Better Medicine, Better Dentistry: Appropriate Analgesic Prescribing

Classification of Pain: Most Americans experience three or four types of pain per year. There are over 50 million Americans partially or totally disable by pain with an annual cost to the system of $336 billion (*American Academy of Pain Medicine 2015*). The goals of therapy for pain are to decrease the intensity, increase physical activity, appropriate use of medications, regulation of sleep patterns and moods, as well as reestablishing work habits.

Acute pain has a treatment goal of a cure. Most of the symptoms associated with chronic pain are not present. **Chronic pain** often results in dependence and tolerance, psychological component is a major problem, a significant environmental change and family involvement and insomnia. The treatment goal for chronic pain is rehabilitation, not a cure.

Treatment may involve one or more of the following **pain management options**: Physical, Psychological or Pharmacological. Physical management involves exercise, cutaneous stimulation, repositioning and counterstimulation (acupuncture). Psychological management involves relaxation techniques, patient education support groups and meditation. Pharmacological management involves **non-opioid analgesics**, **opioid analgesics** and **co-analgesic medications**.

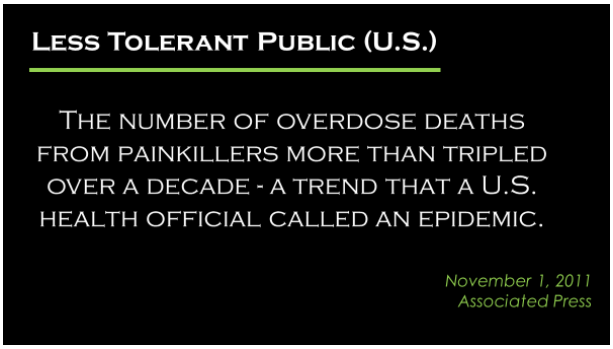
Dentists write approximately 20 million prescriptions for analgesics annually in U.S.. The major indication in dentistry is to manage postoperative pain, requiring a prescription of only a few days duration. Most often the challenge is to give high enough doses over a few short days to cover the inflammatory period, without putting the patient at risk of adverse sequelae. Although the cornerstone of these prescriptions focus on the non-opioid analgesics and opioid analgesics, it is important to remember that most pain of dental origin is due to the inflammatory process, which is why non-steroidal antiinflammatory drugs (NSAIDs) make the most sense for treatment. Opioid-based medications act centrally and do not have antiinflammatory properties.

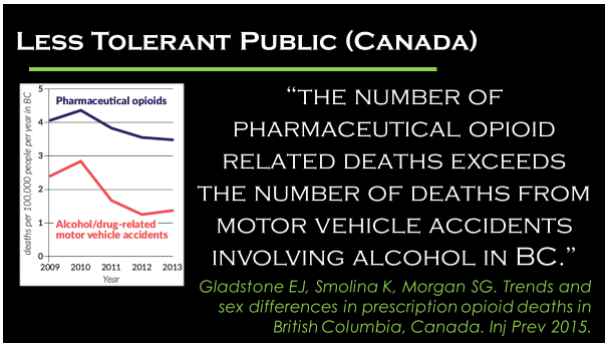
The Drug Armamentarium: We will discuss pharmacological pain management by dividing the discussion into Peripheral Analgesics (non-opioid analgesics), Central Analgesics (opioid analgesics), Co-Analgesics and Local Anesthetics.

Analgesics used for Postoperative Dental Pain

Acetaminophen - Tylenol
Aspirin - Aspirin (various)
Ibuprofen - Advil, Motrin, Nuprin
Flurbiprofen - Ansaid
Diflunisal - Dolobid
Naproxen - Naprosyn, Aleve
Ketorolac - Toradol
Ketoprofen - Orudis
Etodolac – Lodine
Codeine - Codeine (in various)
Oxycodone - Percocet, Percodan
Meperidine - Demerol
Pentazocine - Talwin
Hydrocodone - Lortab, Vicodin
Dihydrocodeine - Synalgos-DC
~~Propoxyphene - Darvon~~

*** Propoxyphene-containing products such as Darvon were removed from the US market in 2010.**

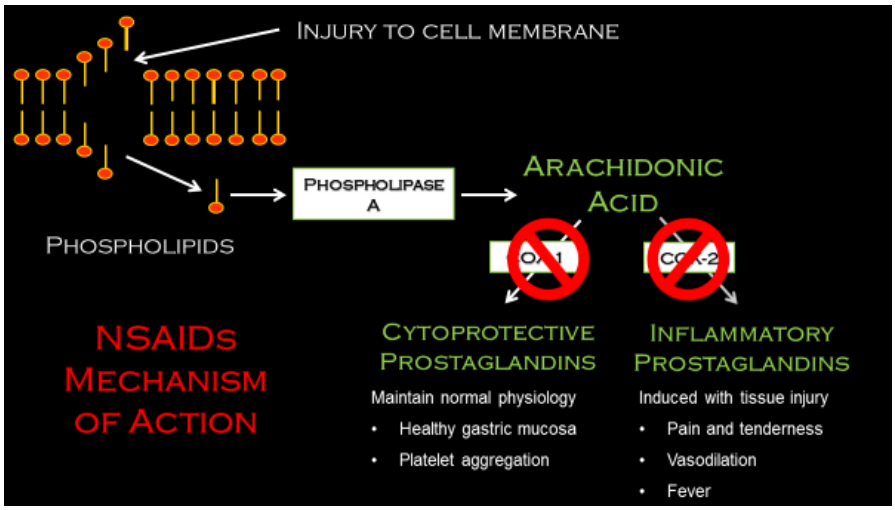




Other Notes or Questions to Ask:

Peripheral Analgesics: non-Opioid Analgesics

Acetaminophen may be the most ubiquitous medication in this category. It is comparable to ASA and NSAIDs in analgesic and antipyretic activity, but only has a weak anti-inflammatory activity. In patients who are maintained on blood thinners or have a history of bleeding complications, acetaminophen dose offer one major advantage over ASA and NSAIDs as it has a minimal antiplatelet effect and does not injure the gastric mucosa. Adult dosages range from 325mg to 1000mg administered three to four times per day, with a maximum daily dose of no more than 4.0 grams (4000mg) to avoid hepatotoxicity. In those patients at risk for liver problems (e.g., Chronic alcoholics, hepatitis patients), the maximum recommended dose should not exceed 2.0 grams (2000mg). The pediatric dose of acetaminophen is 10-15 mg/kg/dose orally every 4-6 hrs (maximum 5 doses/day).



Prostaglandins generated during tissue damage direct some actions of inflammation: fever, pain and vasodilation. Inhibiting prostaglandin synthesis leads to a decrease in this response, which led to the advent of **NSAIDs** as an alternative to acetaminophen.

The mechanism of action of NSAIDs is to block the conversion of arachidonic acid to prostaglandins. Arachidonic acid is a by-product of the breakdown of injured cell membrane phospholipids by the enzyme phospholipase. Non-selective **COX inhibitors** not only block the inflammatory prostanoids which produce pain, tenderness, vasodilation and fever, but they also inhibit the cytoprotective prostanoids that maintain a normal gastric mucosa and normal platelet aggregation. **COX-2** inhibitors only block the inflammatory prostanoids and do not effect the protective gastric mucosa and hemostasis.

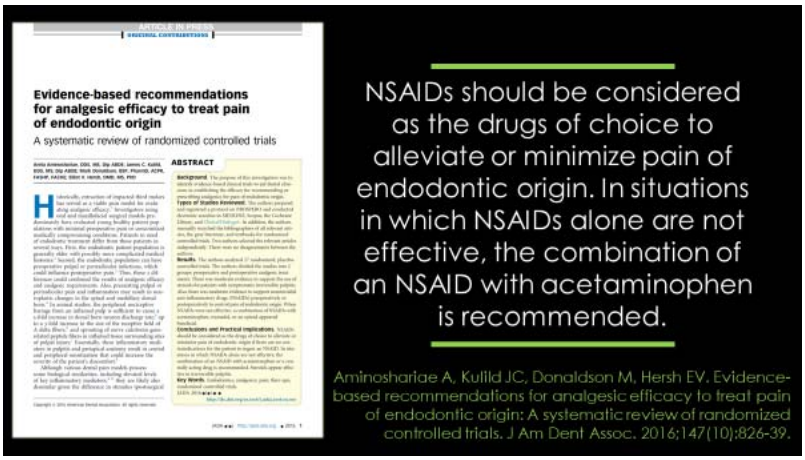
There are a plethora of NSAIDs on the market and rather than reviewing each one individually, some key points should be stressed. Be familiar with at least three agents and their usual dosing regimens and maximum daily dosages. Some examples are:

- Ibuprofen (Motrin) 400-600 mg four times a day (max daily dose is 2400mg)
- Diclofenac (Voltaren) 25-50mg two or three times a day (max daily dose is 200mg)
- Naproxen (Naprosyn) 250-500mg two or three times a day (max daily dose is 1500mg)

Aminoshariae A, Kulild JC, Donaldson M, Hersh EV. Evidence-based recommendations for analgesic efficacy to treat pain of endodontic origin: A systematic review of randomized controlled trials. J Am Dent Assoc. 2016;147(10):826-39

Other Notes or Questions to Ask:

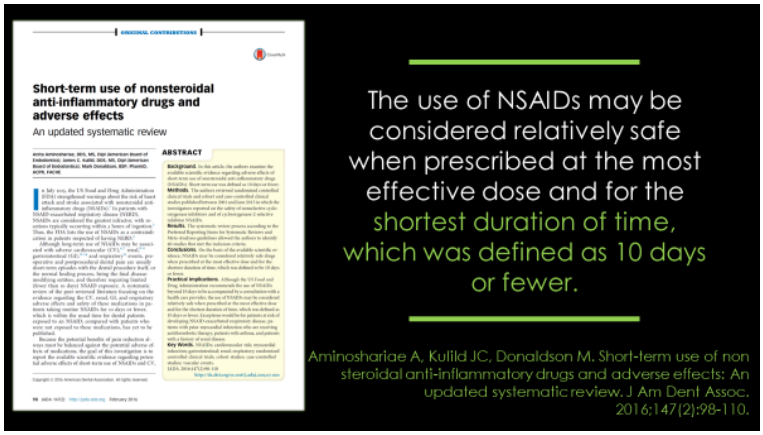
NSAID Mortality: Fortunately or unfortunately, many of these medications are now available without a prescription, which may give prescribers the false sense that they are completely "safe" (without adverse sequelae). In fact, **16,500 people die in US each year due to NSAID complications**. The mechanism of action of NSAID's is to inhibit both COX-1 and COX-2 (cyclooxygenase isoenzymes) which are responsible for the production of prostaglandins: the mediators of inflammation. Some of these prostaglandins are cytoprotective, however, as part of the body's natural homeostatic process. By non-specifically inhibiting both isoenzymes, NSAIDs have been associated with an increased rate of gastritis, gastric erosion and even ulceration.



Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med. 1999 Jun 17;340(24):1888-99.

Baseline Risk of Peptic Ulceration: Hospitalization risk due to peptic ulceration is about 0.2% per year in non-NSAID users. The risk increase to 0.8% in patients currently taking NSAIDs and GI hemorrhage is the most common presentation. The risk is higher in men than women. The range of risk is from 0.5% to 1.7% depending on dose, drug and duration.

NSAID Prescribing: Not all NSAIDs are created equally. The risk of GI toxicity varies from: **ibuprofen → ASA → diclofenac → naproxen → indomethacin → piroxicam → ketoprofen→ ketorolac.** When you prescribe NSAIDs, do so only to patients who do not respond to acetaminophen. Select the NSAID with the lowest toxicity and prescribe the lowest possible dose for the shortest duration of time. The use of NSAIDs may be considered relatively safe when prescribed at the most effective dose and for the shortest duration of time, which was defined as 10 days or fewer



Aminoshariae A, Kulild JC, Donaldson M. Short-term use of nonsteroidal anti-inflammatory drugs and adverse effects: An updated systematic review. J Am Dent Assoc. 2016;147(2):98-110

<u>COX - 2 INHIBITORS</u>:

COX-2 Inhibitors were developed to decrease GI effects of NSAIDS. Older NSAID's inhibit both COX-1 and COX-2 prostanoids. COX-1 is responsible for protecting the GI mucosa (cytoprotective). COX-2 is responsible for inflammatory mediation. COX-2 selectivity increases from:

ketorolac → ketoprofen → indomethacin → ASA → ibuprofen→ piroxicam → diclofenac → celecoxib→ meloxicam

Other Notes or Questions to Ask:

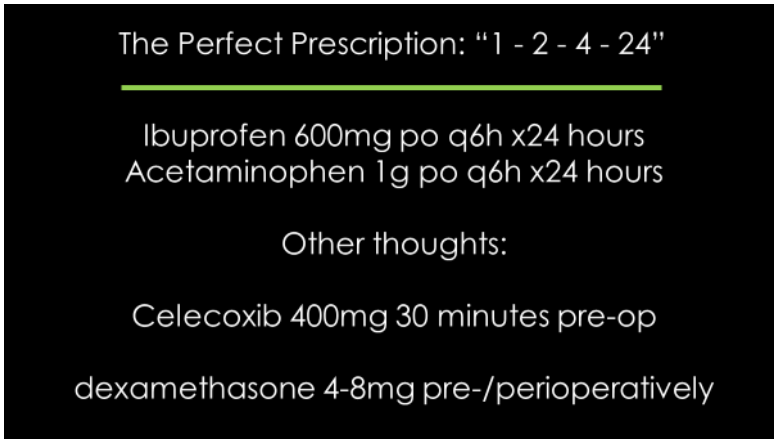
When rofecoxib (Vioxx) was available, it was the most selective of available NSAIDs (>50-fold potency for COX-2 over COX-1) and was is twice as selective as celecoxib. Vioxx was unfortunately removed from the US market in 2004. The COX-2 inhibitor seem to be equally effective as the NSAIDs. There seems to be no difference in overall adverse effects. There seems to be no difference in real effects. In these 3 studies no dyspeptic symptom differences were noted. However, there was an absolute difference in endoscopically proven ulcer of 10 – 25% decrease. Also note that where COX-2 inhibitors were used, they had no effect on platelets.

Differences between the COX-2s: If a patient has a sulfa allergy you should avoid the Celecoxib/Valdecoxib medications. There still is a question if one should not prescribe COX-2s if an aspirin allergy exists. Recognize that Celecoxib has a slightly slower onset of activity. Obviously, with the removal of **Vioxx** & **Bextra** from the market, adverse effects can not be ruled out!

When to use a COX-2? Use a COX-2 inhibitor if other less expensive NSAIDs have been shown to be ineffective or not tolerated. Use a COX-2 inhibitor if cost is not an issue. Use a COX-2 inhibitor if your patient is controlled on a blood thinner like coumadin. Use a COX-2 inhibitor if you are planning to use misoprostol with an NSAIDS.

These newer medications can be up to ten times more expense than the traditional NSAIDs, and should generally be reserved for those patients who have failed prior treatment with NSAIDs, or if they are controlled on a blood thinner like coumadin.

- ~~rofecoxib (Vioxx) 50mg QD~~
- ~~veldecoxib (Bextra) 10mg QD~~
- celecoxib (Celebrex) 200mg BID



Donaldson M and Goodchild JH. Appropriate analgesic prescribing for the general dentist. Gen Dent 2010; 58(4):291-7.

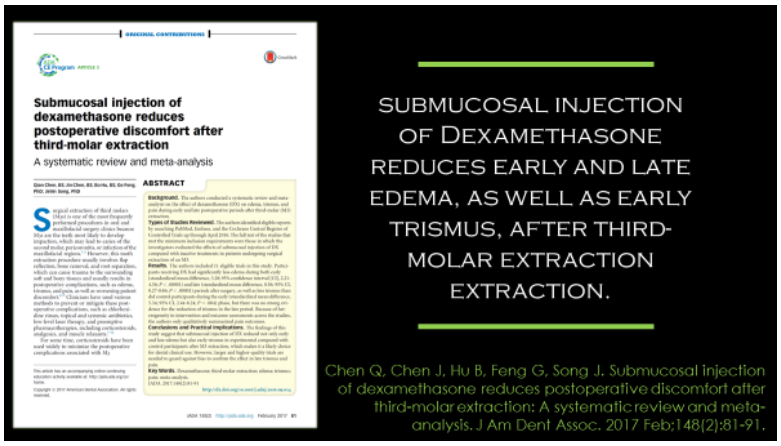
Becker DE. Managing Acute and Postoperative Dental Pain. Anesth Prog 2010; 57(10): 67-79.

Gordon J. Christensen: Clinicians Report. Pain Meds: What Works? February 2015.

What about the use of Steroids?

Dexamethasone is a glucocorticoid (FDA approved 1958). Supplied as Tablets (0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, 6 mg); Injection (4mg/mL, 10mg/mL, 20mg/mL); Elixir (0.5 mg/5 mL)

Plasma Half-Life: 3-5 hours
Duration of Action: 2.5-6 days to treat pain, swelling and trismus.



Chen Q, Chen J, Hu B, Feng G, Song J. Submucosal injection of dexamethasone reduces postoperative discomfort after third-molar extraction: A systematic review and meta-analysis. J Am Dent Assoc. 2017 Feb;148(2):81-91.

Other Notes or Questions to Ask:

Opioid-Based Analgesics: Central Analgesics

When to use them: Opioids such as morphine, meperidine, hydromorphone, fentanyl and others should not always be considered the drugs of choice for all postoperative analgesia cases. They act centrally, have no effect on the inflammatory process, and are associated with adverse sequelae in many patients ranging from constipation to more acute narcotizing effects.

How to use them: Having said this, they may still have a role in pain management, as interpatient response to any type of drug therapy is highly variable. The same general prescribing guidelines described above hold true for opioid-based analgesics: be familiar with at least three agents and their usual dosing regimens. Be aware of drug interactions with other CNS depressant. Most drug interaction software available today does not recognize the obvious interactions between opioid and benzodiazepines.

Pain Control: the site of action for the opioid narcotics is in the brain stem. Where as NSAIDs and COX-2 inhibitors work at the site of injury.

Maximum daily dosages do not readily apply to these agents and it may be more clinically useful to be aware of the minimum effective dosages and potential equiefficacious dosing when switching between agents.

In trying to achieve the best of both worlds there are several combination products which incorporate either acetaminophen or an NSAID with an opioid-based analgesic (eg. Percocet, Vicodin, and Vicoprofen). The practitioner should still decide if an opioid-based analgesic is appropriate therapy for the particular case, and they should also be aware of the maximum recommended daily doses of acetaminophen or the NSAID being used in the combination product. This is especially important in those patients who are ordered both Tylenol and Percocet, for example (since they both contain acetaminophen).

Drug	Route	Equianalgesic dose	Duration of Action (hr)
Morphine	IM, SC PO	10mg 30-60mg	4-6 4-6
Meperidine	IM, SC PO	100mg 200mg	2-4 2-4
Hydromorphone	IM, SC PO	2mg 6-8mg	4-5 4-5
Oxycodone/ Hydrocodone	PO	30mg	3-4
Codeine	IM PO	60mg 120-180mg	4-6 4-6
Fentanyl	IM Transderm	0.1-0.2mg 25μg/hr	Very short 72

Equianalgesic dosing tables are available for opioid-based analgesic medications, which aid in prescribing or changing a patient's regimen to a different agent, but it must be stressed that these are only guidelines and are usually based on single-dose studies in healthy individuals. Some examples of these guidelines are shown below:

Other Notes or Questions to Ask:

1 x Tylenol #3	**=**	**300mg Acetaminophen + 30mg Codeine**
2 x Tylenol #3	**=**	**10mg oral Morphine**
1 x Vicodin	**=**	**500mg Acetaminophen + 5mg Hydrocodone**
2 x Vicodin	**=**	**10mg oral Morphine**
1 x Tylenol #3	**=**	**1 x Vicodin tablet**

Morphine: Morphine is still the gold standard in pain control because of the wide rage of dosage forms and low cost. There are even sustained release preparations that allow a dose once every 12 hours. These sustained release medications are MS Contin, M-Eslon, Kadian. In the elderly M=Eslon offers some advantages because the capsule can be pulled apart and contents mixed as long as the granules are not crushed.

Hydromorphone (Dilaudid): This drug is excellent for patients allergic to morphine. Dilaudid SR (sustained release) comes in 3, 6 and 12mg capsules. The dosing is every 12 hours and the capsules can be opened. This drug is also effective when morphine tolerance develops. You should switch from morphine to hydromorphone when morphine doses needed by the patient are increasing rapidly. In the non-narcotic naïve patient the ratio is about 5:1.

Meperidine (Demerol): There is no advantage with Demerol over morphine for chronic pain. This drug has a shorter half-life, but its active metabolite (normeperidine) has an extended half-life of 8-12 hours. Meperidine may accumulate with repeated administration leading to CNS stimulation that manifests itself as agitation, irritability, nervousness, tremors, twitching and seizures. Since this drug is eliminated by the kidneys, patients with decreased renal function are more susceptible to CNS stimulation from repeated administration. A major contraindication is in patient receiving MAO inhibitors. This may cause severe respiratory depression, coma and decrease in blood pressure.

Fentanyl (Duragesic): Fentanyl can be useful if enteral narcotics are not an option. The dose is limited to 25, 50 75 and 100mcg increments. One need to wait 24 hours to evaluate the effectiveness for pain control. This drug is not for acute pain! It may take 6 days after increasing the dose before a new steady state level is achieved. If the drug is administered in a patch, the serum concentration will take approximately 17 hours to re-equilibrate.

Other Opioids: Codeine is a relatively weak analgesic. Oxycodone and Hydrocodone usually are in combination products such as Percocet and Vicodin. Be aware that because of these combination products a toxicity level may be reached if doses of acetaminophen exceed 4 grams per day.

Constipation: … the eleventh commandment? ***"the hand that writes the narcotic order shall write the laxative order!"***

Other medications for pain: TCA Antidepressants such as amitriptyline, nortriptyline and imipramine are examples. **SSRI** (Selective Serotonin Reuptake Inhibitors) Antidepressants such as fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro) are examples. **Anticonvulsants** such as valproate (Epival), carbamazepine (Tegretol) and gabapentin (Neurontin) are examples. Finally **Glucocorticoids** such as dexamethasone, prednisone, methylprednisolone and hydrocortisone are examples.

Efficacy of Tramadol: Ibuprofen>Tramadol/Acetaminophen>acetaminophen>Tramadol>Placebo

The VERY Latest: "If dentists do prescribe opioid containing analgesics, it is important to consider limiting these prescriptions to 12 doses or fewer, because larger quantities often result in leftover medication that can be at risk for diversion."

Donaldson M, Goodchild JH. Could the prescription you write put you in legal jeopardy? Gen Dent 2018;66(1):9-12.

Other Notes or Questions to Ask: