

## What Should Dentists Know about Medicine...

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## Learning Outcomes

1. Medical Conditions and Their Impact on Dental Care.
2. Medical Emergency & Resuscitation in the Dental Practice.
3. The Special Care Needs Patient.
4. Geriatrics: Oral Medicine and the Ageing Patient.
5. Management of the Oncologic Patient.
6. Oral Soft Tissue Lesions, Temporomandibular Disorders and Orofacial Pain.
7. Infections, Infectious Diseases and Dentistry.
8. Nutrition and Oral Health.
9. **Clinical & Applied Pharmacology and Dental therapeutics.**

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## Pharmacology & Therapeutics in Dentistry

- We are all dealing with an increasing ageing population who are retaining their teeth well into old age. A large proportion of this population will be taking one or two medicines to enable them to continue with their normal daily activities.
- Certain drugs are the mainstay of dental practice. These include **antibiotics**, **analgesics**, **local anesthetics**, and **agents to control anxiety**.

## Pharmacology & Therapeutics in Dentistry

- Many of our patients are medically compromised and this raises **three** important issues with respect to the delivery of routine dental care:
  1. Can the patient's medication cause an **adverse reaction** in the mouth and associated structures?
  2. Can the drugs that I wish to prescribe **interact** with their current medication?
  3. What **medical emergencies** are likely to arise in this population and how should they be dealt with?

## Evidence-Based Dentistry (EBD) on the Use of Analgesics

(CKS Ong, RA Seymour, 2008)

- Management of pain is a critical and challenging component in dentistry.
- Pain, is usually not adequately treated.
- Knowing how well an **analgesic** works and its associated **adverse effects** is fundamental to clinical decision-making.

## Aims of Presentation

1. Are there **clinically important differences** in the **efficacy** and **safety** between different analgesics and techniques?
2. If **there are differences**, which are the ones that are more **effective** and associated with **fewer adverse effects**?
3. Which are the **effective therapeutic approaches** that could reduce the adverse effects?

## Pain Mechanisms Underlying Analgesic Efficacy

Oral Tissue **Insult** Activates the **Inflammatory Process**  
(this is *inflammatory pain* not *nociceptive pain* nor *neuropathic pain*)

- Releases a large series of **pain mediators** (**prostaglandins**, **bradykinins**) → ↑ **sensitivity & excitation of peripheral nociceptors**.
- These usually have little spontaneous activity under normal conditions (**peripheral sensitization**).

## Pain Mechanisms Underlying Analgesic Efficacy

- Repetitive **C-fiber** nociceptor stimulation from the periphery + excitatory amino acids (glutamate and aspartate) + several peptides (**substance P**) increase → activation of **N-methyl-D-aspartate (NMDA)** receptors of the postsynaptic **second-order neuron** in the **dorsal horn**.
- This leads to increased responsiveness of neurons in the central nervous system and to **central sensitization**, which is **responsible for the prolonged pain after dental surgery**.

## Pain Mechanisms Underlying Analgesic Efficacy

The analgesic effect of NSAIDs is primarily the result of their **inhibition of the synthesis of prostaglandins and bradykinins** through the **inactivation of cyclo-oxygenase**

Opioids exert at least part of their effect by inhibiting **substance P** release in the peripheral and the central nervous systems

## Chemical Mediators for Dental Pain

(Seymour et al, 2008)

| Pain mediators       | Source                 | Drug antagonist                          |
|----------------------|------------------------|------------------------------------------|
| Bradykinin           | Plasma kininogen       | Non-steroidal anti-inflammatory drugs    |
| Serotonin            | Platelets              | Non-steroidal anti-inflammatory drugs    |
| Histamine            | Mast cells             | Anti-histamine                           |
| Prostaglandins       | Arachidonic acid       | Non-steroidal anti-inflammatory drugs    |
| Leukotriene          | Arachidonic acid       | Non-steroidal anti-inflammatory drugs    |
| Substance P          | Primary afferent nerve | Opioids                                  |
| Glutamate, aspartate | Primary afferent nerve | N-methyl-D-aspartate receptor antagonist |

## Pain Mechanisms Underlying Analgesic Efficacy

- Once central sensitization is established, **larger doses of analgesics** are required to suppress it.
- The concept of **pre-emptive analgesia** (analgesic intervention **before nociception**) is particularly useful because it can potentially:
  - prevent the **induction of central sensitization** by **blocking the arrival of nociceptive** input to the central nervous system and can
  - prevent **peripheral sensitization** by preventing the formation of **pain mediators in the injured tissues**. (Ong et al, 2003)

## Efficacy of Analgesics for Dental Pain

- Many dentists and patients are **confused** as to **which analgesic is most efficacious** for the pain that needs to be treated.
- Frequently, the **choice** of analgesic is based on **personal preference** rather than **evidence-based information**.
- There is a **wealth of information available** for the **efficacy of analgesics for dental pain**.
- Analgesics available for dental pain management belong to two major groups: the **non-opioid analgesics** (e.g. NSAIDs and acetaminophen) and **opioids**.

## Oxford League Table

(Adapted From: <http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html>)

| Analgesic in Mg                                                          | Number of Patients in Comparison | Percentage With at Least 50% Pain Relief | NNT  | Lower Confidence Interval | Higher Confidence Interval |
|--------------------------------------------------------------------------|----------------------------------|------------------------------------------|------|---------------------------|----------------------------|
| Valdecoxib 40                                                            | 473                              | 73                                       | 1.6  | 1.4                       | 1.8                        |
| Ibuprofen 800                                                            | 76                               | 100                                      | 1.6  | 1.3                       | 2.2                        |
| Diclofenac 100                                                           | 411                              | 67                                       | 1.9  | 1.6                       | 2.2                        |
| Paracetamol 1000 + Codeine 60                                            | 197                              | 57                                       | 2.2  | 1.7                       | 2.9                        |
| Naproxen 440                                                             | 257                              | 50                                       | 2.3  | 2.0                       | 2.9                        |
| Tramadol 150                                                             | 561                              | 48                                       | 2.9  | 2.4                       | 3.6                        |
| Morphine 10 (intramuscular)                                              | 946                              | 50                                       | 2.9  | 2.6                       | 3.6                        |
| Paracetamol 1000                                                         | 2,759                            | 46                                       | 3.8  | 3.4                       | 4.4                        |
| Paracetamol 650 + Dextropropoxyphene (65 hydrochloride or 100 napsylate) | 963                              | 38                                       | 4.4  | 3.5                       | 5.6                        |
| Codeine 60                                                               | 1,305                            | 15                                       | 16.7 | 11.0                      | 48.0                       |

## Efficacy: NSAIDs and Acetaminophen

- Traditional NSAIDs** (ibuprofen, diclofenac, and naproxen) and **COX-2 inhibitors** (rofecoxib, valdecoxib, and lumiracoxib), **do extremely well in this single-dose comparison**, but they *do* differ in efficacy.
- Results from a **recent meta-analysis** also indicate that NSAIDs are **clearly more effective** in **dental surgery** compared with **acetaminophen**, whereas their efficacy appeared to be **without substantial differences** from acetaminophen in **general and orthopedic surgery**. (Hyllsted *et al.*, 2002)

## Efficacy: NSAIDs and Acetaminophen

- COX-2 inhibitors** have equal or better analgesic efficacy compared with **traditional NSAIDs**. (Ong *et al.*, 2005)
- NSAIDs vary in their **time of onset** and their **duration** of analgesic effect:
  - the **longer the half-life** of the drug, the **slower the onset** of effect.
  - a **higher dose** has a **faster onset**, **higher peak effect**, and **longer duration**.

It is advantageous to start with a **high dose of a short half-life drug** and then adjust the dose downward when analgesic efficacy has been achieved, e.g. ibuprofen.

## Efficacy: Opioids

- Opioids perform **poorly in single doses on their own**.
- Oxycodone 15 mg is the only opioid that has a NNT close to that of NSAIDs (2.3) in the Oxford League Table – **high incidence of reported adverse effects**.
- Oxycodone has **10 to 12 fold** greater potency than codeine.
- Codeine phosphate 60 mg and tramadol 50 mg have NNT of 16.7 and 8.3, respectively.
- But* tramadol produced **dose-related analgesia**.

## Efficacy: Opioids

- Oral opioids alone are a **poor choice for acute dental pain** because they provide relatively **inferior analgesia** and **more adverse effects** compared to NSAIDs.
- Opioids may be used as adjunctive analgesics and can be **combined with acetaminophen** to increase its efficacy. For example:
  - Codeine phosphate 60 mg with acetaminophen 1,000 mg increases its efficacy from a NNT of 16.7 to 2.2.
  - Tramadol 75 mg with acetaminophen 650 mg increases its efficacy from a NNT of 8.0 to 3.0

## Effects of Formulation on the Analgesic Efficacy

- Formulations of certain analgesics can have a profound effect on their **efficacy** and the **onset of analgesia**.
  - absorption** of ibuprofen acid is influenced by **formulation**, and certain **salts of ibuprofen** (e.g. lysine and arginine), and **solubilized formulations** have an enhanced **onset of activity**:
    - Ibuprofen lysine** 400 mg produces faster onset and higher peak analgesia than a **conventional ibuprofen**. (Cooper et al, 1994)
    - Diclofenac sodium** softgel has been shown to provide very rapid onset and prolonged analgesic duration compared with conventional **diclofenac potassium**. (Zuniga et al, 2004)

## Effects of Formulation on the Analgesic Efficacy

- Failure to achieve adequate pain relief with **one NSAID** is followed by a trial of **another NSAID** from the **same or different class**. Good management of pain may be achieved with such a second agent. (Mehlich et al, 1999)
- If **two NSAIDs** of **two different classes** have been tried individually, further attempts to obtain benefit from NSAIDs are **unlikely to succeed**. (Mehlich et al, 1999)
- Opioids** may be required when **NSAIDs and acetaminophen are contraindicated**, e.g. because of allergy.

## Effects of Formulation on the Analgesic Efficacy

- Many **opioids** have a **short elimination half-life**, which necessitates **frequent administration** (as frequent as every 2–4 hours).
- Sustained-release** or **controlled-release** formulations have been developed (once-or twice-a-day dosing).
  - Sustained-release oxycodone, codeine, and tramadol have been shown to be effective for **chronic pain**.
  - However, **sustained-release formulations** usually have a **slower onset** of action. **Timed-release formulations** are of **limited value** for treatment of **acute pain**.

## Effects of Formulation on the Analgesic Efficacy

- Improved clinical outcomes have been documented with **combinations of analgesic agents**:
  - Not all combinations or dose ratios lead to enhanced analgesia or reduced adverse events.
    - acetaminophen/opioid** combinations have been shown in RCTs to have **better analgesic efficacy than the single agent alone for dental pain without an increased incidence of adverse events**. (Fricke et al, 2004)
    - acetaminophen/NSAID** combination has shown to act **synergistically** to improve analgesia for **acute postoperative pain**. (Eliak et al, 2005)
    - many studies have not been able to show that a **NSAID/opioid combination is better than NSAIDs alone for dental pain** – combinations of ibuprofen/codeine, ibuprofen/oxycodone, naproxen/codeine have **failed** to show any additive effects in many dental studies. (Dionne et al, 1986; Forbes et al 1986; Walton et al 1990; Petersen et al 1993)

## Adverse Effects of Analgesics

- Dentists need to know the likelihood of adverse effects of analgesics to assess the **Efficacy: Risk** ratio.
- This applies to both **serious clinical effects** that may cause **significant morbidity or mortality**, and to more **trivial symptoms** that may affect **quality of life and drug compliance**.

## Adverse Effects of Non-steroidal Anti-Inflammatory Drugs (NSAID)

- Minor Side Effects**: nausea, vomiting, diarrhea, dizziness, and headache.
- Serious Side Effects**: prolonged bleeding after surgery, kidney failure, and **gastrointestinal and cardiovascular adverse effects**.
- Increased risk of cardiovascular adverse events in patients taking certain NSAIDs, particularly cyclooxygenase-2 (COX-2) inhibitors (Garcia Rodriguez et al, 2005)

## Gastrointestinal Risk of traditional NSAIDs

- **Ibuprofen** has the **lowest risk** among the traditional NSAIDs, **diclofenac** and **naproxen** have **intermediate risks**, and **piroxicam** and **ketorolac** carry the **greatest risk**.
- However, it should be noted that the **advantage of low-risk drugs** may be **lost** once their dosage is **increased**.
- Risk for GI complications increases in the following groups: **≥ 65 years**, **peptic ulcer disease**, **alcoholics**, **on corticosteroids**, **on anticoagulants**, **on aspirin**, **chronic use** (risk develops in a time-dependent manner).

## Gastrointestinal Risk of traditional NSAIDs

- It is advised **not to exceed 3 days** for **fever**, and **10 days** for **analgesia**. Short-term use of 5–10 days of over-the-counter traditional NSAIDs has been shown in several studies to be **extremely safe and well tolerated** (Herish et al, 2000)
- The use of **high-dose short-term traditional NSAIDs** can be associated with serious gastrointestinal toxicity when administered for as **little as 4 days**. (Lewis et al, 2005; Blot et al, 2000)

## Therapeutic Approaches to Reduce GI Toxicity of Traditional NSAIDs

1. Use a **drug other than a traditional NSAIDs** when possible (e.g. **acetaminophen**).
2. Use the **lowest effective dose** because the risk is dose-dependent and the efficacy of traditional NSAIDs has a ceiling effect.
3. **Anti-ulcer co-therapy** and **cyclooxygenase-2 inhibitors** can be used in high-risk GI patients.

## Use of Anti-ulcer Co-therapy

- Proton Pump Inhibitor (PPI), Prostaglandins, Histamine H<sub>2</sub>-blockers, and Antacids
- Co-therapy with **PPIs**, which inhibit acid secretion, has been demonstrated in large-scale RCTs to **promote ulcer healing** in patients with GI ulcers related to use of traditional NSAIDs. (Graham et al, 2002) **Prophylactic use of PPIs in patients with previous GI events or in those at high risk for such events is considered appropriate by major treatment guidelines**. (Scheiman et al, 2005)

## Use of Anti-ulcer Co-therapy

- **Misoprostol** (a synthetic prostaglandin E<sub>1</sub> analogue), effectively reduces GI acid to prevent traditional NSAID dependent Gastropathy. (Silverstein et al, 1995) Because of its non-specific mode of action, a significant proportion of patients reported adverse events such as **diarrhea**, and discontinued it.
- **No evidence** that the concomitant use of **H<sub>2</sub>-blockers** or **antacids** will either prevent the occurrence of GI effects or allow continuation of traditional NSAIDs when and if these adverse reactions occur. (Singh et al, 2006)

## Use of Cyclooxygenase-2 (COX-2) Inhibitors

- Evidence has shown that COX-2 inhibitors have **reduced GI toxicity** compared to traditional NSAIDs.
- VIGOR (Bombardier et al, 2005), CLASS (Silverstein et al, 2000), TARGET (Schnitzer et al, 2004), and SUCCESS-I (Singh et al, 2006) trials have provided evidence that COX-2 inhibitors minimize risk for GI events.
- A recent meta-analysis has shown that treatment with etoricoxib was associated with a significantly lower incidence of GI adverse events than was treatment with traditional NSAIDs. (Ramey et al, 2005)

## Cardiovascular Risk of NSAIDs

- Evidence from several large-scale RCTs of structurally distinct COX-2 inhibitors indicated that such compounds **clearly elevate the risk of MI and stroke**. (IREF Trial by Ott *et al.*, 2003; Juni *et al.*, 2004; VIGOR Trial by Bombardier *et al.*, 2005; APPROVe Trial by Bresalier *et al.* 2005; APC Trial by Solomon *et al.* 2005)
- Worldwide withdrawal of **rofecoxib** and **valdecoxib**.
- Although it seems clear that COX-2 inhibitors increase the risk for CV events, the risk differs to some degree **between individuals** and **across agents**, is **dose-related**, and varies with the **duration** of therapy.

## Cardiovascular Risk of NSAIDs

- the APPROVe (Bresalier *et al.* 2005) clinical trial showed that the risk was only apparent after **18 months of continuous intake of rofecoxib**.
- Risk was highest among patients receiving the **50mg dose**, and less among patients receiving the 25mg dose, and was **not detected** among those receiving 12.5mg.
- In **high-risk patients** (CABG), valdecoxib increased the cardiovascular events threefold even in short-term application for only 10 days.

## Cardiovascular Risk of NSAIDs

- Some studies suggest that **celecoxib**, **etoricoxib**, and **lumiracoxib** have a better safety profile than other COX-2 inhibitors, which is why these drugs have remained on the market (Silverstein *et al.*, 2000; Schnitzer *et al.*, 2004).
- Recent studies have shown that some COX-2 inhibitors are not associated with increased CV risks:
  1. The SUCCESS-1 (Singh *et al.*, 2006) trial found **no increased CV risks** with **celecoxib** compared to either **diclofenac** or **naproxen** in 13,274 patients with osteoarthritis.
  2. The TARGET (Schnitzer *et al.*, 2004) trial found **no significant difference in CV deaths** between **lumiracoxib** and either **ibuprofen** or **naproxen** irrespective of aspirin use in 18,325 patients with osteoarthritis.
  3. The MEDAL (Cannon *et al.*, 2006) trial found **no increased CV risks** of **etoricoxib** compared to **diclofenac** in 34,701 patients with osteoarthritis.

## Cardiovascular Risk of NSAIDs

- With the recent findings of cardiovascular adverse effects of COX-2 inhibitors, a potential **safety concern** has been raised as to whether the increased CV events would be a class effect for all NSAIDs.
- No placebo-controlled RCT** addressing the CV safety of traditional NSAIDs only observational studies, and comparator RCTs.
- Traditional NSAIDs may increase the risk for MI (Singh *et al.*, 2006). In particular, **diclofenac** carries a higher risk than other traditional NSAIDs (because it is more COX-2 selective); this was not the case for **naproxen**.

## Cardiovascular Risk of NSAIDs

- The FDA (USA) and the NICE (UK) have concluded that the increased risk of CV events may be a **class effect** for all NSAIDs and recommended that they all will now carry **stronger warnings for adverse side effects**, including **gastrointestinal** and **cardiovascular adverse** effects.
- These serious warnings for all NSAIDs may have been **'exaggerated'** and have definitely, and perhaps needlessly, frightened NSAID users, because current literature supports the enhanced cardiovascular toxicity of cyclooxygenase-2 inhibitors over traditional NSAIDs.

## Adverse Effects: Acetaminophen

- Acetaminophen **has a safer profile** than NSAIDs. A recent meta-analysis of 47 RCTs **shows no statistically significant differences in the frequency of reported adverse effects** between acetaminophen and placebo. (Barden *et al.*, 2004)
- Overdose can cause **hepatotoxicity**.
- Severe hepatotoxicity has been reported even after therapeutic doses in patients with risk factors such as **chronic alcohol consumption**, **human immunodeficiency virus infection**, and **hepatitis C virus infection**.

## Adverse Effects: Opioids

- Two recent meta-analyses for the adverse effects of opioids in pain management showed that about 1/3 of patients **abandoned** treatment because of **adverse events** (Moore *et al*, 2005; Furlan *et al*, 2006):
  1. Dry mouth (25%)
  2. Nausea (21%), and
  3. Constipation (15%) were most common.
- In view of the frequency of adverse effects, softening laxatives and anti-emetics (e.g. metoclopramide) should be made available at the same time.

## Adverse Effects: Opioids

- Another meta-analysis of analgesics for dental pain shows that **codeine and codeine combinations** were associated with a significant increase in patients suffering **adverse events** compared with NSAIDs alone (Barden *et al*, 2004).
- The **frequency of adverse events with opioids is more common** than with **NSAIDs** and **acetaminophen**, making them a poor choice for dental pain.

## Techniques of analgesic Administration: Routes

- It is a common belief that parenteral NSAIDs would be more efficacious than the oral route.
- A meta-analysis of 26 RCTs compared the analgesic efficacy of NSAIDs given by different routes in acute and chronic pain (Tramer *et al*, 1998) – **there was a lack of evidence for any difference in analgesic efficacy of NSAIDs given by different routes.**
- The intramuscular, intravenous and rectal routes were more likely to have specific local adverse effects.

**The oral route should be used whenever possible!**

## Techniques of analgesic Administration: Timing

- Traditionally, analgesics were given after surgery when patients experienced moderate to severe pain. the **nociception may be upregulated** through both **peripheral and central sensitizations**, leading subsequently to **more intense postoperative pain.**
- Prophylactic Preoperative Analgesics (Pre-emptive Analgesia)**
- A recent meta-analysis of 66 RCTs has concluded that pre-emptive analgesia is effective for NSAIDs but not for opioids (Ong *et al*, 2005).

## Drug Interactions: NSAIDs

- Most NSAID interactions relate to the **antiplatelet** and **gastrointestinal** effects:
  - Aspirin** – NSAIDs (in particular ibuprofen) may **reduce** its **cardioprotective** benefits and **increase GI risk.** diclofenac, rofecoxib, or acetaminophen **do not influence** the effects of aspirin on **platelet function.**
  - The **gastroprotective** benefit of COX-2 inhibitors is **partially or, in some patients, totally lost** if **aspirin** is used for **cardiovascular prophylaxis.**

## Drug Interactions: NSAIDs

- NSAIDs antagonize** the **antihypertensive** effects of **ACE inhibitors.** The risk of **renal impairment** or **hyperkalemia** is increased when patients are treated with these two classes of drugs simultaneously.
- Warfarin** levels are likely to be **increased** if patients are treated with NSAIDs because of competition for protein-binding sites.
- Antidiabetic effects of the oral **sulfonylureas** are **increased** by the co-administration of NSAIDs.

## Drug Interactions: NSAIDs

- **Corticosteroids** – risk of **peptic ulceration** with associated perforation and bleeding is increased in patients taking both drugs.
- **Diuretics** – **nephrotoxicity** is increased, which is probably the result of reduced extracellular fluid volume. The diuretic effect is antagonized and an elevation in serum potassium can occur.
- **Methotrexate** – levels of methotrexate can be **increased** because of the direct competition for renal excretion of the two drugs.

## Drug Interactions: Acetaminophen

- It has the **fewest drug interactions**.
- Acetaminophen is metabolized in the liver, drugs that increase the action of liver enzymes that metabolize acetaminophen (e.g. **carbamazepine**) may **decrease** the action of acetaminophen.
- The potential for acetaminophen to harm the liver is increased when it is **combined with alcohol** or with drugs that also harm the liver.

## Drug Interactions: Opioids

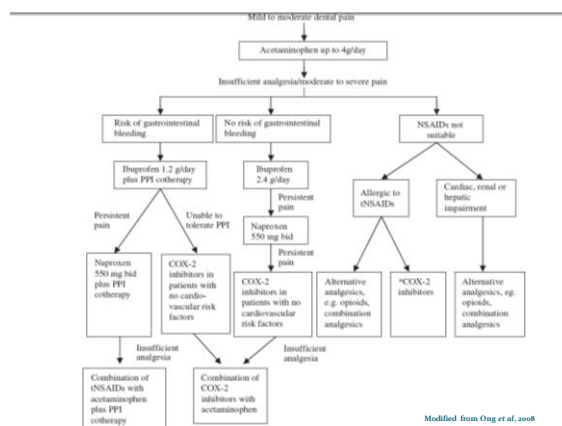
- Most opioid interactions stem from the drugs effects on the liver enzymes, which are largely **responsible for the elimination** of drugs.
- These interactions can either **slow down** or **speed up** that elimination:
  - An example of the former is the sometimes-fatal interaction between **pethidine** and **MAOI** antidepressants, an interaction that can cause an extreme increase in body temperature and seizures.
  - An example of the latter is the **withdrawal symptoms** reported in patients maintained on **methadone** when they are given **phenytoin**.

## Algorithm for Decision Making in Pain Management

- NSAIDs should be first-line analgesics, especially for severe dental pain where no contraindications exist.
- The most **efficacious** and **least toxic** agent should be used first.
- **Availability, cost, and length of action.**
- **Mucosa-protective agents** should be added for those at high risk of developing adverse GI effects because of the possibility of adverse events **even** in short-term use.

## Algorithm for Decision Making in Pain Management

- **COX-2** inhibitors have a place in treatment of high GI risk patients who cannot take mucosa-protective agents.
- If patient compliance is a problem, the once or twice daily formulation is beneficial.
- When NSAIDs are not appropriate, **acetaminophen** should be used and can be combined with **opioids** to increase its efficacy. Opioids should **not** be used as a sole agent.
- Postoperative pain following dental procedures should decrease over the course of **3-5 days** as the inflammatory process subsides.



## Take Home Message

No analgesic, dose, or combination will work for all patients.

Participation by a fully informed patient in the decision-making process is an essential element of good dental practice.

Rational prescribing will result in good pain management with minimal side effects.



## Thank You

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