acetaminophen use remains a serious health problem.[17-20] As a result, the FDA convened a meeting of an advisory committee in June 2009, and new labeling and dosing guidelines are being discussed for this common analgesic.[16]

This article will focus specifically on basic postoperative dental analgesic prescription writing to ensure that the correct drug is selected for all patients and scenarios. Patient safety in general and medication safety in particular will be emphasized to help update prescribers' knowledge base and optimize the efficacy and safety of NSAIDs for postoperative dental pain.

The pathophysiology of acute postoperative dental pain

Tissue damage stimulates the release of inflammatory mediators (such as prostaglandins, kinins, leukotrienes, substance P, and histamine) at the site of injury.[13] These mediators help to initiate and subsequently magnify pain impulses that are transmitted to the central nervous system (CNS) to create the perception of pain. Among these mediators, prostaglandins are especially important for sensitizing peripheral neurons. Prostaglandins are also synthesized in the spinal cord and higher brain centers in response to pain impulses and enhance pain sensitivity by recruiting additional secondary neurons that respond to the primary stimulus.

Aspirin and related NSAIDs work at the site of tissue damage, along the spinal cord, and in the higher brain centers, preventing prostaglandin formation by inhibiting COX activity. COX enzymes mediate the conversion of arachidonic acid to prostaglandins; inhibiting these enzymes essentially inhibits the inflammatory triad process of pain, inflammation, and fever. Unfortunately, arachidonic acid is converted to cytoprotective prostaglandins as well; as a result, aspirin and related NSAIDs have side effects that include delayed wound healing, gastroduodenopathies, an increased risk of cardiovascular events, and prolonged bleeding. With the exception of acetaminophen, which has only minimal anti-inflammatory effects in most settings, these drugs exert a combination of analgesic, antipyretic, and anti-inflammatory effects.

There are two well-known subtypes of tissue COX: COX-1 and COX-2. COX-1 is a constitutive form that promotes hemostasis (in which synthesis of the prostaglandin analogue thromboxane A2 increases platelet degranulation and adhesion), stomach mucosal integrity (where synthesis of prostaglandins protects against acid damage), and kidney function (where prostaglandins help to regulate normal renal blood flow). COX-2 is a largely inducible form that promotes the formation of pro-inflammatory prostaglandins and plays a major role in mediating inflammation, pain, and fever.

Acetaminophen is unique

While the dual COX model resolved many of the issues concerning differences between nonselective NSAIDs and highly selective COX-2 inhibitors, it still could not fully explain the pharmacologic actions of acetaminophen. Many of acetaminophen's actions resemble those of COX-2 selective inhibitors, in that both display analgesic effects, antipyretic effects, and a relative lack of GI toxicity.[21,22] However, acetaminophen has a very weak anti-inflammatory action—an important characteristic of both nonselective NSAIDs and the COX-2 selective drugs—and has no appreciable anti-aggregation or pro-aggregation effects on platelets.[21-25]

There is increasing evidence that one or more additional subtypes of COX may exist. A new COX-3 (produced by the same gene that encodes COX-1) has been described in the literature.[26-29] This COX-3 is found in the brain and is inhibited by clinically achievable concentrations of acetaminophen. While science may be closer to determining the actual mechanism of action for acetaminophen, debate still exists about its primary site of action. This action could be the inhibition of prostaglandin synthesis via this COX-3 pathway, or it could occur through an active metabolite that influences cannabinoid receptors, through reversal of N-methyl-D-aspartate (NMDA), through substance P-induced hyperalgesia, or via the inhibition of nitric oxide pathways.[27,30,31]

The correct drugs in the correct dose

Ideally, selecting an analgesic for the management of acute dental pain is based on the patient's medical history, the drug's pharmacologic profile, the pain's actual or expected intensity, the medication's cost, and the ease with which the medication can be obtained.

For the average adult, analgesia by acetaminophen becomes readily measurable at a dose of 300 mg and plateaus at 1,000 mg.[13] Acetaminophen in the body follows first-order pharmacokinetics, in that metabolism and elimination are constant, regardless of the size of the dose. With a half-life of approximately

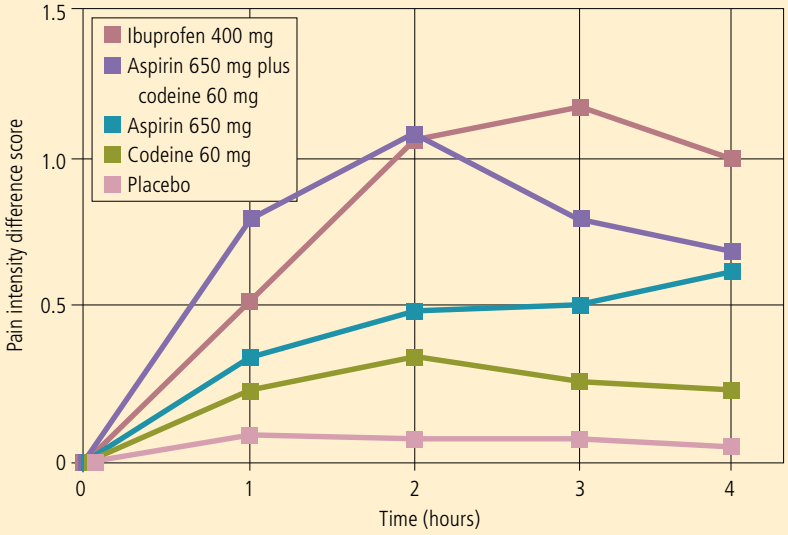
three hours, this medication typically is administered every six hours in order to achieve steady-state blood levels.[32] The maximum effective daily dose is two 500 mg tablets administered every six hours, for a total of 4,000 mg per day.

Ibuprofen was the first NSAID to demonstrate analgesic superiority to aspirin.[33] A 400 mg dose of ibuprofen has been shown to have a greater peak analgesic effect and a longer duration than 600–1,000 mg of aspirin or acetaminophen or 60 mg of codeine and comparable efficacy to traditional opioid analgesic combinations (Chart 1).[23,34] One meta-analysis has suggested there is a dose-dependent increase in analgesia with ibuprofen (up to 800 mg).[35] However, the published source from which the statistically analyzed data were obtained for this declaration actually revealed little analgesic improvement in doses greater than 400 mg.[36] Doses of ibuprofen greater than 400 mg may prolong the duration of maximum analgesia, even though this has not been a consistent finding in the literature. At least one study found that achieving maximum anti-inflammatory action via NSAIDs may require a higher dose than that needed to achieve analgesic action (for example, 200–600 mg of ibuprofen four times per day or 800 mg three times per day for an analgesic effect, compared to 2,400–3,200 mg per day for an anti-inflammatory effect).[8,37]

With a half-life of approximately three hours, ibuprofen is typically administered every six hours to achieve steady-state blood levels.[38] As a result, the maximal effective daily dose would be 600 mg administered every six hours, for a total of 2,400 mg per day.

In rare cases, choosing the most appropriate analgesic drug may be complicated by individual patient factors such as allergy or sensitivity, co-morbid conditions, or past abuse. In situations where aspirin, NSAIDs, acetaminophen, and opioids are contraindicated for the treatment of acute dental pain, the drug tramadol (Ultram, Ortho-McNeil Pharmaceuticals, Inc.) may be an option. For patients that cannot take aspirin, NSAIDs, or opioids, a combination of tramadol and acetaminophen (Ultracet, Ortho-McNeil Pharmaceuticals, Inc.) may be utilized.

Chart 1. Pain relief after removal of impacted third molars. *From:* Cooper SA, Engel J, Ladov M, Precheur H, Rosenheck A, Rauch D. Analgesic efficacy of an ibuprofen-codeine combination. Pharmacotherapy 1982;2(3):162-167. Reprinted with permission.



Ultram is a centrally acting analgesic that is thought to be a weak agonist of the mu opioid receptor and an inhibitor of serotonin and norepinephrine reuptake.[39] It is not classified as a controlled substance, meaning that it carries a low risk of abuse or dependence. Despite less potential to cause respiratory depression at equianalgesic doses of opioids, Ultram does not affect prostaglandins, the primary mediator of acute dental pain.[40] Tramadol is dispensed as either a 50 mg tablet or as a tablet containing tramadol and acetaminophen (37.5 mg and 325 mg respectively), to be taken every eight hours. Ultram should not be used by patients taking monoaminoxidase (MAO) inhibitors or by patients with seizure disorders; judicious dosing is recommended for patients who have a documented opioid dependence.[39]

In dental pain studies, both tramadol (100 mg) and the combination of tramadol (75 mg) and acetaminophen (650 mg) showed lower efficacy than ibuprofen (400 mg). In addition, both tramadol preparations caused a higher number of side effects (that is, nausea, vomiting, and dizziness) than either acetaminophen or ibuprofen.[41,42] Two recent articles rank the efficacy of analgesic preparations as follows: ibuprofen; tramadol/acetaminophen; acetaminophen; tramadol; placebo.[41-43]

At the right dose: Considering efficacy

In a 1999 study, Breivik *et al* described combining acetaminophen with an NSAID.[43] The authors evaluated the combination of 100 mg diclofenac (Voltaren, Novartis Pharmaceuticals) and 1,000 mg acetaminophen and each individual agent used alone against postoperative pain following oral surgery. The pain was defined as moderate to severe, based on the use of a visual analog scale (VAS). The combination resulted in greater analgesia than either drug used alone, as measured by pain intensity scores and total pain relief over eight hours. This combination also offered superior analgesia compared to a combination of 1,000 mg acetaminophen and 600 mg codeine. In addition, the patients' global evaluation of the effectiveness of the treatments was significantly better for the NSAID and acetaminophen combination in comparison to acetaminophen and codeine.[43] Based on these results, the investigators suggested that the additive effects of an NSAID and acetaminophen against oral surgery postoperative pain result in an analgesic effect superior to that of either drug alone.[43]

Dionne has suggested that acetaminophen and ibuprofen in combination can be a useful analgesic regimen for acute dental pain.[44] Since no marketed drug combination contains both an NSAID and acetaminophen, the author proposed taking the usual analgesic dose of ibuprofen (400–600 mg) every four to six hours, not to exceed 2,400 mg over a 24-hour period, and taking acetaminophen (650–1,000 mg) every four hours, not to exceed 4,000 mg (4 g) in 24 hours.[44] This combination of ibuprofen (600 mg) plus acetaminophen (1,000 mg) could be administered every six hours without exceeding the maximum 24-hour dose of either drug.

At the right dose: Considering safety

The combination of acetaminophen and ibuprofen has been ideal in treating postoperative dental pain; the literature contains evidence of the efficacy of this combination.[8-10,12,14,36,44,45] The FDA has recognized that patients with rheumatoid arthritis, osteoarthritis, and other chronic diseases may require ibuprofen in doses as large as 3,200 mg per day; however, based on existing safety data and the FDA's 2005 initiative, the most effective dose for the shortest period of time should be used for acute dental pain: 600 mg orally every six hours, or 2,400 mg per day.[36,45]

At usual doses (that is, ≤4 g per 24 hours) in healthy people, acetaminophen has virtually no adverse effects. Hepatic injury from acetaminophen results primarily from a single toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), which is formed by oxidation of the drug. With therapeutic doses in healthy subjects, oxidation is a minor metabolic pathway, and glutathione conjugates and inactivates the toxic metabolite.[46] The minimum toxic single dose in healthy adults is between 7.5 g and 10 g and >150 mg/kg in children. Single doses of 10–15 g can cause hepatic necrosis, but sometimes even much larger doses do not cause serious liver injury, possibly due to individual variations in terms of glutathione stores or drug metabolism.

Chronic heavy alcohol consumption may lower the threshold for acetaminophen-induced liver damage because it induces the enzymes that oxidize the drug; in addition, alcoholics may have pre-existing hepatic dysfunction and depleted stores of glutathione.[47] Severe liver injury has been reported in alcoholics who claimed to have taken less than 4 g of acetaminophen per day. Fatal hepatic injury has been reported in patients who took 4–10 g of acetaminophen per day and claimed to drink only moderate amounts of alcohol; however, the accuracy of alcohol histories and drug histories from alcoholics is notoriously unreliable.[47-50] The weight of the evidence indicates that recommended doses of acetaminophen do not cause hepatotoxicity, even in chronic alcoholics.[48-50]

Despite this evidence, the FDA's Center for Drug Evaluation and Research convened a Special Advisory Committee in 2009. The committee recommended a maximum single dose of acetaminophen of 650 mg (rather than 1,000 mg) and a maximum daily adult dose of 3,250 mg (instead of 4,000 mg). The recommendation would require the reformulation of currently available products to maximum doses of 325 mg per tablet or liquid dosage. Alternatively, 500 mg dosages could be made a prescription product, while the 325 mg dose remained an OTC product.

While the FDA has argued that decreasing the maximum individual dose from 1,000 mg to 650 mg will decrease the daily exposure of acetaminophen with little loss of efficacy, this suggested decrease would not apply to all indications. In fact, a recent meta-analysis found that 1,000 mg of acetaminophen (two extra-strength 500 mg tablets) was somewhat more effective than 600–650 mg for treating moderate to severe postoperative pain after oral, gynecologic, or orthopedic surgery.[51] Based on safety data to date and the FDA's 2009 initiative, the most effective and safest dose

Table. The amount of acetaminophen in some commercially available compound products.[53]

Medication (manufacturer)	Active ingredient(s)	Amount of acetaminophen per dose (in mg)
Tylenol Regular Strength (McNeil Pharmaceuticals)	Acetaminophen	325
Tylenol Extra Strength (McNeil Pharmaceuticals)	Acetaminophen	500
Darvocet N 50 mg (Eli Lilly and Company)	Propoxyphene and acetaminophen	325
Darvocet N 100 mg (Eli Lilly and Company)	Propoxyphene and acetaminophen	650
Lortab 2.5, 5, 7.5, and 10 (UCB Pharma)	Hydrocodone and acetaminophen	500
Lorcet (Forest Laboratories)	10 mg hydrocodone and acetaminophen	650
Norco 7.5 and 10 (Watson Pharmaceuticals)	Hydrocodone and acetaminophen	325
Percocet 2.5, 5, 7.5, and 10 (Endo Pharmaceuticals)	Oxycodone and acetaminophen	500
Tylox (Ortho-McNeil Pharmaceuticals Inc.)	5 mg oxycodone and acetaminophen	325
Tylenol #3 (McNeil Pharmaceuticals)	30 mg codeine and acetaminophen	300
Tylenol #4 (McNeil Pharmaceuticals)	60 mg codeine and acetaminophen	300
Vicodin (Abbott Laboratories)	5 mg hydrocodone and acetaminophen	500
Vicodin ES (Abbott Laboratories)	7.5 mg hydrocodone and acetaminophen	750
Vicodin HP (Abbott Laboratories)	10 mg hydrocodone and acetaminophen	660
Zydone 5, 7.5, and 10 (Endo Pharmaceuticals)	Hydrocodone and acetaminophen	400

for the shortest period of time (1,000 mg orally every six hours or 4,000 mg per day) should still be used at all times.

Prescribers must remember that acetaminophen is used in more combination products than any other drug—for a number of different indications—and that many of these products are available with a prescription. While the amount of acetaminophen in these doses are appropriate for any single product, taking more than one of these products or taking plain acetaminophen in addition to these products can lead to an accidental overdose (see the table). Patients need to be reminded of the maximum recommended daily doses of these medications, especially for acetaminophen.

When to take medications

Since the majority of postoperative dental pain is acute in nature and typically is accompanied by tissue injury or inflammation, the NSAID/acetaminophen combination prescription described above may be considered the most appropriate analgesic regimen for these patients.[13] Since the natural inflammatory process peaks quickly and is sustained until healing occurs, routine scheduled doses of these medications are required during the initial 24-hour postoperative period to maintain steady blood levels.

To alleviate continuous pain, medications are most effective when given regularly. If a patient can comply with these four doses of two different medications, the majority of cases will not require any further analgesic medication after the first 24 hours.[52] Depending on physician and patient preference, these doses can either be administered together or in a staggered fashion every six hours (for example, an initial 1,000 mg dose of acetaminophen, followed three hours later by 600 mg of ibuprofen, and so on). The staggered approach is sometimes valuable for patients who are "clock-watchers" or for those who might find frequent administration of medications to be more psychologically beneficial following oral surgery. Compliance is truly the key to the success of this analgesic regimen, which may require patients to set alarms so that they do not miss the required doses during the initial 24-hour postoperative period.

After the initial 24-hour postoperative period, patients can reduce their regimen to an "as needed" basis of either drug alone or the two in combination. However, if compliant patients still require routine pain medication more than 48 hours after the dental procedure, the dentist should consider re-examining the patient.

When significant postoperative pain is anticipated, adjunctive preoperative analgesics may be utilized to decrease postoperative pain and postoperative pain medication requirements.[10-12] NSAIDs have been shown to have opioid-sparing effects and can reduce postoperative

nausea and vomiting by 30%.[53-57] This preoperative dosing approach would be an ideal role for the COX-2 selective NSAID (Celebrex), as it will preemptively ameliorate the inflammatory response without causing increased bleeding or delayed wound healing compared to the traditional non-selective NSAIDs. In this case, 400 mg administered orally 30–60 minutes prior to the procedure would maximize this medication's effectiveness. For patients currently taking a blood thinner such as warfarin (Coumadin, Bristol-Myers Squibb), 400 mg of Celebrex taken every 12 hours for the initial 24-hour postoperative period could replace the postoperative ibuprofen prescription described above.[58,59]

Summary

Acetaminophen is an effective analgesic with virtually no adverse effects, except for those related to overdosing. Mild to moderate pain often responds to 650 mg of acetominophen, although 1,000 mg doses may be more effective for treating postoperative dental pain. Recommended doses of acetaminophen are not likely to cause hepatotoxicity in people who drink moderate amounts of alcohol, but they can be dangerous when patients take both acetaminophen and one or more combination products that contain acetaminophen. The efficacy and safety of these analgesic medications for postoperative dental pain can be optimized when taken in combination with an NSAID, such as ibuprofen.

This article provides a regimen for the combination of acetaminophen and ibuprofen to help practitioners manage acute postoperative dental pain more effectively. Dentists must also be aware of maximum cumulative doses of prescribed and OTC analgesic medications, especially for preparations that contain acetaminophen and at least one other active ingredient. Prescribers should always seek the most effective analgesic regimen balanced against potential adverse events for the anticipated length of drug therapy. Postoperative dental pain typically is caused by tissue injury and inflammation and usually has a short duration; as a result, NSAIDs in combination with acetaminophen should be considered the first-line analgesic regimen for most patients.

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References

1. Carr DB, Goudas LC. Acute pain. Lancet 1999; 353(9169):2051-2058.
2. Soxman J, Wolfe S. Update on pain management. Interview by Phillip Bonner. Dent Today 1997;16(11):60-65.
3. Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC, Angelillo IF, Mosteller F. The comparative effects of prospective analgesic therapies on pulmonary outcome: Cumulative meta-analyses of randomized, controlled trials. Anesth Analg 1998;86(3):598-612.
4. Carr DB. Preempting the memory of pain. JAMA 1998;279(14):1114-1115.
5. Dionne RA, Berthold CW. Therapeutic uses of non-steroidal anti-inflammatory drugs in dentistry. Crit Rev Oral Biol Med 2001;12(4):315-330.
6. Dionne RA, Campbell RA, Cooper SA, Hall DL, Buckingham B. Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. J Clin Pharmacol 1983;23(1):37-43.
7. Cicconetti A, Bartoli A, Ripari F, Ripari A. COX-2 selective inhibitors: A literature review of analgesic efficacy and safety in oral-maxillofacial surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97(2):139-146.
8. Mehlisch DR. The efficacy of combination analgesic therapy in relieving dental pain. J Am Dent Assoc 2002;133(7):861-871.
9. Phero JC, Becker D. Rational use of analgesic combinations. Dent Clin North Am 2002;46(4): 691-705.
10. Parsa AA, Sprouse-Blum AS, Jackowe DJ, Lee M, Oyama J, Parsa FD. Combined preoperative use of celecoxib and gabapentin in the management of postoperative pain. Aesthetic Plast Surg 2009;33(1):98-103.
11. Watcha MF, Issioui T, Klein KW, White PF. Costs and effectiveness of rofecoxib, celecoxib, and acetaminophen for preventing pain after ambulatory otolaryngologic surgery. Anesth Analg 2003;96(4):987-994.
12. Attar S, Bowles WR, Baisden MK, Hodges JS, McClanahan SB. Evaluation of pretreatment analgesia and endodontic treatment for postoperative endodontic pain. J Endod 2008;34(6): 652-655.
13. Desjardins PJ, Cooper SA, Peripherally acting analgesics and antipyretics. *In:* Yagiela JA, Neidle EA, Dowd FJ, eds. Pharmacology and therapeutics for dentistry, ed. 4. St. Louis: Mosby;1998: 281-296.
14. Lee Y, Rodriguez C, Dionne RA. The role of COX-2 in acute pain and the use of selective COX-2 inhibitors for acute pain relief. Curr Pharm Des 2005;11(14):1737-1755.
15. FDA announces important changes and additional warnings for COX-2s and NSAIDs. Pharmacist's Letter/Prescriber's Letter 2005;21(5): 210505.
16. Acetaminophen overdose and liver injury—Background and options for reducing injury. Available at: http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4429b1-01-FDA.pdf. Accessed July 21, 2009.
17. Defendi G, Tucker JR. Toxicity, acetaminophen. Available at: http://emedicine.medscape.com/article/1008683-print. Accessed July 3, 2009.
18. Bower WA, John M, Margolis HS, Williams IT, Bell BP. Population-based surveillance for acute liver failure. Am J Gastroenterol 2007;102(11): 2459-2463.
19. Lee W. Drug-induced hepatotoxicity. N Engl J Med 2003;349(5):474-485.
20. Dart RC, Erdman AR, Olson KR, Christianson G, Manoguerra AS, Chyka PA, Caravati EM, Wax PM, Keyes DC, Woolf AD, Scharman EJ, Booze LL, Troutman WG; American Association of Poison Control Centers. Acetaminophen poisoning: An evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2006;44(1):1-18.
21. Graham GG, Scott KF. Mechanisms of action of paracetamol and related analgesics. Inflammopharmacology 2003;11(4):401-413.
22. Botting RM, Mechanism of action of acetaminophen: Is there a cyclo-oxygenase 3? Clin Infect Dis 2000;31:S202-S210.

23. Hersh EV, Moore PA, Ross GL. Over-the-counter analgesics and antipyretics: A critical assessment. Clin Ther 2000;22(5):500-548.
24. Penderson AK, FitzGerald GA. Dose-related kinetics of aspirin. Presystemic acetylation of platelet cyclo-oxygenase. New Engl J Med 1984; 311(19):1206-1211.
25. Warner TD, Mitchell JA. Cyclo-oxygenase-3 (COX-3): Filling in the gaps toward a COX continuum? Proc Natl Acad Sci USA 2002;99: 13371-13373.
26. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS, Simmons DL. COX-3, a cyclo-oxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. Proc Natl Acad Sci 2002;99(21):13926-13931.
27. Anderson BJ. Paracetamol (Acetaminophen): Mechanisms of action. Paediatr Anaesth 2008; 18(10):915-921.
28. Botting RM. Inhibitors of cyclo-oxygenases: mechanisms, selectivity and uses. J Physiol Pharmacol 2006;57 Suppl 5:113-124.
29. Hersh EV, Lally ET, Moore PA. Update on cyclooxygenase inhibitors: Has a third COX isoform entered the fray? Curr Med Res Opin 2005; 21(8):1217-1226.
30. Kis B, Snipes JA, Busija DW. Acetaminophen and the cyclooxygenase-3 puzzle: Sorting out facts, fictions and uncertainties. J Pharmacol Exp Ther 2005;315(1):1-7.
31. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther 2005;12(1):46-55.
32. Albert KS, Sedman AJ, Wagner JG. Pharmacokinetics of orally administered acetaminophen in man. J Pharmacokinet Biopharm 1974;2(5): 381-393.
33. Jasani MK, Downie WW, Samuels BM, Buchanan WW. Ibuprofen in rheumatoid arthritis. Clinical study of analgesic and anti-inflammatory activity. Ann Rheum Dis 1968;27(5):457-462.
34. Cooper SA, Engel J, Ladov M, Precheur H, Rosenheck A, Rauch D. Analgesic efficacy of an ibuprofen-codeine combination. Pharmacotherapy 1982;2(3):162-167.
35. McQuay H, Moore A. An evidence-based resource for pain relief. Oxford: Oxford University Press;1998:35-37.
36. Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N. The correlation between blood levels of ibuprofen and clinical analgesic response. Clin Pharmacol Ther 1986;40(1):1-7.
37. Ganzberg S. Analgesics: Opioids and nonopioids. *In:* Ciancio S, ed. ADA/PDR guide to dental therapeutics. Chicago: Thompson PDR Publishing; 2006:53-111.
38. Motrin [package insert]. Kalamazzo, MI: The Upjohn Company;1999.
39. Becker DE, Phero JC. Drug therapy in dental practice: Non-opioid and opioid analgesics. Anesth Prog 2005;52:140-149.
40. Gutstein HB, Akil H. Opioid analgesics. *In:* Hardman JG, Limbird LE. Goodman and Gilman's the pharmacological basis of therapeutics, ed. 10. New York:McGraw-Hill;2001:590.
41. Medve RA, Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. Anesth Prog 2001;48(3):79-81.
42. Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: Individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. J Pain Symptom Manage 2002;23(2):121-130.
43. Breivik EK, Barkvoll P, Skovlund E. Combining diclofenac with acetaminophen or acetaminophen-codeine after oral surgery: A randomized, double-blind, single-dose study. Clin Pharmacol Ther 1999;66(6):625-635.
44. Dionne R. Additive analgesia without opioid side effects. Compend Contin Educ Dent 2000; 21(7):572-576.
45. Kiersch TA, Halladay SC, Koschik M. A double-blind, randomized study of naproxen sodium, ibuprofen, and placebo in postoperative dental pain. Clin Ther 1993;15(5):845-854.
46. Haas DA. Adverse drug interactions in dental practice: Interactions associated with analgesics. Part III in a series. J Am Dent Assoc 1999; 130(3):397-407.
47. Buckley NA, Srinivasan J. Should a lower treatment line be used when treating paracetamol poisoning in patients with chronic alcoholism? Drug Saf 2002;25(9):619-624.
48. Strom BL. Adverse reactions to over-the-counter analgesics taken for therapeutic purposes. JAMA 1994;272(23):1866-1867.
49. Prescott LF. Paracetamol, alcohol and the liver. Br J Clin Pharmacol 2000;49(4):291-301.
50. Kuffner EK, Dart RC, Bogdan GM, Hill RE, Casper E, Darton L. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients: A randomized, double-blind, placebo-controlled trial. Arch Intern Med 2001;161: 2247-2252.
51. McQuay HJ, Edwards JE, Moore RA. Evaluating analgesia: The challenges. Am J Ther 2002;9(3): 179-187.
52. Bacon TH, Hole JG, Burnett I. Analgesic efficacy of sustained release paracetamol in patients with osteoarthritis of the knee. Br J Clin Pharmacol 2002;53(6):629-636.
53. Sami Mebazaa M, Frikha N, Ben Hammouda N, Mestiri T, Mestiri H, Khalfallah T, Ben Ammar MS. [Postoperative analgesia after laparoscopic cholecystectomy: Comparison of the preoperative administration of celecoxib with paracetamol?] [article in French] Tunis Med 2008;86(10):869-873.
54. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: A qualitative review. Br J Anaesth 2002;88(2):199-214.
55. Romsing J, Moiniche S. A systematic review of COX-2 inhibitors compared with traditional NSAIDs, or different COX-2 inhibitors for postoperative pain. Acta Anaesthesiol Scand 2004; 48(5):525-546.
56. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclo-oxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005;103(6): 1296-1304.
57. Straube S, Derry S, McQuay HJ, Moore RA. Effect of preoperative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: A systematic review of randomized studies. Acta Anaesth Scand 2005; 49(5):601-613.
58. Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: Meta-analysis of randomized controlled trials. Anesthesiology 2005;102(6):1249-1260.
59. Huang YM, Wang CM, Wang CT, Lin WP, Horng LC, Jiang CC. Perioperative celecoxib administration for pain management after total knee arthroplasty—A randomized, controlled study. BMC Musculoskelet Disord 2008;9:77.

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