“Better Medicine, Better Dentistry”

Pharmacology You Can Use!

Dr. Mark Donaldson, BSP, RPH, PHARMD, FASHP, FACHE

Idaho State Dental Association
Continuing Dental Education
Thursday, July 25th, 2013
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Clinically-Useful Pharmacology
Safe Medications for Minimal Sedation
Managing Drug Interactions in the Dental Chair
Intelligent Antibiotic Prescribing
Post-Operative Analgesia and Pain Control

Our Clinician:

Dr. Mark Donaldson, BSP, RPH, PHARMD, FASHP, FACHE, obtained his baccalaureate degree in Pharmaceutical Sciences from the University of British Columbia in Vancouver, and his doctoral degree in Clinical Pharmacy from the University of Washington in Seattle in 2001. After completing a residency and working at Vancouver General Hospital, as well as several small community hospitals as a clinical pharmacy specialist, he relocated to Montana to take his current position of Director of Pharmacy Services at the Kalispell Regional Medical Center in Kalispell, Montana.

Dr. Donaldson is a Clinical Professor in the Department of Pharmacy at the University of Montana in Missoula, and Clinical Associate Professor in the School of Dentistry at the Oregon Health & Sciences University in Portland, Oregon. He has a special interest in dental pharmacology and has lectured internationally to both dental and medical practitioners.

Dr. Donaldson has been a primary author and investigator for the National Institutes of Health (N.I.H.) Consensus Development Committee to define the guidelines for enteral sedation in the United States, and was invited by the Academy of General Dentistry to compose a white paper on enteral conscious sedation with Dr. Stanley Malamed and Dr. John Yageila. He has been published in General Dentistry, the Journal of the Association of Health-System Pharmacists (A.S.H.P.), Journal of the Canadian Dental Association, Anesthesia Progress, Quintessence International and the Journal of the American Dental Association. Dr. Donaldson is currently a reviewer for A.S.H.P. and General Dentistry, and serves on the Editorial Board for the Journal of the American Dental Association (J.A.D.A.).

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Pharmacology is a broad term encompassing the overall study of drugs. The answer to the question, “What Happens When Drugs Enter the Body?” is explained by two branches of pharmacology:

1. **Pharmacokinetics** deals specifically with the absorption of drugs from the outside environment, the distribution to their site of action within the body, their metabolism within the body, and finally their excretion.
2. **Pharmacodynamics** studies the interaction of the drug with the receptors at the site of action.

Once we gain an understanding of the pharmacodynamics and pharmacokinetics, we will concern ourselves with selecting those drugs which are most appropriate for our desired clinical results. Pharmacotherapeutics involves the study of choosing drugs for their desired actions in selective situations.

Patient response to medications can be represented by a bell-shape population curve where about 70% or one standard deviation will demonstrate the intended effect at a particular dose. As we extrapolate this curve out to two and even three standard deviations, we begin to recognize the “outliers”, also referred to as hyper- and hypo-responders: those individuals requiring either much less or much more of the same medication in order to elicit the desired effect. Protocols are very useful to capture the majority of the general population; however, the outliers require a slightly higher level of expertise and experience to determine the most appropriate dosing scheme. This section looks at how to recognize and treat these “outliers”, and more importantly, how to ensure you always practice within the safest possible dosing ranges. Remember our oath, “First, do no harm.”

**Figure 23-2** A normal, bell-shaped distribution curve. For any given drug, approximately 68% of patients experience desirable clinical effects with the usual adult dose, and 95% exhibit desirable effects with a slightly lower or higher dose. A small percentage of patients are hyperresponsive (right side of curve), requiring doses that exceed the “normal” before clinically desirable results occur. More important, however, are those hyporesponsive individuals (left side of curve) who exhibit clinically desirable results at lower than normal doses. Such patients are more likely to experience drug overdose. (From Perlman J: Pharmacology for dental anxious and procedures, Philadelphia, 1980, Lea & Febiger.)

**Figure 23-3** A normal, bell-shaped distribution curve. For any given drug, approximately 68% of patients experience desirable clinical effects with the usual adult dose, and 95% exhibit desirable effects with a slightly lower or higher dose. A small percentage of patients are hyperresponsive (right side of curve), requiring doses that exceed the “normal” before clinically desirable results occur. More important, however, are those hyporesponsive individuals (left side of curve) who exhibit clinically desirable results at lower than normal doses. Such patients are more likely to experience drug overdose. (From Perlman J: Pharmacology for dental anxious and procedures, Philadelphia, 1980, Lea & Febiger.)

Remember: the **HYPER Responder** is fairly easy to recognize preoperatively based on:

- Past Medical History
- Underlying Medical Condition(s)
- Current Medications
- Genetics

In the case of a sedation appointment, a preoperative protocol can account for this since a small amount of medication may be administered prior to the appointment. In general, always stick with the mantra: “Go Low, Go Slow!”

**Other Notes or Questions to Ask:**
Conversely, a significant percentage of patients are hypo-responders after normal or average doses of medications. These patients may require larger than normal doses of medications to achieve a desired effect. Many factors can contribute to a patient’s hypo-response to medication. Again in some sedation cases a combination of factors may culminate to antagonize the clinical effects of sedative drugs leaving the patient needing more medication to tolerate dental treatment.

The **HYPO Responder** is more difficult to recognize preoperatively, but can be inferred if the patient has evidence of the following clues:

- High Anxiety
- Liver Enzyme Inducers
- High Degree of Body Fat
- Use of Stimulants (caffeine, nicotine, and others)
- Past History of Drug Abuse
- Psychiatric Conditions
- Not Following the Preoperative Protocol
- Genetics

### What is Pharmacogenomics? = Pharmacology + Genetics

Since mapping the human genome this new branch of science truly represents the future of medicine since we have the opportunity to prescribe the right drug at the right dose, *the first time* without needlessly exposing patients to the side effects of medications through inappropriate initial dosing. We will be able to individualized pharmacotherapy based on every individual’s genetic make up, thus revolutionizing medicine. Every individual does have a unique genetic predisposition to drug effects and by marrying a patient’s genetic information with a drug’s pharmacological information we can improve outcomes in our patients.

Roche Molecular Diagnostics developed the world’s first pharmacogenomic microarray designed for clinical applications. It provides comprehensive coverage of gene variations and is intended to be an aid for physicians in individualizing treatment doses for patients on therapeutics metabolized through these genes. This tool has now been cleared for in vitro diagnostic use in both the United States and the European Union.

### Other Notes or Questions to Ask:

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Other Notes or Questions to Ask:

The clinical implications of this type of testing and screening are tremendous. A laboratory capable of genetic analysis can complete the test in 8 hours using a standard blood sample and the cost of the test to the laboratory is about $500. The question that still remains, however, is whether it will be covered by insurance carriers. Oncotype DX is a test that examines a breast cancer patient’s tumor tissue at a molecular level, and gives information about her individual disease. This information can help tailor treatment for her breast cancer. Oncotype DX is the first and only gene expression test that has been accepted as demonstrating the ability to predict a patient’s benefit from chemotherapy as well as her risk of recurrence (http://www.genomichealth.com).

Absorption of oral medications occurs in the gastrointestinal tract, specifically the small intestine where most drugs cross the phospholipid bilayer via passive diffusion. Others may be only partially removed from the circulation. The following drugs show poor bioavailability when given orally due to extensive first-pass hepatic elimination:

- Meperidine
- Morphine
- Pentazocine
- Aspirin
- Lidocaine
- Chlorpromazine
- Nitroglycerin
- Isoproterenol
- Propranolol

A small portion of medications and their metabolites may also undergo a cycle of biliary secretion from the liver through the bile duct and back into the small intestine. Here the molecules are either excreted via passage onto the large intestine, or they may be reabsorbed by the small intestine traveling back to the liver via the portal vein again. This cycle is known as enterohepatic circulation.

Pharmacokinetics vs. Pharmacodynamics

Kinetics refers to what the body does to a drug; Dynamics refers to what the drug does to the body. More specifically, Pharmacokinetics is the sequence of events which influence a drug’s ability to reach the receptor in sufficient quantity and for sufficient duration of time. Pharmacokinetics consists of:

- Absorption
- Distribution
- Metabolism
- Elimination

Pharmacodynamics is the study of drug effects on the body. It includes:

- Drug effects (ie. analgesia, sedation, etc)
Absorption

The route of administration is the principle factor which governs rate by which a drug reaches its receptors in sufficient quantity.

- Intravenous (IV) is the fastest route with onset usually within 1 minute.
- Inhalation is almost as fast as IV, administered as a vapor or gas through the pulmonary alveoli in the lungs.
- Subcutaneous and Intramuscular (IM) are similar and require approximately 30 minutes to reach the bloodstream. Absorption is largely governed by how much blood flow is present to allow drug to be carried away. Large volumes cannot be given.
- Enteric routes (oral and rectal) are the slowest way of introducing drugs into the blood stream. Oral ingestion of drug usually requires about 1 hour before effects are discerned.
- Sublingual (SL) has rapid onset, no first-pass effect, but not all drugs can be absorbed this way.

Bioavailability

Bioavailability is the physiological availability of a given amount of a drug. Regardless of the route of administration, usually only a fraction of unchanged drug reaches the systemic circulation:

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>100% by definition</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>75 to ≤ 100%</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>75 to ≤ 100%</td>
</tr>
<tr>
<td>Oral</td>
<td>5 to ≤ 100%</td>
</tr>
<tr>
<td>Rectal</td>
<td>30 to ≤ 100%</td>
</tr>
<tr>
<td>Inhalation</td>
<td>5 to ≤ 100%</td>
</tr>
<tr>
<td>Transdermal</td>
<td>80 to ≤ 100%</td>
</tr>
</tbody>
</table>

The extent of absorption is affected by such factors as: the lipophilicity of the drug; pH-dependent active transport; gut metabolism by bacteria; p-glycoprotein pump and the dissolution of some tablets.

Most drugs are given orally and are absorbed via passive diffusion through cell membranes of the GI tract. These membranes are composed of a lipid bilayer, so the drug’s lipid solubility is crucial for absorption and distribution. Only uncharged drug is lipid soluble.

But do you really care about “pH-dependent active transport”?

Other Notes or Questions to Ask:
Principles of Local Anesthetics

- **pK<sub>a</sub>**
  - All LA are weak bases with a pKa range of 7.7-8.9
  - All LA molecules exist in 2 states:
    1. Cation, positively charged species – impermeable to cells
    2. A free base, uncharged – readily penetrates connective tissues and lipid-rich membranes

\[ \text{RNH}^+ \leftrightarrow \text{RN} + \text{H}^+ \]

- **Example…**

  - Lidocaine pKa = 7.8
  - Injected into an inflamed area with pH = 6.0

    - 98% Cationic species
    - 2% Uncharged species

    - IMPERMEABLE

This may explain in part why it is more difficult to get a patient numb when they have an abscess and the microenvironment in that area has a lower pH than normal.

**Absorption Effected By:**
- Presence of food in the stomach – inhibits absorption
- Mucosal surface area – less surface area will inhibit absorption
- Gastric emptying time – slower emptying time will inhibit absorption
- pH of the tissues – antacids inhibit absorption
- Dosage form of the drug – lipophilic or lipophobic
- Drug inactivation – p450 enzyme complex
- Bioavailability of the drug – plasma protein binding

Drug distribution is often thought of in terms of compartments too, where highly lipophilic drugs cross readily from the plasma compartment to tissue compartments such as the brain. The Blood-Brain Barrier for example, is not a true “barrier”, but more like a selective gatekeeper for highly lipophilic medications whose site of action is the central nervous system.

**Distribution Effected By:**
- Number of drug binding sites on the protein
- Protein concentration
- Weak acids are bound more extensively than weak bases
- Competing molecules
- Disease

**Metabolism:**

Drugs are chemically transformed by the body to make them more water soluble, and thus more easily excretable. The primary organ of metabolism for the oral sedative medications is the liver (although some similar enzymes exist in the cells of the gastrointestinal mucosa).

The enzyme complexes in the liver chemically transform the medication molecules into either active or inactive metabolites. These enzymes are known as the **Cytochrome P<sub>450</sub> (CYP450)** family of enzymes.

**Other Notes or Questions to Ask:**
Drugs can act as either substrates for these enzymes, inducers or inhibitors, and these differences are the basis for drug interactions and the interpatient variability of responses to medication.

Drugs that enter the body parenterally can also be metabolized in the liver, but not until a certain proportion of the drug has had the opportunity to act at the site of action, in the case of sedative agents this would be the central nervous system (CNS). This accounts for the faster onset of action of parenterally administered drugs since the “first-pass effect” is essentially bypassed. This is also true for medications administered via the inhalation, rectal, topical and submucosal routes.

**Metabolism Effected By:**
Individual differences in metabolic rate (genetic polymorphism); Age of the patient (consider the very young and the very old); Liver disease (impairment of enzyme activity or defective formation of enzymes); Cardiac disease (by limiting blood flow to the liver may impair rate of metabolism); Pulmonary disease (especially in the case of inhaled medications); Endocrine dysfunction (hypothyroid patients have a slowed metabolism versus hyperthyroid patients who have a revved up metabolism); Drug interactions (inhibition or induction); Cigarette smokers metabolize some drugs more rapidly than nonsmokers because of enzyme induction.

**Metabolism determines blood levels of active drug and therefore, predictability of response.**

Other Notes or Questions to Ask:
Elimination:

Renal clearance is the major pathway of elimination for most drugs and their metabolites. In fact, the role of the liver in metabolism is to generally convert lipophilic (fat-soluble) molecules into more hydrophilic (water-soluble) molecules for easier excretion via the kidneys. Elimination can also occur via the bile and feces. Sometimes an active metabolite is formed from metabolism and can target the kidney as it is eliminated. Such is the case with Ciprofloxacin, which is used to treat urinary tract infections.

Factors affecting elimination include:

- Age
- Drug Half-Life
- Liver Function
- Compartment Models
- Kidney Disease

This becomes important when considering that different drugs are cleared from the body at different rates, and are therefore dosed differently and with different frequency. In terms of pharmacokinetics, we can then determine the half-life of a drug so that we may dose a patient appropriately. Half-life indicates the time it takes to attain 50% of steady state blood level. After one half-life, one half of the drug in the system will have been eliminated. After four half-lives, greater than 90% of drug in the system will have been eliminated:

\[
\begin{align*}
100\% & \text{ divided by } 2 = 50\% \quad \text{(after one half life 50\% of a drug has been cleared)} \\
50\% & \text{ divided by } 2 = 25\% \quad \text{(after 2 half lives 75\% of a drug has been cleared)} \\
25\% & \text{ divided by } 2 = 12.5\% \quad \text{(after 3 half lives 87.5\% of a drug has been cleared)} \\
12.5\% & \text{ divided by } 2 = 6.25\% \quad \text{(after 4 half lives > 90\% of a drug has been cleared)}
\end{align*}
\]

Therapeutic Levels

- Plasma level is a balance between dose per unit time and factors which will decrease the level of active drug (metabolism, excretion, dilution). Plasma levels of drugs are always changing.

- Steady state: If identical multiple doses of drug are given every half-life, relatively constant levels will be produced after 4 half-lives.

rate of elimination = rate of accumulation

Other Notes or Questions to Ask:
as a balance between dose per unit time and factors which will decrease the level of active drug (metabolism, excretion, dilution). Plasma levels of drugs are always changing.

A **Steady-state** can be achieved when the rate of drug accumulation in a body is equal to the rate of elimination. This is also achievable if identical multiple doses of drug are given every half-life: relatively constant levels will be produced after 4 half-lives.

**Pharmacodynamics**

**Pharmacodynamics** studies the interaction of a drug with a receptor at the site of action. Receptor occupancy explains the response of drugs. Binding to receptors is usually reversible and falls into one of two categories: agonists and antagonists. Agonists have an affinity for receptors and their binding to these receptors leads to the effect and efficacy of the medication. An antagonist only has an affinity for binding to the receptor, but this interaction does not illicit a response and it therefore it antagonizes or blocks an active drug from combining to the receptor and causing an effect.

As we age we may have enhanced sensitivity to drugs due to: changes in receptor numbers; changes in receptor affinity or; alterations in the processes after a drug binds a receptor. For example, the elderly are more sensitive to benzodiazepines, more sensitive to the analgesic effects of narcotics and they have enhanced response to anticoagulants such as warfarin and heparin. In general, elderly patients require a reduction in sedative drug dosage.

Changes in receptor numbers or affinity can also lead to alterations in the processes after a drug binds a receptor. Drug interactions further compound the unpredictability of pharmacodynamics as they too can be: antagonistic (theophylline & propranolol) or synergistic (warfarin and aspirin, benzodiazepines and opiates).

**Other Notes or Questions to Ask:**

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Enteral Conscious Sedation & Sedative Agents

Anxiolysis is a minimal level of sedation whereby the patient has decreased anxiety to facilitate coping skills while retaining interaction ability. Conscious sedation is a moderate level of sedation whereby the patient retains their protective reflexes as well as their own airway, and can respond to physical and verbal stimuli.

The Spectrum of Anesthesia

Relationship Between Efficacy and Safety for Anesthesia and Sedation

Parenteral vs. Enteral Sedation

Parenteral
- IV, IM, SC
- No “First-Pass” effect
- Drug effect is rapid
- Adverse effects can be rapid
- Requires specialty training
- Patient acceptance?

Enteral
- Oral, SL, rectal
- Long latency period
- “First-pass” effect
- Presentation of adverse effects is slow
- Lower incidence of adverse effects
- Requires less specialty training
- Patient acceptance?

All things considered equal, the lower the sedation level, the less chance for a serious adverse event to occur. The adage, “go low and go slow” is an excellent philosophy for the practice of sedating dental patients.

Who is a candidate for oral sedation?

Good
- Pts who have difficulty achieving profound local anesthesia
- Gaggers
- Fearful or anxious patients
- Pts needing longer procedures
- Helpful with invasive procedures

Less Good
- Pts with complex medical histories
- Pts taking medications which may cause adverse reactions
- Severely depressed patients
- Pts with a severe mental handicap
- Pregnant patients

Other Notes or Questions to Ask:
**Oral Route Advantages:**
- Generally the safest route
- Decreased incidence of adverse reactions
- Decreased severity of adverse reactions
- Ease of administration (convenient)
- Almost universal acceptability
- Low cost
- No needles, syringes, equipment
- No specialized training

**Oral Route Disadvantages:**
- Reliance on patient compliance
- Prolonged latent period
- Erratic and incomplete absorption of drugs from the GI tract
- Gastric irritation may cause vomiting
- Inability to titrate
- Adding small doses of drug and being able to determine within seconds if the desired effect was achieved.
- Prolonged duration of action
- Inability to readily lighten or deepen the level of sedation
- Requires cooperation of the patient

**The Drugs**

The goal of conscious sedation dentistry is to create a patient who is calm, and comfortable enough to receive dental care, and who can maintain a patent airway without assistance. Medications used for anxiolysis or conscious sedation should carry an inherent margin of safety such that overdose or unconsciousness is unlikely.

Because there are many medications that are anxiolytic (reduces anxiety) and hypnotic (involves the induction and increase of sleep duration), there may be instances that alternate regimens may be indicated. The decision to use drugs other than triazolam should be based on the practitioners’ level of training and should take into account many factors. The factors that may influence drug selection include:

- Medical History
- Drug interactions
- Allergies
- Length of appointment
- Depth of sedation needed
- Adverse reactions

Anxiolytic and Sedative agents are not new to the practice of medicine. Alcohols have been used for centuries to “numb” the mind to both painful as well as anxiety producing procedures. The use of opium has been traced back to Ancient Egypt. In the nineteenth century, drugs such as bromide (1853), chloral hydrate, paraldehyde, urethane and sulfonal (all pre-1970) were employed with varying degrees of success. Early in the twentieth century, the barbiturates were discovered (Barbital – 1903 and Phenobarbital – 1912), and the age of modern anesthesia was born. While these early drugs were effective, their level of safety was questionable.

Safety of a given medication can be measured pharmacologically by determining the **Lethal Dose 50 (LD50)**. The LD50 is that dose of a given drug that will result in mortality of 50% of the population when administered. Likewise, the **Effective Dose 50 (ED50)** is the dose of a given drug that will cause the desired results in 50% of a population. The two terms can be related to one another by the Therapeutic Index (TI = LD50/ED50), which is a relative measurement of drug safety. The greater the Therapeutic Index of a drug, the greater the margin of safety.

**Chloral Hydrate Induced Arrhythmias**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose (grams)</th>
<th>Arrhythmia</th>
<th>Cardiac Arrest</th>
<th>Antiarry. Drug Res.</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.5</td>
<td>PVC</td>
<td>No</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>6.6</td>
<td>VT</td>
<td>No</td>
<td>Yes</td>
<td>Survived</td>
</tr>
<tr>
<td>17</td>
<td>14</td>
<td>PVC, VT</td>
<td>No</td>
<td>Yes</td>
<td>Survived</td>
</tr>
<tr>
<td>19</td>
<td>17.5</td>
<td>PVC, VF</td>
<td>Yes</td>
<td>Yes</td>
<td>Survived</td>
</tr>
<tr>
<td>21</td>
<td>20</td>
<td>VF</td>
<td>No</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>29</td>
<td>10</td>
<td>PVC, VT</td>
<td>No</td>
<td>-</td>
<td>Survived</td>
</tr>
<tr>
<td>32</td>
<td>20</td>
<td>PVC, VF</td>
<td>Yes</td>
<td>-</td>
<td>Survived</td>
</tr>
<tr>
<td>33</td>
<td>40</td>
<td>PVC</td>
<td>Yes</td>
<td>-</td>
<td>Died</td>
</tr>
</tbody>
</table>

In large doses it shortens the cardiac refractory period and may sensitize heart to circulating catecholamines. *Jastak. JADA 1988 (vol.116)*

**Other Notes or Questions to Ask:**
Chloral Hydrate, a drug that has been used as a sedative for over a century, when compared to a drug in the benzodiazepine class (Diazepam - early 1960s), is an example of the lower degree of safety as demonstrated by drugs of the past. One of the attributes that make newer classes of drugs safer than those in the past is their ability to more selectively depress areas of the central nervous system that affect consciousness. Most anxiolytic and sedative agents, if given in inappropriate doses, have the capacity to elicit undesired effects, including coma and death.

Chlordiazepoxide (1957) was the first drug in the benzodiazepine class to be synthesized. The benzodiazepines, being more selective in their effects on the central nervous system, are much less likely to induce coma and death; therefore they have a much higher LD50 and Therapeutic Index than drugs in other anxiolytic/sedative classes.

The “Ideal” Oral Agent should have the following properties:

- Fast onset
- No adverse effects – large margin of safety (respiratory, cardiovascular, others)
- “Short” acting (for office use)
- Anxiolytic with some amnesic properties
- Reversal agent available

Benzodiazepines meet these requirements and have the following properties:

- Sedative-Hypnotic
- Muscle Relaxant
- Anxiolytic
- Anticonvulsant
- Antidepressant
- Anterograde Amnesia

Medications for Oral Conscious Sedation

The family of medications most commonly used for oral conscious sedation is the benzodiazepines. They were first introduced in the early 1960’s, and are among the most widely prescribed drugs in the world. Like members of your own family they are closely related and share very similar properties due to a common mechanism of action on the gamma amino butyric acid (GABA) receptors in the brain. These GABA receptors are the neuroreceptors responsible for levels of alertness, so the shared pharmacological property of this family of drugs denotes them as sedatives or hypnotics: they cause relaxation, can induce sleep and may even allow for post-hypnotic suggestions. The interaction of the benzodiazepines at the GABA molecule occurs in the limbic, thalamic and hypothalamic levels of the CNS. Specific high-affinity benzodiazepine receptors have been identified. When the benzodiazepine and GABA molecules interact, a macromolecular complex is formed. The complex results in an influx of chloride ions as the chloride ionophore channel in the nerve axon increases in diameter, causing hyperpolarization, and an associated new resting membrane potential.

Other Notes or Questions to Ask:
To further the familial analogy, these medications still maintain their own uniqueness despite their underlying similarity. Each medication may or may not have active metabolites, such as diazepam (Valium), and their individual plasma half-lives and mean peak concentrations vary among agents, which gives rise to different medication properties. It is only through experience that practitioners learn how to match the best medication and dose with each clinical situation and patient.

The Benzodiazepine Family of Medications

All of the benzodiazepine drugs have a similar chemical structure:

**Diazepam (Valium)**

Has high lipid solubility, produces mild sleep and mild amnesia (onset: 30-60 minutes). The half-life is around 50 hours (range: 20-100 hours due to active metabolites) and the duration of action can be 6-8 hours. It is supplied in 2, 5, and 10 mg tablets (usual dosage is 2-40 mg). It is an FDA approved anxiolytic with other indications for use as listed in the Physicians’ Desk Reference (PDR): Preoperative anxiolytic; Night-time sleep (hypnotic) and; as an Anticonvulsant.

Other Notes or Questions to Ask:
**Lorazepam (Ativan)**

Produces mild/moderate sleep with moderate amnesia. It has an onset of action of 60-120 minutes and a half-life of 10-20 hours (no active metabolites). The duration of action is 6-8 hours and it is supplied as 0.5, 1, and 2 mg tablets (typical dosing: 2-6 mg). Compared to diazepam it has moderate lipid solubility and it’s indications for use as listed in the Physicians’ Desk Reference (PDR) include: Preoperative anxiolytic; Night-time sleep (hypnotic) and; as an Anticonvulsant.

**Triazolam (Halcion)**

Has no active metabolites and a plasma half-life is 1.5 – 2.5 hours. It has an effective dose range of 0.125-0.5mg with an onset of action within 45 minutes and a mean peak concentration achieved in 1.3 hours. It has anticonvulsant properties like the other benzodiazepines and does not cause nausea (unlike nitrous oxide). The LD50 is 5 grams per kilogram in rats (very safe). It’s indications for use as listed in the Physicians’ Desk Reference (PDR) include: Preoperative anxiolytic and Night-time sleep (hypnotic).

**Midazolam (Versed)**

Has a high lipid solubility and produces moderate sleep and high amnesia. It’s onset is 15-30 minutes and it has a half-life of 1.5 - 5 hrs. It has no active metabolites and lasts about 1 hour. It is supplied in 118 ml bottles, where each mL contains 2mg midazolam. Typical dosages range from 0.25 to 0.75 mg/kg in children >6 months (relative maximum at 10 mg). It’s indications for use as listed in the Physicians’ Desk Reference (PDR) include: Preoperative anxiolytic; Night-time sleep (hypnotic) and; as an Anticonvulsant.

**Other Medications (non-Benzodiazepines)**

Zaleplon is a pyrazolopyrimidine, differing in structure from the benzodiazepines but still acting selectively at the benzodiazepine receptor. The benefits of this medication are in producing sedation without many of

**Other Notes or Questions to Ask:**
the other effects seen with benzodiazepines. It has modest anxiolytic, myorelaxant, and anticonvulsant properties. Significant drug interactions are uncommon, and synergy with ethanol does not occur. Patients with zaleplon overdose generally do well with supportive care alone. Overdose information for zaleplon is limited and no fatalities have been reported with ingestions of up to 100 mg. Adverse effects with therapeutic use include anterograde amnesia and transient visual hallucinations.

**Zaleplon (Sonata, Starnoc)**

Produces high sleep with only mild amnesia and has an onset of 30 minutes. Its half-life is 1-2 hours and it has no active metabolites. It’s duration of action is up to 6 hours and it is supplied in 5 and 10 mg capsules. Typical dosages are 10 mg (start at 5mg in the elderly or patients with liver disease). Overdosage can be treated with flumazenil. It is not an FDA approved anxiolytic (approved for treatment of insomnia in adults only).

**Cautions:**
- hypersensitivity to zaleplon products
- depressed patients
- elderly or debilitated patients
- hepatic or severe renal impairment
- compromised respiratory condition
- concurrent use of alcohol
- tartrazine sensitivity
- Co-administration with the following medications can effect metabolism: cimetidine, digoxin, and rifampin (diphenhydramine may augment zaleplon’s effects)
- Pregnancy: risk category C

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lipid Solubility</th>
<th>Onset (mins)</th>
<th>T1/2 (hrs)</th>
<th>Site of Metabolism</th>
<th>Active Metabolite</th>
<th>Working Time (hrs)</th>
<th>Usual Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>High</td>
<td>30-60</td>
<td>&gt;24</td>
<td>CYP 1A2, 2C8, 2C19, 3A3-4</td>
<td>Yes</td>
<td>n/a</td>
<td>2-40 mg per day</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Moderate</td>
<td>60-120</td>
<td>10-20</td>
<td>Hepatic glucuronidation</td>
<td>No</td>
<td>4</td>
<td>2-6 mg</td>
</tr>
<tr>
<td>Triazolam</td>
<td>High</td>
<td>15-30</td>
<td>1.5-2.5</td>
<td>CYP 3A4, 5-7</td>
<td>No</td>
<td>2</td>
<td>0.125-0.5 mg</td>
</tr>
<tr>
<td>Midazolam</td>
<td>High</td>
<td>0 (IM)</td>
<td>1.5-5</td>
<td>CYP 3A3-5</td>
<td>No</td>
<td>1</td>
<td>0.25-0.75 mg/kg</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Moderate</td>
<td>30</td>
<td>1-2</td>
<td>Aldehyde oxidase, CYP 3A4</td>
<td>No</td>
<td>1</td>
<td>10-20mg</td>
</tr>
</tbody>
</table>

“Triazolam is chemically related to diazepam and is used for the short-term treatment of insomnia. Its rapid onset, short duration of action, and lack of active metabolites also makes it a near ideal anti-anxiety medication for dental patients”.


**Other Notes or Questions to Ask:**
**Triazolam: Cautions and Contraindications** (Nearly all of these cautions and contraindications apply to all benzodiazepines):

**Absolute Contraindications**
- Known hypersensitivity
- Pregnancy – benzodiazepines are known teratogens (esp. 1st trimester)
- Lack of Knowledge
- Inability to resuscitate
- Concurrent with CYP3A4 inhibitors: grapefruit juice, ketaconazole, itraconazole, nefazodone, cimetidine, and macrolide antibiotics

**Relative Contraindications** (Risk benefit should be considered when the following medical conditions exist):
- Alcohol intoxication – additive CNS
- Glaucoma
- Drug abuse or dependence
- Pediatric patients
- Elderly (oversedation, dizziness, or impaired coordination)
- Psychiatric patients
- Renal impairment
- Severe hepatic impairment
- Lactating patients

**Benzodiazepine Reversal Agent**

**Flumazenil** (Romazicon® in U.S., Anexate® in Canada):
- First clinical trials done in 1979
- Displaces BDZ’s from their receptor site, reversing their sedative action
- Onset of reversal after I.V. injections is 1-2 minutes (neutral ligand)
- Duration of effect depends on the dose of flumazenil and the dose of the BDZ
- Adult dose is 0.2mg q1min up to 5 doses

Flumazenil, a nonspecific competitive antagonist of the benzodiazepine receptor, is used for reversal of benzodiazepine-induced sedation, and overdose. It binds to GABA-receptor sites, but has no agonist activity.

**Other Notes or Questions to Ask:**
The initial adult dose of flumazenil is 0.2 mg given intravenously over 30 seconds. A second dose of 0.2 mg may be given, followed by 0.2mg doses at 45-60 second intervals, to a total of 1mg in twenty minutes. Most patients will respond to less than 1 mg. In children, the initial dose is 0.01 mg/kg. Because the duration of action of flumazenil is short (40-80 minutes), re-sedation occurs in up to 65% of patients and requires either re-dosing or continuous infusion (0.25 to 1.0 mg/hr).

In summary, flumazenil should be used for selected patients with significant symptoms from a known benzodiazepine overdose, and NOT routinely used on patients following an oral sedation procedure.

![Inadequate Sedation](image1)

![Nitrous Oxide Supplementation](image2)

**Dr. Quarnstrom’s Protocol:**

Weight-Based Protocol with oral titration of triazolam and supplemental nitrous oxide:

**Dose (mg) = 0.25mg + 0.125mg (for every 70lb weight increase > 40lbs)**

Therefore mean dose = 0.005mg/lb or 0.5mg for 180-pound man

![Inadequate Halcion Sedation](image3)

![Nitrous Oxide Supplementation](image4)

**Other Notes or Questions to Ask:**

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Tmax (hr)</th>
<th>T(_{1/2}) elim (hr)</th>
<th>Site of metabolism</th>
<th>Pharmacologic antagonist</th>
<th>Usual PO dose</th>
<th>Duration of action (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam (Halcion®)</td>
<td>1.25</td>
<td>2.5 (1.7-4)</td>
<td>CYP 3A4, 5-7</td>
<td>Flumazenil</td>
<td>0.125-0.5 mg</td>
<td>2-4</td>
</tr>
<tr>
<td>Midazolam (Versed®)</td>
<td>0.5-1</td>
<td>1-2</td>
<td>CYP 3A3-5</td>
<td>Flumazenil</td>
<td>0.5 mg/kg</td>
<td>1-2</td>
</tr>
<tr>
<td>Lorazepam (Ativan®)</td>
<td>1.2</td>
<td>15.7 (14-16)</td>
<td>Hepatic gluronidation</td>
<td>Flumazenil</td>
<td>1-3 mg</td>
<td>6-8</td>
</tr>
<tr>
<td>Alprazolam (Xanax®)</td>
<td>1.45</td>
<td>14.5 (12-15)</td>
<td>CYP 3A4</td>
<td>Flumazenil</td>
<td>1 mg</td>
<td>6-8</td>
</tr>
<tr>
<td>Diazepam (Valium®)</td>
<td>1.12</td>
<td>33 (20-100)</td>
<td>CYP 1A2, 2C8, 2C19, 3A3-4</td>
<td>Flumazenil</td>
<td>5-10 mg</td>
<td>6-8</td>
</tr>
<tr>
<td>Zaleplon (Sonata®)</td>
<td>0.5-1.5</td>
<td>1</td>
<td>Aldehyde oxidase, CYP 3A4</td>
<td>Flumazenil</td>
<td>10 mg</td>
<td>4</td>
</tr>
<tr>
<td>Zolpidem (Ambien®)</td>
<td>1.6</td>
<td>2.5</td>
<td>CYP 3A4, 2C9, 1A2</td>
<td>Flumazenil</td>
<td>10 mg</td>
<td>8</td>
</tr>
<tr>
<td>Ramelteon (Rozerem®)</td>
<td>0.3</td>
<td>0.5-2.6</td>
<td>CYP 1A2, 2C, 3A4</td>
<td>Unknown</td>
<td>8 mg</td>
<td>24</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta®)</td>
<td>1-1.5</td>
<td>6</td>
<td>CYP 3A4, 2E1</td>
<td>Flumazenil</td>
<td>2-3 mg</td>
<td>6</td>
</tr>
<tr>
<td>Zopiclone (Imovane®)</td>
<td>1-1.5</td>
<td>3.5-6.5</td>
<td>CYP 3A4, 2E1</td>
<td>Flumazenil</td>
<td>7.5 mg</td>
<td>&lt; 24</td>
</tr>
<tr>
<td>Promethazine (Phenergan®)</td>
<td>2-3</td>
<td>7-15</td>
<td>CYP 2D6, 2B6</td>
<td>None</td>
<td>25 mg</td>
<td>2-8</td>
</tr>
<tr>
<td>Hydroxyzine (Atarax®, Vistaril®)</td>
<td>2.1</td>
<td>7-20</td>
<td>CYP 2D6</td>
<td>None</td>
<td>50 mg</td>
<td>24</td>
</tr>
</tbody>
</table>
Patient Assessment and Drug Interactions

The goal of oral conscious sedation is to create, by pharmacologic or other means, a comfortable environment such that the patient can safely and effectively receive dental care.

There is an inverse relationship between the depth of sedation and the degree of safety associated with it. Clearly, general anesthesia and deep sedation hold the greatest risk of serious morbidity and mortality as well as the highest efficacy. On the other hand, nitrous oxide and oral conscious sedation have the lowest risk and a lower clinical efficacy.

Multiple Agent Protocols
When benzodiazepines are administered alone, only mild changes occur in respiratory rate and oxygen saturation levels. However, adding a barbiturate or a narcotic in a multiple drug regimen with a benzodiazepine creates a statistically significant decrease in both respiratory parameters.

Why should drug interactions concern me? - because polypharmacy is the norm especially in those patients over 65 years old. A Canadian Medical Association policy survey showed that more than 20% of acute care hospital admissions for seniors may result directly from adverse drug reactions. Polypharmacy is used as: complementary therapy; co-morbid conditions and; non-comorbid conditions.

Many of our patients are on multiple drug regimens. The potential for drug interactions increases dramatically with the number of medications prescribed.

Other Notes or Questions to Ask:

July 25, 2013
Chronic illness leads to polypharmacy so that there is a high probability of a drug interaction. But how is this related to dentistry? Almost all of your patients will be on some kind of medication (prescription, OTC, herbals, supplements, recreational). And just because dentists prescribe less than 10% of all available drugs, your patients may be taking others from the 90% you’re not familiar with, and not all of your patients will tell you what they are taking. So who is more “at risk” - you or your patient?

To first understand drug interactions it is important to revisit metabolism. The primary organ of metabolism is the liver (although some similar enzymes exist in the cells of the gastrointestinal mucosa). The enzyme complexes in the liver chemically transform the medication molecules into either active or inactive metabolites. These enzymes are known as the Cytochrome P450 (CYP450) Family of enzymes, and can be further stratified into the individual isoenzymes, which comprise this family. In terms of dental pharmacology, the most prominent isoenzymes to consider are: CYP3A4, CYP2D6, CYP2C9, CYP1A2 and CYP2C19.

Metabolism is also known as biotransformation as some drugs are “pro-drugs”. Drug metabolites are usually more polar and less lipid soluble than the parent molecules (this enhances their excretion and distribution half-life). Hepatic oxidation is the major drug metabolizing process. This process, or what the patient does to the drug (pharmacokinetics), and its balance with what the drug does to the body (pharmacodynamics), determines the effectiveness of the medication.

Drug interactions are common causes of treatment failure and adverse reactions. Most drug interactions remain unrecognized because of a wide margin of safety (therapeutic index) compared to inter- and intra-patient variability seen in practice. The effect of inappropriate drug combinations may lead to drug interactions or inaccurate assessment of the clinical effect.

The therapeutic index of a drug relate its effective dose fifty (ED50) to its lethal dose fifty (LD50) and is a measurement of drug safety. The greater the therapeutic index, the greater

Other Notes or Questions to Ask:
the difference between the ED50 and the LD50, the greater the margin of safety. Chloral Hydrate, an alcohol, has a much lower therapeutic index than the benzodiazepine, diazepam. If, however, the two drugs were to be administered together, the LD50 representing the combination would shift significantly to the left, resulting in a much lower degree of safety.

Some points are important to keep in mind:

✓ The management of a condition with a drug depends on the predicted effect of that drug
✓ The predicted effect depends on the drug being present:
  o in the clinically active dose
  o for the appropriate duration
✓ Anything that changes the dose or duration of effect makes drug management unpredictable

Drug interactions give rise to a modified response from the expected or normal response; can cause increased drug levels leading to an enhanced response or increased side effects (clinical relevance depends on the therapeutic indication) or; can cause decreased drug levels leading to sub-clinical or lack of response. Finally, drug interactions can be permanent because of polymorphism (i.e. patient does not have enzyme). The bottom line is that variability in patient response may be the result of changed metabolism which can be caused by drug interactions.

**Classifying the enzymes responsible for drug metabolism**

- Drugs are usually metabolized to inactive metabolites for excretion
- The main route of metabolism for exogenous substances is the liver by the cytochrome P450 mono-oxygenase system
- The P450 system is made up of many enzymes. However, the majority of drug metabolism is by five enzymes: 1A2, 2C9, 2C19, 2D6, and 3A4

**Relative Proportions of Enzymes**

- CYP3A4
- CYP2C9
- CYP2D6
- CYP1A2
- CYP2C19
- CYP3A4

**Other Notes or Questions to Ask:**
There are significant interpatient and intrapatient variability with respect to effects of medications and current research indicates that the genetic expression of these liver enzymes may play a prominent role in determining who and why different patients react differently. In the case of isoenzyme CYP2D6, for example, this **genetic polymorphism** in metabolism is common, and can lead to 10 times the difference in drug clearance, leading to either therapeutic failures or increased adverse events and toxicities. The ultrarapid metabolizer phenotype (where CYP2D6 activity is overactive) leads to a reduced effectiveness of drug at standard doses. The prevalence of this polymorphism among different patient populations is Northern European countries (2%-4%); Mediterranean area (7%-12%); Ethiopians, (29%) and; Saudi Arabian (21%). Conversely, 5%-10% of the Caucasian population have a CYP2D6 deficiency which often leads to an increased potential for drug interactions and side effects due to an accumulation of CYP2D6 metabolized drugs and higher serum drug concentrations, despite administration of “standard doses”.

**Clinical Relevance of Drug Interactions**
- Drug interactions can be caused by enzyme induction, inhibition, or competition
- If an enzyme is induced by a drug, metabolism occurs faster (e.g. Phenobarbital)
- If inhibition occurs the drug is not metabolized as fast (increased blood levels)
- Two or more drugs (competing for) the same enzyme will lead to variations in blood levels

---

**CYP 1A2**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inducer</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Carbamazepine</td>
<td>BCPs</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Clarithromycin</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Cigarette Smoke</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Erythromycin</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Insulin</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>LAs</td>
<td>Lansoprazole</td>
<td>Ticlopidine</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Omeprazole</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Ritonavir</td>
<td></td>
</tr>
</tbody>
</table>

It is possible for a drug to be both a substrate and an inhibitor of an enzyme.

---

**Other Notes or Questions to Ask:**
**Case Study #1**
A 45 year old woman has been using diazepam intermittently. She has suffered from GERD for 5 years. Her reflux symptoms are controlled by omeprazole but she has recently begun to feel drowsy. She asks if this can be caused by the drugs that she is taking.

Omeprazole is metabolized by CYP 3A4 and by CYP 2C19 and has many interactions with the P450 enzyme system. Omeprazole inhibits the metabolism of drugs (such as diazepam) which are metabolized by CYP 2C19, which can result in increased plasma concentrations.

Not all drugs in the same class are metabolized by the same pathway. Thus when prescribing a second or subsequent drug, potential drug interactions should be considered and drug choice made accordingly. Where a drug interaction occurs, it is often possible to select another drug in the same drug class with a different metabolic pathway. Note that there is also polymorphism with CYP 2C19. 2-6% of Asians do not have the enzyme and are therefore poor metabolizers.

**Case Study #2**
28 year old female who presents for hygiene, operative, and extraction of her wisdom teeth. Past medical history includes: Depression, Social anxiety disorder and Asthma. She takes Prozac, and albuterol prn. She has NKDA.

Surgery went well and she is given codeine syrup postoperatively because, “tablets make me gag”

**Other Notes or Questions to Ask:**
That night there is a frantic phone call to the after-hour service from mother, “my daughter is in excruciating pain!” Recommendation given to double codeine dose to 60mg every six hours and if there is still no relief to come back to the office the following day.

Patient presents to the office the next morning in tears and obvious pain. No noticeable abscess or swelling . . . What could be going on??

Codeine is a “prodrug” that requires “activation” by the liver. The CYP 2D6 isoenzyme is responsible for converting codeine to it’s active form, morphine (Br J Anaesth 2002; 89: 839–45). Up to 10% of the Caucasian population have a deficiency in this isoenzymes so they cannot activate codeine. Since pain of dental origin is primarily related to inflammation and narcotics like codeine are not antiinflammatory agents, ibuprofen and acetaminophen should be the combination of choice (helps avoid “codeine failures” also). Donaldson M and Goodchild JH. Appropriate analgesic prescribing for the general dentist. Gen Dent 2010; 58(4):291-7.

**Case Study #3**

A 73-year old man who has been on lovastatin (Mevacor®) 20mg daily for the past seven years is given six courses of erythromycin (9 grams over 2 weeks) for subacute bacterial endocarditis (SBE) prophylaxis. Most of the procedures involved simple crowns and fillings. Doses were all appropriate as per the old American Heart Association guidelines (J Am Dent Assoc. 1997 Aug;128(8):1142-51).

One day after his last erythromycin dose he experiences generalized muscular weakness, anorexia, nausea and vomiting. Four days after his last erythromycin dose he presents to the Emergency Room at his local hospital complaining of muscle weakness with noticeable abdominal distension. He was admitted to hospital and rapidly deteriorated, developing rhabdomyolysis, acute renal failure, pancreatitis, ileus, and elevated liver function tests.

He spent the next ten days in the intensive care unit, where his condition ultimately stabilized and the severity of his condition was down-graded as slow improvements were noted. It took a further seven days as hospital inpatient before he had recovered enough to be appropriately discharged. Happily he survived the ordeal.

**Other Notes or Questions to Ask:**

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**CYP 3A4**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inducer</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Barbiturates</td>
<td>CCBs (esp. Diltiazem)</td>
</tr>
<tr>
<td>Astemizole</td>
<td>Cyclophosphamide</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Dexamethasone</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Lansoprazole</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>CCBs (not diltiazem)</td>
<td>Erythromycin</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Fentanyl</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Halothane</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Erythromycin</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Fentanyl, Halothane</td>
<td>Grapefruit Juice</td>
</tr>
<tr>
<td>Fentanyl, Halothane</td>
<td>HIV Protease</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>HIV Protease</td>
<td>Inducers and</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Lanthrubicin</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Loratidine, Lovastatin</td>
<td>Midazolam</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Midazolam, SSRIs</td>
<td>Nebivolol</td>
<td>Midazolam</td>
</tr>
<tr>
<td>Simvastatin, TCAs</td>
<td>Nefazodone</td>
<td>Nefazodone</td>
</tr>
<tr>
<td>Terfenadine, Triazolam</td>
<td>Omeprazole</td>
<td>Omeprazole</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>Taperifex</td>
</tr>
<tr>
<td></td>
<td>Sex Steroids</td>
<td>TCAs</td>
</tr>
</tbody>
</table>

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Grapefruit Juice is considered a **Suicide Inhibitor** because it completely destroys some of the CYP3A4 in the small intestine. Normal enzyme levels of this isoenzyme are reestablished after body makes more, usually in 2 to 3 days after the juice leaves body. Juice from the frozen concentrate is a more potent inhibitor than fresh juice or ½ grapefruit.

Besides the liver, metabolism also occurs in other parts of the body such as: the intestinal epithelium, biliary canaliculi, renal proximal tubules, blood-brain barrier, and some tumor cells. The mechanism responsible for this is the **P-Glycoprotein** efflux pump, which has gained particular notoriety in explaining the interaction between grapefruit juice and some medications.

There are, of course, risk factors for drug interactions. The high risk situations are: administration to the very young and elderly; administration to medically compromised patients; the use of drugs with small margins of safety (digoxin, warfarin, opioids, lithium, theophylline, thyroid medications) and; the use of chronic drug therapies involving drugs that are excreted slowly.

Other points to note: The majority of drug interactions occur with chronic therapy (antibiotics are the exception) and; most drug interactions occur with cardiovascular, NSAIDs and CNS drugs.

**Summary**
- Be careful: titrate to minimize the possibility of severe reaction occurring (go low, go slow)

**Other Notes or Questions to Ask:**
• Be aware: If patients come back and say, “I don’t feel well on this medication”, drug interactions should be one of your considerations
• The less that a drug is metabolized, the lower the chance of a drug interaction
• If the drug is not producing the anticipated results, altered metabolism is a possibility (whether inhibition, or induction of the substrate or absence of the enzyme)
• In polypharmacology, drugs with fewer potential drug interactions should always be considered (e.g., Escitalopram, pantoprazole, other…)

Unique Characteristics of Dental Therapeutics
• Usually single dose or short-term therapy (5-10 days)
• Most dental drugs have large margin of safety
• Use of IV drugs is limited
• Procedures are usually elective
• Drug armamentarium is limited

There are numerous potentially dangerous medication interactions and clinically significant factors to consider:

- Metronidazole and Alcohol
- Tetracycline and certain cations
- Antibiotics and Birth Control Pills
- NSAIDS & ASA and Warfarin
- Always consider a drug’s therapeutic index
- Watch for duplications
- Ask about ALL the drugs your patient takes
- Consider theoretical vs. clinical significance
- Consider age, weight, renal and liver function

Consider Your Resources

- Texts (Lexicomp’s Drug Information Handbook for Dentists)
- Lexicomp Dental Drug Database
- Web-based Services (Drug Reax by Micromedex)
- www.naturaldatabase.com
- Clinical Pharmacology by Gold Standard Multimedia
- order1@adecllc.info by Dr. Michael Glick
- PDAs (Epocrates, Tarascon and others)

Other Notes or Questions to Ask:
Lexi-Comp’s Drug Information Handbook for Dentistry: Oral Medicine for Medically-Compromised Patients and Specific Oral Conditions is one of the most compact text references available. This resource contains abbreviated monographs on prescription medications and is well known for its useful charts and comparison tables. It is easy to use and is organized in alphabetical order according to a drug’s generic name. The handbook provides useful information when looking for a quick response to a simple drug information request, such as indications, dosages, general adverse effects, and drug interactions. The Drug Information Handbook provides an updated edition annually to include new drugs and updates to current medications.

Physicians’ Desk Reference (PDR): The PDR is a compilation of drug package inserts. It does not include all prescription medications because of space limitations. A new PDR is published every year; however, it is important to note that the information may not be updated with each annual publication. It is also important to note that only FDA-approved indications and dosages can be found within the PDR.

Lexi-Comp Online: In addition to the compact handbook, Lexi-Comp also provides Web-based and PDA resources with annual subscriptions. Lexi-Comp Online offers a convenient way to search medications quickly and easily. Once a medication is searched, the user can scroll through various parts of the drug monograph using the simple drop-down menu. This allows the user to move from section to section with ease and speed. Other features included are a drug-interaction reviewing tool, patient education leaflets, a drug-identification database, lists of drug recalls and shortages, and recent drug news.

Micromedex: Micromedex is a popular Web-based resource. Using one search box, a clinician is able to search many different databases that include detailed and summarized drug information, toxicology, alternative medicine, and reproductive risk evaluation. Micromedex’s detailed information highlights Drugdex, PDR, and Martindale’s (for use in searching foreign medications). The toxicology information that is included with these resources is trademarked as Poisindex and Identidex. Poisindex identifies ingredients for commercial, biological, and pharmaceutical products and delivers summarized toxicology data. Identidex allows the clinician to identify a medication using its embossed lettering or numbering and other descriptive characteristics, such as color and shape. Other useful tools in this resource include a drug interaction reviewing tool, patient education leaflets for both prescription drugs and dietary supplements, and clinical calculators to help determine body mass index, ideal body weight, metric conversions, and others.

Clinical Pharmacology: Clinical Pharmacology is a Web-based application providing a vast array of information that is both thorough and practical. It has multiple functions, allowing users to obtain product information, view monographs, identify medications, and print patient education materials. The site also contains drug class overviews, various interactions (including drug–drug, drug–herbal, drug–nutritional, and drug–food interactions), and full-color product images.

Other Notes or Questions to Ask:
Antibiotics and Dentistry

Sulphonamides
- Sulphonamides first used in the 1930’s.
- Penicillin first used in 1941, although Fleming had discovered it in 1929.
- Today we have more than 100 agents being used therapeutically.
- The development of newer antibiotics is in part due to the increased incidence of acquired bacterial resistance.

Untoward Reactions to Sulphonamides
- Disturbances of urinary tract.
- Disorders of hematopoietic system: acute hemolytic anemia, agranulocytosis, and aplastic anemia.
- Hypersensitivity reactions.
- Drug interactions: oral anticoagulants, sulfonylurea hypoglycemic agents, and hydantoin anticonvulsants.

Classification of Penicillins

<table>
<thead>
<tr>
<th>Acid Stable</th>
<th>Broad Spectrum</th>
<th>Penicillinase-Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin V</td>
<td>Ampicillin</td>
<td>Methicillin</td>
</tr>
<tr>
<td>Phenethicillin</td>
<td>Amoxicillin</td>
<td>Nafcillin</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Carbenicillin</td>
<td>Oxacillin</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Ticarcillin</td>
<td>Cloxacillin</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>Piperacillin</td>
<td>Dicloxacillin</td>
</tr>
<tr>
<td>Floxacillin</td>
<td>Azlocillin</td>
<td>Floxacillin</td>
</tr>
<tr>
<td></td>
<td>Mezlocillin</td>
<td></td>
</tr>
</tbody>
</table>

Example of Penicillin Resistant Mechanism
1. β-lactamases (penicillinas): inactivate penicillins by cleavage of the β-lactam ring.
2. Decreased affinity of PBPs for penicillin or decreased ability of penicillin to reach its site of action.

β-lactamase Inhibitors
Clavulanic acid: a product of Streptomyces clavuligerus, has poor intrinsic antimicrobial activity, but it is a “suicide” inhibitor (irreversible binder) of β-lactamases and inactivates them, thus preventing the destruction of β-lactam antibiotics.
- Augmentin: amoxicillin + clavulanic acid
- Timentin: ticarcillin + clavulanic acid

Resistant strains of bacteria are not necessarily more virulent than the susceptible strains of the same organism. Resistance makes these organisms more difficult to treat and limits our therapeutic options. One U.S. study estimated that the annual cost of antibiotic resistance was at least $100 million (Med Care 1999;27:194-203).

“Much of the resistance problem that we are facing today has been attributed to the overuse and misuse of antibiotics” (JAMA 1997;277:1794)

Other Notes or Questions to Ask:
**Therapeutic Uses in Dentistry**

1. Treatment of an acute dental infection.
2. Prophylaxis in patients at risk of developing SBE or other problems as the result of bacteremia caused by dental procedures or traumatic injury.
3. Prophylaxis in patients with compromised host defense mechanisms caused by certain diseases or drug therapy.

The common infection, particularly those occurring as the result of carious lesions, are caused by a variety of aerobic gram-positive cocci and anaerobic microorganisms. Penicillin V has been historically the most frequently prescribed antibiotic for therapy of infections of dental origin. Some dental infections are caused by penicillinase-producing organisms: penicillinase-resistant penicillin or non-penicillin antibiotics such as erythromycin or clindamycin.

Oral Erythromycin and the Risk of Sudden Cardiac Death ([NEJM 2004;351:1089-96]): “The adjusted rate of sudden death from cardiac causes was twice as high as placebo and amoxicillin . . . The adjusted rate of sudden death from cardiac causes was 5 times as high among those who concurrently used CYP3A4 inhibitors.”

**Adverse Reactions of Penicillins**

- Nausea, vomiting, and diarrhea.
- Penicillin G (in heroic doses): congestive heart failure (sodium cause), and cardiac toxicity (potassium cause, especially in patient with renal impairment).
- Neurotoxic effect (penicillin G in exceptionally high doses).
- Superinfections by nonsusceptible bacteria.

**Acute allergic reactions** (within 30 min): urticaria, angioedema, bronchoconstriction, gastrointestinal disturbances, and shock.

**Accelerated allergic reactions** (arise 30 min to 48 hrs): urticaria, pruritus, wheezing, mild laryngeal edema, and local inflammatory reactions.

**Delayed allergic reactions** (take 2 or more days to develop): skin rashes, may also be seen in oral cavity (acute glossitis, furred tongue, black and brown tongue, cheilosis, and severe stomatitis with loss of buccal mucosa).

**The Bugs**

**Acute Dental Infections**

Tooth decay: *Streptococcus mutans*

Pulpitis: *Streptococci or Staphylococci*

Periapical Abscess: α-hemolytic *Streptococci or Staphylococci*

Gingivitis: *Peptococcus spp., Bacteroides*

**Prophylaxis for SBE** ([J Am Dent Assoc. 2007 Apr;138(4):458-74.])

*Streptococcus viridans* is the most common cause of infective endocarditis following dental procedures (more recently *Staphylococcus epidermidis*). Antibiotics are thought to provide protection by decreasing the number of organisms reaching the damaged heart valve from a primary source.

**Prophylaxis in the Immunocompromised**

- Neutropenia: Organ Transplantation
- HIV Infection: Long-term immunosuppression (corticosteroid use)

**Other Notes or Questions to Ask:**
The Drugs:

<table>
<thead>
<tr>
<th>Penicillins</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
</tr>
</tbody>
</table>

Concentration-dependant killing

Also known as dose-dependant killing, bacterial eradication is more rapid and efficient when the drug concentration is appreciably greater than the organisms MIC (e.g., Flouroquinolones, Aminoglycosides).

Time-dependant killing

Also known as concentration-independent killing, bacterial eradication is best when the drug concentration remains constantly above the MIC (usually four times greater) during the dosing interval (e.g., β-lactams, vancomycin).

### Bactericidal

<table>
<thead>
<tr>
<th>Penicillins</th>
<th>Macrolides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Imipenem</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Trimethoprim</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>(Chloramphenicol)</td>
</tr>
</tbody>
</table>

### Bacteriostatic

<table>
<thead>
<tr>
<th>Macrolides</th>
<th>Tetracyclines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>(Chloramphenicol)</td>
</tr>
</tbody>
</table>

Other factors affecting a drug's efficacy:

- Diagnosis & initial antibiotic choice
- Route & time of administration
- Dose, frequency & duration of treatment
- Distribution of drug in the body
- Allergy status of the patient
- Side effects of the medication
- Patient compliance

### AHA Guidelines: at-risk patients

**No penicillin allergy & able to take oral medication: Amoxicillin**

- Adult: 2g, 1h prior to procedure.
- Child*: 50mg/kg 1h prior to procedure

**No penicillin allergy & unable to take oral medication: Ampicillin**

- Adult: 2g IM or IV, 30 min before procedure
- Child*: 50mg/kg IM or IV, 30 min before procedure

**Allergic to penicillin and able to take oral medication: Clindamycin**

- Adult: 600mg, 1h prior to procedure
- Child*: 20mg/kg, 1h prior to procedure
- Or
- **Cephalexin† or Cefadroxil†**
  - Adult: 2g, 1h prior to procedure
  - Child*: 50mg/kg, 1h prior to procedure
  - Or
- **Azithromycin or Clarithromycin**
  - Adult: 500mg, 1h prior to procedure
  - Child*: 15mg/kg, 1h prior to procedure

### Other Notes or Questions to Ask:
Allergic to penicillin and unable to take oral medication:

**Clindamycin**
- Adult: 600mg IV, within 30 min prior to procedure
- Child*: 20mg/kg IV, within 30 min prior to procedure

**Cefazolin**
- Adult: 1g IM or IV, within 30 min prior to procedure
- Child*: 25mg/kg IM or IV, within 30 min prior to procedure

---

**No definitive, scientific basis exists for the use of prophylactic antibiotics before dental procedures for these eight groups of patients:**

- Cardiac: native heart valve disease, prosthetic heart valves and pacemakers;
- Hip, knee and shoulder prosthetic joints;
- Renal dialysis shunts;
- Cerebrospinal fluid (CSF) shunts;
- Vascular grafts;
- Immunosuppression secondary to cancer and chemotherapy;
- Systemic lupus erythematosus (SLE);
- Insulin-dependent (type 1) diabetes mellitus.

---

**Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is recommended.**

- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease (CHD) *
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

* Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
† Prophylaxis is recommended because endothelialization of prosthetic material occurs within six months after the procedure.

“We found that although most patients reported receiving instructions for infectious endocarditis (IE) prophylaxis use consistent with American Heart Association guidelines, IE prophylaxis overuse among negligible-risk patients and underuse among moderate-risk patients was common. Continued physician and patient education may lead to improved adherence to the current American Heart Association recommendations.”


**Other Notes or Questions to Ask:**
Antibiotic Prophylaxis (AP) Prior to Dental Procedures for Joint Replacement Patients

In 1988, a group of selected orthopaedic surgeons (AAOS), dentists and infectious diseases specialists (IDSA) held a workshop in Chicago, sponsored by the American Dental Association (ADA), to address the issue of Antibiotic Prophylaxis (AP) prior to dental procedures for their joint replacement.1,2 As a result of this meeting, a paper was published in 1990 stating that there was limited evidence to support AP but still recommended it until additional information became available.3


Later in 1990, the Council on Dental Therapeutics of the ADA published the results of the 1988 meeting stating that there was very limited data to support the continuation of the use of AP for dental patients with prosthetic joints.1 In 1997, after continued collaboration, the ADA and American Academy of Orthopaedic Surgeons (AAOS) published an advisory statement on the dental management of patients with prosthetic joints.2 This statement was slightly modified in 2003 and exists as our current guidelines.3


According to these current guidelines, prophylaxis is not recommended for pins, plates, and screws, or for otherwise healthy patients with total joint replacements. Patients at “greater” risk could be considered for prophylaxis:

Prostheses were less than two years old or those with “high risk” conditions such as:

- Inflammatory arthropathies (rheumatoid arthritis, SLE)
- Drug- or radiation-induced immunosuppression
- Previous joint infection
- Malnourishment
- HIV infection
- Insulin-dependant diabetes
- Hemophilia
- Malignancy

Other Notes or Questions to Ask:

In February 2009, without any involvement with organized dentistry or non-orthopaedic physician specialties, the AAOS published an “Information Statement” entitled “Antibiotic Prophylaxis for Bacteremia in Patients with Joint Replacements”.1

“…it was developed as an educational tool based on the opinions of the authors. Readers are encouraged to consider the information presented and reach their own conclusions”.


While the 2003 ADA/AAOS guidelines state:

“The risk/benefit and cost/effectiveness ratios fail to justify the administration of routine antibiotic prophylaxis.”

This new 2009 AAOS Information Statement suggested a very different position:

“Given the potential adverse outcomes and cost of treating an infected joint replacement, the AAOS recommends that clinicians consider antibiotic prophylaxis for all total joint replacement patients prior to any invasive procedure that may cause bacteremia.”

There is no clear explanation or scientific basis for this change in position and herein lies the current controversy: which paper is the most correct?

Other Notes or Questions to Ask:
If one were to follow the informational statement of the AAOS authors, the following four assumptions would need to be met to believe the actions are in the best interest of the patient . . .

1. Bacteremia from oral flora arising from dental procedures causes “late prosthetic joint infections” (infections occurring 3 months after joint replacement surgery).

   **Fact:** Analysis of reported cases of LPJIs demonstrates that joint infections are rarely caused by bacterial species common to the mouth and there is no credible evidence to link LPJIs with dental procedures.\(^1\)-\(^4\)


2. There is a temporal relation between dental procedures and “late prosthetic joint infections” (infections occurring 3 months after joint replacement surgery).

   **Fact:** evidence of a temporal relationship between dental procedures and the onset of LPJIs is circumstantial.\(^1\)


3. Antibiotic Prophylaxis prevents bacteremia from dental procedures and subsequent “late prosthetic joint infections” (infections occurring 3 months after joint replacement surgery).

   **Fact:** there are case reports of late prosthetic joint infections occurring after dental procedures despite Antibiotic Prophylaxis.\(^1\)-\(^2\)


4. One cannot compare “late prosthetic joint infections” and infective endocarditis because of differing anatomy, blood supply, microorganisms and mechanisms of infection.

   **Fact:** Even if there are differences in the anatomy, microbiology and possible pathogenesis of LPJI and IE, they do have in common the underlying mechanism of putative hematogenous spread from the mouth.

Of greatest interest is that the 2007 AHA recommendations reduce by about 90% the number of cardiac patients recommended for AP by the 1997 AHA guidelines, in spite of the fact that as many as 50% of cases of IE are caused by oral bacterial species.

An analogy could be made to infections of cardiovascular implantable electronic devices (CIED) which, like LPJIs, are almost exclusively caused by *Staphylococcus* and other non-oral flora. A recent AHA Statement on CIED-related infections states that,

**Other Notes or Questions to Ask:**
“the predominance of Staphylococci as pathogens ... rather than oral flora suggests that antibiotic prophylaxis for dental procedures is of little or no value...” and “… there is currently no scientific basis for the use of prophylactic antibiotics prior to routine invasive dental, gastrointestinal, or genitourinary procedures to prevent CIED infections” 1-5


Given the opinion nature of the 2009 Information Statement, the AAOM (American Academy of Oral Medicine) feels that it should not replace the 2003 Joint Consensus Statement prepared by the three relevant organizations, the ADA, the AAOS and the IDSA.

J Am Dent Assoc 2011;142:159-165

Continue to follow the 2003 guidelines and make sure to consider Patient Factors as described above as well as Procedure Factors and Drug Factors to ensure appropriate prescribing if antibiotics are indicated.


Other Notes or Questions to Ask:
Medications for Postoperative Analgesia

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 $70 billion (Lancet 1999;353(9168):1959). 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 16 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

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (Tylenol)</td>
<td>325mg</td>
</tr>
<tr>
<td>Aspirin (various)</td>
<td>325mg</td>
</tr>
<tr>
<td>Ibuprofen (Advil, Motrin, Nuprin)</td>
<td>500mg</td>
</tr>
<tr>
<td>Flurbiprofen (Ansaid)</td>
<td>500mg</td>
</tr>
<tr>
<td>Diflunisal (Dolobid)</td>
<td>500mg</td>
</tr>
<tr>
<td>Naproxen (Naprosyn, Aleve)</td>
<td>500mg</td>
</tr>
<tr>
<td>Ketorolac (Toradol)</td>
<td>500mg</td>
</tr>
<tr>
<td>Ketoprofen (Orudis)</td>
<td>500mg</td>
</tr>
<tr>
<td>Etodolac (Lodine)</td>
<td>500mg</td>
</tr>
<tr>
<td>Codeine (various)</td>
<td>500mg</td>
</tr>
<tr>
<td>Oxycodone (Percocet, Percodan)</td>
<td>500mg</td>
</tr>
<tr>
<td>Meperidine (Demerol)</td>
<td>500mg</td>
</tr>
<tr>
<td>Pentazocine (Talwin)</td>
<td>500mg</td>
</tr>
<tr>
<td>Hydrocodone (Lortab, Vicodin)</td>
<td>500mg</td>
</tr>
<tr>
<td>Dihydrocodeine (Synalos-DC)</td>
<td>500mg</td>
</tr>
</tbody>
</table>

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

Adding Up Doses: Amount of Acetaminophen Per Pill

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol Regular Strength</td>
<td>325mg</td>
</tr>
<tr>
<td>Tylenol Extra Strength</td>
<td>500mg</td>
</tr>
<tr>
<td>Vicodin / Vicodin ES</td>
<td>500mg / 750mg</td>
</tr>
<tr>
<td>Lortab</td>
<td>500mg</td>
</tr>
<tr>
<td>Lorcet</td>
<td>650mg</td>
</tr>
<tr>
<td>Tylox / Percocet</td>
<td>325mg / 500mg</td>
</tr>
<tr>
<td>Tylenol #3</td>
<td>300mg</td>
</tr>
</tbody>
</table>

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).

Acetaminophen Toxicity

- Gastrointestinal Toxicity
  - Epidemiology 2001;12:570-576
  - 11,500 control subjects were matched by age and gender (N=23,000 total)
  - 2105 patients ages 40-79, diagnosed with peptic ulcer

Acetaminophen at any dose → RR 1.3 for GI Bleed
≥ 2 grams per day → RR 3.6 for GI Bleed
≥ 2 grams per day + NSAID → RR 13.2 for GI Bleed

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)

Other Notes or Questions to Ask:

NSAID Mortality

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.

**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. Mucosal lesion may be caused in as little as one week.

**COX - 2 INHIBITORS:**

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

**Merck Announces Voluntary Worldwide Withdrawal of VIOXX®**

- Sept. 30, 2004—Merck & Co., Inc. announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company’s decision, which is effective immediately, is based on new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.
- The trial, which is being stopped, was designed to evaluate the efficacy of VIOXX 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labeling for VIOXX.

**Pfizer Announces Voluntary Worldwide Withdrawal of BEXTRA®**

- FDA Alert [4/7/2005];
- FDA has requested that Pfizer voluntarily withdraw Bextra from the United States market. Pfizer has agreed to suspend sales and marketing of Bextra in the United States, pending further discussion with the Agency. At this time, the Agency has concluded that the overall risk versus benefit profile of Bextra is unfavorable. This conclusion is based on the potential increased risk for serious cardiovascular (CV) adverse events, which appears to be a class effect of non-steroidal anti-inflammatory drugs (NSAIDs) (excluding aspirin), an increased risk of serious skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other NSAIDs, and the fact that Bextra has not been shown to offer any unique advantages over the other available NSAIDs.

**Prostaglandin I₂**

- Predominantly found in the endothelium
- Inhibits platelet aggregation, causes vasodilation, prevents proliferation of vascular smooth-muscle cells
- Thromboxane A₂ does the opposite: it is the major COX-1 product of platelets which causes platelet aggregation, vasoconstriction and vascular proliferation.
- COX-2 specific inhibitors upset this balance!
When rofecoxib (Vioxx) was available, it was the most selective of available NSAIDs (>50-fold potency for COX-2 over COX-1) and was 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

### AN OVERVIEW OF COX-2 INHIBITORS

<table>
<thead>
<tr>
<th>GENERIC NAME (BRAND NAMES)</th>
<th>DOSSING REGIMEN</th>
<th>PHARMACOKINETICS</th>
<th>COST PER DAY ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute Pain</td>
<td>Osteoarthritis</td>
<td>Peak Time (Hours)</td>
</tr>
<tr>
<td>Ibuprofen (Advil, Motrin)</td>
<td>400-600 mgs q4-6h</td>
<td>400-800 mg tid</td>
<td>1-2</td>
</tr>
<tr>
<td>Celecoxib (Celebrex)</td>
<td>200mg bid prn</td>
<td>100 mg bid or 200 mg qd</td>
<td>3</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx)</td>
<td>50 mg qd</td>
<td>12.5–25 mg qd</td>
<td>2-3</td>
</tr>
</tbody>
</table>

**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.

**Other Notes or Questions to Ask:**
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).

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

**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:

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.

**Other Notes or Questions to Ask:**
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, nortriptiline 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


Other Notes or Questions to Ask: