Day 1: Getting Started with Sedation: Inhalational Sedation

- Introduction to Sedation
- Clinically-Useful Pharmacology
- Patient Assessment
- Applied Physiology & Anatomy of Respiration
- Nitrous Oxide Equipment: Plumbed and Portable
- First Demonstration – Incremental Technique
- When Fail-Safe Isn't Safe

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

- Physiologic Monitoring
- Contamination and Scavenging
- Nitrous Oxide and Oxygen Pharmacology
- Rapid Induction Technique
- Keeping Patients Safe: The Dental Emergency Kit
- Beyond Sedation: Local Anesthesia Update
- Avoiding Drug Interactions

Day 3: Inhalational Sedation & Sedation – Putting it All Together

- Pharmacology of Oral Sedatives
- Oral Sedation Protocols
- Beyond Sedation: Appropriate Analgesic Prescribing
- Improving your Post-Operative Success
- Keeping Patients Safe: Flumazenil & Naloxone
- Sedation Regulations
Our Clinicians

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 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, PHARMD, ACPR, 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 enhanced the principles and ideals of the Academy of General Dentistry.

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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
The course manual is intended to follow the agenda and slides. Additional information and reference reading is given in your workbooks.

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 dosing of enteral drugs is no more than the maximum recommended dose (MRD) of a drug that can be prescribed for unmonitored home use.

The use of preoperative sedatives for children (aged 12 and under) prior to arrival in the dental office, except in extraordinary situations, must be avoided due to the risk of unobserved respiratory obstruction during transport by untrained individuals.

Children (aged 12 and under) can become moderately sedated despite the intended level of minimal sedation; should this occur, the guidelines for moderate sedation apply.

For children 12 years of age and under, the American Dental Association supports the use of the American Academy of Pediatrics/American Academy of Pediatric Dentistry Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures.

Notes:
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.

**More on Minimal Sedation and Moderate Sedation**: (From the ADA Guidelines, October 2017)

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** - 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.
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.

The following definition applies to the administration of moderate or greater sedation:

**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.

<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><strong>Airway</strong></td>
<td>Unaffected</td>
<td>No intervention required</td>
<td>Intervention may be required</td>
<td>Unrousable even with painful stimulation</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>
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.”

![Image of bell-shape population curve](image)

**Figure 28-3.** A normal, bell-shaped distribution curve. For any given drug, approximately 60% of patients experience desirable clinical effects with the usual adult dose, and 10% exhibit desirable effects with a slightly lower or higher dose. A small percentage of patients are either hyper- or hypo-responders: those individuals requiring either much less or much more of the same medication in order to elicit the desired effect. Protocols are 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.

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!”
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

Since mapping the human genome this new branch of science truly represents the future of medicine since we have the opportunity to prescribe the right drug at the right dose, the first time without needlessly exposing patients to the side effects of medications through inappropriate initial dosing. We will be able to individualized pharmacotherapy based on every individual's genetic make up, thus revolutionizing medicine. Every individual does have a unique genetic predisposition to drug effects and by marrying a patient's genetic information with a drug's pharmacological information we can improve outcomes in our patients.
Roche Molecular Diagnostics developed the world's first pharmacogenomic microarray designed for clinical applications. It provides comprehensive coverage of gene variations and is intended to be an aid for physicians in individualizing treatment doses for patients on therapeutics metabolized through these genes. This tool has now been cleared for in vitro diagnostic use in both the United States and the European Union.

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.
Notes:

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:
  1. Cation, positively charged species – impermeable to cells
  2. A free base, uncharged – readily penetrates connective tissues and lipid-rich membranes

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

- When \( pH=pK_a \) then the proportion of the two species is 50:50
- If \( pK_a \uparrow \) or \( pH \downarrow \) of the surrounding environment then a greater proportion of the charged form will exist

Example...

Lidocaine \( pK_a = 7.8 \)

Injected into an inflamed area with \( pH = 6.0 \)

98% Cationic species – IMPERMEABLE

2% Uncharged species

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."

Differences in Bicarbonate?

<table>
<thead>
<tr>
<th>Solution</th>
<th>No Buffering</th>
<th>Hand Buffered</th>
<th>Mean pH</th>
<th>% Difference (Buffered/Onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% Lido 1:100 epi</td>
<td>4.27</td>
<td>6.96</td>
<td>7.10</td>
<td>63/66.3</td>
</tr>
<tr>
<td>4% Septo 1:100 epi</td>
<td>3.62</td>
<td>6.87</td>
<td>6.97</td>
<td>90/92.5</td>
</tr>
<tr>
<td>4% Prilo</td>
<td>6.31</td>
<td>6.86</td>
<td>7.05</td>
<td>8.7/11.7</td>
</tr>
<tr>
<td>3% Mepi</td>
<td>6.37</td>
<td>7.02</td>
<td>7.01</td>
<td>10.2/10</td>
</tr>
</tbody>
</table>

All solutions mixed to 9:1 anesthetic to sodium bicarbonate ratio

Goodchild JH, Donaldson M. Accepted by Compendium 2015
Notes:

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

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

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

Metabolism

Drugs are chemically transformed by the body to make them more water soluble, and thus more easily excretable. The primary organ of metabolism for the oral sedative medications is the liver (although some similar enzymes exist in the cells of the gastrointestinal mucosa). The enzyme complexes in the liver chemically transform the medication molecules into either active or inactive metabolites. These enzymes are known as the Cytochrome P<sub>450</sub> (CYP450) family of enzymes.

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.

Drugs available to general circulation to have effect

Metabolism

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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:

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

The binding of drugs to receptors cannot be quantified, so clinically we describe a drug's **therapeutic level** in terms of plasma levels. The therapeutic level for a drug is the plasma concentration at which we know a majority of the population will have a desired clinical effect. Although, there is a wide interpatient variability in response to medications, referenced plasma levels of medications help us guide treatment and are recorded as a balance between dose per unit time and factors which will decrease the level of active drug (metabolism, excretion, dilution). Plasma levels of drugs are always changing.

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

**Pharmacodynamics**

Pharmacodynamics studies the interaction of a drug with a receptor at the site of action. Receptor occupancy explains the response of drugs. Binding to receptors is usually reversible and falls into one of two categories: agonists and antagonists. Agonists have an affinity for receptors and their binding to these receptors leads to the effect and efficacy of the medication. An antagonist only has an affinity for binding to the receptor, but this interaction does not illicit a response and it therefore it antagonizes or blocks an active drug from combining to the receptor and causing an effect.
As we age we may have enhanced sensitivity to drugs due to: changes in receptor numbers; changes in receptor affinity or; alterations in the processes after a drug binds a receptor. For example, the elderly are more sensitive to benzodiazepines, more sensitive to the analgesic effects of narcotics and they have enhanced response to anticoagulants such as warfarin and heparin. In general, elderly patients require a reduction in sedative drug dosage.

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

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
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</td>
<td>None (Stress reduction as indicated)</td>
</tr>
<tr>
<td>II</td>
<td>Possible stress reduction and other modifications as indicated</td>
</tr>
<tr>
<td>III</td>
<td>Possible strict modifications; stress reduction and medical consultation are priorities</td>
</tr>
<tr>
<td>IV</td>
<td>Minimal emergency care in office; hospitalization for stressful elective treatment; medical consultation urged</td>
</tr>
<tr>
<td>V</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>
</table>
| MC-1A      | Controlled and stable condition/disease  
No anticipated complications |
| MC-1B      | Controlled and stable condition/disease  
Anticipated/possible minor complications |
| MC-1C      | Controlled and stable condition/disease  
Anticipated/possible major complications |
| MC-2A      | Poorly controlled and/or unstable condition/disease  
No anticipated complications |
| MC-2B      | Poorly controlled and/or unstable condition/disease  
Anticipated/possible minor complications |
| MC-2C      | Poorly controlled and/or unstable condition/disease  
Anticipated/possible major complications |
| MC-3       | Cardiac or other conditions needing continuous monitoring |

**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

Nitrous Oxide: Applied Physiology of Respiration
Nasal Cavities
- Warm (37°C)
- Humidify
- Filter

Larynx Functions
- Prevents entry of large particles into lungs
- Makes speech possible
- Removal of dust particles by cilia and mucous
- Air conduction

Functions of Trachea & Bronchi
- Removal of dust particles by cilia and mucous
- Air conduction
- Anatomical Dead Space
- The space from pharynx to terminal bronchioles
- Air conduction only
- About 150mL of air

Bronchial Lining
- Cilia
- Mucous Cells (Goblet Cells)
- Alveolar Phagocytes (Dust Cells)
- Bronchial Walls
- Cartilage support replaced by smooth muscle

Chronic Obstructive Pulmonary Disease (COPD)
- Emphysema (“Pink Puffers”)
- Chronic Bronchitis (“Blue Bloaters”)
Progression of COPD

“Pink Puffer” → “Blue Bloater”

Pulmonary Capacities

Volumes
- Tidal Volume (500mL)
- Anatomical Dead Space (150mL)

Flows
- Frequency (15/min)
- Minute Volume (T.V. x Freq) = 7,500mL/min
- Alveolar Frequency
  5,250mL/min

Stretch Receptors (X Nerve)
- Situated in smooth muscle in airways
- Stimulated by inflation of lung
- Slowly-adapting nerve ending
- Inhibit respiration

Irritant Receptors (A Nerve)
- Situated by irritants
- Rapidly-adapting nerve ending inhibits respiration
- Produces:
  - Coughing
  - Bronchoconstriction
  - Rapid breathing

Peripheral Chemo Receptors
- Carotid Bodies (IX)
- Aortic Bodies (X)
- Both stimulated by:
  - Low Oxygen
  - High Carbon Dioxide
  - Low pH
- Increase rate & depth of respiration

Central Chemo Receptors
- Close to ventral surface of medulla
- Stimulated by H⁺ in C.S.F.
- H⁺ move accentuated in C.S.F. because no buffering capacity
- Response to CO2 slow (3-7 minutes)
Nitrous Oxide: Historical Perspective and Equipment
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”.

It was not until the mid-1840’s that a dentist named Horace Wells while attending a demonstration was exposed to N₂O. During this demonstration a man named Samuel Cooley, after inhaling the gas, injured his leg and appeared not to notice. Horace Wells instantly envisioned the gas as an adjunct to the field of dentistry.

Horace Wells was the first person to have a tooth extracted under Nitrous Oxide anesthesia. He termed this revelation the “greatest discovery ever made,” and tried over the next year to prove the efficacy of N₂O to the medical community.

1845, Harvard Medical School – Horace Wells’ demonstration to prove the efficacy of Nitrous oxide. The demonstration was a failure, because the patient felt discomfort, and Wells was labeled a “charlatan” and a “fake”

Description of Nitrous Oxide

**Therapeutic Category** - Sedative, Anxiolytic

**Uses** - To induce sedation and analgesia in the anxious dental patient, a principal adjunct to inhalation and IV general anesthesia (GA) in medical patients

**Route of Administration** – Inhalation

**Dosage** - 20 - 70% administered via nasal hood, cannula, or mask

**Drug Uptake** - N₂O is rapidly absorbed via the lungs, onset 1-2 mins

**Armamentarium**

Nitrous Oxide is supplied in blue cylinders
- 95% liquid, 5% vapor
  - Gauge will read 750 psi at 70° F
  - Gauge will not accurately reflect the contents of the tank until tank is less than 20% full

Oxygen is supplied in green cylinders
- 100% compressed gas
  - Gauge will read 2000 psi at 70° F
<table>
<thead>
<tr>
<th>DRUG</th>
<th>ONSET (Min)</th>
<th>MAC (%)</th>
<th>OIL/WATER</th>
<th>BLOOD/GAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2O</td>
<td>0.5</td>
<td>1-2</td>
<td>1.4</td>
<td>103</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.8</td>
<td>3-5</td>
<td>98</td>
<td>1.7</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.3</td>
<td>3-5</td>
<td>224</td>
<td>0.8</td>
</tr>
<tr>
<td>Ether</td>
<td>12</td>
<td>15-20</td>
<td>65</td>
<td>1.9</td>
</tr>
<tr>
<td>Metohylure</td>
<td>13</td>
<td>15-20</td>
<td>970</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Physical Constants of N2O

- Molecular Weight: 44.013
- Boiling Point @ 1.0 atm (° F): -129.1
- Freezing Point @ 1.0 atm (° F): -131.5
- Vapor Pressure @ 70 ° F: 745 psi
- Density (gas): 1.997 g/l
Two ways of delivering Nitrous Oxide in the dental office:
- Central System
- Portable System

Central Delivery System
- Multiple tanks positioned upright in a locked closet or storage area
- Each tank with a pressure reducing valve and pressure gauge connected to a manifold (allows for switching of tanks when one becomes empty)
- Connected to central plumbing to each operatory and flowmeter

Portable Delivery System
- 4 small tanks (2 N2O, 2 O2) attached to a yoke with a flow meter
- Tanks fit into a metal pin system, which serves as a pressure release valve or regulator

Flowmeter
- Many different types, but basic principle is the mixing of gases at an appropriate flow rate
- Average flow rate is 3-6 L/min

Reservoir Bag
- Serves several functions:
  - Provides inspiratory reserve for the patient
  - Provides a means for assessing the proper flow rate for each patient
  - Serves as an emergency means of producing positive pressure gas when compressed

After the gas is mixed via the flowmeter it must pass through rubber tubing to the patient.

Nitrous oxide can either be delivered via face mask, nasal hood, or nasal cannula.

Practitioners should always be aware of kinks, twists, or holes in the tubing as it decrease the effectiveness of the gas and may expose the operator and staff to the gas.

Nitrous oxide should never be given without oxygen.

Surgical anesthesia is impossible with N2O alone without causing hypoxia

**Occupational Exposure**

How can we minimize occupational exposure?

- Nitrous oxide badge or vial – Can be worn by the personnel and will monitor the levels of exposed nitrous
- Proper maintenance of the equipment
- Proper evacuation/scavenging of expired gas – the accepted flow rate for scavenger systems is 45 L/min
- The use of a well-fitting nose mask
- Minimize the use of nitrous oxide
- Educate staff about handling techniques of the equipment and tanks
- Discourage speaking, or mouth breathing when patient is on nitrous oxide
- Perform frequent leak testing
- Make sure of room ventilation, and fresh air dilution
- Provide in-office training to staff about ways to reduce exposure

Notes:
Nitrous Oxide Administration
Objectives

- Anxiolysis / Conscious Sedation
- Maintain all Reflexes
- Maintain Verbal Communication
- Does not take the place of local anesthetics

Nitrous Oxide Levels

- Adult Sedation: 20-50%
- Pediatric Sedation: 20-30%
- Adverse Effects: >60%

Incremental Technique

- 100% Oxygen for 2 minutes
- 10% Nitrous Oxide for 1 minute
- 20% Nitrous Oxide for 1 minute
- 25% Nitrous Oxide for 1 minute
- 30% Nitrous Oxide for 1 minute
- 35% Nitrous Oxide for 1 minute

At 50% take 3 deep breathes

10% We do not expect to see any signs at this time

20% Nitrous for one Minute

We would not normally expect any signs or symptoms at this level

but

Since 20% of the population over react and 20% under react to nitrous oxide/oxygen……

Explain possible Symptoms of:

- Warmth
- Relaxation
- Paraesthesia

Explain the effect of mouth breathing!
Continue increasing at the rate of 5% each minute until some signs of sedation are felt
- If No Sedation by 50% Check:
  - Mouth Breathing
  - Shallow Breathing
  - Loose Mask
  - Ask patient to take three deep breaths
  - Increase flow rate to accommodate increased intake
  - If no symptoms increase at 5% each minute

At Completion of Sedation
- Give 100% Oxygen for five minutes
- Sit patient up at 45 degrees for a few minutes then upright
- Assess recovery

“There has never been a reported mortality in a dental office while using nitrous oxide – oxygen sedation as the sole sedative and dentistry is being performed.”
John A. Yagiela, DDS, PhD (1948-2012)

Early attempts to use nitrous oxide as a sole anesthetic were not successful because of its low potency. With a minimum alveolar concentration (MAC50) of 104% in humans, N2O by itself would require high volume percentage and hyperbaric conditions to achieve anesthesia in 50% of subjects. This scenario is unlikely in any dental office: a characteristic that gives the gas its large, inherent margin of safety.

Two Main Types of Systems: Installed (Central) Systems and Portable Systems.

The 12 Safety Features of Nitrous Oxide – Oxygen Sedation

1. Alarms
2. Color coding
3. Diameter index safety system (DISS)
4. Emergency air inlet
5. Locks
6. Minimum oxygen liter flow
7. Minimum oxygen percentage
8. Oxygen fail-safe
9. Oxygen flush button
10. Pin index safety system
11. Quick-connect for positive-pressure oxygen
12. Reservoir bag
#1 Alarms (Audible and visual)
- Ritchie whistle
  - Low oxygen pressure alarm
  - Oxygen Failure Warning Device (OFWD)
  - Oxygen failure protection device – Dräger
  - Pressure sensor shut off valve – Datex-Ohmeda
- High pressure oxygen alarm
- Low nitrous oxide pressure alarm
- High nitrous oxide pressure alarm

At least one case is reported of hypoxia occurring during anaesthesia in a spontaneously breathing ASA I patient. The patient became cyanotic twice when breathing a gas mixture delivered by a safety mixer. Changing the machine solved the immediate problem. The diagnosis was difficult to make because the rotameters all showed normal delivery of oxygen and nitrous oxide. Oximetry elucidated the cause, which was found to be a defective rapid oxygen control. Because these machines do not appear to be absolutely reliable, the use of gas analysers should become more systematic.


#2 Color coding
Gas cylinders are often color coded, but the codes are not standardized across different jurisdictions. In the United States, for example, oxygen cylinders are typically green, even though oxygen cylinders internationally are typically white. For this reason, cylinder color alone cannot safely be used for positive product identification; cylinders have labels which identify the gas they contain and the label should be used for positive identification. The original anoxic technique of anesthesia with nitrous oxide alone often made patients cyanotic which is where the term “blue nitrous” originates and one of the reasons why nitrous oxide tanks are easily identified as blue cylinders in the United States.

- Cylinders (tanks)
- Hoses (lines, pipes)
- Wall plates (outlets)
- Machine knobs

#3 Diameter-Index Safety System (DISS)
The Compressed Gas Association (CGA) developed DISS to establish a standard for non-interchangeable, removable connections for medical gases, vacuum (suction), and evacuation service. Each type of gas and connector is assigned a DISS number (1040 for nitrous oxide and 1240 for oxygen). Nitrous oxide has been assigned the 3/4”-16 thread connection; oxygen has been assigned the 9/16”-18 thread connection.
Regardless, there have been DISS failures reported in the literature:


#4 Emergency Air Inlet
There is an emergency air outlet that is designed to remain closed as long as gas(es) are being administered to the patient. However, when the oxygen fail safe system turns the gases off, room air is allowed to enter the system so that the patient can continue to breathe through the nasal hood or mask.

#5 Locks
Similar to other psychotropic drugs, nitrous oxide may be abused by individuals with access to the drug, including those in the dental profession. According to State fire codes, nitrous oxide and other compressed gases must be kept in locked rooms, but many manufacturers supply additional locks for the machines themselves to dissuade staff from accessing nitrous oxide inappropriately. Examples of some of these locking mechanisms are occur at the tanks themselves, the manifold, or at the level of the mixer.

#6 Minimum Oxygen Liter Flow
Nitrous oxide – oxygen machines are required to provide a minimum oxygen liter flow of 2.5-3 liters per minute. Since oxygenation of the patient is paramount, this safety feature ensures that the patient always has access to 100% oxygen when the machine is turned on. Regardless of the percentage of gas mix that the patient is receiving, if the nitrous oxide tank were to become empty, this minimum amount of oxygen would continue to flow while the nitrous alarm was alerting the clinician to attend to the tanks.

#7 Minimum Oxygen Percentage
This was one of the initial safety features employed by all manufacturers of nitrous oxide machines to ensure that during gas delivery concentrations of oxygen never fall below 30%. While earlier machines had the ability to give 100% nitrous oxide, they were more commonly found in oral surgery offices or sold as sedation equipment to general dentists in the 1970s. In the 1700s-1800s, the term “Blue Nitrous” was coined as this was the hypoxic technique used to cause sedation and by giving the patient less oxygen than what was available in ambient air, patients would often turn blue. These early anesthesia machines had both nitrous oxide and oxygen flush valves; currently only oxygen flush valves are permitted. The back-ups to this minimum oxygen percentage safety feature are the low oxygen pressure alarm, the pressure sensor shut off valve (oxygen fail-safe) which stops the flow of any other gas, and the emergency air inlet safety feature. In fact, “nitrous oxide sedation” is a misnomer and is more correctly referred to as “nitrous oxide – oxygen sedation” since these two gases must now be given in combination. During gas delivery concentrations of oxygen never fall below 30%. Room air has 21% oxygen.
#8 Oxygen Fail-Safe
The oxygen fail-safe is designed so that the nitrous oxide will automatically turn off when oxygen delivery is compromised or is depleted. It senses only pressure and does not check whether the supplied gas is actually oxygen, however. See “A” in the diagram:

There have been failures of the oxygen fail-safe valve, however, where the internal diaphragm ruptured and the empty oxygen tanks were then back-filled with nitrous oxide. This is perhaps the worst possible scenario since nobody would suspect this flaw, and shutting off the nitrous to give 100% oxygen would actually result in the patient receiving 100% nitrous.

This example emphasizes the benefit of simply taking the mask off of the patient thereby allowing them to breathe room air, rather than providing what you believe to be 100% oxygen.

#9 Oxygen Flush Button
The oxygen flush button is a mechanism that allows for 100% oxygen to be administered through the reservoir bag in the event of an emergency. It delivers oxygen straight from the pipeline or cylinder regulator at 45-50 psi. The flow rate will be between 35-75 L/min. Unfortunately, there have also been reported failures of this fail-safe mechanism: Anderson CE, Rendell-Baker L. Exposed O2 flush hazard. Anesthesiology. 1982; 56(4):328.

#10 Pin Index Safety System
The Pin Index Safety System uses geometric features on the yoke to ensure that pneumatic connections between a gas cylinder and a machine that uses pressurized gases are not connected to the wrong gas yoke. The units for the pin configurations are in millimeters and for oxygen these pins are at 2 and 5 mm respectively, while they are at 3 and 5mm for nitrous oxide.

Unfortunately, there have also been reported failures of this fail-safe mechanism when either the pins that are meant to engage the holes have fallen off, or if there is a build-up of washers such that the pins cannot engage the holes at all.

#11 Quick-Connect for Positive-Pressure Oxygen
Most nitrous oxide – oxygen delivery systems have quick connectors which allow supply hoses to be connected to specific gas connection points. Insertion into an incorrect outlet is prevented by the use of different shapes for mating portions, different spacing of mating portions, or some combination of these: similar in concept to the DISS. In an emergency situation where positive-pressure oxygen is required, perhaps to augment CPR (cardiopulmonary resuscitation) the unique quick-connect compatibility assures immediate access to positive-pressure oxygen anywhere in the office. Caution
as your caverject may also fit in this connection and the last thing you want to do in an emergency situation is fill an unconscious patients’ lungs with water rather than with air!

**#12 Reservoir bag**

The reservoir bag, also called the breathing bag, is typically an inflatable rubber reservoir bladder where fresh gas entering the circuit is conveyed. The bag is gradually filled as gases enter the circuit and is deflated with inhalation. The reservoir bag is easier for the patient to breathe from than a continuous flow of gas(es). The bag should be maintained partly full. It should not be allowed to overfill as it is difficult for the patient to breathe against this positive pressure. This may also lead to escape of gases around the nose/mouth-piece, causing unnecessary contamination of the ambient office air.

Complete emptying of the bag is also undesirable as this defeats its purpose as a reservoir. An empty bag may indicate that the gas flow is inadequate or a leak is present in the system. Breathing against an empty bag can be very frightening, and this is particularly true for apprehensive patients whom we are trying to relax by administering nitrous oxide – oxygen sedation. With the advent of emergency air inlet valves to allow room air to enter the system if the bag is empty or if the gas flow is inadequate to meet minute volume, this is no longer a problem.

**Best Practices**

Before the initial use of the system for each day, all of the nitrous oxide delivery system components should be inspected for wear, cracks, holes or tears. High-pressure line connections can be tested for leaks quarterly. A portable infrared spectrophotometer can also be used to test for leaks.


**How does nitrous oxide cause teratogenesis?** Chronic abuse by dentists show signs similar to vitamin B12 deficiency.


- Vit B12 = increases human sperm motility
- Vit B12 = increases human infertility


- Effect of 20% N2O on rat spermatogenesis after 5-week exposure:
- Decreased sperm count
- Abnormal multinucleated giant cells
- Total recovery after 3 days


- Showed that rat litter size and weight were reduced and number of abortions increased when male previously exposed to nitrous oxide.
- Concentrations at which there were no longer significant effects of nitrous oxide on rat litter size over a 10-day exposure period were between 3250-3500 ppm.


- Deoxyuridine suppression test on dentists using nitrous oxide suggest 400 ppm as a safe level.
- Provided the first direct evidence that occupational exposure to N2O can result in altered vitamin B12 metabolism and impaired synthesis of methionine synthase (a crucial enzyme for DNA formation).


- Evidence is overwhelming that prolonged exposure to clinical concentrations of N2O inhibits cellular proliferation of the formed elements of the blood and can lead to megaloblastic anemia, leukopenia and thrombocytopenia.
- A time-weighted average of 100 ppm for an eight-hour workday and/or a time-weighted average of 400 ppm per anesthetic administration would provide adequate protection of dental personnel.

Rowland AS, Baird DD, Weinberg CR, et al. Reduced fertility among women employed as dental assistants exposed to high levels of N2O. NEJM 1992;327(14):993-7)

- All women who wanted to conceive did conceive within 12 months of trying as long as a scavenger system was used, or even when a scavenger system was not used but nitrous was not on for more than 5 hours per week. Remember: this study simply looked at rates of conception. It has already been shown that nitrous oxide exposure during pregnancy is safe.

ADA guidelines are 50 ppm TWA for offices, 25 ppm TWA for hospital settings.

<p>| Effect of N2O on rat testicular methionine synthetase activity after 1 hour exposure: |
|----------------------------------------|--------|-------|------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Level</th>
<th>Exposure</th>
<th>Reduction</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>1 hour</td>
<td></td>
<td>29%</td>
<td>48 hours</td>
</tr>
<tr>
<td>50%</td>
<td>1 hour</td>
<td></td>
<td>63%</td>
<td>72 hours</td>
</tr>
</tbody>
</table>

Notes:
Physiologic Monitoring For Adult Enteral Sedation
Protective reflexes intact  
Patient can independently and continuously maintain an airway  
Patient can respond appropriately to verbal commands

<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>
</tbody>
</table>

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

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 patient’s 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 patient’s esophagus through their nose or mouth

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

- \( \text{PaO}_2 \) = partial atmospheric pressure of oxygen that is dissolved in the blood. Measured in mmHg
- \( \text{SaO}_2 \) = oxygen saturation of the blood as defined as % of heme sites occupied by an oxygen molecule
- \( \text{SpO}_2 \) = 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 (PaO\(_2\)) \( \rightarrow \) Normal
- 90% saturation = 60 mmHg (PaO\(_2\)) \( \rightarrow \) Danger!
- 80% saturation = 45 mmHg (PaO\(_2\)) \( \rightarrow \) Severe Hypoxia!
Changes in this curve can be caused by:

1. Alkalosis/Acidosis
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
  - Indocarmine

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
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%.$^6$

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

Source: Anesthesia Progress 2000;47:143-150

---

Notes:
What is Methemoglobinemia?

- 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 (Sulfonamides)

**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

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:

---

55
End-Tidal CO$_2$ Monitoring (ET CO$_2$)

The ability to measure a patient’s exhaled carbon dioxide (CO$_2$)

Advantages
- Measures ventilation via detecting exhaled CO$_2$
- Rate
- Alarm

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

Capnography:
Refers to the comprehensive measurement & display of CO$_2$, including end-tidal, inspired, and the capnogram (real time CO$_2$ waveform)

Capnometry:
Refers to the measurement and display of CO$_2$ in numeric form only

Normal PaCO$_2$ = 40 ± 5 mmHg

ET CO$_2$ = 0 mmHg indicates the patient is not being ventilated
- Upper airway obstruction
- Apnea
- ET misplaced
- Ventilator disconnect / malfunction
- Disconnect of sample line
Nitrous Oxide: Contamination and Scavenging
Introduction to potential health hazards of trace anesthetics and proposed techniques for limiting occupational exposure.

Animal Studies

Several studies have examined the effects of nitrous oxide on the development of animal embryos with inconsistent results. Discrepancies between these conclusions are due to:

- Different animals
- Different gas concentrations
- Different times during pregnancy of exposure
- Different durations of exposure

Mutagenicity tests of other inhalational anesthetics have also provided no evidence of carcinogenicity or organ toxicity, although some animal studies indicated that chronic exposure to nitrous oxide concentrations of 1000 ppm or higher can result in teratogenicity.

Human Studies

Cohen 1975: Retrospective Questionnaire defined Levels of Exposure as:

- 0 None
- 1-2999 hours Light
- >3000 Hours Heavy

Return Rate: 70%

Dentists: 21,000/120,000
Assistants: 22,000/150,000

Epidemiological Errors:
- Retrospective
- Inadequate Control
- Incomplete Return
- Biased Return
- Unknown Exposure
- Unsupported by other studies
- Unsupported Diagnosis of defect
Cohen 1980 (Heavily Exposed is redefined as >8 hours per week):

<table>
<thead>
<tr>
<th>HEAVILY EXPOSED DENTIST</th>
<th>FEMALE ASSISTANTS EXPOSED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7 fold increase in liver disease</td>
<td>1.6 fold increase in liver disease</td>
</tr>
<tr>
<td>1.2 fold increase in kidney disease</td>
<td>1.7 fold increase in kidney disease</td>
</tr>
<tr>
<td>1.9 fold increase in neurological disease</td>
<td>2.8 fold increase in neurological disease</td>
</tr>
<tr>
<td>1.5 fold increase in spontaneous abortions in wives</td>
<td>2.3 fold increase in spontaneous abortions in wives</td>
</tr>
<tr>
<td>1.5 fold increase in Cancer Rates</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N₂O CONTAMINATION FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>movement</td>
</tr>
<tr>
<td>talking</td>
</tr>
<tr>
<td>mask leakage</td>
</tr>
<tr>
<td>poor suction</td>
</tr>
<tr>
<td>laughing</td>
</tr>
<tr>
<td>mouth breathing</td>
</tr>
<tr>
<td>moustache</td>
</tr>
</tbody>
</table>

**Brown Mask System Mean and S.D. of N₂O Concentration versus Time**

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂O Concentration (p.p.m.)</td>
<td>50</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
</tr>
</tbody>
</table>

**Fraser-Harlake Mean N₂O Concentration versus Time**

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂O Concentration (p.p.m.)</td>
<td>50</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
</tr>
</tbody>
</table>

**COMPARISON OF THE TESTED MASKS**

<table>
<thead>
<tr>
<th>N Mask Type</th>
<th>Mean ppm N₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 Brown</td>
<td>43.4</td>
</tr>
<tr>
<td>29 Porter</td>
<td>48.2</td>
</tr>
<tr>
<td>24 Parkell</td>
<td>54.4</td>
</tr>
<tr>
<td>23 Dupaco</td>
<td>61.2</td>
</tr>
<tr>
<td>33 Fraser-Harlake</td>
<td>62.7</td>
</tr>
</tbody>
</table>
Carbon Dioxide Absorber
How can we minimize occupational exposure?


- ↑ Vit B12 = increases human sperm motility
- ▼ Vit B12 = increases human infertility


- Effect of 20% N2O on rat spermatogenesis after 5-week exposure:
  - Decreased sperm count
  - Abnormal multinucleated giant cells
  - Total recovery after 3 days


“Concentrations at which there were no longer significant effects of nitrous oxide on rat litter size over a 10-day exposure period were between 3250-3500 ppm”
ADA guidelines are 50 ppm TWA for offices, 25ppm TWA for hospital settings.

<table>
<thead>
<tr>
<th>Level</th>
<th>Exposure</th>
<th>Reduction</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>1 hour</td>
<td>29%</td>
<td>48 hours</td>
</tr>
<tr>
<td>50%</td>
<td>1 hour</td>
<td>63%</td>
<td>72 hours</td>
</tr>
</tbody>
</table>


• Deoxyuridine suppression test on dentists using nitrous oxide suggest 400 ppm as a safe level
• Provided the first direct evidence that occupational exposure to N2O can result in altered vitamin B12 metabolism and impaired synthesis of methionine synthase (a crucial enzyme for DNA formation)


• Evidence is overwhelming that prolonged exposure to clinical concentrations of N2O inhibits cellular proliferation of the formed elements of the blood and can lead to megaloblastic anemia, leukopenia and thrombocytopenia.
• A time-weighted average of 100ppm for an eight-hour workday and/or a time-weighted average of 400ppm per anesthetic administration would provide adequate protection of dental personnel.

ADA Workshop Panel Conclusions

1. N2O/O2 is a very valuable tool for pain and anxiety control and it should continue to be taught at all levels of dental education.
2. Chronic occupational exposure to N2O/O2 in offices without scavenging units may be associated with deleterious neurological and reproductive effects on the health of dental personnel.
3. Where scavenging systems are used there has been no such evidence to date. Appropriate scavenging systems and methods of administration should be adopted.
4. It should be clearly indicated that potential health hazards of N2O do not apply to the patient.
5. N2O levels vary significantly among offices using scavenging systems. Therefore a protocol should be implemented.
6. State dental boards regulate certification programs requiring evidence of satisfactory completion of educational programs.

Recommended Checklists

**On Installation**
- Whole system (spectrophotometer)

**Daily**
- Rubber hoses
- Nasal masks
- Connectors (high and low pressure)
- Reservoir bags (visual)

**Quarterly**
- Whole system (spectrophotometer)

References and Recommended Reading for Medications for Nitrous Oxide Contamination & Scavenging


Gillman M. Nitrous oxide/oxygen conscious sedation without adequate scavenging. SADJ. 2005 Mar;60(2):68, 77


Nitrous Oxide Pharmacology
1. **Nitrous oxide is stable and inert at room temperature**

Inherent Molecular Stability

Density of Nitrous oxide = 1.997 g/L  
Density of Air = 1.239 g/L

Because nitrous oxide is more dense than air, the greatest concentration of unscavenged gas will be low and near the floor

2. **No metabolism in the body, with no organ specific toxic effects?**

Volatile gases move through the body based on partial pressures

The gas moves to other compartments after the first compartment is saturated

Nitrous oxide is not metabolized within the body. 99.9% of absorbed nitrous oxide is eliminated unchanged, 0.004% is recovered as metabolites

After the nitrous oxide is removed delivery is stopped, the gas will diffuse back into the lungs and be exhaled unchanged

There are some organ-specific effects within the body from nitrous oxide use:
- Respiratory
- Cardiovascular
- CNS
- GI
- Respiratory Effects

---

**Characteristics of Nitrous Oxide**

1. Inherent molecular stability
2. Organ-specific toxic effects
3. Non-flammable
4. Low blood-gas coefficient and onset
5. Potency
6. Long-term effects?
7. No unpleasant smell or irritating vapor
8. Cardio-respiratory effects?
9. Analgesic and hypnotic effects?
10. Diffusion Hypoxia & CNS effects reversible?
11. Xenon vs. Nitrous Oxide

---

**Inherent Molecular Stability**

**Physical Constants of N2O**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight</td>
<td>44.013</td>
</tr>
<tr>
<td>Boiling Point @ 1 atm (°F)</td>
<td>-129.1</td>
</tr>
<tr>
<td>Freezing Point @ 1 atm (°F)</td>
<td>-131.5</td>
</tr>
<tr>
<td>Vapor Pressure @ 76° F</td>
<td>745</td>
</tr>
<tr>
<td>Density (gas)</td>
<td>1.997 (g/L)</td>
</tr>
</tbody>
</table>

www.combox.com/frames/technical/gases/nitrous.htm

---
2. **No metabolism in the body, with no organ specific toxic effects? (continued)**

- Can cause direct depression of medullary ventilatory center at concentrations >50%
- Relaxes bronchial smooth muscle
- Can cause direct myocardial depression at concentrations >40%
- When combined with a volatile agent, there is usually less circulatory depression than if either agent is used alone
- Causes increased cerebral blood flow
- Increases intracranial pressure due to increased cerebral blood volume
- Nausea and vomiting are common adverse events when nitrous oxide is given at high concentrations
- Can cause intestinal rupture if administered to patient with bowel obstruction or abdominal distension

Contraindications to nitrous oxide:

**Pregnancy** – No evidence of fetotoxic effects with low-dose, short-term exposure. Chronic effects have proven to be teratogenic resulting in spontaneous abortion, low birth weights, fetal abnormalities, and low conception rates for prospective mothers and fathers. Can cross the placenta rapidly and cause fetal depression.

**Head injuries** – Patients with impaired level of consciousness and/or mentation should not receive nitrous oxide because CBF and intracranial pressure could be increased

**Malnourishment (alcoholics) or Vitamin B12 deficiency** - Patients with Pernicious anemia, and/or are malnourished are at an increased risk of neurologic disease and bone marrow suppression with exposure to N2O

**Presence or suspicion of pneumothorax** – Nitrous oxide diffuses into air-containing spaces 34 times faster than nitrogen can diffuse out, and can lead to potentially dangerous airspace expansion
- Air embolus, intraocular air bubble, intracranial air bubble

**COPD or emphysema** – Administration of N2O may cause rupture of blebs, and/or the administration of augmented inspiratory oxygen concentrations may result in depression of ventilatory drive
  “Bleb” = intrapleural air space

**Severe abdominal pain and distension suspicious of bowel obstruction** – A very serious situation that could ultimately lead to ruptured intestines

**Otitis media** – specifically in children because N2O can readily diffuse into air-filled spaces, including the middle ear. Will be very painful in this instance.

No metabolism in the body, with no organ specific toxic effects?

**Contraindications to nitrous oxide:***

**Scuba diving within the last 24 hours** – N2O should not be used on patients who have been scuba diving in the last 24 hours to avoid decompression sickness
3. **Non-flammable**
   - Nitrous oxide is stable and inert at room temperature
   - It is classified by the Department of Transportation (DOT) as a nonflammable gas
   - However, nitrous oxide can combust at temperatures in excess of 1202° F

4. **Has a low blood-gas coefficient ensuring rapid induction and elimination, with the ability to titrate in a reasonable time**

   The blood/gas coefficient is not related to potency but is calculated by the amount of gas needed to saturate the blood divided the amount of gas

   As blood/gas coefficient increases ♦, onset of action increases ♦

5. **Is reasonably potent**

   Factors that will **not** affect the MAC:
   1. No effect from gender
   2. No time affect
   3. No effect from pH or pCO2
   4. Elevations or mild drops in BP
   5. Hypothyroidism
   6. Chronic alcoholism
   7. Anemia (unless severe)

   Factors that will affect the MAC:
   1. Significant hypoxia decreases the MAC
   2. Increasing age decreases MAC
   3. Circadian rhythms alter MAC +/- 10%
   4. Benzodiazepines and opioids reduce the MAC
   5. Pregnancy decreases the MAC
   6. MAC's are additive (i.e. 50% N2O + .5 MAC Halothane = 1 MAC of anesthetic)

   **MACawake** - The minimum alveolar concentration at which patients still respond to commands
   
   \[
   \text{MACawake} = 0.2 - 0.6 \text{ MAC}
   \]

   MACawake N2O = 20-60%
6. Should have no long-term adverse effects with chronic exposure at low dose MOST of nitrous oxide’s unfavorable characteristics are based on long-term toxicity

Possible long term toxic effects of nitrous oxide
- Bone marrow changes (Vit B12)
- Peripheral neuropathy
- Teratogenic effects
- Greenhouse effect?

Bone Marrow Changes:
Nitrous oxide can be degraded by the interaction with Vit B12 in intestinal bacteria
(B12 is converted from its monovalent to covalent form = inactivation)
This results in signs of B12 deficiency

Bone marrow suppression
- Megaloblastic changes with possible pancytopenia
- Signs of malnourishment
- Pernicious anemia-like symptoms (glossitis, chelitis)

Peripheral neuropathy
- Thought to be the result of nitrous oxide with vitamin B12
- Temporary

Teratogenic effects
- Nitrous oxide has shown to be teratogenic in animal models (70% concentration)
- Vitamin B12 inactivation during the first trimester interferes with organogenesis
- Spontaneous abortion
- Low birth weights
- Pre-term delivery

Does nitrous oxide worsen the Greenhouse Effect?
- Nitrous oxide can contribute to ozone depletion
- Anesthetic-related nitrous oxide represents 1% of global production
- This accounts for .05% of Greenhouse Effect

7. No unpleasant smell or irritating vapor

Nitrous oxide is:
- Colorless
- Odorless (Sometimes referred to as slightly sweet smelling)
- No unpleasant smell or irritating vapor
8. No cardio-respiratory effects

Cardio-Respiratory Effects
- Cardiac effects from nitrous oxide are generally not observed clinically
- Although N2O exerts a negative ionotropic effect on the heart, this is counteracted by the stimulatory effects of nitrous oxide on the sympathetic nervous system

Nitrous oxide cause only modest increases to respiratory rate and tidal volume
- Net effect = Unchanged minute ventilation
- Normal paCO2

9. Analgesic and Hypnotic Effects
- Nitrous oxide is a weak anesthetic agent
- Cannot produce surgical anesthesia under normal atmospheric conditions (MAC = 103%)
- Surgical anesthesia possible only under hyperbaric conditions
- Nitrous oxide will cause significant analgesia at concentrations as low as 20%

Nitrous oxide is sedative/hypnotic at concentrations of 30-80%
Nitrous oxide should not be given at concentrations above 80%
At concentrations > 80%, an adequate amount of oxygen may not be delivered

10. Diffusion Hypoxia & CNS Effects reversible?

Diffusion hypoxia (Fink Phenomenon – 1955) – 100% post-operative O2?

As nitrous oxide diffuses out of the body, it reduces the amount of oxygen within the airways, and there is a relative diffusion hypoxia

It is recommended that after the procedure is finished, that the patient be placed on 100% oxygen to help diminish this diffusion hypoxia

Diffusion hypoxia is a very rare occurrence

In fact, because the phenomenon is so rare and the chances of occurrence are further reduced by post-operative oxygen, the topic is largely academic

Because nitrous oxide is merely absorbed and not metabolized, its effects are completely reversible with discontinuation of the nitrous oxide and/or the administration of 100% oxygen

Is nitrous oxide the ideal inhalation anesthetic?
11. What about Xenon?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nitrous Oxide</th>
<th>Xenon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure + Cheap</td>
<td>✓</td>
<td>NO</td>
</tr>
<tr>
<td>Molecular Stablility</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>No metabolism or toxic effects</td>
<td>NO</td>
<td>✓</td>
</tr>
<tr>
<td>Not flammable</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Low blood/gas coefficient</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Potent</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>No long-term effects</td>
<td>NO</td>
<td>✓</td>
</tr>
<tr>
<td>No unpleasant smell</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cardio-resp effects minimal</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Analgesic and hypnotic</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CNS effects reversible</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Nitrous Oxide Administration
**Objectives**
Anxiolysis / Conscious Sedation
Maintain all Reflexes
Maintain Verbal Communication
Does not take the place of local anesthetics

---

**Nitrous Oxide Levels**

- Adult Sedation: 20-50%
- Pediatric Sedation: 20-30%
- Adverse Effects: >60%

---

**Rapid Induction Technique**

To be used when the patient’s effective concentration of nitrous oxide has been established

Establish Tidal Volume with 100% Oxygen
Increase flow to 10 liters per minute

(Collapse Bag)

Increase % of Nitrous to Maximum (70%)
Have patient take 3 deep breaths
Reduce % to normal required level (e.g. 35%)
Sedation should occur after a few breaths

At Completion of Sedation

- Give 100% Oxygen for five minutes
- Sit patient up at 45 degrees for a few minutes then upright
- Assess recovery

---

**Alternate Rapid Induction Technique**

Establish tidal volume
Take patient to usual end-point for sedation e.g. 35-40%
Wait for few minutes

---

Notes:
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.

Why Should You Care About Emergencies?

• 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.

How Do You Manage 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.
• Equipment - Less is better.
• Phone – Cell.
• Medication - Only what you will use and are comfortable using . . .

Notes:
Stress-Reduction Protocol

- Recognize medical risk.
- Consult patient’s physician(s).
- Pharmacosedation, as indicated.
- Short appointments.
- Morning appointments.
- Excellent 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>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>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>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 recommend-ed 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.

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
#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%

**#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.
#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.

#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?

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 benzo diazepines.”

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.”


#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

#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 preanesthetic 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!!

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**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 q5-10 minutes until respiratory rate > 10/minute. Continue to monitor respiratory rate q1.5 minutes 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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#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 patients 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</td>
</tr>
<tr>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Prednisolone</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>Triamcinolone</td>
</tr>
<tr>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Betamethasone</td>
</tr>
</tbody>
</table>

**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.
Good to Great:
Tips & Tricks to Improve Local Anesthesia Success
Local Anesthetics - Historical Perspective
• The first local anesthetic was Cocaine
• Carl Koller (September 1884) used cocaine as a local anesthetic during a surgical procedure (for glaucoma)
• William Halsted (November 1884) developed the principles of nerve block using Cocaine
• Infraorbital and IA blocks were performed on him as a “guinea pig” it took him 3 years to overcome his resulting Cocaine addiction
• Due to the unfavorable therapeutic index of Cocaine the search was on for a less toxic compound with LA properties:
  o 1904 – Alfred Einhorn synthesized the ester Procaine (Novocaine)
  o 1943 – Nils Lofgren synthesized Lidocaine which possessed:
    • Less allergenicity
    • More potency
    • More rapid onset of action
  o 2000 – Articaine granted FDA approval in the US
  o 2008 – OraVerse (phentolamine mesylate) approved

<table>
<thead>
<tr>
<th>Local Anesthetics</th>
<th>ESTERS</th>
<th>AMIDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td></td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Procaine (Novocaine)</td>
<td>Mepivacaine</td>
<td></td>
</tr>
<tr>
<td>Benzocaine</td>
<td></td>
<td>Prilocaine</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td></td>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Dyclonine (Cēpacol Maximum Strength)</td>
<td>Etidocaine</td>
<td></td>
</tr>
<tr>
<td>Tetracaine (Cēpacol Viractin, Pontocaine)</td>
<td>Articaine</td>
<td></td>
</tr>
</tbody>
</table>

Notes:

Local Anesthesia
Mechanism of Action

B + H⁺ ⇌ BH⁺

CHARGED Form, lipid soluble and penetrating nerve membranes

At Injection

Local Anesthesia
Mechanism of Action

B + H⁺ ⇌ BH⁺

Na⁺

B + H⁺ ⇌ BH⁺

After Injection
Principles of Local Anesthetics

- Local anesthetic solutions prepared at low pH are believed to pinch or sting during injection
- Plain solutions have pH ~ 6
- Solutions with vasoconstrictor have pH ~ 4
- Local anesthetics are marketed in solutions of pH 4-6 to increase shelf-life
- Local anesthetics are unstable when pH increases (when uncharged form dominates)
  - precipitation
  - photodegradation
  - aldehyde formation
  - denaturing

Why Buffer Local Anesthetics?
There have been reports of:
- Faster anesthetic onset
- Less injection pain
- Better quality of anesthesia

Buffered 2% Lido 1:100k (9:1 ratio)
- pH 3.85 buffered to 7.31
- 20 pts, IANB, cross-over design
- Outcomes: onset, injection pain
- 44% of subjects reported zero injection pain with the buffered solution
- 72% of subjects preferred the buffered solution (11% non-buffered, 17% no preference)

Studies on Buffering
- Buffered vs. non-buffered 2% Lido with 1:100k epi
- IANB, Buffered at 5:1 ratio
- No difference in anesthetic success, onset time, or injection pain
- Buffered vs. non-buffered 2% Lido w/ 1:100k epi
- MX infiltration, Buffered at 9:1 and 19:1
- No difference in onset time, or injection pain

Why do we wiggle the cheek during local anesthetic administration?

Local anesthetics reversibly bind to the voltage-gated Na⁺ channel, block Na⁺ influx, and thus block action potential and nerve conduction.
Gate Control Theory was described by Melzack and Wall in 1965. This theory explains about a pain-modulating system in
which a neural gate present in the spinal cord can open and close thereby modulating the perception of pain

Nerve Fibers Involved:
- The smaller, unmyelinated A (delta) and C nerve fibers sense pain such as sharp burning and aching feelings
- Larger, myelinated A (beta) skin nerves which carry senses of touch, heat, cold and pressure

---

**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>A: Alpha</td>
<td>Proprioception, motor</td>
<td>Heavy</td>
<td>12-20</td>
<td>70-120</td>
<td>+</td>
</tr>
<tr>
<td>A: Beta</td>
<td>Touch, pressure</td>
<td>Heavy</td>
<td>5-12</td>
<td>30-70</td>
<td>++</td>
</tr>
<tr>
<td>A: Gamma</td>
<td>Muscle spindle</td>
<td>Heavy</td>
<td>3-6</td>
<td>15-30</td>
<td>++</td>
</tr>
<tr>
<td>A: Delta</td>
<td>Nociception, autonomic</td>
<td>Heavy</td>
<td>2-5</td>
<td>12-10</td>
<td>+++</td>
</tr>
<tr>
<td>Type B</td>
<td>Pain, temperature</td>
<td>Light</td>
<td>&lt;3</td>
<td>3-15</td>
<td>++++</td>
</tr>
<tr>
<td>Type C:</td>
<td>Sensory</td>
<td>None</td>
<td>0.3-1.3</td>
<td>0.7-2.3</td>
<td>++++</td>
</tr>
</tbody>
</table>

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**Using the Gate Control Theory**

“...when vibration is applied as a counter stimulation to an anesthetic injection, it will reach the brain before the pain sensation does. The brain can perceive only one sensation at a time; therefore, the sensation that arrives at the brain first is the one that will be felt.” (Ann Surg Innov Res. 2011; 5: 1-5.)

Gate Control Theory and Local Anesthesia Administration
- Transcutaneous Electronic Nerve Stimulation (TENS)
- Vibration Devices
- DentalVibe
- VibraJect

Transcutaneous Electronic Nerve Stimulation (TENS)

“Patient-controlled TENS reduced but did not eliminate discomfort experienced during inferior dental block and lingual block compared with 20% benzocaine topical anaesthetic” (J Dent 1998;26:417-20.)

“TENS is extremely useful in some dental procedures, such as TMJ syndrome and tooth extraction; however, its use is not prac-
tical in all situations. The dentist must remember that TENS is an adjunctive form of treatment. When applied correctly and with care, TENS is useful in the management of pain in the head and face.” (Anesth Prog 1986;33(3):156-60.)

**DentalVibe®**

“When compared to a conventional approach, DentalVibe significantly lowered self-reported pain during local anesthesia injection for adolescent subjects in this study” (Pediatr Dent 2014;36:51-5.)

“It is much louder than the Vibraject which is a deliberate feature to help distract the patient. In addition the frequency and strength of the vibration is varied, unlike the Vibraject. It is claimed that this increases the efficacy of the device. A real advantage over the Vibraject is that vibration is applied to the tissues before needle contact which helps with initial penetration. However, it means that you cannot use your fingers to retract or palpate structures such as the internal oblique ridge. This results in a seriously high learning curve. I have really struggled with this.” (http://www.dentalanxiety.net/gadgets/dentalvibe-vs-vibraject/)

**VibraJect**

“Subjects receiving the conventional injection methods had a mean pain score of 4.6 ± 0.41. The vibraject group had a mean pain score of 1.71 ±0.24. Certain sites had larger decreases in the mean pain score using the vibraject. These included the upper anterior segment infiltrations and lower right IDB injections.” (Murray P, et al. Efficacy of a Vibrating Dental Syringe Attachment on Pain Levels. IADR 2003. Abstract #1177.)

“We evaluated the effectiveness of VibraJect in combination with an electrical injection device. No statistically significant decrease in pain scores was found at needle insertion or anesthetic injection. The clinical efficacy of VibraJect remains controversial” (Anesth Prog 2005;52(2):62-64.)

A Few Words on the Local Anesthetic Armamentarium:
Does Size Matter?

“There is no statistically or clinically significant difference between perceived pain of injection based on the needle gauges commonly used in dentistry.”

(General Dentistry 2006;55(3):216-7.)
Will the odds be ever in your favor?

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, herbs, 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?

“67% of patients do not discuss complementary and alternative medicine (CAM) with their health care providers because the clinicians did not ask.”


Notes:
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.**
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.

Relative Proportions of Enzymes

<table>
<thead>
<tr>
<th>Relative Proportions of Enzymes</th>
<th>CYP1A2</th>
<th>CYP2D6</th>
<th>CYP2C19</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP 1A2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Substrate</strong></td>
<td>Caffeine</td>
<td>Chlordiazepoxide</td>
<td>Diazepam</td>
<td>Enrofloxacin</td>
</tr>
<tr>
<td><strong>Inducer</strong></td>
<td>Carbamazepine</td>
<td>Clarithromycin</td>
<td>Cigarette Smoke</td>
<td>Erythromycin</td>
</tr>
<tr>
<td><strong>Inhibitor</strong></td>
<td>BCPs</td>
<td>Cimetidine</td>
<td>Ciprofloxacin</td>
<td>Flavoxamine</td>
</tr>
<tr>
<td><strong>CYP 2C9</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Substrate</strong></td>
<td>ASA</td>
<td>Diazepam</td>
<td>Diazepam</td>
<td>Most NSAIDs</td>
</tr>
<tr>
<td><strong>Inducer</strong></td>
<td>Carbamazepine</td>
<td>Phenobarbital</td>
<td>Phenobarbital</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td><strong>Inhibitor</strong></td>
<td>Amiodarone</td>
<td>Azole Antifungals</td>
<td>Cimetidine (weak)</td>
<td>Statins</td>
</tr>
</tbody>
</table>

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

Notes:
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”.

### 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.
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**

**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.

Consider Your Resources

➢ Texts (Lexicomp’s Drug Information Handbook for Dentists)
➢ Lexicomp Dental Drug Database
➢ Web-based Services (Drug Reax by Micromedex)
➢ www.naturaldatabase.com
➢ Clinical Pharmacology by Gold Standard Multimedia
➢ order1@adecllc.info by Dr. Michael Glick
➢ PDAs (Epocrates, Tarascon and others)
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.
Pharmacology of Sedatives and Reversal Agents
Anxiolysis is a minimal level of sedation whereby the patient has decreased anxiety to facilitate coping skills while retaining interaction ability. Conscious sedation is a moderate level of sedation whereby the patient retains their protective reflexes as well as their own airway, and can respond to physical and verbal stimuli.

### The Spectrum of Anesthesia

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

### Parenteral vs. Enteral Sedation

<table>
<thead>
<tr>
<th></th>
<th>Parenteral</th>
<th>Enteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV, IM, SC</td>
<td></td>
<td>Oral, SL, rectal</td>
</tr>
<tr>
<td>No “First-Pass” effect</td>
<td>Long latency period</td>
<td>“First-pass” effect</td>
</tr>
<tr>
<td>Drug effect is rapid</td>
<td></td>
<td>Presentation of adverse effects is slow</td>
</tr>
<tr>
<td>Adverse effects can be rapid</td>
<td></td>
<td>Lower incidence of adverse effects</td>
</tr>
<tr>
<td>Requires specialty training</td>
<td></td>
<td>Requires less specialty training</td>
</tr>
<tr>
<td>Patient acceptance?</td>
<td></td>
<td>Patient acceptance?</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.
The goal of conscious sedation dentistry is to create a patient who is calm, and comfortable enough to receive dental care, and who can maintain a patent airway without assistance. Medications used for anxiolysis or conscious sedation should carry an inherent margin of safety such that overdose or unconsciousness is unlikely.

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

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

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

Chloral Hydrate, 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.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Dose (grams)</th>
<th>Arrhythmia</th>
<th>Cardiac Arrest</th>
<th>Antiarry. Drug Res.</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.5</td>
<td>PVC</td>
<td>No</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>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 catecholamines. *Jastak. JADA 1988* (vol.116)
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:

![Macromolecular Complex](image1)

![Neuron Action Potentials](image2)

Benzodiazepines

![Benzodiazepine Structure](image3)
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

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)
- $LD_{50}$ 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

Goodchild JH and Donaldson M. The Use of Sedation in the Dental Outpatient Setting: A Web-based Survey of Dentists. Dent Im-

Notes:
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

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).


Goodchild JH and Donaldson M. Calculating and justifying total anxiolytic doses of medications for in-office use. General Dentistry 2006 Jan-Feb;54-57.
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>10-20 mg</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: golu 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".


Notes:
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), resedation 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 (Benedryl) 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.

<table>
<thead>
<tr>
<th>Antihistamines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydroxyzine (Atarax or Vistaril)</strong></td>
</tr>
<tr>
<td>- Diphenylmethane, unrelated to benzodiazepines, phenothiazines, or opiates</td>
</tr>
<tr>
<td>- H1-receptor antagonist</td>
</tr>
<tr>
<td>- Bronchodilator</td>
</tr>
<tr>
<td>- Antisialogogue (anticholinergic)</td>
</tr>
<tr>
<td>- Antiarhythmic</td>
</tr>
<tr>
<td>- Anxiolytic</td>
</tr>
<tr>
<td>- Even at high doses produces minimal CV and respiratory depression</td>
</tr>
<tr>
<td>- High therapeutic index</td>
</tr>
<tr>
<td>- Produces moderate sleep with no amnesia</td>
</tr>
<tr>
<td>- Antihistaminic, Decongestant, and Anti-emetic actions</td>
</tr>
<tr>
<td>- Onset: 1 hour</td>
</tr>
<tr>
<td>- Half-Life: 3-7 hours</td>
</tr>
<tr>
<td>- No active metabolites</td>
</tr>
<tr>
<td>- Duration: 3-6 hours</td>
</tr>
<tr>
<td>- Supplied in 10, 25, and 100 mg tablets and a 10mg/5mL syrup</td>
</tr>
<tr>
<td>- Dosage: Adults 50-100 mg, Children 10-50 mg</td>
</tr>
<tr>
<td>- Overdosage: No specific antidote</td>
</tr>
<tr>
<td>- FDA approved anxiolytic and as a pre- and postoperative adjunctive medication</td>
</tr>
</tbody>
</table>

<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>
**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.

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

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 to 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 N₂O 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 N₂O. 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 N₂O anesthesia. He termed this revelation the “greatest discovery ever made,” and tried over the next year to prove the efficacy of N₂O 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 N₂O sedation. From that time until the late 1950’s, the medical field predominately used N₂O as a preanesthetic gas for Halothane. Dental schools began teaching inhalation anesthesia in the early 1960’s and it is estimated that “56% of GP’s and 85% of oral surgeons” use N₂O 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
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: ________________
**Case Example 3**

triazolam

- 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: ________________
**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)

<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>Diazepam</td>
<td>2.5 mg</td>
<td>Lorazepam 0.5 mg</td>
<td>Hydroxyzine 25 mg</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10 mg</td>
<td>Lorazepam 2 mg</td>
<td>Hydroxyzine 100 mg</td>
</tr>
</tbody>
</table>

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 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.: 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

\[ F = 44\% \]
\[ \text{Dose} = 0.25\text{mg} \]
\[ V_d = 70 \text{ L} \]
\[ K_{ab} = 1.5 \text{ h}^{-1} \]
\[ K_{el} = 0.35 \text{ h}^{-1} \]
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 (ie, 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/halcindex.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.

Inadequate Sedation Nitrous Oxide Supplementation
Medications for Postoperative Analgesia
Classification of Pain: Most Americans experience three or four types of pain per year. There are over 50 million Americans partially or totally disable by pain with an annual cost to the system of $70 billion (Lancet 1999;353(9168):1959). The goals of therapy for pain are to decrease the intensity, increase physical activity, appropriate use of medications, regulation of sleep patterns and moods, as well as reestablishing work habits.

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

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

Dentists write approximately 16 million prescriptions for analgesics annually in U.S. The major indication in dentistry is to manage postoperative pain, requiring a prescription of only a few days duration. Most often the challenge is to give high enough doses over a few short days to cover the inflammatory period, without putting the patient at risk of adverse sequelae. Although the cornerstone of these prescriptions focus on the non-opioid analgesics and opioid analgesics, it is important to remember that most pain of dental origin is due to the inflammatory process, which is why non-steroidal antiinflammatory drugs (NSAIDs) make the most sense for treatment. Opioid-based medications act centrally and do not have antiinflammatory properties.

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

### Analgesics used for Postoperative Dental Pain

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

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

### Adding Up Doses: Amount of Acetaminophen Per Pill

- Tylenol Regular Strength 325mg
- Tylenol Extra Strength 500mg
- Darvocet N 50mg 325mg
- Darvocet N 100mg 650mg
- Vicodin / Vicodin ES 500mg / 750mg
- Lortab 500mg
- Lorcet 650mg
- Tylox / Percocet 325mg / 500mg
- Tylenol #3 300mg
Acetaminophen may be the most ubiquitous medication in this category. It is comparable to ASA and NSAIDs in analgesic and antipyretic activity, but only has a weak anti-inflammatory activity. In patients who are maintained on blood thinners or have a history of bleeding complications, acetaminophen dose offer one major advantage over ASA and NSAIDs as it has a minimal antiplatelet effect and does not injure the gastric mucosa. Adult dosages range from 325mg to 1000mg administered three to four times per day, with a maximum daily dose of no more than 4.0 grams (4000mg) to avoid hepatotoxicity. In those patients at risk for liver problems (e.g., Chronic alcoholics, hepatitis patients), the maximum recommended dose should not exceed 2.0 grams (2000mg). The pediatric dose of acetaminophen is 10-15 mg/kg/dose orally every 4-6 hrs (maximum 5 doses/day).

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

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

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

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

**Mechanism of Action of NSAIDS**

![Diagram of COX-1 and COX-2 inhibitors](image)

**NSAID Mortality**

![Graph showing NSAID mortality](image)

*Figure 1. U.S. Mortality Data for Seven Selected Disorders in 1997. A total of 16,956 patients with rheumatoid arthritis or osteoarthritis died from the gastrointestinal toxic effects of NSAIDs. Data are from the National Center for Health Statistics and the Arthritis, Rheumatism, and Aging Medical Information System.*
**NSAID Mortality:** Fortunately or unfortunately, many of these medications are now available without a prescription, which may give prescribers the false sense that they are completely “safe” (without adverse sequela). In fact, 16,500 people die in US each year due to NSAID complications. The mechanism of action of NSAID’s is to inhibit both COX-1 and COX-2 (cyclooxygenase isoenzymes) which are responsible for the production of prostaglandins: the mediators of inflammation. Some of these prostaglandins are cytoprotective, however, as part of the body’s natural homeostatic process. By non-specifically inhibiting both isoenzymes, NSAIDs have been associated with an increased rate of gastritis, gastric erosion and even ulceration.

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

**NSAID Prescribing:** Not all NSAIDs are created equally. The risk of GI toxicity varies from: ibuprofen ➡ ASA ➡ diclofenac ➡ naproxen ➡ indomethacin ➡ piroxicam ➡ ketoprofen ➡ ketorolac. When you prescribe NSAIDs, do so only to patients who do not respond to acetaminophen. Select the NSAID with the lowest toxicity and prescribe the lowest possible dose for the shortest duration of time. Mucosal lesion may be caused in as little as one week.

**COX - 2 INHIBITORS:**

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

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

---

**Prostaglandin I2**

- Predominantly found in the endothelium
- Inhibits platelet aggregation, causes vasodilation, prevents proliferation of vascular smooth-muscle cells
- Thromboxane A2 does the opposite: it is the major COX-1 product of platelets which causes platelet aggregation, vasoconstriction and vascular proliferation.
- COX-2 specific inhibitors upset this balance!
When rofecoxib (Vioxx) was available, it was the most selective of available NSAIDs (>50-fold potency for COX-2 over COX-1) and was twice as selective as celecoxib. Vioxx was unfortunately removed from the US market in 2004. The COX-2 inhibitor seems to be equally effective as the NSAIDs. There seems to be no difference in overall adverse effects. There seems to be no difference in real effects. In these 3 studies no dyspeptic symptom differences were noted. However, there was an absolute difference in endoscopically proven ulcer of 10 – 25% decrease. Also note that where COX-2 inhibitors were used, they had no effect on platelets.

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

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

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

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

**AN OVERVIEW OF COX-2 INHIBITORS**

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

Opioid-Based Analgesics: Central Analgesics

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

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

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

Maximum daily dosages do not readily apply to these agents and it may be more clinically useful to be aware of the minimum effective dosages and potential equivalficious dosing when switching between agents.
In trying to achieve the best of both worlds there are several combination products which incorporate either acetaminophen or an NSAID with an opioid-based analgesic (eg. Percocet, Vicodin, and Vicoprofen). The practitioner should still decide if an opioid-based analgesic is appropriate therapy for the particular case, and they should also be aware of the maximum recommended daily doses of acetaminophen or the NSAID being used in the combination product. This is especially important in those patients who are ordered both Tylenol and Percocet, for example (since they both contain acetaminophen).

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

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

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

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

**Hydromorphone (Dilaudid):** This drug is excellent for patients allergic to morphine. Dilaudid SR (sustained release) comes in 3, 6 and 12mg capsules. The dosing is every 12 hours and the capsules can be opened. This drug is also effective when morphine tolerance develops. You should switch from morphine to hydromorphone when morphine doses needed by the patient are increasing rapidly. In the non-narcotic naïve patient the ratio is about 5:1.
Meperidine (Demerol): There is no advantage with Demerol over morphine for chronic pain. This drug has a shorter half-life, but its active metabolite (normeperidine) has an extended half-life of 8-12 hours. Meperidine may accumulate with repeated administration leading to CNS stimulation that manifests itself as agitation, irritability, nervousness, tremors, twitching and seizures. Since this drug is eliminated by the kidneys, patients with decreased renal function are more susceptible to CNS stimulation from repeated administration. A major contraindication is in patient receiving MAO inhibitors. This may cause severe respiratory depression, coma and decrease in blood pressure.

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

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

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

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

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

Notes:

Searchable database
you do NOT need to have all of the information
As of July 31, 2015, the Montana Prescription Drug Registry (MPDR):

- Over 7.2 million prescriptions in the database.
- Two thousand seven hundred twenty-eight users are registered, which is 28.3% of all eligible users.
- 40.9% of eligible health care providers who live in Montana are registered to use the MPDR, and 61.5% of in-state pharmacists have registered.
- In July, 13,635 patient history searches were conducted (290,356 since 2012) and staff responded to 16 subpoenas (526 since 2012).

Case Study

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

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

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 antiinflammatory agents, ibuprofen and acetaminophen should be the combination of choice (helps avoid “codeine failures” also).

Corticosteroids in Dentistry
**Corticosteroids:** Man-made drugs that closely resemble cortisol, a hormone that the adrenal glands produce naturally. Corticosteroids are often referred to by the shortened for “steroids” but are different from the sex hormones. Steroids generally work by decreasing the production of chemicals that cause inflammation. This helps keep tissue damage to minimum. They reduce the activity of the immune system by affecting the way white blood cells work.

1. **Glucocorticoids:** Corticosteroids with a relatively greater effect on carbohydrate metabolism than on water and electrolyte regulation.

2. **Mineralocorticoids:** Corticosteroids characterized by their similarity to aldosterone and their influence on water and electrolyte balances.

**Steroids in Dentistry**
- Immunosuppressive: erosive lichen planus, SLE, pemphigus vulgaris, rheumatoid arthritis, scleroderma
- Anti-inflammation: mucositis, oral ulcerations, post-op edema
- Analgesia: post-op pain
- Replacement therapy: adrenal insufficiency

**Glucocorticoids**

They are effective in relieving the common postoperative dental sequelae of:
- Pain
- Edema
- Trismus

To be effective, they must be given in adequate doses
- Normal daily output of cortisol is 15-25 mg/day
- Up to 300 mg/day in times of crisis

**Dexamethasone**

Drug Class: Glucocorticoid (FDA approved 1958). Available as:
- Tablets (0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, 6 mg)
- Injection (4mg/mL, 10mg/mL, 20mg/mL)
- Elixir (0.5 mg/5 mL)

Brand Name: Decadron

Storage: 68-77°F. Do not refrigerate

Plasma Half-Life: 3-5 hours

Duration of Action: 2.5-6 days
Question: What benefit do corticosteroids play in Dentistry?

- Dan et al. (2010): Meta-analysis on the effects of corticosteroids after oral and orthognathic surgery:

“The administration of corticosteroids in oral surgery decreases edema and pain significantly, with no higher risk of infection and with minimal risk of other side effects”

What about if we pre-treat with Dexamethasone & Ibuprofen?

Local Dexamethasone Infiltration After Dental Implant Placement – A Comparative Study

Two groups:
A: Pre-op Abx, NSAID
B: Pre-op Abx, NSAID, and post-op Dex (16mg total)

A: 66% had severe pain at 12h
Swelling peaked at 36h
B: 8% had severe pain at 12h
Lower swelling at every time measurement


Do corticosteroids impact implant osseointegration? Two studies…

- White Rabbits
- Implants into the mandible and tibia
- Two groups: One group treated with prednisolone for 4 days before surgery, then 4 days one month and two months after surgery and then a Control group
- Outcome measure: (evaluated at 3 months) Bone density, Removal torque

Results: All implants osseointegrated. No difference in bone density, removal torque of tibia implants less than mandible
Conclusion: Osseointegration of titanium implants in the mandible is not affected strongly by steroid administration

- White Rabbits
- Designed to mimic osteoporosis
- Tibia implants in four groups (one control, 3 experimental): Steroid injections 2 weeks before thru 4 weeks post-op; Steroid injections daily for 4 weeks are placement; Steroid injections daily for 4 weeks, starting 4 weeks after surgery
- Outcome measures: Bone contact with implant and Pull-out force

Results: All implants osseointegrated. Significantly less bone contact in the experimental groups. No difference in pull-out force.
Conclusion: Dental implants may successfully integrate in osteoporosis-like bone.

Notes:
Does corticosteroid use correlate with disturbances in surgical wound healing?

Thorén et al. (J Oral Maxillofac Surg 2009;67:1884-1888.)
- Total of 280 patients undergoing open reduction for mandibular or zygomatic fracture (both IO and EO approaches)
- 100 patients (35.7%) were administered peri-operative steroids
- Most common steroid was Dexamethasone, doses were 5-30 mg (or equivalent)

Results: The steroid group had 6 instances of disturbed healing (6%). The non-steroid group had 5 instances of disturbed healing (2.8%)
Conclusions: No statistical difference between the two groups. All 6 of the healing disturbances were in the highest dose group (30mg Dexamethasone)

- Consider the administration of a corticosteroid for the mitigation of pain and swelling
- Timing:
  - 4mg Dexamethasone one day before surgery, after surgery 4mg submucosal injection in surrounding area
  - Some authors suggest administering additional steroids for 2 days post-op to avoid rebound edema
Keeping Patients Safe: Flumazenil & Naloxone
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 0.2 mg doses at 1-minute intervals, to a total of 1 mg 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 (0.7 to 1.3 hours), re-sedation occurs in up to 65% of patients and requires either re-dosing or continuous infusion (0.25 to 1.0 mg/hr).

In summary, flumazenil should be used for selected patients with significant symptoms from a known benzodiazepine overdose and not routinely used in patients with altered mental status.

Other points to note are:

1. Insoluble in water
2. Slightly soluble in acidic solutions
3. Dilute concentration of 0.1 mg/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 5 mL vials and be aware of expiry dates!

“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.”


PURPOSE: The purpose of this study was to examine intralingual (IL) and submucosal (SM) delivery of flumazenil as viable alternatives to immediate intravenous (IV) administration for reversing benzodiazepine sedation in an animal model. METHODS: A dog animal model was chosen based upon comparable body weight to children (12-17 kg) and the ease of oral access in this species. Research design was a non-randomized matched pair study. This type of “before and-after study” allowed the dogs to receive 3 different routes of flumazenil administration (IV, IL, and SM) following an initial dose of midazolam (0.5 mg/kg IV). Blood samples were obtained (at 0, 2, 4, 8, 15, and 30 minutes) for high performance liquid chromatography (HPLC) analysis of flumazenil and midazolam, and oxygen saturation values were recorded. RESULTS: Both IL and SM delivery of flumazenil were determined to be viable alternatives to immediate IV administration for reversing benzodiazepine-induced oxygen saturation (SaO2) desaturation. For flumazenil to be able to reverse the SaO2 desaturation, the plasma levels must be greater than 5ng/ml, which was exceeded by IL and SM drug delivery. CONCLUSION: In a benzodiazepine-induced desaturation, the submucosal and intralingual routes are viable alternatives to intravenous administration of flumazenil in an animal model.


PURPOSE: This study was performed to determine the bioavailability and local tissue toxicological safety of flumazenil (Romazicon) when administered by oral submucosal (SM) as opposed to intravenous (i.v.) injection. METHODS: Six dogs each received SM flumazenil (0.2mg), and their serum was collected at predetermined time intervals (0-2 h) and frozen (-70 degrees C). Seven days later, the dogs received an identical dose of i.v. flumazenil, and serum samples were again collected, as above. Comparative quantitation of flumazenil levels (i.v. vs SM) was made using a sensitive HPLC assay (UV detection). Direct/local drug toxicity was visually scored by unbiased raters of color photographs (test and control mucosa) taken at 1, 2, and 7 days following SM flumazenil injection. An oral pathologist examined slides processed from control and treatment tissues (hematoxylin and eosin staining) taken (punch biopsy) 1 week following SM injection to compare with direct clinical scores. RESULTS: Serum flumazenil levels reached a plateau (8.5 +/- 1.5 ng/mL, mean +/- SD) within 4 min of SM drug injection and declined thereafter to -2 ng/mL by 2 h. Bioavailability of SM flumazenil was 101 +/- 14%, based upon measuring the area under the serum concentration-time curves over 1.5 h (AUC 0-1.5 h, SM vs. i.v. drug). Thus, serum drug levels following SM drug administration were broadly comparable to those obtained during the elimination phase of corresponding i.v. drug delivery. Regarding drug tissue toxicity, no evidence of direct drug toxicity was observed by unbiased raters of color photographs (test and control mucosa) taken at 1, 2, and 7 days following SM flumazenil injection. Following pathologic review, no difference was seen in the degree of inflammation between treatment and control tissue. CONCLUSION: At the quantity and concentration used, SM drug flumazenil administration appears to be both a safe and a viable alternative to bolus i.v. drug delivery and worthy of further investigation.


OBJECTIVE: To determine whether flumazenil, a drug used to reverse benzodiazepine-induced respiratory depression and approved only for i.v. use, is effective by alternative routes. METHODS: A randomized, controlled, nonblinded, crossover canine trial was performed to evaluate reversal of midazolam-induced respiratory depression by flumazenil when administered by alternative routes. Mongrel dogs were sedated with thiopental 19 mg/kg i.v., then tracheally intubated. With the dogs spontaneously breathing, tidal volume, end-tidal CO2, and O2 saturation were observed until a stable baseline was achieved.

Notes:
Incremental doses of midazolam were administered until respiratory depression (30% decline in tidal volume, 10% decrease in O2 saturation, and 15% increase in end-tidal CO2) occurred. Flumazenil was administered by a randomly selected route [0.2 mg followed 1 minute later by 0.3 mg i.v., sublingual (s.l.) or intramuscular (i.m.); or 1 mg followed 1 minute later by 1.5 mg per rectum (PR)]. Time to return to baseline respiratory functions was recorded (“time to reversal”). Each of 10 dogs was studied using all 4 routes of flumazenil administration with a washout period of at least 7 days. An additional dog served as a control (no flumazenil). RESULTS: The control time to reversal was 1,620 seconds. The i.v. route was significantly faster (mean 120 +/- 24.5 sec) than the other 3 routes (p<0.005). The SL route was the second fastest (mean 262 +/- 94.5 sec), the IM route was the third fastest (mean 310 +/- 133.7 sec) and the PR route was the slowest (mean 342 +/- 84.4 sec). The SL, IM, and PR routes did not differ significantly from one another. CONCLUSIONS: Flumazenil administered by all 4 routes reversed midazolam-induced respiratory depression in a dog model. For the selected dosages used, the i.v. route was significantly faster than all 3 other routes, and SL was the second fastest.


In an open design, randomised, two-way cross-over study, a single 2 mg i.v. dose and a single 30mg oral dose of flumazenil were each administered to a group of healthy young (n = 6) and elderly (n = 12) volunteers (male: female 2/1). Plasma samples were collected at intervals and intact drug was assayed. Both the i.v. and oral doses of flumazenil were very well tolerated by both age groups and no severe or unexpected adverse effects were observed. The main complaints were dizziness and headache, mainly after oral dosing, probably due to the higher Cmax and AUC following this route of administration. After 2 mg i.v. the disposition parameters in the two age groups (elderly/young) were very similar: volume of distribution (Vss): 0.88/0.90 L/kg; total body clearance (ClPL): 0.86/0.99 L/min; terminal elimination half-life (t1/2 beta): 1.02/0.91 h. After the 30 mg oral dose the mean Cmax of 87.6 ng/mL (elderly) and 78.4 ng/mL (young) were generally reached within 0.5 to 1 h. In 26% (elderly) and 23% (young), the absolute bioavailability of flumazenil was very similar. It is concluded that the absorption and disposition parameters of flumazenil were not significantly affected by aging.


Triazolam is increasing in popularity as a premedication prescribed by dentists to help their fearful and anxious patients tolerate the potentially aversive nature of some dental procedures. Recent anecdotal reports suggest that incremental sublingual dosing of triazolam may be an effective technique for producing conscious sedation in the dental setting. Although promising, no laboratory or clinical data have been available to evaluate the efficacy or safety of this approach. This study was designed to determine the pharmacokinetics and sedative effects of incremental sublingual dosing of triazolam (total, 1.0 mg) in healthy adults. Ten healthy adult volunteers received sublingual triazolam (0.25 mg) followed by additional doses after 60 (0.50 mg) and 90 (0.25 mg) minutes. Plasma triazolam concentrations, clinical effects (Observer’s Assessment of Alertness/Sedation score), and processed electroencephalogram (bispectral index score) were measured intermittently for 3 hours. Plasma triazolam concentrations (mean +/- SD, 5.1 +/- 1.1 ng/mL) and drug effects (Observer’s Assessment of Alertness/Sedation score, 2 +/- 1; and the bispectral index score, 62 +/- 16) were greatest in all subjects at the end of the 3-hour evaluation period. Eight of the subjects had Observer’s Assessment of Alertness/Sedation scores consistent with the definition of deep sedation or general anesthesia (Observer’s Assessment of Alertness/Sedation score, <3) at some of the later time points in the 180 minutes of data collection. In comparison, 4 of the subjects had bispectral index scores less than 60 during these later time points of data collection. Given the considerable intersubject variability in triazolam concentrations and effects, additional research is needed to assess this multidosing strategy before it can be endorsed as a useful and safe sedation technique for managing fearful and anxious patients in dental practice.
Can we make sedation even safer?

- Start with intrinsically safe medications that have the best evidence for use.
- Ensure that you and your staff are well-educated, trained and up to date with your certifications (BLS, HCPBLS, ILS, PALS, ACLS).
- Practice, practice, practice
- Monitoring will keep your patients safer too: Blood pressure, pulse, heart rate, oxygen saturation (pulse oximetry).
- Regardless, you need to know what to look for clinically, and how your monitoring equipment works.
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%.

Affinity of carbon monoxide for hemoglobin is 200x that of oxygen.

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 (HbO2) and deoxyhemoglobin (HHb); carboxyhemoglobin (COHb) is not being measured.
- The pulse oximeter will grossly overestimate the oxygen saturation in chronic smokers!
- Pulse oximeter shows the combination of HbO2 + COHb, not the individual components.
- Example: Pulse oximeter reads 99% on a chronic smoker. If they have 10% COHb then the true reading of HbO2 is 89%!!!

New, non-invasive co-pulse oximetry measures:
- Oxyhemoglobin
- Reduced Hemoglobin
- Methemoglobin
- Carboxyhemoglobin

Rainbow-Set Rad-57 Pulse CO-Oximeter

Masimo Inc, Irvine, CA
Can we make sedation even safer?

- Bispectral Index System (BIS) Monitoring Video (courtesy of Aspect Technologies).
- Clinical Interpretation of Bispectral Analysis


And, of course, there will always be new drugs . . .

Ramelteon (Rozerem®)
- Approved for use by the FDA in October 2005
- First in a new drug class of melatonin receptor agonists.
- More potent than melatonin. It helps people FALL asleep, but doesn’t necessarily help them STAY asleep.
- People take Rozerem 8 mg a half hour before bedtime - higher doses don’t work any better.
- ONSET. Generally works within 30 minutes.
- LENGTH OF USE. Only Rozerem is NOT limited to short-term use in true insomniacs.
- DEA. Rozerem is the only anxiolytic/sedative that’s NOT a controlled substance.
- COST. Less than Ambien, Sonata, or Lunesta but generics are always on the horizon.

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 overdose
- 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 q15seconds until no naloxone given x 1 hour

Notes:
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