Minimal Oral Sedation:
The Art of Anxiolysis in the Dental Office

by Jason H. Goodchild, DMD
&
Mark Donaldson, BSP, ACPR, PHARMD, FASHP, FACHE
Day 1: What is Minimal Oral Sedation All About?

- Introduction to Minimal Sedation
- Pharmacology 101
- Patient Assessment
- Pharmacology of Sedatives & Reversal Agents
- Minimal Oral Sedation – Protocols Parts 1 & 2

Day 2: How Can I Keep My Patients and This Practice Safe?

- Physiologic Monitoring
- Drug Interactions
- Bleeding Disorders, Anticoagulants & Antiplatelets
- Herbal Concerns in Dentistry
- Beyond Sedation (Update on Local Anesthesia)
- What’s in Your Emergency Kit – and Why
Jason H. Goodchild, DMD is a graduate of Dickinson College in Carlisle, Pennsylvania. He received his dental training at the University of Pennsylvania School of Dental Medicine where he still holds a faculty position as a Clinical Associate in the Department of Oral Medicine. As part of his training and service in the Department of Oral Medicine he was educated in enteral sedation and completed numerous cases at the dental school and the Hospital of the University of the University of Pennsylvania. As a part of his faculty duties he treats patients with complex medical histories, and oversees students and residents.

He is also Clinical Assistant Professor in the Division of Oral Diagnosis, Department of Diagnostic Sciences at the New Jersey Dental School. He teaches the next generation of dentists excellence in patient care, and introduces the concepts of enteral sedation to fourth-year dental students in the classroom.

Dr. Goodchild has published numerous articles and spoken to many State Dental Boards on the topic of enteral sedation dentistry. He has been an invited speaker for the Academy of General Dentistry and American Association of Dental Examiners. He is a reviewer for the Journal of the American Dental Association, General Dentistry, and Quintessence International. He has also served as a grant reviewer for the National Institute of Health.

Dr. Goodchild maintains an active private practice in Havertown, Pennsylvania

Mark Donaldson, BSP, ACP, PHARMD, FASHP, FACHE received his baccalaureate degree from the University of British Columbia and his Doctorate in Clinical Pharmacy from the University of Washington. He completed a residency at Vancouver General Hospital, and has practiced as a clinical pharmacy specialist, clinical coordinator and director of pharmacy services at many healthcare organizations in both Canada and the United States. He is currently the Director of Clinical Pharmacy Performance Services for Vizient, in Whitefish, 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. He has spent the last 18 years focusing on dental pharmacology and dental therapeutics, and is a leader in the field.

Dr. Donaldson has published numerous peer-reviewed works and textbook chapters. He currently serves on the Editorial Board for the Journal of the American Dental Association, is board certified in healthcare management and is the Past-President of the American College of Healthcare Executives’ Montana Chapter. Dr. Donaldson was named as the 2014 recipient of the Bowl of Hygeia for the state of Montana and is the 2016 recipient of the Dr. Thaddeus V. Weclew Award. This award is conferred upon an individual who has made outstanding contributions to the art and science of dentistry and/or enhanced the principles and ideals of the Academy of General Dentistry.

Notes:
Introduction to Minimal Oral Sedation

Questions

1. What was the first drug used for oral sedation?
   a. Benzodiazepines
   b. Barbiturates
   c. Alcohol
   d. Nitrous Oxide
   e. Opioids

2. What is the goal of oral sedation?
   a. To put the patient to sleep
   b. To shut the patient up
   c. To reduce anxiety
   d. To facilitate coping

3. What organ is chiefly responsible for drug metabolism?
   a. Stomach
   b. Liver
   c. Kidney
   d. Blood
   e. Intestines

4. What basic equipment must you have to perform oral sedation?
   a. Emergency drugs
   b. Positive pressure oxygen
   c. Pulse oximeter
   d. Automated external defibrillator

5. After delivering oral sedation to a patient for a dental appointment, when is the patient ready to be dismissed?
   a. When they are awake
   b. After they have paid their bill
   c. When the drugs have worn off
   d. When they are ambulatory
   e. When sedation has waned

Notes:
Case Example:
- C.O. 46 yo female
- Tx Plan: Complete extractions and insertion of full upper and lower immediate dentures
- Tx length: 5 hours
- MHx:
  - MVP with regurgitation
  - No meds
  - No Known Drug Allergies (NKDA)
  - Patient smokes 1 ppd x 25 years
- Preoperative Vitals
  - BP 127/82 mmHg
  - Pulse 80 bpm
  - SpO2 98%

Drug Regimen:
Triazolam 0.50 mg total

*Why Oral Sedation?*
- Many people require additional measures to minimize anxiety and fear
- Anxious and fearful patients underserved
  - Costs to the patient are typically less than IV sedation or general anesthesia
  - How many people in need? Up to 100M?
  - Not enough O.S. & Anesthesiologists. Out of approximately 190,000 dentists in the US, only 10,000 are OS and DA.
**Definitions**

**Enteral** – any method for the introduction of pharmacological agents which relies on absorption through the skin or other mucous membrane [i.e., oral, rectal, sublingual].

**Parenteral** – a technique of administration in which the drug bypasses the gastrointestinal (GI) tract [i.e., intravenous (IV), intramuscular (IM), intranasal (IN), submucosal (SM), subcutaneous (SC), intraosseous (IO)].

*(From the ADA Guidelines, October 2005)*

**Anxiolysis** - the diminution or elimination of anxiety.

**Conscious Sedation** - a minimally depressed level of consciousness that retains the patient's ability to independently and continuously maintain an airway and respond appropriately to physical stimulation or verbal command and that is produced by a pharmacological or non-pharmacological method or a combination thereof.

In accord with this particular definition, the drugs and/or techniques used should carry a margin of safety wide enough to render unintended loss of consciousness unlikely. Further, patients whose only response is reflex withdrawal from repeated painful stimuli would not be considered to be in a state of conscious sedation.

**Deep Sedation** – an induced state of depressed consciousness accompanied by partial loss of protective reflexes, including the inability to continually maintain an airway independently and/or to respond purposefully to physical stimulation or verbal command.

**General Anesthesia (GA)** – General anesthesia consists of the deliberate use of any drug, combination of drugs, element, or other material with the specified intent to induce a loss of sensation or consciousness.

*(From the ADA Guidelines, October 2012)*

**Minimal Sedation** - a minimally depressed level of consciousness, produced by a pharmacological method, that retains the patient’s ability to independently and continuously maintain an airway and respond normally to tactile stimulation and verbal command. Although cognitive function and coordination may be modestly impaired, ventilatory and cardiovascular functions are unaffected.

*Note:* In accord with this particular definition, the drug(s) and/or techniques used should carry a margin of safety wide enough never to render unintended loss of consciousness. Further, patients whose only response is reflex withdrawal from repeated painful stimuli would not be considered to be in a state of minimal sedation.

When the intent is minimal sedation for adults, the appropriate initial dosing of a single enteral drug is no more than the maximum recommended dose (MRD) of a drug that can be prescribed for unmonitored home use.

Nitrous oxide/oxygen may be used in combination with a single enteral drug in minimal sedation.

**Moderate Sedation** - a drug induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

**Titration** - administration of incremental doses of a drug until a desired effect is reached. Knowledge of each drug's time of onset, peak response and duration of action is essential to avoid over sedation. Although the concept of titration of a drug to effect is critical for patient safety, when the intent is moderate sedation one must know whether the previous dose has taken full effect before administering an additional drug increment.

*Notes:*
More on Minimal Sedation and Moderate Sedation: (From the ADA Guidelines, October 2012)

The following definitions apply to administration of **minimal sedation**:

- **Maximum recommended (MRD)** - maximum FDA-recommended dose of a drug, as printed in FDA-approved labeling for unmonitored home use.

- **Incremental dosing** - administration of multiple doses of a drug until a desired effect is reached, but not to exceed the maximum recommended dose (MRD).

- **Supplemental Dosing** – during minimal sedation, supplemental dosing is a single additional dose of the initial dose of the initial drug that may be necessary for prolonged procedures. The supplemental dose should not exceed one-half of the initial dose and should not be administered until the dentist has determined the clinical half-life has passed. The total aggregate must not exceed 1.5X the MRD on the day of treatment.

*For Moderate Sedation*…Note: In accord with this particular definition, the drugs and/or techniques used should carry a margin of safety wide enough to render unintended loss of consciousness unlikely. Repeated dosing of an agent before the effects of previous dosing can be fully appreciated may result in a greater alteration of the state of consciousness than is the intent of the dentist. Further, a patient whose only response is reflex withdrawal from a painful stimulus is not considered to be in a state of moderate sedation.

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<table>
<thead>
<tr>
<th>Continuum of Depth of Sedation (Developed by the American Society of Anesthesiologists)</th>
<th>Minimal Sedation (Anxiolysis)</th>
<th>Moderate Sedation / Analgesia (Conscious Sedation)</th>
<th>Deep Sedation / Analgesia</th>
<th>General Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responsiveness</strong></td>
<td>Normal response to verbal stimulation</td>
<td>Purposeful response to tactile or verbal stimulation</td>
<td>Purposeful response to repeated or painful stimulation</td>
<td>Unrousable even with painful stimulation</td>
</tr>
<tr>
<td><strong>Airway</strong></td>
<td>Unaffected</td>
<td>No intervention required</td>
<td>Intervention may be required</td>
<td>Intervention often required</td>
</tr>
<tr>
<td><strong>Spontaneous Ventilation</strong></td>
<td>Unaffected</td>
<td>Adequate</td>
<td>May be adequate</td>
<td>Frequently inadequate</td>
</tr>
<tr>
<td><strong>Cardiovascular Function</strong></td>
<td>Unaffected</td>
<td>Maintained</td>
<td>Usually maintained</td>
<td>May be impaired</td>
</tr>
</tbody>
</table>

*Available at:*
http://www.asahq.org/publicationsAndServices/sedation1017.pdf
The Art of Dental Therapeutics: Pharmacology 101
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.”

![Diagram of bell-shape population curve](image1)

**Figure 23.2**: A normal, bell-shaped distribution curve. For any given drug, approximately 60% 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 hyper- or hypo-responders, requiring doses that exceed the “normal” (blue shaded area). More important, however, are those hyperresponsive individuals (left side of curve) who exhibit clinically desirable results at lower-than-normal doses. Such patients are more likely to experience drug overdoses. (From Pulaski TJ: Pharmacology for dental students and practitioners, Philadelphia, 1990, 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!**”

![Diagram of bell-shape population curve](image2)

**Figure 23.3**: A normal, bell-shaped distribution curve. For any given drug, approximately 60% 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 hyper- or hypo-responders, requiring doses that exceed the “normal” (blue shaded area). More important, however, are those hyperresponsive individuals (left side of curve) who exhibit clinically desirable results at lower-than-normal doses. Such patients are more likely to experience drug overdoses. (From Pulaski TJ: Pharmacology for dental students and practitioners, Philadelphia, 1990, Lea & Febiger.)

Notes:
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.

**Affymetrix GeneChip® Probe Array**
Image courtesy of Affymetrix
1-888-DNA-CHIP

**Human Genome U133 Plus 2.0 Array**
See also: Genomic Health Inc.
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.

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

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 blood stream. 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 &lt; 100%</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>75 to &lt; 100%</td>
</tr>
<tr>
<td>Oral</td>
<td>5 to &lt; 100%</td>
</tr>
<tr>
<td>Rectal</td>
<td>30 to &lt; 100%</td>
</tr>
<tr>
<td>Inhalation</td>
<td>5 to &lt; 100%</td>
</tr>
<tr>
<td>Transdermal</td>
<td>80 to &lt; 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.
Principles of Local Anesthetics

- 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

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

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”?

This may explain in part why it is more difficult to get a patient numb when the have an abscess and the microenvironment in that area has a lower pH than normal.
Should I buffer local anesthetic? How? The easy answer to “should I”—YES! “How” is a bit more difficult ...
- OnPharma (elegant but expensive)
- By-Hand (super cheap but tedious)
- Anutra Local Anesthetic Delivery System (brand new, not enough information)

1. Less sting or pinch on injection
   a. Buffered pH (closer to 7.4)
   b. CO2 at tip of the needle
2. Improves lipid solubility (uncharged form dominates)
   a. Faster onset
   b. More profound anesthesia
   c. More forgiving for mandibular blocks
3. May work better in infected areas
   a. Low pH situations

Can We Buffer Local Anesthetics By Hand? (9:1 anesthetic to sodium bicarbonate ratio)

- 50mL vial of 8.4% Sodium Bicarbonate (approx. $9)
- ½ cc 28G x ½” needle (Box of 100 @ $29.99)

Buffering Conclusions

- Easy to do and may decrease onset, decrease injection pain, and improve efficacy (Lidocaine only?)
- Can be done by hand or via Onpharma mixing device.

"Increasing the pH of lidocaine reduced pain and improved patient comfort and satisfaction. No adverse events were reported. Therefore, increasing the pH of commercial lidocaine solutions with bicarbonate immediately prior to their use should be considered."
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 P450 (CYP450) family of enzymes.

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.
Top 3 “disease” states (induced metabolism):

- Hyperthyroidism
- Acute alcoholism
- Young patients

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.

Top 3 “disease” states (inhibited metabolism):

- Hypothyroidism
- Chronic alcoholism
- Older patients

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

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:

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

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).
Medical Assessment of Dental Patients
The challenge for practicing dentists is to evaluate the stability of patients in order to provide safe dental care.

Dentists are faced with several problems that make risk assessment difficult:

- Patients are getting older
- Patients are retaining their teeth later in life
- More ambulatory patients with medical conditions
- More patients on polypharmacology

More patients will present to the dental office with chronic medical conditions:

**Chronic Diseases**

- 90 million Americans live with chronic illnesses
- Account for 70% of all deaths in the U.S.
- Account for 60% of the nation's medical costs
- Account for 1/3 of the years of potential life lost before age 65
Question...Do your patients tell you the truth on the medical history questionnaire?

<table>
<thead>
<tr>
<th>Reasons noted for refusing to reveal information on a health history form</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unimportant information</td>
<td>17%</td>
</tr>
<tr>
<td>Privacy</td>
<td>62%</td>
</tr>
<tr>
<td>Afraid of refusal of treatment</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>14%</td>
</tr>
</tbody>
</table>

23% of respondents would be reluctant to note current drug abuse on a dental history questionnaire!

10% of respondents believed that dental health professionals do not need to be fully aware of a patient’s health status!

Medical History Questionnaire

- Screening for medical problems
- Monitoring medical conditions
- Assessing and evaluating medical conditions and diseases that may create risks to the dental patient
- Assessing and evaluating modifications to dental care
- Verify history with verbal interview

ASA Physical Status Classification

1. A normal healthy patient
2. A patient with a mild systemic disease
3. A patient with a severe systemic disease that limits activity, but is not incapacitating.
4. A patient with an incapacitating systemic disease that is a constant threat to life.
5. A moribund patient not expected to survive 24 hours with or without operation.
6. A declared brain-dead patient whose organs are being removed for donor purposes

In the event of an emergency, precede the number with an “e”

ASA Physical Status Classification. American Society of Anesthesiologists. Available at: www.asahq.org/clinical/physical status.htm

ASA Physical Status Classification

- Devised in 1941 as a statistical tool for retrospective analysis of hospital records; the ASA physical status classification was revised in 1961 (JAMA 1961;178:261-6).
- Originally, ASA classification was not intended to assign “operative risk”, but merely to describe the “physical status” of a patient prior to an operation.

Limitations of ASA Classifications

The classification makes no adjustments for:
- Age
- Sex
- Weight
- Pregnancy
- Type of operation
- Type of anesthesia
- Skill or training or surgeon

Therefore, the same assignment of “risk” cannot be given to a single patient undergoing different surgical procedures
ASA Classification Examples

ASA 1: Patient without systemic disease; a normal, healthy patient

ASA 2: Patient with mild systemic disease

- Type II Diabetes Mellitus
- Controlled or exercise induced asthma
- Controlled epilepsy
- Controlled HTN

ASA 3: Patient with severe systemic disease that limits activity but is non-incapacitating

- Stable angina
- Myocardial infarction or Stroke (>6 mos)
- Type 1 Diabetes Mellitus
- Congestive Heart Failure (CHF)
- Chronic Obstructive Pulmonary Disease (COPD)
- Uncontrolled asthma
- BP > 160/95

ASA 4: Patient with an incapacitating systemic disease that is a constant threat to life

- Myocardial infarction or Stroke (<6 mos)
- Unstable angina
- BP > 200/115
- CHF or COPD on O2
- Uncontrolled epilepsy
- Uncontrolled Diabetes Mellitus

ASA 5: Moribund pt. who is not expected to survive 24 hours with or without an operation

- Ruptured aortic aneurysm
- Massive pulmonary embolism

ASA 6: A declared brain dead pt. whose organs are being removed for donor purposes

An “E” can be assigned to any classification to denote emergency status

Notes:
Medical Risk Assessment for Dentistry

Operative Risk should be assigned based on:
- Medical Complexity (Controlled vs. Uncontrolled)
- Potential severity of adverse events
  - None
  - Minor
  - Major
- Potential modifications needed (e.g. before, during, and/or after)

### USC Physical Evaluation System

<table>
<thead>
<tr>
<th>ASA Physical Status Classification</th>
<th>Therapy Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>I  A normal healthy patient</td>
<td>None (Stress reduction as indicated)</td>
</tr>
<tr>
<td>II A patient with mild to moderate systemic disease</td>
<td>Possible stress reduction and other modifications as indicated</td>
</tr>
<tr>
<td>III A patient with severe systemic disease that limits activity but is not incapacitating</td>
<td>Possible strict modifications; stress reduction and medical consultation are priorities</td>
</tr>
<tr>
<td>IV A patient with severe systemic disease that limits activity and is a constant threat to life</td>
<td>Minimal emergency care in office; hospitalization for stressful elective treatment; medical consultation urged</td>
</tr>
<tr>
<td>V A moribund patient not expected to survive 24 hours with or without an operation</td>
<td>Treatment in the hospital is limited to life support only; for example, airway and hemorrhage management</td>
</tr>
</tbody>
</table>

### Medical Complexity Status

<table>
<thead>
<tr>
<th>MC-0</th>
<th>No significant medical problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC-1A</td>
<td>Controlled and stable condition/disease</td>
</tr>
<tr>
<td></td>
<td>No anticipated complications</td>
</tr>
<tr>
<td>MC-1B</td>
<td>Controlled and stable condition/disease</td>
</tr>
<tr>
<td></td>
<td>Anticipated/possible minor complications</td>
</tr>
<tr>
<td>MC-1C</td>
<td>Controlled and stable condition/disease</td>
</tr>
<tr>
<td></td>
<td>Anticipated/possible major complications</td>
</tr>
<tr>
<td>MC-2A</td>
<td>Poorly controlled and/or unstable condition/disease</td>
</tr>
<tr>
<td></td>
<td>No anticipated complications</td>
</tr>
<tr>
<td>MC-2B</td>
<td>Poorly controlled and/or unstable condition/disease</td>
</tr>
<tr>
<td></td>
<td>Anticipated/possible minor complications</td>
</tr>
<tr>
<td>MC-2C</td>
<td>Poorly controlled and/or unstable condition/disease</td>
</tr>
<tr>
<td></td>
<td>Anticipated/possible major complications</td>
</tr>
<tr>
<td>MC-3</td>
<td>Cardiac or other conditions needing continuous monitoring</td>
</tr>
</tbody>
</table>

### Potential for Adverse Events
- Drug actions and interactions of medication patients are taking and oral sedative given by the dentist
- Patient’s ability to withstand the stress of dental care
- Patient’s ability to achieve hemostasis
- Patient’s susceptibility to infections

### Modification of dental care or when to institute changes to protocol
- Before Treatment
- During Treatment
- After Treatment

### Setting or the most appropriate place to treat
- Patient can be treated as an out-patient in a general dental office
- Patient can be treated as an out-patient in a hospital dental setting
- Patient requires continuous monitoring in an operating room or short-procedure unit

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Notes:

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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

<table>
<thead>
<tr>
<th>Normal</th>
<th>Minimal Sedation</th>
<th>Moderate Sedation</th>
<th>Deep Sedation</th>
<th>General Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protective reflexes intact</td>
<td>Partial loss of protective reflexes</td>
<td>Loss of protective reflexes</td>
<td>Loss of protective reflexes</td>
<td></td>
</tr>
<tr>
<td>Patient can independently and continuously maintain an airway</td>
<td>Inability to independently maintain an airway</td>
<td>May not respond to verbal commands</td>
<td>No pain sensation or reflex withdrawal from stimuli</td>
<td></td>
</tr>
<tr>
<td>Total unconsciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Relationship Between Efficacy and Safety for Anesthesia and Sedation

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>General anesthesia</td>
<td>Serious morbidity and mortality possible</td>
</tr>
<tr>
<td>Deep sedation</td>
<td>Transient morbidity</td>
</tr>
<tr>
<td>Parenteral premedication</td>
<td>Low morbidity</td>
</tr>
<tr>
<td>Oral premedication</td>
<td>Nitrous oxide</td>
</tr>
</tbody>
</table>

### Parenteral vs. Enteral Sedation

<table>
<thead>
<tr>
<th>Parenteral</th>
<th>Enteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV, IM, SC</td>
<td>Oral, SL, rectal</td>
</tr>
<tr>
<td>No “First-Pass” effect</td>
<td>Long latency period</td>
</tr>
<tr>
<td>Drug effect is rapid</td>
<td>“First-pass” effect</td>
</tr>
<tr>
<td>Adverse effects can be rapid</td>
<td>Presentation of adverse effects is slow</td>
</tr>
<tr>
<td>Requires specialty training</td>
<td>Lower incidence of adverse effects</td>
</tr>
<tr>
<td>Patient acceptance?</td>
<td>Requires less specialty training</td>
</tr>
</tbody>
</table>

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.

Feck AS and Goodchild JH. The use of anxiolytic medications to supplement local anesthesia in the anxious patient. Compendium 2005, 26(3);81-87.
Who is a candidate for oral sedation?

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

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


- Dentists: 1:260,000
- Physicians: 1:248,000
- Single Operator/Anesthetist: 1:143,000
- One Operator & One Anesthetist: 1:598,000
- Conscious Sedation: 1:1,000,000

- patient died on a motorcycle later the same day
- this study was pre pulse oximeter usage


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

Notes:
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, 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.

Chloral Hydrate Induced Arrythmias

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Dose (grams)</th>
<th>Arrhythmia</th>
<th>Cardiac Arrest</th>
<th>Antiarrhythm 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>0.6</td>
<td>SVT</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>VT</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 catastrophes. Jastak. JADA 1988 (vol.116)

Chloral Hydrate vs Diazepam

<table>
<thead>
<tr>
<th>Dose (grams)</th>
<th>Response</th>
<th>Margin of Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>50</td>
<td>LGD50</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
<td>LD50</td>
</tr>
</tbody>
</table>

Notes:
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

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.
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:

Benzodiazepines

![Chemical Structure of Benzodiazepines]
**Diazepam (Valium)**
- Produces mild sleep and mild amnesia
- Onset: 30-60 minutes
- Half-Life: 50 hours (20-100) due to active metabolites
- Duration of action can be >8 hours
- Supplied in 2, 5, and 10 mg tablets
- Usual Dosage is 2-40 mg
- FDA approved anxiolytic
- High Lipid Solubility

Indications for use of diazepam as listed in the Physicians’ Desk Reference (PDR):
- Preoperative anxiolytic
- Night-time sleep (hypnotic)
- Anticonvulsant

**THE BLOOD-BRAIN BARRIER**

A complex group of blood-brain barrier mechanisms closely controls both the kinds of substances which enter the extra-cellular space of the brain and the rate at which they enter. This mechanism is not a true “barrier” but acts like a selective gatekeeper, and comprises both anatomical structures and physiological transport systems which handle different classes of substances in different ways. The blood-brain barrier mechanisms precisely regulate the chemical composition of the extra-cellular space of the brain and prevent harmful substances from reaching neural tissue, and gives rise to a second and third compartment model for the benzodiazepines.

**Lorazepam (Ativan)**
- Produces mild/moderate sleep with moderate amnesia
- Onset: 60-120 minutes
- Half-Life: 10-20 hours
- No active metabolites
- Duration: 6-8 hours
- Supplied in 0.5, 1, and 2 mg tablets
- Dosage: 2-6 mg
- Moderate Lipid Solubility

Indications for use of lorazepam as listed in the Physicians’ Desk Reference (PDR):
- Preoperative anxiolytic
- Night-time sleep (hypnotic)
- Anticonvulsant

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**Notes:**
Triazolam (Halcion)
- No active metabolites
- Plasma half-life is 1.5 – 2.5 hours
- Wide effective dose range
- Mean peak concentration is achieved at 1.3 hours
- Has anticonvulsant properties – can be used with the epileptic patient
- May act as a respiratory depressant at very high doses (greater than 2mg)
- Relaxation for adequate pain control – important for hard to numb patients
- Does not cause nausea (unlike nitrous oxide)
- \( \text{LD}_{50} \) is 5 grams per kilogram in rats (very safe)

Respiratory depression represents the principal negative that is introduced with conscious sedation and left unrecognized and untreated is the cause of the most serious complication!

Indications for use of triazolam as listed in the Physicians’ Desk Reference (PDR):
- Preoperative sedation
- Night-time sleep
- Onset: 1 hour
- Peak effect: 1.3 hours
- Duration: 2-3 hours

Dosage (PDR):
- Adult: 0.5 mg Healthy adult
- Elderly or debilitated 0.125 mg
- Always use the lowest effective dose
- Child: Safety and efficacy not tested for patients below the age of 18

**Midazolam (Versed)**
- Produces moderate sleep and high amnesia
- Onset: 15-30 minutes
- Half-Life: 1.5 - 5 hrs.
- No active metabolites
- Duration: 1 hr.
- Supplied in 118 ml bottles, each mL contains 2mg midazolam
- Dosage: 0.25 to 0.75 mg/kg in children >6 months (relative maximum at 10 mg)
- High Lipid Solubility
- Not an FDA approved anxiolytic

Indications for use of midazolam as listed in the Physicians’ Desk Reference (PDR):
- Preoperative anxiolytic
- Night-time sleep (hypnotic)
- Anticonvulsant

**Midazolam (Versed®)**

*Fused imadazo ring enhances metabolism*

*Very electron- withdrawing group increase potency*

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Goodchild JH and Donaldson M. Calculating and justifying total anxiolytic doses of medications for in-office use. General Dentistry 2006 Jan-Feb;54-57.

**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 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. Other non-benzodiazepines include Eszopiclone (Lunesta), Zopiclone (Imovane) and Zolpidem (Ambien).
Zaleplon (Sonata, Starnoc)
- Produces high sleep with only mild amnesia
- Onset: 30 minutes
- Half-Life: 1-2 hours
- No active metabolites
- Duration: up to 6 hours
- Supplied in 5 and 10 mg capsules
- Dosage: 10 mg (start at 5mg in the elderly or patients with liver disease)
- Overdosage can be treated with flumazenil
- 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
- Coadministration 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) 15-30 (PO)</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 a near ideal sedative agent due to its pharmacological properties, which make it not only highly effective for dental sedation purposes, but it also comes with a high margin of safety.

**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, ketoconazole,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

**Precautions**
- Cardiovascular Disease (tachycardia 0.5%)
- Patients on Steroids (stimulation, mania, increased agitational state)
- Potential Drug Interactions: alcohol & CNS depressants
- Potential Herb Interactions: gulu kola, kava, melatonin, SAMe, St. John's Wort, valerian (may increase CNS depression)
- Food may decrease the rate of absorption

“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”.

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.

*** It is not recommended for routine reversal as seizures and cardiac dysrhythmias can occur with flumazenil administration, and although the majority of these effects are uncommon and well tolerated. Co-ingestion of drugs with proconvulsant properties is associated with an increased risk of seizures, presumably due to loss of the benzodiazepine’s protective anticonvulsant effect when the antagonist is administered. Combined overdose of benzodiazepines with tricyclic antidepressants accounts for 50% of these seizures. Coingestants possessing prodysrhythmic properties, such as carbamazepine or chloral hydrate, may increase the likelihood of cardiac effects by a similar mechanism.

*** Although flumazenil reverses benzodiazepine-induced sedation, it does not consistently reverse respiratory depression. 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 redosing 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.
**Flumazenil** -- Other points to note are:

1. Insoluble in water
2. Slightly soluble in acidic solutions
3. Dilute concentration of 0.1mg/mL
4. 5 mL and 10 mL vials
5. One hour duration (triazolam's half-life is about 2 hours so patients could re-sedate)
6. Can be given sublingual in the canine to first molar area, 2-3 mm under the mucosa, not in the midline
7. Buy the 5mL vials and be aware of expiry dates!

**Contraindications:**
- Known hypersensitivity to benzodiazepines
- Patients with known seizure disorders treated with a benzodiazepine

Several studies support the use of flumazenil in the treatment of benzodiazepine overdose.:

- “Respiratory depression mediated by benzodiazepines can be reversed using the specific antagonist flumazenil (Romazicon). It can be titrated intravenously or injected sublingually in 0.2 mg increments every 2-3 minutes, up to 1 mg. Flumazenil should not be administered to patients with a history of seizure disorder or dependence on benzodiazepines.”
- “Clinical trials using flumazenil to reverse the CNS depression associated with intravenous diazepam sedation for third molar extractions have demonstrated its efficacy.”
- “Although intended for intravenous administration in 0.2 mg increments up to 1 mg, it may be injected submucosally as well.”
- “Intraoral submucosal injection of flumazenil appears to be a viable concept based upon the following findings. The drug is rapidly and complete absorbed into the systemic circulation, as evidenced by comparable serum concentrations to those obtained by IV administration.”

*Dionne R, Phero J, Becker D; Management of Pain and Anxiety in the Dental Office. WB Saunders 2002;18:289*

Some Definitions

**Synergism:** When two or more drugs with similar pharmacologic effects act together to produce a greater effect than either drug alone. Synergism can either be additive or potentiating.

- **Additive:** The combined drug effects are essentially the algebraic sum of their individual effects (eg. $1 + 1 = 2$).
- **Potentiating:** The combined drug effects are greater than the sum of their individual effects (eg. $1 + 1 > 2$).

**Antihistamines**

There are several other drugs that are effective for oral sedation, but don't fall into the previous drug classes that have been discussed. The H1-receptor antagonist hydroxyzine (Atarax) has both sedative and hypnotic properties. The OTC anti-histamine diphenhydramine (Benadryl) have hypnotic properties and can be an inexpensive and safe adjunct to sedation. Both Atarax and Benadryl are useful in allergic rhinitis and urticaria, and are antiemetic.

### Antihistamines

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Half-Life (hrs)</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>Benadryl</td>
<td>2-8</td>
<td>25-50 mg</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Dramamine</td>
<td>4-6</td>
<td>50-100 mg</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Atarax, Vistaril</td>
<td>3-7</td>
<td>50-100 mg</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Phenergan</td>
<td>2-6</td>
<td>25-50 mg</td>
</tr>
</tbody>
</table>

**Hydroxyzine (Atarax or Vistaril)**

- Diphenylmethane, unrelated to benzodiazepines, phenothiazines, or opiates
- H1-receptor antagonist
- Bronchodilator
- Antisialagogue (anticholinergic)
- Antihistaminic, Decongestant, and Anti-emetic actions
- Onset: 1 hour
- Half-Life: 3-7 hours
- No active metabolites
- Duration: 3-6 hours
- Supplied in 10, 25, and 100 mg tablets and a 10mg/5mL syrup
- Dosage: Adults 50-100 mg, Children 10-50 mg
- Overdosage: No specific antidote
- FDA approved anxiolytic and as a pre- and postoperative adjunctive medication
**Contraindications:**
- Early Pregnancy
- Known Hypersensitivity
- Nursing Mothers
- Children <1 year
- Acute narrow angle glaucoma
- Use with other CNS depressants cautiously

*Phenergan* is from the phenothiazine class but has H₁-receptor effects. It has strong antihistamine properties and is commonly used in conjunction with opioid anesthesia, due to its antiemetic properties. Phenergan's antiemetic protection is primarily due to its interaction with dopaminergic receptors in the CTZ (Chemotactic Trigger Zone).

Some important points about Phenergan:
- Will not produce unconsciousness, and even at higher doses will not cause respiratory or CV depression
- Sedative
- Antisialagogue (Anticholinergic effects)
- Strong antiemetic

**Nitrous Oxide**

"I am sure the air in heaven must be this wonder working gas of delight"

- *Robert Southey, about Nitrous Oxide*

**Historical Perspective**

The discovery of nitrous oxide (and also oxygen) is credited to Joseph Priestley in 1793. During experiments with iron filings, ammonium nitrate, and water, he found that a residual gas was given off which later became known as nitrous oxide.

\[
\text{NH}_4\text{NO}_3 + \text{H}_2\text{O} + \text{Fe} \rightarrow \text{N}_2\text{O} + \text{Fe(OH)}_3 + \text{H}_2\text{O}
\]

Ammonium nitrate is heated in the presence of iron filings. The resultant gas is then passed through water to remove toxic by-products. The result is nitrous oxide.

The first person to inhale pure nitrous oxide was Humphrey Davy (at the Pneumatic Institute in Bristol, England), in 1798. At that time, nitrous oxide (N₂O) was thought to be responsible for many diseases, however after breathing the gas he reported a euphoric feeling, and "overwhelming joy."
For the first half of the 19th century, the analgesic properties of N\textsubscript{2}O went unnoticed and nitrous was widely used as a recreational drug. It was not until the mid-1840’s that a dentist named Horace Wells while attending a demonstration was exposed to N\textsubscript{2}O. During this demonstration a man named Samuel Cooley, after inhaling the gas, injured his leg. Dr. Wells noticed that Mr. Cooley appeared to be unaware of the injury to his leg, and he instantly envisioned the gas as an adjunct to the field of dentistry. Horace Wells in fact became the first person to have a tooth extracted while under N\textsubscript{2}O anesthesia. He termed this revelation the “greatest discovery ever made,” and tried over the next year to prove the efficacy of N\textsubscript{2}O to the medical community. After a failed experiment at Harvard Medical School in 1845 in which the patients “felt some discomfort,” Wells was labeled as a “charlatan” and a “fake.” He died some years later, never receiving the credits for his discovery.

Nitrous oxide lost favor and was very seldom used outside of dentistry until the 1930’s. It was then that medical schools began teaching the techniques of N\textsubscript{2}O sedation. From that time until the late 1950’s, the medical field predominately used N\textsubscript{2}O as a preanesthetic gas for Halothane. Dental schools began teaching inhalation anesthesia in the early 1960’s and it is estimated that “56% of GPs and 85% of oral surgeons” use N\textsubscript{2}O in their practice today.

**Advantages of Combination Oral-Inhalation Sedation**

- Decreased dose required of either medication alone
- Decreased overall side effects
- Potentiation vs Synergy
**Anxiolysis**
A pharmacologically induced state of consciousness where an individual is awake but has decreased anxiety to facilitate coping skills, retaining interaction ability. Anxiolysis = the elimination of anxiety

**Medications**
Diazepam - Valium
Zaleplon - Sonata
Triazolam - Halcion
Hydroxyzine - Atarax or Vistaril
Lorazepam - Ativan
Alprazolam - Xanax
Nitrous Oxide - Laughing Gas
Ramelteon - Rozerem

The same anxiolytic drug given in different doses can cause different responses. In the case of benzodiazepines, a small dose will cause anxiolysis, while larger doses may cause sedation.
• Medical history reviewed (including past anesthesia history)
• Complete Airway Evaluation (eg, Mallampati classification)

Difficult Airway Patients
- Previous difficult airway
- Obesity (BMI > 30)
- Retrognathia, micrognathia
- Severe Rheumatoid Arthritis (TMJ, cricoarytenoid joint)
- Obstructive Sleep Apnea
- Uncontrolled diabetics (with “Prayer Sign”)

Mallampati Classifications

Class 1: Entire uvula vestibule, as well as hard palate, soft palate, and tonsillar pillars are visible

Class 2: Only part of the uvula and part of the tonsillar pillars are visible

Class 3: Uvula invisible, but soft palate and hard palate remain visible

Class 4: Soft palate invisible, only hard palate remains visible

Notes:
Pre-Sedation Checklist (continued)

- All potential drug interactions researched
  - When assessing potential drug interactions for oral sedation the two main types of interactions are: 1) Additive CNS depression, and; 2) Cytochrome p450 inhibition/induction
  - In addition to prescribed medications, interactions with herbals and nutritional supplements should be also considered
- All drug allergies or intolerances noted
- Baseline vitals taken
- Pre-operative instructions reviewed with the patient
- Dietary, habit, or medicine restrictions reviewed with the patient
- Informed consent given and signed
- Responsible companion identified for transportation to/from the appointment
- Post-operative condition is described
  - When to resume normal activity
  - When to resume eating/hydration
  - Pain management
- How to recognize a problem and when/how to contact the office

Early published directions for triazolam dental sedation
(CDAJ 1988;54(7):511-4.)

1. The drug should be given one hour before the procedure begins
2. The drug should be administered with a small amount of water on a stomach that has been empty for at least 4 hours
3. As fear “slows” gastric emptying, it is often advantageous to administer a “night before” dose, and then treat the patient in the morning, following a restful sleep. In this case, the patient should be driven to the office for the treatment appointment.
4. Following treatment, the patient should be escorted from the office by a responsible adult companion and cautioned against operating a vehicle or similar activities for the remainder of the day.
5. Do not combine triazolam with other CNS depressants, especially ethanol
6. The drug, ideally, should be administered in the dental office with the patient being placed under observation in a recovery-type facility

According to the authors, “Doses should be individualized on the basis of age, size, anxiety, and medical history.”
Table 2. Total triazolam anxiolytic dosing guidelines (in mg).

<table>
<thead>
<tr>
<th>Weight (lb./kg)</th>
<th>18–40</th>
<th>41–64</th>
<th>65 and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100≤45</td>
<td>0.3125*</td>
<td>0.250*</td>
<td>0.1250*</td>
</tr>
<tr>
<td>110/50</td>
<td>0.3438</td>
<td>0.275</td>
<td>0.1375</td>
</tr>
<tr>
<td>120/55</td>
<td>0.3750</td>
<td>0.300</td>
<td>0.1500</td>
</tr>
<tr>
<td>130/60</td>
<td>0.4063</td>
<td>0.325</td>
<td>0.1625</td>
</tr>
<tr>
<td>140/65</td>
<td>0.4375*</td>
<td>0.350</td>
<td>0.1750</td>
</tr>
<tr>
<td>150/70</td>
<td>0.4688</td>
<td>0.375*</td>
<td>0.1875*</td>
</tr>
<tr>
<td>160/75</td>
<td>0.5000*</td>
<td>0.400</td>
<td>0.2000</td>
</tr>
<tr>
<td>170/80</td>
<td>0.5313</td>
<td>0.425</td>
<td>0.2125</td>
</tr>
<tr>
<td>180/85</td>
<td>0.5625*</td>
<td>0.450</td>
<td>0.2250</td>
</tr>
<tr>
<td>190/90</td>
<td>0.5938</td>
<td>0.475</td>
<td>0.2375</td>
</tr>
<tr>
<td>200+95+</td>
<td>0.6250*</td>
<td>0.500*</td>
<td>0.2500*</td>
</tr>
</tbody>
</table>

*Indicates possible triazolam dosing increments based on available tablet strength. Note: Always round down to the the nearest tablet strength.

Table 3. Total lorazepam anxiolytic dosing guidelines (in mg).

<table>
<thead>
<tr>
<th>Weight (lb./kg)</th>
<th>18–40</th>
<th>41–64</th>
<th>65 and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100≤45</td>
<td>1.250*</td>
<td>1.0*</td>
<td>0.50*</td>
</tr>
<tr>
<td>110/50</td>
<td>1.375</td>
<td>1.1</td>
<td>0.55</td>
</tr>
<tr>
<td>120/55</td>
<td>1.500*</td>
<td>1.2</td>
<td>0.60</td>
</tr>
<tr>
<td>130/60</td>
<td>1.625</td>
<td>1.3</td>
<td>0.65</td>
</tr>
<tr>
<td>140/65</td>
<td>1.750*</td>
<td>1.4</td>
<td>0.70</td>
</tr>
<tr>
<td>150/70</td>
<td>1.875</td>
<td>1.5*</td>
<td>0.75*</td>
</tr>
<tr>
<td>160/75</td>
<td>2.000*</td>
<td>1.6</td>
<td>0.80</td>
</tr>
<tr>
<td>170/80</td>
<td>2.125</td>
<td>1.7</td>
<td>0.85</td>
</tr>
<tr>
<td>180/85</td>
<td>2.250*</td>
<td>1.8</td>
<td>0.90</td>
</tr>
<tr>
<td>190/90</td>
<td>2.375</td>
<td>1.9</td>
<td>0.95</td>
</tr>
<tr>
<td>200+95+</td>
<td>2.500*</td>
<td>2.0*</td>
<td>1.00*</td>
</tr>
</tbody>
</table>

*Indicates possible lorazepam dosing increments based on available tablet strength. Note: Always round down to the the nearest tablet strength.

Goodchild JH, Donaldson M. Calculating and justifying total anxiolytic doses of medications for in-office use. General Dentistry 2006 Jan-Feb; 54-57.
Total Anxiolytic Dose is calculated by:

- Considering age, weight, and medical status
- Three age groups
  - 18-40 (dose increased by 25% to account for ↑ metabolism)
  - 41-64
  - 65+ (dose reduced dose 50% bc of sensitivity, and ↓ metabolism)
- ASA 3 patients – reduce dose on the chart by an additional 50%
- ASA 4 patients – contraindicated
- Relative potency of triazolam to lorazepam is 4:1

**Case Example 1**
triazolam

- 34 yr H female
- 160 lbs
- PMHx: Mitral valve prolapse (MVP) w/o regurgitation, verified by Echo 5 years ago
- No medications
- No known drug allergies
- Vitals: BP 110/65 mmHg, pulse 60 bpm

Correct Dose: ______________________

**Case Example 2**
triazolam

- 42 yr AA male
- 200 lbs
- PMHx: Asthma
- Meds: Albuterol prn
- No known drug allergies
- Vitals: BP 135/85 mmHg, pulse 100 bpm

Correct Dose: ______________________

Notes:
### Case Example 3

**Tria zolam**

- 65 yr male
- **PMHx:**
- Type 2 Diabetes Mellitus
- BG range 215-250 mg/dL
- HgA1C 12%
- Meds: glimepiride 4 mg q.d.
- No known drug allergies
- Vitals: BP 135/82 mmHg, pulse 87 bpm, Height 6’0”, Weight 275 lbs.

**Correct Dose:**

---

### Case Example 4

**Lorazepam**

- 22 yr male, 160 lbs
- **PMHx:**
- Inguinal hernia repair 5 years ago
- Prolapsed mitral valve w/ regurgitation
- Seasonal allergies
- Meds: Fexofenadine
- No known drug allergies
- Vitals: BP 120/75 mmHg, pulse 90 bpm

**Correct Dose:**

---

### Case Example 5

**Lorazepam**

- 74 yr male, 225 lbs
- **PMHx:** Angina (2-3 attacks/week)
- Meds:
  - Metoprolol 200 mg bid
  - Atorvastatin 20 mg qd
  - Aspirin 81 mg qd
  - Nitroglycerin prn
- No known drug allergies
- Vitals: BP 129/85 mmHg, Pulse 80 bpm

**Correct Dose:**

---

Notes:  

---

---
Case Example 6
Lorazepam
- 21 yo female, 140 lbs
- PMHx: Recently gave birth (3 weeks ago) and is breastfeeding
- Meds:
  - Multivitamins
  - Herbal diet medication
  - Allergic to PCN → hives
- Vitals: BP 105/60 mmHg, Pulse 85 bpm
- SHx: Quit smoking 9 mos. ago. Before that 1 ppd x 3 years

Correct Dose: ____________________

Case Example 7
Lorazepam
- 58 yo male, 215 lbs
- PMHx:
  - CABG x 4
  - MVP w/ regurgitation
  - Joint replacement (Right knee and hip)
- Meds:
  - Cyclobenzaprine 10 mg
  - Viagra prn
- Allergies:
  - PCN
  - Clindamycin (intolerance)
- Vitals: BP 150/87 mmHg, Pulse 90 bpm
- SHx: Smokes 1 cigar/day x 30 yrs

Correct Dose: ____________________
Are there other strategies?

• A dose of medication could be given the night before the sedation
  – May help anxious patients to relax and get to sleep
  – Establishes a blood level of the medication that can be added to the next morning
  – Reduces total drug amounts
• Incremental dosing – “oral titration” (usually not allowed without conscious sedation permit)

What medications could be used the night before the sedation?

• Stick with a Benzodiazepine or Hydroxyzine
• Use longer half-life drugs
• For patients who smoke, use Hydroxyzine the night before

<table>
<thead>
<tr>
<th>Dose</th>
<th>Elderly/Debilitated/CNS depressants</th>
<th>Average</th>
<th>High Fear/Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diazepam 2.5 mg</td>
<td>Diazepam 5 mg</td>
<td>Diazepam 10 mg</td>
</tr>
<tr>
<td></td>
<td>Lorazepam 0.5 mg</td>
<td>Lorazepam 1 mg</td>
<td>Lorazepam 2 mg</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine 25 mg</td>
<td>Hydroxyzine 50 mg</td>
<td>Hydroxyzine 100 mg</td>
</tr>
</tbody>
</table>
### Table 4. Protocol for Incremental Oral Administration

This example is for an 8 a.m. appointment when dentistry is planned to begin at 9 a.m.

**Prior to appointment:** The patient (Adult ASA 1 or 2) has been evaluated by the dentist preoperatively and accepted for oral sedation dentistry; prior to appointment, the patient has received a single dose of triazolam (0.25 mg; for elderly, debilitated, or patients with potential drug interactions, 0.125 mg should be dispensed).

7:00 a.m.: The patient, having gone six hours without eating, takes 0.25 mg triazolam; a responsible companion escorts the patient to the office

8:00 a.m.: The patient arrives at the office with the companion and compliance with preoperative instructions is verified

8:03 a.m.: The patient is seated in the operatory for the beginning of continuous physiologic monitoring; at that time, the patient’s wristwatch and glasses are removed and given to a companion

8:06 a.m.: The patient is assessed for susceptibility to the sedative medication; additional medication may be provided sublingually

8:35 a.m.: The patient’s sedation state is reassessed; if additional medication is necessary, the dentist should deliver it sublingually

8:54 a.m.: Oxygen is introduced with the appropriate protocol

8:57 a.m.: Nitrous oxide is introduced with the appropriate protocol

9:00 a.m.: Local anesthesia is administered; at this point, nitrous oxide administration is terminated and dentistry begins

The above graph represents a rough kinetic model of an additional dose of triazolam (ie, supplemental dosing) to maintain sedation for a longer dental appointment.

Pharmacokinetic modeling of oral triazolam:

- $F = 44\%$
- Dose = 0.25mg
- $V_d = 70\text{ L}$
- $K_{ab} = 1.5\text{ h}^{-1}$
- $K_{el} = 0.35\text{ h}^{-1}$
- Number of doses = 8
- Dose interval = 2hrs

The above graph is a representation of what the plasma concentration may be after multiple doses of oral triazolam. At a dose of 0.25mg given every 2 hours, the plasma concentration approaches 2.5 μg/mL. A single 0.5mg dose typically results in plasma concentrations of approximately 4.0 μg/mL.
Pre-Sedation Instructions

- NPO for 6-8 hours (clear liquids ok), exception – diabetic patients
- No CNS depressants or sedatives for 24 hours before/after (other than night-time anxiolytic prescribed by treating dentist)
  - Smokers
  - Coffee drinkers
  - Herbal diet medications (eg, Ephedra)
  - Herbal medications
    - (eg, Kava Kava, Valerian, Chamomile, Melatonin, St. John’s Wort)
  - Nutritional supplements
- No chance of pregnancy (triazolam is pregnancy factor X)
- No allergies to the sedative medications (possible, but very rare)
- Must have a responsible person to bring them to the office and take them home (no exceptions!)
- No contact lenses (anticholinergic effects → dry eyes)
- No driving for 24 hours after the sedation appointment
- Because of prolonged psychomotor impairment - No operating hazardous machinery
- No heavy lifting (balance disturbances)
- No stairs without assistance (balance disturbances)
- No important decisions (amnesia)

Reminders

- Always remember the definition of anxiolysis…pt is conscious, responds to verbal commands, patent airway at all times
- Patients may respond that they are still awake. (“You are an excellent patient”)
- Do not treat any patient that has a questionable or complex medical history! (ASA 1 and 2, ASA 3 with possible medication consult)
- Sedation patients are never left unattended
- If a reversal agent for any reason, no additional sedative should be administered, and the patient should be monitored for the appropriate time (at least 1 hour)

Patient Dismissal

Patient readiness for discharge needs to be addressed in a simple, clear, reproducible manner that meets accepted guidelines

Aldrete Score (Phase 1 discharge)
Postanesthesia Discharge Scoring System (PADSS)
Aldrete Scoring System Designed for assessment of patients for Phase 1 discharge (i.e., discharge from ICU or post-anesthesia care unit.

Aldrete's score is not intended to determine home-readiness.

The modified PADSS differs from its original form by not including oral intake of fluids as a criterion for discharge.
Patient Dismissal

The patient is always escorted by their companion, or a team member, while walking in the office. Team member helps companion assist (or via wheelchair/companion chair) patient into departing vehicle. Patient is taken directly home. Make follow-up calls to all patients that night and remind them to hydrate. Unconditional positive regard (always be encouraging!). Review all post-operative instructions with the patient’s companion. Flumazenil should not routinely be used to aid in patient dismissal (short duration and possible re-sedation).

A Second Single Dose Appointment

Adjust on the following variables:

- Pt. Good/office good = Rx remains the same
- Pt. Good/office bad = Rx adjustment by increasing or decreasing dosage appropriately
- Pt. Bad/office bad = reassess for referral (different type of sedation) or test appt. with adjustments to protocol

Dr. Fred Quarnstrom’s Triazolam Manual

http://faculty.washington.edu/quarn/halindex.html

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

- Dosing is simple (based on the “Q-factor”)
- Good body of evidence reporting it’s successful use
- Does not require the same “risks” and costs you may be currently undertaking

Some Important Caveats to Remember:

- Increased number of drugs lowers safety.
- Respiration most likely source of anesthetic mishap.
- Be careful not to practice beyond your Level of Training.

Nitrous Oxide Supplementation

Inadequate Sedation Nitrous Oxide Supplementation
# Oral Sedation Record

## Pre-Op

<table>
<thead>
<tr>
<th>Date</th>
<th>Patient Name</th>
<th>Patient Date</th>
<th>Height</th>
<th>Weight</th>
<th>Age</th>
<th>American Society of Anesthesiologists' Classification (ASA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th>Drug Allergies or Intolerances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Vitals:</th>
<th>Pulse (bpm)</th>
<th>BP (mmHg)</th>
<th>SpO₂ (%)</th>
</tr>
</thead>
</table>

## Peri-Op

Use the table below to record both the medications used and the times administered. (eg, sedatives, nitrous oxide/oxygen, and local anesthesia)

<table>
<thead>
<tr>
<th>Name of Medication &amp; Dosage</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Post-Op

Vital signs at discharge:

<table>
<thead>
<tr>
<th>Pulse (bpm)</th>
<th>BP (mmHg)</th>
<th>SpO₂ (%)</th>
</tr>
</thead>
</table>

- ☐ Discharge criteria satisfied
- ☐ Post-operative Instructions given to patient and companion
- ☐ Patient instructed when to resume normal eating and drinking
- ☐ Patient given emergency contact phone numbers
- ☐ Patient released to responsible adult companion

Dentist Name (Sign & Print)  Assistant’s Name
Physiologic Monitoring For Adult Enteral Sedation
**Minimal Sedation**

- Moderate Sedation
- Deep Sedation
- GA

**Protective reflexes intact**
- Patient can independently and continuously maintain an airway
- Patient can respond appropriately to verbal commands

Loss of protective reflexes
- Inability to independently maintain an airway
- No pain sensation or reflex withdrawal from stimuli
- Total unconsciousness


---

<table>
<thead>
<tr>
<th>Responsiveness</th>
<th>Minimal Sedation (Anxiolysis)</th>
<th>Moderate Sedation / Analgesia (Conscious Sedation)</th>
<th>Deep Sedation / Analgesia</th>
<th>General Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway</td>
<td>Unaffected</td>
<td>No intervention required</td>
<td>Intervention may be required</td>
<td>Intervention often required</td>
</tr>
<tr>
<td>Spontaneous Ventilation</td>
<td>Unaffected</td>
<td>Adequate</td>
<td>May be adequate</td>
<td>Frequently inadequate</td>
</tr>
<tr>
<td>Cardiovascular Function</td>
<td>Unaffected</td>
<td>Maintained</td>
<td>Usually maintained</td>
<td>May be impaired</td>
</tr>
</tbody>
</table>

Source: American Society of Anesthesiology (www.asahq.org)
Monitoring: In office conscious sedation mortality & serious morbidity are exceedingly rare in modern practice

Blood Pressure:
- Systolic Blood Pressure (SBP)
  - Reflects peak pressure in vascular system
- Diastolic Blood Pressure (DBP)
  - Reflects resting pressure in vascular system
- Mean Arterial Pressure (MAP)
  - Reflects average pressure in system
  - MAP = SBP + (2 × DBP) / 3

Heart Rate:
- Normal 60-100 bpm
- Bradycardia <60 bpm
- Tachycardia >100 bpm

---

**JNC 8 Recommendations**

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Target SBP (mm Hg)</th>
<th>Target DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 years</td>
<td>&lt;150</td>
<td>&lt;90</td>
</tr>
<tr>
<td>&lt; 60 years</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
<tr>
<td>&gt; 18 years with CKD</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
<tr>
<td>&gt; 18 years with diabetes</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease, SBP = systolic blood pressure, DBP = diastolic blood pressure

*JAMA. 2014 Feb 5;311(5):507-20*
Definitions:

Ventilation – refers to carbon dioxide elimination and is monitored by a stethoscope and/or end-tidal CO2

Oxygenation – refers to O2 being delivered to cells and is monitored by a pulse oximeter

Respiration

• Monitoring the respiratory status of the patient is vitally important for sedation patients!

• During sedation, changes in breathing are often noted well before cardiovascular changes

Respiration may be monitored by:

1. Determining the respiratory rate
2. Observing rise and fall of the chest wall
3. Observing the color of mucous membranes
4. Observing inflation and deflation of the reservoir bag if inhalation sedation is used

Visualization of inflation/deflation of the reservoir bag is a valid method of determining air exchange if an airtight seal of the mask is maintained

Holding a mirror or an ungloved hand in front of the patients mouth or nose so that air is felt (or seen fogging the mirror) is a good method of determining exchange of air is occurring

Respiration - devices used to assess respiration include:

• Precordial stethoscope
• Pretracheal stethoscope
• Esophageal stethoscope

A precordial / pretracheal stethoscope involves a weighted stethoscope head secured in place with tape to either the precordial or pretracheal area

The esophageal stethoscope is designed for placement into the patients esophagus through their nose or mouth

- This obviously would not be tolerated during oral sedation, but is excellent for general anesthesia

Source: www.SedationResource.com
Pulse Oximeter

- **PaO₂** = partial atmospheric pressure of oxygen that is dissolved in the blood. Measured in mmHg
- **SaO₂** = oxygen saturation of the blood as defined as % of heme sites occupied by an oxygen molecule
- **SpO₂** = estimate of oxygen saturation as calculated by the pulse oximeter

The relationship between the amount of oxygen dissolved in the blood and the amount attached to the hemoglobin is called the oxyhemoglobin dissociation curve

- 97% saturation = 97 mmHg (PaO₂) → Normal
- 90% saturation = 60 mmHg (PaO₂) → Danger!
- 80% saturation = 45 mmHg (PaO₂) → Severe Hypoxia!
Changes in this curve can be caused by:
1. Alkalosis/Acidosi
2. Changes in PaCO₂
3. Hypothermia/Hyperthermia
4. Increased or decreased 2-3-DPG (a normal by-product of red blood cell metabolism)

Considerations for Pulse Oximetry:

- Effect of non-functioning hemoglobin:
- Pulse ox only measures oxygenated hemoglobin (HbO₂) and deoxygenated hemoglobin (Hb)
- When patients have large amounts of non-functioning hemoglobin pulse oximeter readings can vary widely!
  - Carboxyhemoglobin (HbCO)
  - Methemoglobin (METHb)

Anemia (a lack of red blood cells causes anemia)

↓ Hemoglobin

The small of amount of hemoglobin may be well saturated with oxygen

Pulse ox readings will be normal

Changes in pulse ox are concerning b/c pt may not have enough O₂ going to tissues

Dyes

Some surgical dyes can impact Pulse Ox use

Dyes can alter light transmission thru blood

If the patient's blood contains the following dyes, pulse oximetry cannot be used:
- Methylene blue
- Indocyanine green
- Indiocarmine

Bilirubin, the breakdown product of RBC, does not affect Pulse Ox readings

Common sources of error:

- Light interference – consider covering the site
- Movement artifacts – usually pulse readings
- Sensor application – tight vs. loose
- Inadequate blood flow – BP cuff, tight clothing
- Nail polish
What else is out there for patient assessment during in-office sedation?

Bispectral Index Monitoring (BIS)

BIS Monitoring measures EEG on a dimensionless scale from 0-100. A BIS reading of 0 corresponds to flat-line EEG (no brain activity). A BIS of 95 to 100 is normal. A BIS reading of ≤ 60 is commonly considered general anesthesia.

What about Pulse CO-Oximetry?

Pulse CO-Oximeter measures:
1. Pulse
2. Oxygen saturation
3. Carboxyhemoglobin
4. Methemoglobin

Notes:
Remember that pulse oximeters show oxygen saturation as \( \text{SpO}_2 \) (an estimate of the true oxygen saturation)

“True” oxygen saturation is written as \( \text{SaO}_2 \)

In the blood, carbon monoxide combines with hemoglobin to form carboxyhemoglobin (COHb)

In smokers, the amount of COHb in the blood ranges from 5-15%.

In non-smokers the level is 0.3-1.6%
Even in places of environmental pollution the level does not exceed 1.9%
Affinity of carbon monoxide for hemoglobin is 200x that of oxygen

High levels of carboxyhemoglobin causes a left shift in the oxyhemoglobin dissociation curve – more difficult for tissues to extract oxygen. Result is chronic tissue hypoxia – body compensates with more RBC

**Net effect** = increased oxygen availability at the expense of plasma viscosity

Currently pulse oximeters can only measure oxyhemoglobin (HbO\(_2\)) and deoxyhemoglobin (HHb); COHb can not be measured.

The pulse oximeter will grossly overestimate the oxygen saturation in chronic smokers!

For every 1% of circulating carboxyhemoglobin, the pulse oximeter over reads by 1%. Fifty percent of cigarette smokers have a carboxyhemoglobin concentration of 6%.

*Source: Anesthesia Progress 2000;47:143-150*

**Pulse oximeter will show HbO\(_2\) + COHb (normal pulse oximeters can not differentiate the two hemoglobin species)**

**Example:** Pulse oximeter reads 99% on a chronic smoker. If they have 10% COHb then the true reading of HbO\(_2\) is 89%!!!

How do Pulse Oximeters calculate \( \text{SpO}_2 \)?

\[
\text{Fractional SpO}_2 = \frac{\text{O}_2\text{Hb} \times 100\%}{\text{O}_2\text{Hb} + \text{Hb} + \text{COHb} + \text{MetHb}}
\]

Clinically… \( \text{SpO}_2 = \text{O}_2\text{Hb} - \text{COHb} \)
• Can occur in patients given extremely large doses of Prilocaine (>8 mg/kg or >8 carps in a 70 kg adult)
• The metabolite of Prilocaine, o-toludine, causes oxidation of the iron atom in hemoglobin from the reduced to the oxidized state. \( \text{Fe}^{2+} \rightarrow \text{Fe}^{3+} \)

**Medications associated with Methemoglobinemia:**

- Local Anesthetics (Prilocaine, Benzocaine)
- Analgesics (Acetaminophen, Celecoxib)
- Antibiotics (Sulphonamides)

**Methemoglobinemia:**

- The resultant species of hemoglobin - Methemoglobin is unable to transport oxygen
- Patient appears cyanotic
- Blood takes on a bluish hue

*Fortunately, for most patients methemoglobinemia is well tolerated*

Of concern are pediatric patients, patients with cardiovascular or pulmonary disease, or patients with hereditary methemoglobinemia

For compromised patients or patients with hereditary methemoglobinemia, Prilocaine should be avoided

Treatment of Methemoglobinemia = IV methylene blue

Organs with high oxygen demands (ie CNS, cardiovascular) usually are the first systems to manifest toxicity

Normal methemoglobin fraction = 1%

- At 3-15% signs may include changes in skin color
- At 15-20% patients may be relatively asymptomatic, but cyanosis is likely present
- At 25-50%, the signs and symptoms are:
  - Headache
  - Dyspnea
  - Lightheadedness
  - Weakness
  - Confusion
  - Palpitations, Chest pains
  - Methemoglobinemia

- At 50-70%, the signs and symptoms are:
  - Altered mental status
  - Delirium
- Death occurs when methemoglobin fractions approach 70%

Notes:
**End-Tidal CO₂ Monitoring (ET CO₂)**
The ability to measure a patient’s exhaled carbon dioxide (CO₂)

**Advantages**
- Measures ventilation via detecting exhaled CO₂
- Rate
- Alarm

**Disadvantages**
- Non-intubated patient – difficult and inaccurate if patient is a mouth breather
- Expensive

**Capnography:**
Refers to the comprehensive measurement & display of CO₂, including end-tidal, inspired, and the capnogram (real time CO₂ waveform)

**Capnometry:**
Refers to the measurement and display of CO₂ in numeric form only

Normal PaCO₂ = 40 ± 5 mmHg

ET CO₂ = 0 mmHg indicates the patient is not being ventilated
- Upper airway obstruction
- Apnea
- ET misplaced
- Ventilator disconnect / malfunction
- Disconnect of sample line

Notes:

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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.**

**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 P<sub>450</sub> (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 relates 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 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:
  - in the clinically active dose
  - 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.**
Relative Proportions of Enzymes

- 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

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
**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 Caucasians 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 post-operatively because, “tablets make me gag.”

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 its 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 anti-inflammatory 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.

CYP 3A4

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<tr>
<th>Substrate</th>
<th>Inducer</th>
<th>Inhibitor</th>
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<td>Alprazolam</td>
<td>Barbiturates</td>
<td>CCBs (esp. Diltiazem)</td>
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<td>Atropine</td>
<td>Cyclophosphamide</td>
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<td>Atorvastatin</td>
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<td>Barbiturates</td>
<td>Lansoprazole</td>
<td>Cyclosporine</td>
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<td>CCBs (not diltiazem)</td>
<td>Midazolam</td>
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<td>Cisapride</td>
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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.

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 chronic drug therapies involving drugs that are excreted slowly and; the use of drugs with small margins of safety:

*digoxin, warfarin, opioids, lithium, theophylline, thyroid medications*

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)
• 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

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.

**ICE’s Medical Support System,** a website providing resources on medical conditions as they relate to oral health care. “This unique software will enhance oral health care professionals’ ability to help a patient population that presents with medical conditions that impact the provision of dental care,” said Dr. Michael Glick, author of the content on the site. Dr. Glick is professor of oral medicine and dean, School of Dental Medicine, University at Buffalo, N.Y., and editor of The Journal of the American Dental Association. The site is located at “www.icemedicalsupport.com”.

The Medical Support System provides up-to-date, point-of-care oral care information that is continually updated in more than 50 languages. Using the information available on the site, dentists and other dental team members can assess a patient’s potential for medical complications and the need for dental modifications. Additionally, subscribers can amass up to three hours of continuing education credits through use of the site. A demo of the site is available at www.icemedicalsupport.com/demo.

For more information about the Medical Support System, visit http://icemedicalsupport.com/ada or you can call 1-866-292-9725 or email info@icehealthsystems.com.

**Notes:**
An Evidence-Based Challenge: Treating Patients on Anticoagulants
**Definition:**
Evidence-based dentistry (EBD) is an approach to oral health care that requires the judicious integration of systematic assessments of clinically relevant scientific evidence, relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences.

*Isn't this what we already do?*

*Is EBD just a new name for something we are already doing, or should be doing?*

**What is Evidence?**
Do you consider Evidence to be:
- Scientific articles
- Literature reviews
- Textbooks

And do you consider these things plus continuing education, what your colleagues may have said, and other journal articles when you make treatment decisions?

Or, do you consider Evidence to be:
1. All available knowledge on a specific clinical problem
2. Synthesized to provide unbiased treatment guidelines
3. That can be used to evaluate outcomes

**Evidence-Based Dentistry Implications**
- Practice Guidelines will decrease practice variations while improving outcomes
- Purchasers may insist on these Practice Guidelines
- Performance measures and outcome assessment
- The “in my hands” argument no longer is acceptable
- Treatment will be evidence driven (ie, “Best Practices”) rather than being left solely to the personal preference of the practitioner
- Performance measures?
Another Definition of EBD:
Evidence-based dentistry is defined as the practice of dentistry that integrates the best available evidence with clinical experience, and the patient’s treatment needs and preferences.

How does this apply to the treatment of medically complex dental patients?

The projected percentage increase between 2000 and 2050 of the 65+ senior population is 147%

As the population ages and medical science advances, more patients with complex medical histories will be seeking dental care

Management of Medically Complex Patients

Notes:
The dentist retains the primary responsibility for the procedures actually carried out and for the immediate management of any untoward complications.  
(Burkett's Oral Medicine)

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<th>ASA CLASSIFICATION</th>
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<td>Class 5</td>
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<td>Class 6</td>
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Let's look at an example…

**How are you treating patients taking warfarin (Coumadin) or antiplatelet therapy?**

- How do you treat a patient who presents with a history of taking Coumadin?
- Can dental treatment be performed on patients taking warfarin or antiplatelet drugs?
- Should patients discontinue warfarin or antiplatelet drugs 3-6 days prior to treatment?
- Is there an appropriate INR level for dental treatment?
- Are there drug interactions?
Let’s Review the Literature:

**NEJM 1957;256(8):351-3.**
“Two cases are reported in which dental extraction, performed during the course of coumarin therapy, was followed by excessive and serious bleeding.”

**JADA 1961;62:172-180.**
“Experience indicates that with careful medical management and prescribed surgical technique, dental surgery may be carried out safely while PT levels are maintained at therapeutic levels.”

(1.5-2x normal)

**Ann Intern Med 1963;59(6):911-3.**
“No complication was recorded in any patient who had either single or multiple extractions. The maximum number of teeth extracted at one sitting was 7.”

**JADA 1996;127(5):625-38.**
“Although studies have repeatedly shown that patients who continuously take anticoagulants can safely undergo general dental treatments, many physicians in this study said they would suggest patients alter medication routines before several dental procedures.”

Wahl MJ. JADA 2000;131:77-81.

![ABSTRACT]

**Background.** Continuous anticoagulant therapy with warfarin is administered to prevent a variety of medical complications, including thromboembolisms and stroke. When patients receiving continuous anticoagulant therapy are scheduled for dental surgery, a decision must be made whether to continue or interrupt the anticoagulant therapy.

**Methods.** The author reviewed the literature, focusing on dental surgery in patients receiving continuous anticoagulant therapy and in patients whose anticoagulant therapy was withdrawn before they underwent dental procedures.

**Results.** Of more than 950 patients receiving continuous anticoagulant therapy (including many whose anticoagulant levels were well above currently recommended therapeutic levels) who underwent more than 2,400 surgical procedures, only 12 (< 1.3 percent) required more than local measures to control hemorrhage. Only three of these patients (< 0.31 percent) had anticoagulation levels within or below currently recommended therapeutic levels.

Of 526 patients who experienced 575 interruptions of continuous anticoagulant therapy, five (0.95 percent) suffered serious embolic complications; four of these patients died.

**Conclusions.** Serious embolic complications, including death, were three times more likely to occur in patients whose anticoagulant therapy was interrupted than were bleeding complications in patients whose anticoagulant therapy was continued (and whose anticoagulation levels were within or below therapeutic levels). Interrupting therapeutic levels of continuous anticoagulation for dental surgery is not based on scientific fact, but seems to be based on its own mythology.

**Clinical Implications.** Dentists should recommend that therapeutic levels of anticoagulation be continued for patients undergoing dental surgery. Practitioners should consult with the patient’s physician if necessary to determine his or her level of anticoagulation before performing dental surgery.
Oral surgery in patients on anticoagulant therapy

Crispian Scully, CBE, MD, PhD, MDS, MRCS, FDSRS, FDSRCPS, FFDRCSI, FDSRCSE, FRCPath, FMedSci, and Andy Wolff, DMD, London, United Kingdom, and Tel Aviv, Israel
EASTMAN DENTAL INSTITUTE AND MACCABI HEALTH FUND AND ASSUTA HOSPITAL

Table V. Management of patients on coumarins needing oral surgery in dental clinics

1. Careful history taking including:
   - Underlying medical condition (need of antibiotic prophylaxis?)
   - Presence of increasing bleeding risk factors
   - Previous bleeding experience in oral surgery procedures
   - Habits (ie, alcohol intake)
   - Mental condition
2. Careful oral examination to determine:
   - Degree of urgency of planned surgical procedure
   - Extent of planned surgical procedure
   - Gingival condition
3. Order INR
4. Decision of whether to treat or to refer with consideration of following factors:
   - Result of history taken
   - Result of oral examination
   - Result of INR
   - Logistical considerations: distance to hospital or emergency care facility, patient mobility
5. Referral always to hospital in presence of either one of following conditions:
   - INR > 3.5
   - Need of more than simple surgical procedure
   - Presence of additional bleeding risk factors or logistic difficulties
6. Performance of surgery in office without INR provided:
   - Need of surgery cannot be postponed
   - History of stable INR up to 2.5
   - Previous available INR value obtained within last week
7. If surgery to be performed in office, following materials should be used:
   - Absorbable packing hemostatic agents
   - Sutures
   - Hemostatic mouth washes
More on the INR: The international normalized ratio, or INR, was introduced in 1983 by the World Health Organization, or WHO, Committee on Biological Standards to more accurately assess patients receiving anticoagulation therapy. The INR mandates the universal standardization of prothrombin time.

The Normal INR Range is 1.0-1.5 (Source: JADA 1997;128:1121-2.)

JADA 2003;134:1492-7. (Prepared by the ADA Council of Scientific Affairs)

Conclusions and Clinical Implications: The scientific literature does not support routine discontinuation of oral anticoagulation therapy for dental patients. Use of warfarin sodium therapy as it relates to dental oral surgery procedures has been well-tolerated. Some dental studies of antiplatelet therapy are consistent with the findings in warfarin sodium studies. Dental therapy for patients with medical conditions requiring anticoagulation or antiplatelet therapy must provide for potential excess bleeding. Routine discontinuation of those drugs before dental care, however, can place these patients at unnecessary medical risk. The coagulation status – based on the INR – of patients who are taking these medications must be evaluated before invasive dental procedures were preformed. Any changes in anticoagulation therapy must be undertaken in collaboration with the patient’s prescribing physician.

Oral Surgery in Patients on Anticoagulant Treatment Without Therapy Interruption

Giovanni B. Ferrieri, MD, DMD,* Stefano Castiglioni, DDS,† Daniela Carmagnola, DDS, PhD,‡ Marco Cargnel, DDS,∫ Laura Strobimenger, MD, DMD,** and Silvio Abati, MD, DMD††

Purpose: Conflicting opinions exist in literature concerning the management of oral surgery in patients on oral anticoagulants because no consensus on perioperative protocols is available, including precise guidelines regarding the need for therapy modification or withdrawal. The aim of this study was to evaluate bleeding complications associated with oral surgery performed on patients on oral anticoagulants without therapy modification or withdrawal but following a standardized comprehensive perioperative management protocol.

Patients and Methods: Patients on oral anticoagulant therapy with warfarin and in need of oral surgery underwent a thorough general and oral clinical evaluation to assess thromboembolic and bleeding risk; 255 subjects who, on the morning of surgery, had INR values ≤5.5 were included in the study. An atraumatic surgical technique was carried out and all patients received postoperative careful instructions.

Results: Five cases (1.96%) of bleeding complication were observed in patients with moderate to high thromboembolic and bleeding risk.

Conclusion: The findings from this study suggest that a comprehensive perioperative management protocol for oral surgery in patients on oral anticoagulants including 1) thromboembolic and bleeding risk assessment, 2) an atraumatic surgical technique, and 3) postoperative careful instructions, can lead to safe and successful results with minimal complications.

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Notes:
Conclusion: For most patients undergoing simple single dental extractions, the morbidity of potential thromboembolic events if anticoagulant therapy is discontinued clearly outweighs the risk of prolonged bleeding if anticoagulant therapy is continued.

**Risk of Thromboembolism With Short-term Interruption of Warfarin Therapy**

David A. Garcia, MD; Susan Regan, PhD; Lori E. Henault, MPH; Ashish Upadhyay, MD; Jaclyn Baker, MD; Mohamed Othman, MD; Elaine M. Hylek, MD, MPH

- When all 1293 interruptions are considered, the proportion associated with thromboembolism within the 30-day follow-up period is 0.5%.
- Among patients whose warfarin therapy was interrupted for 5 days or fewer, the proportion experiencing thromboembolism was 0.4% compared with 2.2% for those with an interruption interval of 7 days or more.

**Dentoalveolar Procedures for the Anticoagulated Patient: Literature Recommendations Versus Current Practice**

Brent B. Ward, DDS, MD,* and Miller H. Smith, DDS†

*How often do you routinely recommend interruption of Warfarin?*

- For Low Risk Procedures: 23.6% recommend routine discontinuation
- For Moderate Risk Procedures: 48.8% recommend routine discontinuation
- For High Risk Procedures: 70.5% recommend routine discontinuation
<table>
<thead>
<tr>
<th>Dental Treatment</th>
<th>Suboptimal INR Range</th>
<th>Normal Target INR Range</th>
<th>Out of Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1.5</td>
<td>1.5 to &lt; 2.0</td>
<td>2.0 to &lt; 2.5</td>
</tr>
<tr>
<td>Exam, Radiographs, study models</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple restorative, supragingival prophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex restorative, SCRP, endodontics</td>
<td></td>
<td>Local Measures</td>
<td></td>
</tr>
<tr>
<td>Simple extraction, gingivoplasty</td>
<td></td>
<td>Local Measures</td>
<td>Local Measures</td>
</tr>
<tr>
<td>Multiple extractions, removal of a single bony impaction</td>
<td></td>
<td>Local Measures</td>
<td>Local Measures</td>
</tr>
<tr>
<td>Gingivectomy, apicoectomy, minor perio flap surgery, placement of single implant</td>
<td></td>
<td>Probably Safe (IR)</td>
<td>Probably Safe (IR)</td>
</tr>
<tr>
<td>Full-mouth/full-arch extractions</td>
<td>Probably Safe (IR)</td>
<td>Local Measures</td>
<td></td>
</tr>
<tr>
<td>Extensive flap surgery, extraction of multiple bony impactions, multiple implant placement</td>
<td>Probably Safe (IR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open fracture reduction, orthognathic surgery</td>
<td>Not Advised</td>
<td>Not Advised</td>
<td>Not Advised</td>
</tr>
</tbody>
</table>

* IR = Insufficient Research to draw a conclusion

The Challenge…

Case Example
Information from the patient
77 yo H male
5’7”, 185 lbs
BP:
- 1st Reading: 121/77 mmHg, 70 bpm
- 2nd Reading: 141/90 mmHg, 79 bpm
Meds:
- Digoxin 0.25 mg
- Glyburide / Metformin 1.25/250 mg
- Warfarin 5 mg
- Atenolol 50 mg
- Lotrel 5-20 mg
No Known Drug Allergies (NKDA)

- Can this patient receive dental care?
- What are your concerns?

Affairs are easier of entrance than of exit; and it is but common prudence to see our way out before we venture in
-Aesop 620-560 BC, Greek Fabulist

Treatment Rendered – 5 hour length
- Remaining lower teeth extracted, Gelfoam placed, no sutures
- Maxillary teeth scaled and polished
- Caries removal
- RCT 6, 10
- Maxillary teeth prep’d and provisionalized
- Immediate FL inserted
With pressure, hemostasis achieved

Patient satisfied discharge criteria and was released at 2:45 PM

Your pager goes off at 11 PM from the patient’s spouse
She says the patient is bleeding uncontrollably and she is scared

You tell them to go to the emergency room of the local hospital and you will meet them there…

The attending dentist applies pressure but the bleeding will not stop
Stat CBC reveals:
- RBC 3.0 (normal 4.5-11)
- HCT 27 (normal 40-51)
- HGB 8.4 (normal 12-16)

- Pt is beginning to feel sluggish, lethargic, and nauseated
- Pt is admitted at 12:30 AM
- Warfarin therapy is discontinued and patient is heparinized
- Pt receives 3 units of blood to raise the RBC and hemoglobin (8.4 → 12)
- 2 weeks later the dental board contacts you and asks you to submit a report on the incident

What could have been done differently?
The Challenge…

Case Example:
57 yo male taking warfarin 7.5 mg
MHx involves myocardial infarction 5 years ago
Otherwise medically stable
Vitals: BP 117/85 mmHg, Pulse 90 bpm

Consultation with the physician yields the following laboratory values:
- PT = 17 secs
- INR = 3.0
- Platelets = 225,000 / cu mm

Should you stop the Coumadin?
Why?
For how long?
When do they start again?
What are the chances of having a thromboembolic event while the patient is not anticoagulated?

Should you not alter the Coumadin?
Why?
Will the surgical field be harder to see?
What can I use to control bleeding?
Will I get hemostasis?
Will the patient have post-operative bleeding?

And the winner is….

Don’t stop the Coumadin
There is overwhelming literature to support the practice of routine oral surgery while patients are taking Coumadin

But…

Routine oral surgery should be performed without interruption of Coumadin if:
- INR 1.0-3.5
- Patient not taking Clopidrogel (Plavix) or ASA concurrently…if so, drug alterations may be needed
- 5 or less teeth to be extracted (simple)
- 1 quadrant of SRP
Another Challenge…

60 yo female
Takes aspirin 81 mg daily
PMHx involves a CVA 3 years ago
Vitals are within normal limits
Needs 3 teeth extracted

How do you treat this patient?

And the winner is…

Don’t stop the aspirin
Up to 100 mg has been shown to be OK

More concerning if patient is on additional anticoagulants or has congenital coagulopathy

Also, If patient is taking Plavix alone, then there is no need to interrupt dosing

General Recommendations

INR at or below 3.5, warfarin therapy need not be modified
INR> 3.5, should be referred to their physician for dose adjustment
Use tranexamic acid (Cyklokapron®)
Low dose aspirin need not be discontinued
Plavix need not be modified

Dental Considerations

• Minimum number of platelets needed for dental care = 50,000 /cu. mm
• Spontaneous bleeding possible when platelets < 20,000
• Oral complications involve ecchymoses, petechiae, and hematoma
• If patient takes ASA or Plavix, there is no need to stop either
• In most cases, if patient takes ASA and Plavix there is no need to stop either…unless procedure with significant potential for bleeding (eg, full mouth extractions)

Aspirin (81 mg) – Ibuprofen Co-administration

Dental Considerations:
Ibuprofen for post-op dental pain is usually short-term
Probably little cause for concern
Pts should avoid taking ASA for at least 8 hrs after Ibuprofen

Notes:
General Dental Management

• Medical consultation…
  • Know what to ask for!
  • Appropriate laboratory studies
• Emphasize preventive care
• Aspirin/NSAID-containing analgesics should be used judiciously postoperatively
• When procedures that may cause bleeding are performed, consider local means to aid hemostasis:
  • Pressure
  • Sutures
  • Packing (Gelfoam, Surgicel)
  • Tranexamic Acid Rinse (Cyklokapron®)
  • Topical thrombin

• If a patient calls you at home after a difficult extraction and says they are still bleeding despite biting on gauze…

  Tell them to bite on a wet tea bag!!!
  (Tannic acid is a hemostatic agent)

• Infiltration local anesthesia is generally safe, but inferior alveolar blocks should only be done with good coagulation control
• Dental scaling should proceed only when coagulation status is controlled
  → One quadrant per visit if INR < 3.5, or if patient on ASA and/or Plavix
• Restorative dentistry alone is not in indication for hemorrhage control. Potential for gingival bleeding or hematoma formation from anesthesia is the primary factor
• Dental extractions should only be done with good coagulation control
  → Simple extractions of 5 or less teeth with INR < 3.5, Plavix or ASA
• When you are properly prepared and have good pre-op information, post-operative hemorrhage control should be good
All cultures on all continents have herbal healing traditions. Until the 20th century, most people everywhere had close contact with foods and herbs where they were grown. Through the 1930s, MDs in US studied and relied on plant drugs as primary medicines. Medical schools taught plant taxonomy and medicinal plant therapeutics (pharmacognosy). In 1870, the US Pharmacopeia listed 636 herbal entries. The 1990 edition listed 58. Some were found unsafe, most were replaced by pharmaceuticals.

Dietary Supplement Health and Education Act of 1994 (DSHEA) allows 4 types of statements:
1. Role of nutrient in affecting “structure and function” in humans.
2. Documented mechanism that supplement acts on to affect “structure and function”.
3. Benefits due to dietary deficiency—must report the prevalence of disease in USA.
4. Statements of general well-being from consumption of the supplement.

Dietary Supplement Health and Education Act of 1994 (DSHEA) allows 4 types of statements:

<table>
<thead>
<tr>
<th>Statement</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevate mood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A is essential to proper eye function</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Calcium is essential for bone health</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Saw palmetto promotes prostate health</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Depression Example:
- Treat depression: No
- Elevate mood: Yes

Vitamin A is essential to proper eye function: Yes
Calcium is essential for bone health: Yes
Saw palmetto promotes prostate health: Yes

But “disease” claims not permitted:
- Saw palmetto cures or relieves BPH: Not OK
- CardioHealth: OK, Hepaticure: Not OK
- “Reduces the stiffness of arthritis” not permitted
- “Promotes joint health” is permitted

Depending on state law, these kinds of distinctions may also apply to health care practitioners such as chiropractors. Any structure/function claims must also include:

“This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”

Under the US Dietary Supplement Health and Education Act of 1994, the FDA can:
- Promulgate good manufacturing practices.
- Refer for criminal action the sale of toxic products.
- Obtain injunction against false claims.
- Seize products that pose unreasonable risk.
- Sue company making claims of cure or treating disease.

The FDA cannot regulate supplements as drugs, requiring the same level of proof of efficacy in order for the supplements to be marketed (this applies to vitamins, minerals, herbs, nutriceuticals etc.). The FDA is therefore developing the National Center for Complementary and Alternative Medicine (NCCAM) which can deal with issues of safety, labeling, enforcement, science based research so that some self-regulation/standards exist.

Notes:
Up to 42% of Americans are using some sort of dietary supplement for both prevention and therapeutic purposes, a 6.4 billion dollar industry in 2008.

1. General Health
2. Colds
3. Arthritis
4. Energy Enhancement
5. Cholesterol Lowering
6. Cancer Prevention
7. Allergies
8. Weight Management

Many conventional medications are derived from herbs:
- 35% prescription drugs
- 60% OTC drugs

Over 50 population: average of 7 or more supplements. Someone turns 50 every 10 seconds in the US.

### Differences Between Herbs and Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Herbs</th>
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<tr>
<td>Dose established</td>
<td>Efficacy proof</td>
</tr>
<tr>
<td>Efficacy proof</td>
<td>Monosubstance</td>
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<td>FDA-approval before marketing</td>
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<td>FDA-approval before marketing</td>
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<tr>
<td>Patentable</td>
<td>Potency standardized</td>
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<tr>
<td>Potency standardized</td>
<td>Proof of efficacy not required</td>
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<tr>
<td>Proof of efficacy not required</td>
<td>Complex compound</td>
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<tr>
<td>Complex compound</td>
<td>No FDA pre-approval</td>
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<td>Post-marketing Notification for structure-function claims</td>
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<td>Post-marketing Notification for structure-function claims</td>
<td>Not patentable</td>
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<tr>
<td>Not patentable</td>
<td>Potency varies</td>
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</table>


<table>
<thead>
<tr>
<th>Common Name</th>
<th>Latin Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic</td>
<td>Allium sativum</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Echinacea spp.</td>
</tr>
<tr>
<td>Saw palmetto</td>
<td>Serenoa repens</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Ginkgo biloba</td>
</tr>
<tr>
<td>Cranberry</td>
<td>Vaccinium macrocarpon</td>
</tr>
<tr>
<td>Soy</td>
<td>Glycine max</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Panax ginseng</td>
</tr>
<tr>
<td>Black cohosh</td>
<td>Actaea racemosa</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Hypericum perforatum</td>
</tr>
<tr>
<td>Milk thistle</td>
<td>Silibum marianum</td>
</tr>
<tr>
<td>Green tea</td>
<td>Camellia sinensis</td>
</tr>
<tr>
<td>Evening primrose</td>
<td>Oenothera biennis</td>
</tr>
<tr>
<td>Valerian</td>
<td>Valeriana officinalis</td>
</tr>
<tr>
<td>Horny goat weed</td>
<td>Trifolium pratense</td>
</tr>
<tr>
<td>Grape seed extract</td>
<td>Epimedium spp.</td>
</tr>
<tr>
<td>Bilberry</td>
<td>Vitis vinifera</td>
</tr>
<tr>
<td>Red clover</td>
<td>Pausynystalia johimbe</td>
</tr>
<tr>
<td>Black cohosh</td>
<td>Aesculus hippocastanum</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Zingiber officinalis</td>
</tr>
<tr>
<td>Milk thistle</td>
<td></td>
</tr>
<tr>
<td>Ginger</td>
<td></td>
</tr>
</tbody>
</table>


1. Garlic
2. Echinacea
3. Saw palmetto
4. Ginkgo
5. Cranberry
6. Soy
7. Ginseng
8. Black cohosh
9. St. John’s wort
10. Milk thistle
11. Green tea
12. Evening primrose
13. Valerian
14. Horny goat weed
15. Grape seed extract
16. Bilberry
17. Red clover
18. Yohimbine
19. Horse chestnut seed extract
20. Ginger

### Herbals and Dentistry: What are we really worried about?

1. Bleeding / Hemostasis (Patients on Anticoagulants)
2. Thromboembolism (Patients on Blood Thinners)
3. CNS Interactions (Patients who may receive Sedatives)
4. Blood Pressure Issues (Patients who may be receiving Antihypertensives)
### Top 20 Selling Herbals that may affect Bleeding / Hemostasis (Patients on Anticoagulants)

1. Garlic
2. Echinacea
3. Saw palmetto
4. Ginkgo
5. Cranberry
6. Soy
7. Ginseng
8. Black cohosh
9. St. John's wort
10. Milk thistle

11. Green tea
12. Evening primrose
13. Valerian
14. Horny goat weed
15. Grape seed extract
16. Bilberry
17. Red clover
18. Yohimbine
19. Horse chestnut seed ext.
20. Ginger

**Honorable mentions:** Alfalfa, Beer, Danshen, Dong Quai, EDTA, Glucosamine, Licorice, Policansol, Vitamin K, Willow Bark, Wintergreen.

### Top 20 Selling Herbals that may affect Blood Pressure (Patients on Antihypertensives)

1. Garlic
2. Echinacea
3. Saw palmetto
4. Ginkgo
5. Cranberry
6. Soy
7. Ginseng
8. Black cohosh
9. St. John's wort
10. Milk thistle

11. Green tea
12. Evening primrose
13. Valerian
14. Horny goat weed
15. Grape seed extract
16. Bilberry
17. Red clover
18. Yohimbine
19. Horse chestnut seed ext.
20. Ginger

**Honorable mentions:** Dolomite, Hawthorn, Indian Snakeroot, Oleander, Thuja, Yellow Dock

### Top 20 Selling Herbals that may affect Cognition (Patients on Sedatives)

1. Garlic
2. Echinacea
3. Saw palmetto
4. Ginkgo
5. Cranberry
6. Soy
7. Ginseng
8. Black cohosh
9. St. John's wort
10. Milk thistle

11. Green tea
12. Evening primrose
13. Valerian
14. Horny goat weed
15. Grape seed extract
16. Bilberry
17. Red clover
18. Yohimbine
19. Horse chestnut seed ext.
20. Ginger

**Honorable mentions:** 5-HTP, Ergot, Hawaiian baby woodrose, Kava Kava, L-tryptophan, Lithium, SAMe, Thuja

### Top 20 Selling Herbals that may affect Thromboembolism (Patients on Blood Thinners)

1. Garlic
2. Echinacea
3. Saw palmetto
4. Ginkgo
5. Cranberry
6. Soy
7. Ginseng
8. Black cohosh
9. St. John's wort
10. Milk thistle

11. Green tea
12. Evening primrose
13. Valerian
14. Horny goat weed
15. Grape seed extract
16. Bilberry
17. Red clover
18. Yohimbine
19. Horse chestnut seed ext.
20. Ginger

**Honorable mentions:** Danshen, Dong Quai, Policansol, Willow Bark

### Top Selling Herbals that are Most Prone to Drug Interactions - Indications

- Garlic – Atherosclerosis; Colorectal & Gastric Cancer; HT
- Echinacea – Common Cold; Vaginal Candidiasis
- Ginkgo – Memory; Dementia; Retinopathy; Glaucoma; PMS
- Soy – Breast CA; Diabetes; Hyperlipidemia; Menopausal symptoms; Osteoporosis
- Ginseng – Diabetes; Respiratory tract infections
- St. John’s wort - Depression
- Evening primrose – Mastaglia; Osteoporosis
- Horny goat weed - Osteoporosis
- Yohimbine – Erectile Dysfunction (ED); sexual dysfunction

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**Notes:**

- [Image 12x521 to 275x718]
- [Image 11x301 to 273x500]
- [Image 287x301 to 556x499]
- [Image 288x518 to 556x718]
Top Selling Herbals that are Most Prone to Drug Interactions - EBM

Garlic – Atherosclerosis; HT
Echinacea – No Evidence
Ginkgo – No Evidence
Soy – Possibly Effective
Ginseng – No Evidence
St. John’s wort - Depression
Evening primrose – Possible Effective
Horny goat weed – No Evidence
Yohimbine – Possibly Effective

The H.E.R.B.A.L. Mnemonic

• H ear the Patient out with respect
• E ducate the patient
• R ecord and document
• B e aware
• A gree to discuss
• L earn about new & popular supplements

Web Resources on Herbs

• American Herbalists Guild: www.americanherbalistsguild.com
• Herb Research Foundation www.herbs.org
• Natural Medicines Comprehensive Database www.naturaldatabase.com
• National Center for Complementary and Alternative Medicine www.nccam.nih.gov
• Office of Dietary Supplements www.ods.od.nih.gov

Which Drugs Do You REALLY Have to Worry About?

Warfarin, Cyclosporine, Digoxin, HIV protease inhibitors, Theophylline, Carbamazepine, Lithium, Thyroid medications, Opioids

Steps for Detecting and Advising on Herbal/Drug Interactions

• Is the patient taking any herbal supplements?
• Does the herbal have efficacy for the intended use?
• Is the product reliable? (i.e., what are they REALLY taking?)
• Is the Rx drug one with a narrow therapeutic margin (warfarin, cyclosporine, digoxin, HIV protease inhibitors, theophylline, carbamazepine, lithium, thyroid medications, opioids)?

General Guidelines on Use of Herbal Medicines

• Take a good history of patient use of herbs and supplements.
• Diagnosis needed before using herbs for symptomatic treatment.
• Natural does not equal safe.
• Generally avoid herbs during pregnancy and lactation.
• In children, pay close attention to dosage according to weight.

Notes:
Local Anesthesia
Local Anesthesia – Historical Perspective

- Cocaine was the first local anesthetic, discovered by Carl Koller in 1884 (eye drops)
- The first dental use was by Dr. William Halsted on Nov 26, 1884
- The “caines” developed subsequent to cocaine have no relationship to cocaine other than an etymological and pharmacological one; that is they cause anesthesia.

Structure-Activity Relationship

1. Aromatic portion – Responsible for lipophilicity of compounds, i.e., lipid/water distribution and protein binding characteristics.

2. Intermediate linkage – connected to aromatic residue via an ester or amide linkage. Type of linkage important in determining the route of metabolism and the allergic potential of the compounds.

3. Amine portion – usually a secondary or tertiary amine and is associated with water solubility of the compounds, but is not necessary for anesthetic activity. Compounds lacking the amine portion are insoluble in water and useful only topically.
Mechanism of Action: Local anesthetics block the sensation of pain by interfering with the propagation of impulses along peripheral nerve fibers. This is accomplished by a reduction in the permeability of the nerve cell membrane to sodium ions. This results in a decreased rate of rise in the depolarization phase of the action potential causing a failure of a propagated action potential to develop.

Local anesthetics reversibly bind to the voltage-gated $\text{Na}^+$ channel, block $\text{Na}^+$ influx, and thus block action potential and nerve conduction.

Relative size and susceptibility to block of nerve fibers

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Function</th>
<th>Myelination</th>
<th>Diameter (µm)</th>
<th>Conduction Velocity (m/s)</th>
<th>Sensitivity to Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A: Alpha</td>
<td>Proprioception, motor</td>
<td>Heavy</td>
<td>12 - 20</td>
<td>70 - 120</td>
<td>+</td>
</tr>
<tr>
<td>Type A: Beta</td>
<td>Touch, pressure</td>
<td>Heavy</td>
<td>5 - 12</td>
<td>30 - 70</td>
<td>++</td>
</tr>
<tr>
<td>Type A: Gamma</td>
<td>Muscle spindles</td>
<td>Heavy</td>
<td>3 - 6</td>
<td>15 - 30</td>
<td>++</td>
</tr>
<tr>
<td>Type A: Delta</td>
<td>Pain, temperature</td>
<td>Heavy</td>
<td>2 - 5</td>
<td>12 - 30</td>
<td>+++</td>
</tr>
<tr>
<td>Type B</td>
<td>Preganglionic autonomic</td>
<td>Light</td>
<td>&lt;3</td>
<td>3 - 15</td>
<td>++++</td>
</tr>
<tr>
<td>Type C: Dorsal Root</td>
<td>Pain</td>
<td>None</td>
<td>0.4 - 1.2</td>
<td>0.5 - 2.3</td>
<td>++++</td>
</tr>
<tr>
<td>Type C: Sympathetic</td>
<td>Postganglionic</td>
<td>None</td>
<td>0.3 - 1.3</td>
<td>0.7 - 2.3</td>
<td>++++</td>
</tr>
</tbody>
</table>
Factors affecting Local Anesthetic action:

- $pK_a$
- Lipid Solubility
- Protein Binding
- Vasodilator Activity
- Principles of Local Anesthetics

$pK_a$

All LA are weak bases with a $pK_a$ range of 7.7-8.9. All LA molecules exist in 2 states:

A free base (uncharged) that readily penetrates connective tissues and lipid-rich membranes; and a cation (positively charged species) that is unable to cross membranes.

When the pH = $pK_a$ then the proportion of the two species is 50:50. If $pK_a$ increases, or the pH of the surrounding environment decreases then a greater proportion of the charged form will exist.

**Example…**
Relationships between pKa, Ionization, and Local Anesthesia onset at pH 7.4

<table>
<thead>
<tr>
<th>Drug</th>
<th>pKa</th>
<th>% Cationic</th>
<th>% Free Base</th>
<th>Onset time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepivicaine</td>
<td>7.7</td>
<td>67</td>
<td>33</td>
<td>2-4</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7.8</td>
<td>71</td>
<td>29</td>
<td>2-4</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>7.8</td>
<td>71</td>
<td>29</td>
<td>2-4</td>
</tr>
<tr>
<td>Articaine</td>
<td>7.8</td>
<td>71</td>
<td>29</td>
<td>2-4</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>7.9</td>
<td>76</td>
<td>24</td>
<td>2-4</td>
</tr>
<tr>
<td>Bupivicaine</td>
<td>8.1</td>
<td>83</td>
<td>17</td>
<td>5-8</td>
</tr>
</tbody>
</table>


Lipid Solubility

The major determination of potency for LA is their intrinsic lipid solubility. The general rule is: More lipid solubility = More potency. As a result, agents with lower solubility are generally marketed at higher concentrations.

Relationships between lipid solubility and clinically effective LA concentration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lipid Solubility</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articaine</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Mepivicaine</td>
<td>42</td>
<td>2-3</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>55</td>
<td>4</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>110</td>
<td>2</td>
</tr>
<tr>
<td>Bupivicaine</td>
<td>560</td>
<td>0.5</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>1853</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Protein Binding

Increased protein binding allows anesthetic molecules to be more firmly attached to proteins at receptor sites. The general rule is: Increased protein binding = longer duration of action.

Duration of Local anesthesia is based on several factors:
- Affinity of the LA to the nerve membrane (Lipid and protein components)
- Type of injection
- Presence or absence of vasoconstrictor
- Pulpal vs. soft tissue anesthesia?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approx. Protein Binding</th>
<th>Duration of action (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prilocaine</td>
<td>55</td>
<td>40-220</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>65</td>
<td>60-190</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>75</td>
<td>25-165</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>94</td>
<td>30-470</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>95</td>
<td>40-440</td>
</tr>
<tr>
<td>Articaine</td>
<td>95</td>
<td>60-220</td>
</tr>
</tbody>
</table>

### Average Durations of Local Anesthesia after Intraoral Injection (mins)

<table>
<thead>
<tr>
<th></th>
<th>Maxillary Infiltration</th>
<th>Inferior Alveolar Block</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulpal</td>
<td>Soft Tissue</td>
</tr>
<tr>
<td>2% Lidocaine w/ 1:100K or 1:50k epi</td>
<td>60</td>
<td>170</td>
</tr>
<tr>
<td>3% Mepivacaine</td>
<td>25</td>
<td>90</td>
</tr>
<tr>
<td>4% Prilocaine</td>
<td>20</td>
<td>105</td>
</tr>
<tr>
<td>0.5% Bupivacaine w/ 1:200k epi</td>
<td>40</td>
<td>340</td>
</tr>
<tr>
<td>1.5% Etidocaine w/ 1:200k epi</td>
<td>30</td>
<td>280</td>
</tr>
<tr>
<td>4% Articaine w/ 1:100k or 1:200k epi</td>
<td>60</td>
<td>170</td>
</tr>
</tbody>
</table>

*Jastak JT et al. Local Anesthesia of the Oral Cavity, 1995.*

<table>
<thead>
<tr>
<th><strong>Local Anesthetic</strong></th>
<th><strong>Elimination Half-life (mins)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>96</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>114</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>96</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>210</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>156</td>
</tr>
<tr>
<td>Articaine</td>
<td>27 mins (Hepatic 108 mins)</td>
</tr>
</tbody>
</table>


Notes:
<table>
<thead>
<tr>
<th>Relative Vasodilating Values of Amide-Type Local Anesthetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilatory Activity</td>
</tr>
<tr>
<td>Articaine</td>
</tr>
<tr>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Etidocaine</td>
</tr>
<tr>
<td>Lidocaine</td>
</tr>
<tr>
<td>Mepivacaine</td>
</tr>
<tr>
<td>Prilocaine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maximum Recommended Dosages of Common Local Anesthetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Anesthetic</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Lidocaine w/ 1:100k epii (2%-36 mg)</td>
</tr>
<tr>
<td>Lidocaine w/ 1:50k epi</td>
</tr>
<tr>
<td>Lidocaine w/o epi</td>
</tr>
<tr>
<td>Mepivacaine (3% - 54 mg)</td>
</tr>
<tr>
<td>Mepivacaine (2% w/ 1:20k levo)</td>
</tr>
<tr>
<td>Prilocaine plain (4% - 72 mg)</td>
</tr>
<tr>
<td>Prilocaine w/ 1:200k epi</td>
</tr>
<tr>
<td>Bupivacaine (0.5%)</td>
</tr>
<tr>
<td>Articaine (4% - 72 mg)</td>
</tr>
</tbody>
</table>

Maximum Recommended Dosages of Vasoconstrictors

<table>
<thead>
<tr>
<th></th>
<th>Concentration</th>
<th>Parts / Thousand</th>
<th>Maximum Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/mL</td>
<td></td>
<td>mg</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.02</td>
<td>1:50,000*</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>1:100,000</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>0.005</td>
<td>1:200,000</td>
<td>0.2</td>
</tr>
<tr>
<td>Levonordefrin</td>
<td>0.05</td>
<td>1:20,000</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* 1:50,000 should be reserved for local hemostasis
† Max no. of carps is limited by the LA

Hersh EV. Local Anesthetics.
In: Fonseca RJ. Oral and Maxillofacial Surgery, 2000
Pregnancy and Breastfeeding Risk Classification of Local Anesthetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Category</th>
<th>Use during breastfeeding?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>B</td>
<td>Yes</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>C</td>
<td>Yes</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>B</td>
<td>Yes*</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>C</td>
<td>Yes</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>B</td>
<td>Yes</td>
</tr>
<tr>
<td>Articaine</td>
<td>C</td>
<td>With Caution</td>
</tr>
</tbody>
</table>

*JADA 2012;143:858-71.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Category</th>
<th>Use during breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>B</td>
<td>Yes</td>
</tr>
<tr>
<td>Dyclonine</td>
<td>C</td>
<td>Yes</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>C</td>
<td>With Caution</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>C</td>
<td>With Caution</td>
</tr>
</tbody>
</table>

*JADA 2012;143:858-71.*
What’s in Your Emergency Kit and Why
What is an Emergency? Any condition which if left untreated may lead to patient morbidity or mortality.


• In a survey of 2,704 dentists throughout North America, a total of 13,836 emergencies occurring within a 10-year period was reported.

• None of these emergencies were truly dental emergencies. They were potentially life-threatening medical problems that patients developed while they were in a dental office.

• Almost all medical emergencies that occur in a dental office are fear-related.

• If fear and apprehension are reduced, the chances of having a medical emergency are also reduced.

• Three-quarters of all of these medical emergencies developed as sequelae of pain (i.e., inadequate local anesthesia), the dentist’s failure to recognize and treat a patient’s fear of dental care, or both.

Medical emergencies reported by 2,704 dentists.*

<table>
<thead>
<tr>
<th>EMERGENCY SITUATION</th>
<th>NO. (%) OF EMERGENCIES REPORTED†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope‡</td>
<td>4,161 (30.1)</td>
</tr>
<tr>
<td>Mild Allergic Reaction</td>
<td>2,583 (18.7)</td>
</tr>
<tr>
<td>Postural Hypotension</td>
<td>2,475 (17.9)</td>
</tr>
<tr>
<td>Hyperventilation‡</td>
<td>1,326 (9.6)</td>
</tr>
<tr>
<td>Insulin Shock (Hypoglycemia)</td>
<td>709 (5.1)</td>
</tr>
<tr>
<td>Angina Pectoris§</td>
<td>644 (4.6)</td>
</tr>
<tr>
<td>Seizures</td>
<td>644 (4.6)</td>
</tr>
<tr>
<td>Asthmatic Attack (Bronchospasm)§</td>
<td>385 (2.8)</td>
</tr>
<tr>
<td>Local Anesthetic Overdose</td>
<td>204 (1.5)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>187 (1.4)</td>
</tr>
<tr>
<td>Anaphylactic Reaction</td>
<td>169 (1.2)</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>148 (1.1)</td>
</tr>
</tbody>
</table>

* Source: Malamed.†
† A few emergencies with low numbers were omitted from the tables.
‡ Emergencies that potentially are stress related.

Why Should You Care About Emergencies?

The Best Preparation is Prevention:
• Know your patient: get a complete medical and pharmacological history.
• Review any problem areas.
• Take training.
  • Practice
  • Practice
  • Practice
• Manual - Simple with flow charts.
• Emergency Kit.
• Equipment - Less is better.
• Phone – Cell.
• Medication - Only what you will use and are comfortable using . . .
Stress-Reduction Protocol

- Recognize medical risk.
- Consult patient’s physician(s).
- Pharmacosedation, as indicated.
- Short appointments.

Morning appointments.
Excellence intraoperative pain control.
Minimize waiting room time.
Excellent post-operative pain control.

Rosenberg, M. Preparing for Medical Emergencies: Essential Drugs and Equipment for the Dental Office. J Am Dent Assoc 2010; 141;14S-19S.

Suggested basic emergency drugs for the general dental office

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>DRUG</th>
<th>ACTION</th>
<th>ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchospasm (Severe Allergic Reaction)</td>
<td>Epinephrine</td>
<td>α- and β- adrenergic receptor agonist</td>
<td>Autoinjectors or preloaded syringes, ampules; 1:1,000 solution subcutaneously, intramuscularly or sublingually; adults, 0.3 milligram; children, 0.15 mg</td>
</tr>
<tr>
<td>Bronchospasm (Mild Asthma)</td>
<td>Bronchodilator such as albuterol</td>
<td>Selective β₂- adrenergic receptor agonist</td>
<td>Two or three inhalations every one to two minutes, up to three times if needed</td>
</tr>
<tr>
<td>Bronchospasm (Severe Asthma)</td>
<td>Epinephrine</td>
<td>α - and β- adrenergic receptor agonist (bronchodilator)</td>
<td>Autoinjectors or preloaded syringes, ampules; 1:1,000 solution subcutaneously, intramuscularly or sublingually; adults, 0.3 mg; children, 0.15 mg</td>
</tr>
<tr>
<td>Mild Allergic Reaction</td>
<td>Diphenhydramine</td>
<td>Histamine blocker</td>
<td>50 mg intramuscularly; 25 to 50 mg orally every three to four hours</td>
</tr>
<tr>
<td>Angina</td>
<td>Nitroglycerin</td>
<td>Vasodilator</td>
<td>Sublingual tablet: one every five minutes up to three doses; translingual spray: one spray every five minutes up to three times</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Glucose, as in orange juice</td>
<td>Antihypoglycemic</td>
<td>If the patient is conscious, ingest</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Aspirin</td>
<td>Antiplatelet</td>
<td>One full-strength tablet (165-325 mg) chewed and swallowed</td>
</tr>
<tr>
<td>Syncope</td>
<td>Aromatic ammonia</td>
<td>Respiratory Stimulant</td>
<td>Inhalant crushed and held four to six inches under nose</td>
</tr>
<tr>
<td>Almost Anything</td>
<td>Oxygen</td>
<td>Respiratory Support</td>
<td>Ad Lib</td>
</tr>
</tbody>
</table>

#1: Epinephrine 1:1,000 Injection

- **Uses:** to reverse hypotension, bronchospasm, and laryngeal edema that result from an acute anaphylactoid type reaction. Also used to reduce bronchospasm resulting from an acute asthmatic episode that is refractory to inhaler therapy.

- **Pharmacology:** Causes vasoconstriction that in turn increases blood pressure, heart rate, and force of contraction. Also causes bronchial dilatation. Reduces the release of histamine. Can be ineffective if the patient is taking beta-blocker.

- **Adverse Effects:**
  1. Cardiovascular: Tachycardia, Tachyarrhythmia’s, and hypertension.
  2. Central Nervous System: Agitation, headache, and tremors.
  3. Endocrine System: Increased blood glucose.
  4. Pregnant Female: Can decrease placental blood flow.

- **Dose:** Supplied in vials, ampules, or pre-loaded syringes in concentration of 1:1000 (1mg/mL); 0.3mg for adults, 0.15mg for children. IV give 0.5-2.0mg (0.5mL-2.0mL) depending on severity of hypotension, titrate to effect repeat in 2 minutes if needed.

Notes:
#1: EpiPen Instead??


**CONCLUSION:** The needle on epinephrine auto-injectors is not long enough to reach the muscle in a significant number of children. Increasing the needle length on the auto-injectors would increase the likelihood that more children receive epinephrine by the recommended intramuscular route.

#2: Diphenhydramine (Benedryl) 50mg Injection

- **Uses:** To reduce the affects of histamine release that is associated with allergic reactions, anaphylaxis, and acute asthma attack precipitated by exogenous causes.
- **Pharmacology:** An antihistamine that blocks the release of histamine in the body. It does not prevent the action of the histamine once released and thus must be given quickly. Prevents histamine responses such as bronchospasm, hypotension, rash, and edema.
- **Adverse Effects:**
  2. Central Nervous System: CNS depression (sedative effects including drowsiness, lethargy, and mental confusion).
- **Dose:** 50-100mg IM or IV. For mild cases of pruritis, urticaria, or erythema an oral dose of 50mg every 6 hours can be used.

#3: Nitroglycerin

If patients have a history of angina and you are considering giving them their nitro or yours (from the EMG kit), what MUST you know?

- For Viagra and Levitra, at least 24 hours should have elapsed since the last dose of a PDE5 inhibitor.
- For Cialis, allow at least 48 hours before using nitrates.

*J Am Coll Cardiol 1999; 33:273-82
J Am Coll Cardiol 2003; 42:1855-60*
• **Uses:** Used to relieve or eliminate chest pain associated with angina pectoris, to differentiate between angina and a myocardial infarction.

• **Pharmacology:** A coronary and peripheral vasodilator and as such helps increase the flow of oxygenated blood to the heart muscle.

• It also causes venous pooling of blood decreasing venous return to the heart thus improving the pumping efficiency of the heart. Because of this improved efficiency myocardial oxygen demand is decreased.

• **Adverse Effects:**
  a. Cardiovascular: Rapid heart rate, facial flushing, and orthostatic (Postural) hypotension.
  b. Central Nervous System: Dizziness and headache.

• **Dose:**
  a. Tablet: Tablet: 1 tablet sublingually repeat after 2 minutes if no relief up to 3 doses.
  b. Metered Dose Spray: 1 spray sublingually repeat after 2 minutes if no relief up to 3 doses.

**Angina**

**Symptoms/Signs:** chest pain

<table>
<thead>
<tr>
<th>Position</th>
<th>comfortable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway</td>
<td>N/A</td>
</tr>
<tr>
<td>Breathing</td>
<td>N/A</td>
</tr>
<tr>
<td>Circulation</td>
<td>check pulse, monitor BP</td>
</tr>
</tbody>
</table>

**Definitive Treatment:**

1. Let patient take their nitro
2. Administer O₂ or O₂ with N₂O
3. Chew one aspirin tablet (81mg or 325mg)
4. Call 911
5. Terminate appointment

**M.I. “Heart Attack”**

**Symptoms/Signs:** Crushing sensation in chest, tingling or numbness of left arm or hand, rapid breathing, sweating, ashen color, may be nauseated and vomit. Clenched fist on chest is 80% predictive! Call 911!

<table>
<thead>
<tr>
<th>Position</th>
<th>Comfortable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway</td>
<td>Monitor</td>
</tr>
<tr>
<td>Breathing</td>
<td>Assist if they stop breathing</td>
</tr>
<tr>
<td>Circulation</td>
<td>Check pulse, monitor BP</td>
</tr>
</tbody>
</table>

**Definitive Treatment:**

1. Call 911
2. Administer O₂
3. Chew one aspirin tablet 81 or 325mg
4. Monitor and record vital signs
5. Be prepared to administer CPR

Called “remote ischemic preconditioning,” the procedure developed by Toronto's Hospital for Sick Children was found to significantly limit the amount of damage to the heart muscle caused by a blockage in a cardiac blood vessel.

Ischemic preconditioning involves using the device to interrupt blood flow in the arm, off and on over a period of 35 to 40 minutes: the cuff is inflated for five minutes, then deflated for five minutes, with the procedure being repeated consecutively four times.

[http://www.cbc.ca/health/story/2010/02/26/heart-attack-blood-pressure-cuff.html#ixzz0gfLoHNbP](http://www.cbc.ca/health/story/2010/02/26/heart-attack-blood-pressure-cuff.html#ixzz0gfLoHNbP)
**#4: Oxygen**

Bag-Valve Concentrations:

- Without oxygen - 21%
- With oxygen, no reservoir - 60%
- With oxygen and reservoir - 90 to 95%
- With demand valve attachment - 100%

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**#5: Aspirin (for Acute Coronary Syndromes)**

- **Pharmacology:** Irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, via acetylation, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandin derivative, thromboxane A2, via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation; has antipyretic, analgesic, and anti-inflammatory properties.

- **Uses:** Treatment of mild-to-moderate pain, inflammation, and fever; prevention and treatment of myocardial infarction (MI), acute ischemic stroke, and transient ischemic episodes; management of rheumatoid arthritis, rheumatic fever, osteoarthritis, and gout (high dose); adjunctive therapy in revascularization procedures (coronary artery bypass graft [CABG], percutaneous transluminal coronary angioplasty [PTCA], carotid endarterectomy), stent implantation.

- **Precautions:**
  - Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.
  - Dehydration: Use with caution in patients with dehydration.
  - Ethanol use: Heavy ethanol use (>3 drinks/day) can increase bleeding risks.
  - Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer disease.
  - Hepatic impairment: Avoid use in severe hepatic failure.
  - Renal impairment: Use with caution in patients with mild-to-moderate renal impairment (only at high dosages); avoid in severe impairment.

Notes:
#6: Albuterol Inhaler (bronchodilator)

- **Uses:** Used during acute asthma or Anaphylaxis to reduce or control bronchospasm.

- **Pharmacology:** A β₂-adrenergic drug that relaxes the bronchial smooth muscle. It has rapid onset and duration of action of up to 6 hours. Also reduces the stimulation of mucous production.

- Albuterol and Beta-Blockers tend to inhibit each other.

- **Adverse Effects:** Should be used with caution in patients with cardiovascular disorders especially coronary artery disease, arrhythmias, and hypertension.

- **Dose:** 2 puffs every 2 minutes to a maximum of 20 puffs. Hold inhaler about 2 inches from mouth. Have patient take two deep breaths and then exhale forcefully. Dispense one puff on slow deep inhalation. Hold breath for 10 seconds and repeat.

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#7: Glucose (for hypoglycemia)

- **Symptoms:**
  - Appears confused
  - Cool, moist skin
  - May be hungry
  - May seem “drunk” but not alcohol breath odor
  - Slurred speech

If patient becomes unconscious or does not respond readily after sugar/carbohydrate administration, activate EMS. They will give IV treatment. Never give unconscious patient anything orally!

**Should I Have Other Drugs?**

- Flumazenil (Romazicon®) - YES
- Naloxone (Narcan®) - YES
- Nitrous Oxide?
- Midazolam (Versed®)?
- Corticosteroids?
- Aromatic Ammonia?

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Do Not Get Yourself Locked Into A Serious Drug Collection!
#8: Flumazenil (Romazicon®) for Benzodiazepine Sedation Reversal

- **Uses:** Selectively blocks benzodiazepine receptors, reversing sedation and respiratory depression
- **Preparation:** 0.1 mg/ml, in 5 ml and 10 ml MDV
- **Dose:** IV or sublingual, 0.2 mg every 1 minutes up to 5 doses

“Respiratory depression mediated by benzodiazepines can be reversed using the specific antagonist flumazenil (Romazicon). It can be titrated intravenously or injected sublingually in 0.2 mg increments every 2-3 minutes, up to 1 mg. Flumazenil should not be administered to patients with a history of seizure disorder or dependence on benzodiazepines.”

Dionne R, Phero J, Becker D; Management of Pain and Anxiety in the Dental Office. WB Saudners 2002;18:289

“Intraoral submucosal injection of flumazenil appears to be a viable concept based upon the following findings. The drug is rapidly and complete absorbed into the systemic circulation, as evidenced by comparable serum concentrations to those obtained by IV administration.”


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#9 Naloxone (Narcan®) – Narcotic Antagonist

**Indications:**
- Reversal of narcotic depression including respiratory depression induced by opioids, (both natural and synthetic narcotics), propoxyphene, and narcotic-antagonist analgesics
- Diagnosis of suspected acute narcotic overdosage
- Not effective in counter-acting depression due to barbiturates, tranquilizers or other non- narcotic anesthetics or sedatives

**Routes of Administration:**
- IM, SC - when IV route not feasible; onset of action not as prompt as with IV and may be delayed in patients who are hypotensive and have impaired peripheral circulation
- IV direct - slowly over at least 1 minute

**Dosage - Adults:**
- Known or suspected overdose: 0.4-2 mg IV; if no response, repeat 2-4 mg in minutes; in cases of large narcotic overdoses, or methadone, pentazocine, propoxyphene overdose, higher doses may be required; if no response after 10 mg, reassess diagnosis; effective dose may be repeated every 20-60 minutes
- Post-operative respiratory depression: 0.1-0.2 mg at 2-3 minute intervals until desired response is obtained; repeat doses may be required at 1-2 hour intervals
- Partial reversal of opioid-associated respiratory depression in palliative patient: if respiratory rate < 6/minute, administer 0.1-0.2mg IV q2-3 minutes or 0.1-0.2mg SC q5-10minutes until respiratory rate > 10/minute. Continue to monitor respiratory rate q15minutes until no naloxone given x 1 hour.

**Dosage - Children:**
- Known or suspected overdose:
  - Birth to 5 yrs or 20 kg: 0.1 mg/kg/dose; repeat at 2-3 minute intervals until desired response obtained
  - > 5 yrs or > 20 kg: 2 mg; repeat as above
- Post-operative respiratory depression: 0.005-0.01 mg/kg IV repeated if necessary at 2-3 minutes intervals
- Onset of effect: within 1-2 minutes following IV, within 2-5 minutes following IM or SC
- Duration of effect: 45 minutes to 3-4 hours
- Since duration of action of narcotic agent may exceed that of naloxone, repeated doses or administration of naloxone via IV infusion may be required

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### #9: Midazolam (Versed®) for Seizures

- **Uses:** For seizures, since it can be injected IM or subcutaneously or swallowed (orally). Realistically you want to call 911 if the seizure lasts more than a minute or if it is the first seizure for a patient.

- **Pharmacology:** A short-acting hypnotic-sedative drug with anxiolytic and amnesic properties. It is used in dentistry, cardiac surgery, endoscopic procedures, as preanaesthetic medication, and as an adjunct to local anesthesia. The short duration and cardiorespiratory stability makes it useful in poor-risk, elderly, and cardiac patients.

- **Dose:** Inject 1-1.5mg (1-1.5mL) into buccal fold and repeat after a minute or two if the seizure has not stopped. If buccal fold is too difficult due to patient clenching inject IM on upper arm.

- **Beware:** Midazolam is also available as a 5mg/mL vial in which case 5mL would be 25mg: too much!!
#10: Corticosteroids for Acute Adrenal Insufficiency

The adrenal cortex produces over 25 different steroids. These steroids are broken into three groups: sex steroids, mineralocorticoids, and glucocorticoids. Of primary concern in dentistry are the glucocorticoids. A physiologic dose of approximately 20mg/day of cortisol is produced. This plays a key role in the body's ability to adapt to stress. Cortisol provides a chemical link within the cells of the body allowing regulation of vital functions including blood pressure and glucose utilization.

Cortisol production is triggered by real or threatened “stress” such as trauma, illness, fright, and anesthesia. In a patient with suppressed adrenal function a failure of this cortisol production eliminates the chemical link to regulate vital functions resulting in sudden shock and possibly death. Suppressed adrenal function or Adrenal Failure is classified as either Primary (Addison’s disease caused by Disease states such as TB, Bacteremia, Carcinoma, and Amyloidosis.) or Secondary (caused by Pituitary disorders, Hypothalmic disorders, or Steroid Therapy).

Steroid therapy suppresses the function of the adrenal cortex reducing the production of natural cortisol. Because of this suppression patient's who have been on long term steroid therapy lose their ability to respond to stress. If these patients are stressed symptoms of acute adrenal insufficiency may result.

Signs and Symptoms of Acute Adrenal Insufficiency:

1. Mental confusion
2. Muscle weakness
3. Fatigue
4. Nausea and vomiting
5. Hypotension
6. Intense pains in abdomen, lower back, and/or legs
7. Mucocutaneous pigmentation
8. Hypoglycemia
9. Hyperkalemia
10. Increase heart rate, decreased blood pressure

Dental Treatment Considerations

For patients with a history of glucocorticoid therapy use stress reduction protocols. The following guidelines can be used to determine if replacement therapy is indicated but it is always a good idea to get a medical consult in such cases.

If the patient has undergone supraphysiologic (more than 20mg/day) glucocorticoid therapy that was discontinued more than 30 days prior to the planned dental treatment no supplementation is required.

If the patient has undergone supraphysiologic glucocorticoid therapy within 30 days of the planned dental procedure considered the patients suppressed and provide steroid supplementation equivalent to 100mg of cortisol.

If the patient has undergone or is undergoing alternate day dosing schedule glucocorticoid therapy no supplementation is required but it is best to provide dental treatment on the off day of the patient's dose schedule.

If the patient is currently receiving daily glucocorticoid therapy at a supraphysiologic level (more than 20mg) supplementation is required. If the daily dose is subphysiologic supplementation is not required.

<table>
<thead>
<tr>
<th>Equivalent Doses of Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone __________________________ 25mg</td>
</tr>
<tr>
<td>Hydrocortisone ______________________ 20mg</td>
</tr>
<tr>
<td>Prednisolone ________________________ 5mg</td>
</tr>
<tr>
<td>Prednisone __________________________ 5mg</td>
</tr>
<tr>
<td>Methylprednisolone ___________________ 4mg</td>
</tr>
<tr>
<td>Triamcinolone ________________________ 4mg</td>
</tr>
<tr>
<td>Dexamethasone _______________________ 0.75mg</td>
</tr>
<tr>
<td>Betamethasone ______________________ 0.6mg</td>
</tr>
</tbody>
</table>

Notes:

Fundamentals of Emergency Preparation

- Training (BLS, ILS, ACLS, PALS).
- Development and implementation of an emergency plan.
- Purchase and maintenance of emergency equipment and drugs.
- Periodic mock emergency drills.
- Training new staff members.
- Monitoring and Patient Assessment.
Emergency Kit Setup & Directions
Take all your emergency drugs and tape them to cards with a brief description of what they are, how they are used, how much you give, and can they be repeated. The paragraphs below can be printed then pasted to a card. Tape a syringe and needle to the card if required so you are already to use the drug. Place each card in a clear zip lock bag just large enough to hold the card, meds, and syringes.

Place all the bags in a brightly colored plastic tool box and label the box “EMERGENCY KIT” in large letters. The kit must be centrally located and visible, so do not place in a cupboard. All staff MUST know where this kit is at all times!

Do not have any drug in your kit you do not know and are comfortable giving. Do have every drug you know how to use and might want. It is too late to order the drug when the patient is having a problem.

Refresh your emergency kit every year. You need to bind it to a date or you will put off replacing old drugs. We have been in offices with kits that are over 20 years old and have never had the seal broken.

Realize that dentists see very few medical emergencies so it is hard to maintain competence in handling them. You cannot practice too often. However, the paramedics prefer to be called while the patient is still alive, so call them early.

1. **EpiPen 2-Pak 0.3mg/0.3mL (contains 2 Adult pens)**
   
   *Call 911 - Call 911 - Call 911*
   
   **Inject one pen in to front outside of thigh. Ok to repeat if needed after 3-5 minutes.** Used for anaphylaxis: severe, rapid onset (less than 1 hour) allergic reaction, swollen throat, tongue, or lip or if patient has difficulty breathing allergic reaction. Note that the EpiPen is expensive at $120 for the 2 pens if you see children you must also carry the EpiPen Jr 2-pak 0.15mg/0.3mL. **Call 911.**
   
   OR

1. **Epinephrine 1:1000 ampule (contains 1mg epinephrine)**
   
   *Call 911 - Call 911 - Call 911*
   
   **Inject into outer thigh. Dose is 0.3mg for an adult, 0.15mg for a child. Repeat every 5 minutes or more often. (Maximum of 3 injections).** Used for anaphylaxis: severe, rapid onset (less than 1 hour) allergic reaction swollen throat, tongue, or lip or if patient has difficulty breathing allergic reaction. or if patient has difficulty breathing with slow onset allergic reaction. **Call 911.**

2. **Diphenhydramine Injectable 50mg/mL. Inject 1mL (for kids aged 1-7 use 0.5mL) IM in upper arm.**
   
   Used for moderate, slow onset (takes one hour or more) allergic reaction: Itching throat, swollen tongue, or lip. Be ready for anaphylaxis if breathing difficulty starts. **Observe for 1 hour to ensure recovery. May need to terminate appointment or refer to MD for oral antihistamine or steroids for 3 days.**
3. **One bottle of nitroglycerine spray.** Pump once or twice to prime (you should see a mist come out) then spray 1-2 doses into the floor of mouth. May repeat every 5 minutes up to 3 times. Call 911 if chest pain does not resolve. Used for angina. Also, check to be sure no Viagra or Levitra within the last 24 hours (48 hours for Cialis) before giving the nitro.

4. **A bottle of Aspirin (325mg tabs).** In the case of angina or a heart attack the patient is to chew one tablet while the staff calls 911.

5. **O2 portable tank w/mask and ambu bag.**

6. **One albuterol inhaler.** Shake dispenser, have patient exhale, spray as they inhale. May repeat every 10 seconds. Used for asthma, bronchial spasm.

7. **A can of non-diet, carbonated soda.** Have patient drink 4 oz per minute until can is empty. Hypoglycemia in a diabetic patient is best treated with this. The carbonation gets it through the stomach faster than any uncarbonated source of sugar. It is absorbed from the small intestine. This requires a CONSCIOUS patient.

8. **2 vials Flumazenil (0.1mg/mL - Supplied in either 5mL or 10 mL vials).** Give 1-2mL in floor of mouth off midline adjacent to bicuspid/cuspid area. Observe for 60 seconds. Repeat as needed up to five doses, or until desired effect is realized. Patient must be kept in office for 2 hours to see if they resedate. Used to reverse benzodiazepines including Triazolam, Midazolam, Diazepam, Alprazolam, Lorazepam and at least one non-benzodiazepine, Zaleplon.

9. **2 vials Naloxone 0.4 mg/mL (1 mL).** Give 0.4-2 mg I.V., I.M. or SubQ; may need to repeat doses every 2-3 minutes; after reversal, may need to readminister dose(s) at a later interval (i.e., 20-60 minutes) depending on type/duration of opioid. Give to patient when concerned about a potential narcotic overdose. If no response is observed after 10 mg total, consider other causes of respiratory depression.

Optional:
**An AED (Automated External Defibrillator).** The patient’s chance of leaving the hospital after cardiac arrest drops 10% for every minute the patient is in ventricular fibrillation. You are probably the oldest person in the office so you may be doing this for yourself. It is expected that within a few years AEDs will be mandatory in all dental offices.

**One 5mL vial of Midazolam 1mg/mL for seizures.** Inject 5-7.5mL into buccal fold and repeat after a minute or two if the seizure has not stopped. If buccal fold is too difficult due to patient clenching inject IM on upper arm. Use for seizures, since it can be injected IM or subQ or swallowed (orally). Realistically you want to call 911 if the seizure lasts more than a minute or if it is the first seizure for a patient. Beware: Midazolam is also available as a 5mg/mL vial in which case 5mL would be 25mg: too much!!