Science of Sedation

**Pharmacology** is a broad term encompassing the overall study of drugs.

This course specifically emphasizes the use of anxiolytic drugs to safely and effectively achieve a level of anxiolysis – a pharmacologically induced state of consciousness where the patient remains awake, but has decreased anxiety to facilitate coping skills, retaining interaction ability.

**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.

**Pharmacodynamics** studies the interaction of the drug with the receptors at the site of action.

**Pharmacotherapeutics** involves the study of choosing drugs for their desired actions in selective situations.

---

Routes of Drug Administration include Enteral (absorption across the enteric membranes of the GI tract) or Parenteral (bypassing the enteric membranes). Enteral routes can involve either the oral and rectal pathways, while parenteral can be Intramuscular (IM), Intravenous (IV), Subcutaneous (SC), or inhalation. More than 90% of medications are administered via the oral route.

---

**Oral Route Advantages:**
- Ease of administration
- Almost universal acceptability
- Low cost
- Decreased incidence of adverse reactions
- Decreased severity of adverse reactions
- No needles, syringes, equipment
- No specialized training

**Oral Route Disadvantages:**
- Reliance on patient compliance
- Prolonged latent period
- Erratic and incomplete absorption of drugs from the GI tract
- Inability to titrate
- Prolonged duration of action
- Inability to readily lighten or deepen the level of sedation
Pharmacokinetics

How a drug enters the body (its route of administration) is the primary determinant governing the rate by which drug molecules reaches its receptors in sufficient quantity, thereby directly affecting the quantity of drug needed to effect its actions, as well as the onset of symptoms.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Rate of Action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous (IV)</td>
<td>~ 1 minute</td>
<td>Most direct route into the body, thus requiring relatively less drug to effect actions (potency)</td>
</tr>
<tr>
<td>Inhalation</td>
<td>~ 1-3 minutes</td>
<td>Dependent on gas exchange mechanisms and pressure gradients across alveolar membranes</td>
</tr>
<tr>
<td>Subcutaneous (SC)</td>
<td>~ 30 minutes</td>
<td>Large volumes cannot be given and rate of action is determined by blood flow to area of administration</td>
</tr>
<tr>
<td>Intramuscular (IM)</td>
<td>~ 30 minutes</td>
<td>Includes sublingual which can significantly reduce time of onset of symptoms</td>
</tr>
<tr>
<td>Enteric</td>
<td>~ 60 minutes</td>
<td></td>
</tr>
</tbody>
</table>

The extent of absorption is further affected by the **First Pass Effect**, which involves partial inactivation by liver enzymes before the drug enters the general circulation on its way to its primary site of action. Almost all drugs that are absorbed from the intestine enter the hepatic portal vein and pass through the liver before they are distributed systemically. Some drugs are almost completely inactivated while others may be only partially inactivated as a result of their first passage through the liver. Some medications, as a result of metabolism by liver enzymes, are transformed into metabolites that have efficacy equal to or even greater than the parent drug compound.

Drugs that enter the body parenterally can also be metabolized in the liver, but not until a certain portion 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 largely bypassed. This is also true for medications administered via the inhalation, rectal, topical, submucosal, and sublingual routes.
Absorption Effected By:

- Presence of food in the stomach – lessens absorption
  - Mucosal surface area – less surface area will lessen absorption
  - Gastric emptying time – slower emptying time will slow absorption in the small intestine
- pH of the tissues – antacids inhibit absorption
- Dosage form of the drug – lipophilic or lipophobic (lipophobic inhibits absorption)
- Drug inactivation – p450 enzyme complex
- Bioavailability of the drug – plasma protein binding

The primary organ of *metabolism* for the oral sedative medications is the liver. 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*$_{450}$ (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. Of these, the isoenzyme most responsible for the metabolism of the anxiolytic medications we will be discussing is CYP3A4.

Once the drug reaches the general circulation, it is *distributed* throughout the body and a certain percentage of the administered drug is bound by plasma proteins. While bound to these large plasma molecules, the drug molecule is unavailable to work at the site of action. Only free, unbound drug molecules are available to bind to receptors at the site of action in order to exert a pharmacological effect.

Drug distribution is often thought of in terms of compartments, where highly lipophilic drugs cross readily from the plasma compartment to tissue compartments such as the brain. The *Blood-Brain Barrier* separates the plasma and brain compartments and acts as a selective gatekeeper for highly lipophilic medications whose site of action is the central nervous system.
Pharmacodynamics

The site of action for most of the sedative medications in our techniques are the Gamma Amino Butyric Acid (GABA) receptors in the limbic system of the brain. GABA is a substance which when activated causes a decrease in alertness. Certain sedative medications, cause heightened GABA activity when in close proximity to the GABA molecule. Remember that GABA is an inhibitory neurotransmitter, so a heightened GABA effect translates into a deeper level of anxiolysis or sedation.

The relationship between the dose of a drug and the intensity of effect is referred to as the Dose/Effect Curve. The dose of a given drug required to achieve a given maximum effect describes its potency. The magnitude of the desired effect is an indication of a drug's efficacy. Another way of stating the previous definitions is that Potency is Dose Related, while Efficacy is Effect Related.

The Time/Concentration Curve relates time after a dose of a given drug with the concentration of that drug in the plasma. The particular curve depicted below is for orally administered medications. There is a level at which the signs and symptoms of sedation begins to occur. This is the minimum effective concentration. There is also a level at which despite increases in the plasma concentration, no increase in drug effect will be noticed. This is the maximum effective concentration. The point in the curve at which the highest concentration for a given dose is reached is called the mean peak concentration. The point at which one-half of the drug has been eliminated from the plasma is termed the plasma half-life, and is useful in determining the longevity of the drug in the patient’s system. It is a more descriptive and useful term than duration of action (length of time that the drug exerts noticeable effects). The shape and height of the curve will vary
depending on the specific drug, dosage, route of administration, as well as individual patient characteristics.

TIME/CONC. CURVE – Single Dose Oral Sedation

As previously stated, the point at which one-half of the drug has been eliminated from the plasma is termed the **plasma half-life**, and is useful in determining the longevity of the drug in the patient’s system. Half-life is rarely an absolute constant; however, as it is affected by physiologic, pathologic, and environmental factors, so individual patients have their own half-life values for each drug. The rate of elimination of a drug from the plasma is not constant; therefore, it is oversimplified to say that a drug is totally eliminated from the system at two times the plasma half-life. In actuality, at four times the half life, about 90% of a given drug has been eliminated.

**Benzodiazepines**

The benzodiazepine class of drugs constitutes the majority of medications currently used for oral conscious sedation in dentistry today.

- The Benzodiazepines were first introduced in the early 1960’s, and are among the most widely prescribed drugs in the world.
- They have sedative (relaxes) as well as hypnotic properties (induces sleep & allows for post-hypnotic suggestion)
- Benzodiazepines affect gamma amino butyric acid (GABA) receptors in the brain, which are responsible for the level of alertness.
Benzodiazepines may or may not have active metabolites (Valium, for example does, whereas triazolam and lorazepam do not).

Plasma half-life and time for mean peak concentration varies for each member of this class.

Medications for Oral Conscious Sedation

Triazolam (Halcion)

- Sedative, hypnotic
- Effects gamma amino butyric acid (GABA) receptors
- No long-term active metabolites
- Plasma half-life is 2-3 hours (1.6 to 5.4)
- Wide effective dose range (minimum effective concentration varies widely)
- Mean peak concentration arrived at on average of 1.3 hours
- Anticonvulsant – can be used with the epileptic patient
- Respiratory Depressant – Not as important orally, except in high doses
- Relaxation for adequate pain control – important for hard to numb patients
- No nausea! Nitrous oxide nausea only!
- LD 50 is 5 grams per kilogram in rats (very safe)

The Lethal Dose 50 (LD50) is that dose of a drug that will result in mortality to 50% of the population when administered. Likewise, the Effective dose 50 (ED50) is the dose that will cause the desired effect in 50% of a given 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

- There are 20,000 0.25mg tablets of Triazolam in 5 grams!
Key Point!
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 (PDR):
- Preoperative sedation
- Night-time sleep

Cautions (PDR):
- Overdose may occur at four times the maximum recommended dose of 0.5 mg (2.0 mg or #8 0.25mg tablets)
- Hallucinations, paranoia, and depression (several reports with extended medication time)
- Anterograde amnesia
- Elderly or debilitated patients start with 0.125 mg
- Dry mouth

Contraindications:
- Acute narrow angle glaucoma
- Known hypersensitivity
- Psychosis
- Pregnancy
- Excreted in human milk
- Alcohol (patient self-induced premedication) leads to very serious respiratory depression

Cautions (Medications):
- Antidepressants cause CNS depression (additive effect)
- Tagamet (inhibits CYP 3A4)
- Antacids (ph affects absorption and inhibit p450 enzymes)

Contraindications (Medications):
- Erythromycin (inhibits CYP 3A4)
- Protease inhibitor - HIV tx. (inhibits p450 enzymes)
- Cyclosporine - anti-rejection (inhibits p450 enzymes)
- Grapefruit juice (inhibit p450 enzymes)
- St. John's Wort (induces liver enzymes)
- Antifungal (inhibit liver enzymes 22-27X in plasma concentration)

*There are several pharmacology software products available on the market for desktop, portable computer or palm use. These products are an invaluable source of assistance when evaluating the interaction potential of various medications. DOCS recommends:
Lexi-Comp Dental Reference Library On CD-ROM

This CD-ROM contains a comprehensive compilation including the following reference materials:

- Drug Information Handbook for Dentistry (10th ed.)
- Dental Office Medical Emergencies
- Natural Therapeutics Pocket Guide
- Clinician’s Endodontic Handbook
- Oral Soft Tissue Diseases
- Manual of Clinical Periodontics
- Manual of Dental Implants
- Roadmap to Financial Integrity in the Dental Office
- Drug Identification
- Stedman’s Medical Dictionary
- Patient Education Leaflets
- Electronic Calculator
- Network Access
- Designed for DOCS with Oral Sedation in mind
- Easy to install and use

This product may be purchased directly from the company or through the Dental Organization of Conscious Sedation (DOCS members receive a discount).

Triazolam continued:

How Supplied:
- Tablets: 0.125mg (pale lavender) and 0.25 mg (blue)

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

Ordering Triazolam:
- Darby Dental Supply: Fax Order Form enclosed to 206-812-7759
  o Order bottle of 100 tablets of 0.25 mg for in-office use
  o Order blister packs of 10 to dispense for take-home pre-op use
Reversal Agents

Flumazenil (Romazicon in U.S., Anexate in Canada):
1. Binds to GABA receptor sites
2. Competitive antagonist to Benzodiazepines – has higher affinity for GABA than other benzodiazepines
3. No agonist activity
4. Does not affect other GABA receptor sites (EtOH, Barbiturates, Opiates)
5. Insoluble in water
6. Slightly soluble in acidic solutions
7. Dilute concentration of 0.1mg/cc
8. 5 ml and 10 ml vial
9. No active metabolites
10. Metabolized in liver
11. Does not cause hypertension or tachycardia
12. May cause agitation
13. May cause seizures in susceptible patients
14. 0.2 mg IV or IM initial dose (2 cc)
15. 0.2 mg IV or IM second dose (2 cc)
16. Maximum dose 1.0 mg (10 cc)/20 minutes
17. One hour duration (remember – triazolam’s half-life is about 2 hours)
18. Can be given sublingual in the canine to first molar area, 2-3 mm under the mucosa, not in the midline
Several studies support the viability of sublingual administration of flumazenil:

*Dionne R, Phero J, Becker D; Management of Pain and Anxiety in the Dental Office. WB Saudners 2002;9:135


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

Buy the 5 ml vials (longer shelf-life)

---

**Diazepam (Valium)**
- Benzodiazepine
- Works on GABA Receptors
- Produces Mild Sleep
- Onset: 1 hour
- Active Metabolites
- Half-Life: 50 hours (20-100)
- Duration: 6-8 hours
- Mild Amnesia
- Supplied in 2, 5, & 10 mg tabs
- Dosage: 2.5 -10 mg
- Overdosage treated with flumazenil
- FDA approved anxiolytic

**Contraindications:**
1. Pregnancy
2. Known hypersensitivity
3. Pediatric patients <6 mo.
4. Acute narrow angle glaucoma

**Warnings:**
1. Elderly/debilitated pts.
2. Other CNS depressants
3. Tagamet
**Lorazepam (Ativan)**
- Benzodiazepine
- Works on GABA receptors
- Produces Mild/Moderate sleep
- Onset: 1 hour
- No active metabolites
- Half-Life: 12-14 hours
- Duration: 6-8 hrs.
- Moderate amnesia
- Supplied in 0.5, 1, & 2 mg tabs
- Dosage: 1-3 mg (elderly ½)
- Overdosage reversed with flumazenil
- FDA approved anxiolytic

**Contraindications:**
1. Known hypersensitivity
2. Pregnancy
3. Children less than 12
4. Acute Narrow Angle Glaucoma

**Warnings:**
1. Impaired renal and hepatic dysfunction
2. Elderly/debilitated patients

*Lorazepam is not affected as much as other benzodiazepines by liver enzyme inhibitor/inducers due to differences in its metabolic pathways

---

**Hydroxyzine (Atarax or Vistaril)**
- Diphenylmethane - unrelated to benzos, phenothiazines, or opiates
- Produces Moderate Sleep
- Anxiolytic, Antihistaminic, and Anti-emetic actions
- Onset: 1 hour
- No active metabolites*
- Half-Life: 3-7 hours
- Duration: 3- hours
- No Amnesia
- Supplied in 10, 25, 50, & 100 mg tabs & caps
- Dosage: 10-50 mg
- Overdosage: No specific antidote
- FDA approved anxiolytics

*Cetirizine, a metabolite of Hydroxyzine, has minimal sedation activity
Contraindications:
1. Early Pregnancy
2. Known Hypersensitivity
3. Nursing Mothers
4. Children <1 year
5. Acute narrow angle glaucoma

Warnings:
1. Other CNS depressants

Zaleplon (Sonata)
- Pyrazolopyrimidine
- Works on BZDZ GABA receptor sites
- Produces High Sleep
- Onset: 1/2 hour
- No active metabolites
- Half-Life: 1-2 hours
- Duration: 1-2 hrs.
- Moderate Amnesia
- Supplied in 5 & 10 mg caps
- Dosage: 5-15 mg
- Overdosage treated with flumazenil
- Not an FDA approved anxiolytic

Contraindications:
1. Children < 18
2. Severely depressed patients

Warnings:
1. Hepatic Impairment
2. CYP450 inhibitors
3. Aldehyde Oxidase Inhibitors (diphenhydramine)
4. Elderly Patients

Nitrous Oxide
- Has a long history of use in dentistry as a sedative and analgesic agent.
- Is the safest of all inhalation anesthetics. It’s Mean Alveolar Concentration (the equivalent of ED50 for volatile gases where 50% of the population will not respond to surgical stimuli) is 105%, making it theoretically impossible for it to elicit general anesthesia, even at high doses.
- In dentistry, it is administered in concentrations of 20% - 70%.
• Passes rapidly through body compartments (lungs, blood, and other body tissues) by passive gradient diffusion.
• Is not metabolized by the body and once partial pressure gradients allow for it, is exhaled by the lungs chemically unchanged.
• The mechanism of action is poorly understood.
• Nitrous Oxide can be administered in the dental office through central as well as portable delivery systems.
• The application of nitrous oxide during the sedation experience is to supplement the sedative actions of the enterally administered agents as well as provide mild analgesia for short periods of time.

**Technique**

The technique for effective nitrous oxide anxiolysis involves “flushing” the patient’s system with 100% oxygen for three minutes. This creates a favorable partial pressure gradient for nitrous oxide to be absorbed across the pulmonary alveoli and lung capillaries.

Following 100% Oxygen administration through a nasal hood or cannula, three minutes of nitrous oxide administration is usually enough time for maximum absorption of nitrous oxide. On a patient with an orally administered sedative agent on board, no more than 30% nitrous oxide is necessary. Given for short intervals during local anesthesia administration and other invasive procedures, nitrous oxide is a valuable adjunct to the successful sedation experience.

**Adverse Events**

If however, the nitrous oxide concentration administered exceeds recommended levels (30%), then the possibility exists that the additive effect results in a level of sedation deeper than intended - up to and including deep sedation. This phenomenon can be explained by visualizing the shrinking spectrum of sedation that results from multiple administered sedative agents (polypharmacology).

Increased concentrations, as well as extended duration of administration, can result in the most common adverse event encountered with nitrous oxide administration, nausea and vomiting. This most unpleasant event can result in regurgitation of any sedative agent that is still in the stomach, and can lead to dehydration and electrolyte imbalance in the patient who has been NPO for the last several hours. The most serious potential complication from nausea and vomiting in a sedated patient, however, is the aspiration of vomitus.
Nitrous Oxide Hygiene

Long-term occupational exposures to trace concentrations of nitrous oxide are believed to have adverse health effects on exposed individuals. Such adverse effects include a potential for change in production of DNA precursors, spontaneous abortions, and impaired fertility. Nitrous oxide levels in the office should not exceed 25 ppm.

Nitrous oxide levels in the dental office can be maintained at a safe level through:

• **Use of a scavenging system** that redirects N2O outside the office is the most effective means of reducing ambient gas.
• **Good ventilation** in the operatory dilutes the concentration of gas in one area of the office.
• **Well-fitting masks** reduce leakage.

One of the newest advances in nitrous oxide administration is the **Safe-Sedate Nasal Hood**. This apparatus provides more efficient delivery of gases into the nasal nares, while reducing extraneous nitrous oxide into the operatory. The **Safe-Sedate Nasal Hood** also is latex-free and disposable, preventing cross-contamination.

• **Reduced talking** by the patient decreases exhalation of nitrous oxide into the operatory environment.

In addition, there are several commercially available monitoring systems to alert office personnel of potential unsafe levels of trace N2O.

Contraindications

Nitrous oxide is less effective in patients whose respiratory systems have compromised ability to exchange gases (COPD), or restricted nasal airways (mucous secretions and swollen nasal membranes as a result of upper respiratory infections or seasonal allergies)

As previously cited, chronic exposure to nitrous oxide can lead to spontaneous abortions and impaired fertility. In addition, long-term exposure can result in neurologic disease and in the malnourished patient (pernicious anemia) can cause bone marrow suppression.

As nitrous oxide can readily diffuse into air-filled spaces like the middle ear, its use can result in additional discomfort in the patient with otitis media.
NITROUS OXIDE – ADDITIONAL INFORMATION

BENEFITS OF NITROUS OXIDE SEDATION

Nitrous Oxide/Oxygen sedation has many advantages over other forms of anxiety/pain control, while the disadvantages are few in number.

1. Safety - Nitrous oxide (N\textsubscript{2}O) analgesia/sedation in dentistry and medicine enjoys an impeccable safety record, which has withstood the test of time longer than any other drug.
   a. Gardner Quincy Colton (1864-1897) was the first to study the safety of nitrous oxide, and documented 193,000 cases with no adverse reactions.
   b. Ruben, a Danish researcher, reported 3 million cases in which N\textsubscript{2}O/O\textsubscript{2} was used in the dental office with no adverse reactions.
   c. Niels Bjorn Jorgensen cited 4 million episodes without complications.
   d. Today, more than 24 million surgical procedures are performed each year in the United States, and nitrous oxide/oxygen continues to provide safe, effective analgesia/sedation.

When used properly, the patient is mildly sedated and responds to verbal commands. Protective defenses such as the cough and gag reflexes remain intact.

N\textsubscript{2}O/O\textsubscript{2} sedation may be used safely with other forms of sedation including oral premedication. The only drug interactions between nitrous oxide and other drugs have to do with accentuation of the side effects of nitrous oxide (CNS depression, nausea and vomiting).

2. Ease of use – The equipment used in nitrous oxide delivery is straightforward, as is the administration technique.

For the clinician, the drug is easily titrated to the level of sedation/analgesia required for the procedure. Titration is the process of precisely administering a drug incrementally to a specific level or endpoint of sedation. Because titration is easily accomplished with N\textsubscript{2}O/O\textsubscript{2}, nitrous oxide sedation and analgesia is more efficient and less likely to result in over-sedation.

Due to its ease of use and wide margin of safety, minimal training for nitrous oxide delivery is required.

3. Effectiveness – In addition to being used to induce general anesthesia in combination with other anesthetic agents, many health
disciplines use N$_2$O/O$_2$ sedation alone as an effective means of alleviating patient anxiety and mild discomfort during ambulatory and outpatient procedures.

- **Pain Relief** – While the level of pain control afforded by N$_2$O can vary from patient to patient, the analgesic properties of N$_2$O are well documented. Multiple studies report that a mixture of 20%-50% N$_2$O has the same analgesic efficacy as 15 mg of morphine. These analgesic properties are useful in alleviated the severe pain associated with myocardial infarction.

- **Anxiety Relief** – N$_2$O/O$_2$ sedation can significantly impact fear and anxiety by producing sedation and/or a sense of well-being. Sedation enables the patient to become calm, relaxed, and able to tolerate the situation better and with less difficulty. This relaxed feeling has a positive effect on the patient’s pain threshold.

Nitrous oxide is especially effective when combined with other forms of pain and anxiety control. Such an example is N$_2$O/O$_2$ and local anesthesia. Local anesthesia and N$_2$O/O$_2$ combined offer a superior pain and anxiety management alternative compared to either alone.

4. **Quick onset of action and recovery** – N$_2$O/O$_2$ sedation has a rapid onset of action, with clinical effects often beginning within 30 seconds, and peak effects usually occurring in less than 5 minutes. Upon termination, N$_2$O/O$_2$ is quickly and easily reversed. It is virtually completely eliminated from the body with 100% pure oxygen for a minimum of 5 minutes after termination of the drug. Upon conclusion of recovery, cognitive function returns completely back to normal.

5. **Amnesic properties** – After N$_2$O/O$_2$ sedation/analgesia, patients often remark how quickly time passed during a long procedure, nor can they recall the severity of their pain or anxiety or its duration. The passage of time tends to become unclear or compressed with nitrous oxide use.

6. **Acceptance** – Patient acceptance of N$_2$O/O$_2$ use is well documented. In general, patients view its use as pleasant and effective.

7. **Few side effects** – Nitrous oxide has very few side effects, all of which are mild when used properly. These include CNS depression and nausea and vomiting. In addition, N$_2$O/O$_2$ sedation analgesia may be advantageous when other sedative/analgesic drugs are contraindicated (i.e. allergy).
PHARMACOLOGY OF NITROUS OXIDE

PHYSICAL & CHEMICAL PROPERTIES
Nitrous Oxide (Dinitrogen Monoxyde - N₂O) is a sweet smelling, colorless gas. When compressed into a cylinder, it becomes a liquid. Its specific gravity is 1.53, which indicates that it is heavier than air (specific gravity of 1). Because of this, the greatest concentration of unscavenged gas will be near the floor.

Although nonflammable itself, N₂O supports combustion. If the gas were to come in contact with a combustible source at a high temperature and elevated pressure, such as inside a cylinder, an explosion could occur.

Absorption & Distribution
Inhaled gases such as N₂O enter and move around the body through partial pressure gradients (See Figure II-4, next page). There are two dimensions to these gradient differences – degree and direction. Gases move in a higher to lower pressure direction. The degree refers to the magnitude of the pressure difference – the greater the difference, the more efficient the transfer. This same mechanism accounts for the passage of gases necessary for normal respiration.

The difference between the partial pressures of N₂O in the lungs and the pulmonary blood circulation dictate how quickly the nitrous oxide crosses the pulmonary membrane and enters the bloodstream. N₂O crosses the alveolar membrane easily. The solubility of the drug then determines how quickly equilibration occurs, and clinical action begins.

If a drug is highly insoluble, it will reach equilibrium rapidly, cross the blood-brain barrier quicker, and reach the brain faster. Therefore, the more insoluble a drug is, the quicker it works. Consider the following example: Imagine two cups of warm water: Into one cup you put a spoon of sugar and into the other a spoon of sand. Which will be in higher concentration in the bottom of the cup? The sand, of course, since it is insoluble in water. The sugar dissolves, so very little reaches the bottom. Eventually, the water will
become saturated with sugar, and sugar will collect in the bottom of the cup. For the purposes of the subject of this discussion, bottom of cup, read brain.

The interaction between a drug, the brain, and other tissues until equilibrium is reached is expressed in values called partition coefficients. These values indicate the efficiency of drug transfer to various body compartments.

The Blood-Gas Partition Coefficient (BGPC) is calculated by the amount of gas needed to saturate the blood divided by the amount of gas (See Table II-5 below). If the blood-gas partition coefficient is high, more drug and/or more time will be necessary to achieve equilibration or the level necessary for movement of the agent to the brain. In the example cited above, the partition coefficient of sand is low compared to sugar.

<table>
<thead>
<tr>
<th>Drug</th>
<th>BGPC</th>
<th>Onset (Mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous Oxide</td>
<td>0.5</td>
<td>1-2</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.8</td>
<td>3-5</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.3</td>
<td>3-5</td>
</tr>
<tr>
<td>Ether</td>
<td>12</td>
<td>15-20</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>13</td>
<td>15-20</td>
</tr>
</tbody>
</table>

Table II-5. Blood-Gas Partition Coefficients Of Some Inhalation Anesthetics.

N₂O is an example of a relatively insoluble drug. Its blood-gas partition coefficient is 0.47. It remains unchanged in the blood and does not combine with any blood elements. Uptake by the body is limited, resulting in equilibrium being achieved quickly. This explains why the peak clinical effects of nitrous oxide may be seen within 3-5 minutes after administration.

**Metabolism & Elimination**

Nitrous oxide is not metabolized in the liver as many drugs are. Ninety-nine percent of it is eliminated through the lungs without biotransformation. A very small (0.004%) amount of N₂O is metabolized in the gastrointestinal tract by anaerobic bacteria, resulting in potentially toxic free radicals. This minute amount does not pose any significant threat to the body.

The partition coefficients of N₂O between tissues, muscles, and fat are low. Equilibration occurs quickly in these tissues due to the inability of the tissues to hold N₂O. Because of this, N₂O is not stored in the body to any extent resulting in rapid and complete elimination at the end of administration.

**PHARMACODYNAMICS**

Pharmacodynamics describes the action of a drug - the mechanisms of chemical and physical transformation at the effector site within the organism.
The complete mechanism of the pharmacodynamics of nitrous oxide is yet to be determined.

Findings to date indicate that N\textsubscript{2}O induces opioid peptide release in the brain stem leading to the activation of descending noradrenergic neurons, which results in modulation of the nociceptive process in the spinal cord. In addition, several receptor-effector mechanisms including dopamine receptors, alpha-2 adrenoreceptors, benzodiazepine receptors (GABA) and N-methyl-d-aspartate (NMDA) receptors have been implicated in the pharmacodynamic action of N\textsubscript{2}O, although the relationship of one with the other is not known.

The potency of an anesthetic agent reflects the relative amount of drug necessary to achieve a defined action. For gaseous agents, drug potency is measured by its minimum alveolar concentration (MAC). MAC is defined as the amount of drug necessary to prevent movement in 50\% of subjects responding to a surgical incision.

Nitrous oxide is the least potent (weakest) of all inhalation anesthetics (See Table II-6 below). The MAC for N\textsubscript{2}O is 103\%. This value indicates that at normal atmospheric pressure N\textsubscript{2}O alone is not able to produce profound surgical anesthesia.

<table>
<thead>
<tr>
<th>Drug</th>
<th>MAC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous Oxide</td>
<td>103</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.7</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.8</td>
</tr>
<tr>
<td>Ether</td>
<td>1.9</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Table II-6. Minimum Alveolar Concentrations Of Some Inhalation Anesthetics**

An inhalation anesthetic's MAC, may or may not be affected by various factors:

**Factors that will not affect the MAC:**
1. Gender
2. Time (MAC after 10 hours is the same as during the first hour)
3. pH or pCO\textsubscript{2}
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 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. MACs are additive (i.e. 50% N₂O + .5 MAC Halothane = 1 MAC of anesthetic)

From a practical standpoint, the desired action from N₂O administration is to decrease anxiety and increase the pain threshold, while remaining within the level of minimum or moderate sedation. At both of these levels of CNS depression, the patient responds to verbal commands. The term MAC<sub>awake</sub> refers to the minimum alveolar concentration at which patients still respond to commands. For N₂O, the MAC<sub>awake</sub> of N₂O = 0.2-0.6 MAC or 20-60% N₂O.

Nitrous Oxide & Other Gases

The partial pressure of N₂O is approximately 31 times greater than that of nitrogen (N₂). Because of this, N₂O rapidly replaces the N₂ occupying any body space, including the blood. Not only does N₂O rapidly replace N₂, but it also increases the volume and/or pressure of the space formerly occupied by nitrogen.

Higher concentrations of N₂O promote a more rapid uptake of the gas, and there is a simultaneous effect occurring with the other gases being administered. The rapid uptake of N₂O allows the second gas to be drawn in much faster than it would normally if it were being administered alone. This is because the rapid uptake of N₂O results in an increased concentration of the second gas in the alveoli. This phenomenon, called the “second-gas effect”, allows minimal amounts of a more potent anesthetic to be administered simultaneously with N₂O.

Nitrous Oxide & Altitude

Extreme altitudes above 10,000 feet do affect the use of N₂O. Because of the barometric pressure change, those administering N₂O/O₂ sedation at significant elevations must be aware of the need for an increase in N₂O concentration to obtain the same effects as at sea level. In Denver, Colorado, where the elevation is 5,280, a 5% increase in N₂O may be necessary relative to locations at seal level.

Diffusion Hypoxia

It has been hypothesized that headache, lethargy, and nausea can occur because of decreased O₂ saturation levels in the blood caused by the rapid exit of N₂O on its termination. The application of 100% pure O₂ for the first 3-
5 minutes after N₂O termination has been traditionally advocated to prevent O₂ desaturation of blood.

However, there is research that questions the clinical significance of diffusion hypoxia and whether these symptoms are even associated. Indeed, several researchers have reported no diffusion hypoxia when breathing room air instead of 100% O₂. Despite the doubts raised as to the validity of diffusion hypoxia, it can be argued that it is prudent to administer 100% O₂ postoperatively for a minimum of 5 minutes.

THE EFFECT OF NITROUS OXIDE ON BODY SYSTEMS

When administered with oxygen, nitrous oxide is compatible with human physiology, actually improving a patient’s perfusion while decreasing his or her anxiety.

Cardiovascular System

N₂O does not negatively affect the cardiovascular system to produce any significant physiologic changes. The interaction between N₂O and
contractility, cardiac output, stroke volume, heart rate, and rhythm is minimal, and in the case of cardiac disease, insignificant. It has been shown that N₂O with O₂ has a positive effect on myocardial ischemia by providing supplemental O₂ and can be very helpful in myocardial infarction.

**Respiratory System**

Any condition such as an upper respiratory tract infection that affects air exchange through the nose can result in insufficient amounts of N₂O/O₂ entering the respiratory system and causing its desired effect. In addition, the drying effect of the gas administration may result in mucous plugs that interfere with air exchange, and increased pressure in infected sinus cavities may result in additional discomfort.

Because vomiting during N₂O administration is possible, the potential for aspiration, although unlikely, exists. If the patient is adequately oxygenated, prevented from entering deeper levels of sedation, nitrous oxide is used judiciously (% & time), and follows the pre-sedation guidelines, the risk of aspiration is extremely small.

Nitrous oxide use is not contraindicated in asthmatic patients, because it is nonirritating to mucous membranes. In fact, its sedative nature can reduce the likelihood of an asthmatic event caused by anxiety.

For patients with debilitating respiratory conditions (eg. COPD), the use of N₂O/O₂ may be a relative contraindication. These individuals may be on a hypoxic drive, therefore the richer concentration of oxygen delivered with nitrous oxide may impair their stimulus to breathe. It is prudent to seek a medical consultation with the physician treating their respiratory condition. Patients with cystic fibrosis or emphysema may present with bullae on the lungs that contain air and fluid. N₂O may irritate these conditions due to the expansive nature of the gas.

**Central Nervous System**

N₂O is a CNS depressant, although its exact mechanism is unknown. It is known that its effects on cerebral blood flow, velocity, and perfusion pressure are minimal. Its effects on intracranial pressure is less significant than with other inhaled anesthetics, and when used appropriately is clinically insignificant.

Due to the rapid replacement of N₂ with N₂O in air spaces, notable intracranial pressure increases have been found in cases of pneumoencephalography (medical procedure where cerebrospinal fluid is drained and replaced with air, oxygen, or helium to allow investigators to
better see the brain on a radiograph). \( \text{N}_2\text{O} \) should not be used for one week after this procedure.

Chronic exposure to \( \text{N}_2\text{O} \) as in the case of its abuse has shown evidence of CNS injury. This CNS damage manifests itself in the forms of numbness and weakness in extremities as well as ataxic gait.

**Hematopoietic System**

Megaloblastic and pernicious anemia have been found in patients who have been exposed to high concentrations of \( \text{N}_2\text{O} \) for an extended period. \( \text{N}_2\text{O} \) has been implicated in the interference of the enzyme methionine synthase, an enzyme necessary for DNA synthesis and Vitamin B12 metabolism. Pernicious anemia and megaloblastic anemia are conditions that are associated with this vitamin deficiency.

**Gastrointestinal System**

Because of its expansive nature and its propensity for infiltrating air spaces within the body, \( \text{N}_2\text{O} \) could adversely affect the non-rigid air space contained in the bowel in the case of bowel obstruction. As a result, it is less desirable to use \( \text{N}_2\text{O}/\text{O}_2 \) sedation in such a patient in order to avoid increasing expansion, pressure, and discomfort.

**Genitourinary And Reproductive Systems**

\( \text{N}_2\text{O}/\text{O}_2 \) sedation does not pose any negative effect on the genitourinary system itself, however there are concerns with nitrous oxide administration and pregnancy.

It should be pointed out that the \( \text{N}_2\text{O}/\text{O}_2 \) combination has been a commonly used pharmacologic agent in obstetrics. Research confirms its safety with pregnant women during labor and delivery.

Regarding pregnancy and the delivery of dental care, the following considerations regarding \( \text{N}_2\text{O}/\text{O}_2 \) sedation should be considered:

Most pharmacologic agents cross the placental barrier; \( \text{N}_2\text{O} \) is no exception. Low levels of oxygen can affect organogenesis during the first trimester. Although \( \text{N}_2\text{O} \), when delivered appropriately, should not physiologically threaten the fetus, it can, as in the case of radiation, be blamed should fetal anomalies occur.

Therefore, it is prudent, if for no other reasons, the peace of mind of the patient and to minimize potential liability to the practitioner, to forego the use of nitrous oxide during pregnancy.
If for emergency purposes, these risks are less than the need for N₂O, then N₂O use should be avoided during the first trimester, and appropriate medical consultation should be obtained and documented.

The chronic exposure of nitrous oxide and its effect on the genitorurinary and reproductive systems of dental personnel will be considered later in this workbook.

**Neuromuscular System**

N₂O/O₂ does not directly affect muscle action, but given in high enough concentrations can cause muscle relaxation secondary to CNS depression.

**Cancer**

N₂O has never been shown to cause or affect cancerous cell growth. However, the incidence of pulmonary fibrosis and other pulmonary diseases can increase in patients taking bleomycin sulfate, an antineoplastic agent used typically for the treatment of lymphomas, testicular tumors, and squamous cell carcinomas. This occurs indirectly if the O₂ administered with N₂O is administered in concentrations greater than 30%.

**Allergies**

There have been no known reported allergies to N₂O. Individuals sensitive to latex may experience contact dermatitis from the administration armamentarium. Latex-free nasal hoods, conduction tubing and reservoir bags are available to avoid this occurrence.

**Malignant Hyperthermia**

Malignant hyperthermia is a genetic condition consisting of extreme muscle hyperactivity, leading to a potentially fatal increase in body temperature after exposure to certain volatile anesthetic agents. Patients who know of familial tendencies and history can be tested to avoid this problem. N₂O/O₂ sedation is not considered a trigger for malignant hyperthermia and can be safely administered to susceptible individuals.

**Psychological and other Mental Disorder Conditions**

Nitrous oxide itself is a substance that produces euphoria. If the patient is suffering or recovering from addiction or mental illness, the relaxing euphoric sensations from nitrous oxide may exacerbate or trigger undesirable tendencies or encourage addictive behaviors. Discretion in such cases is warranted.
For patients with a mental deficiency such as Down’s Syndrome, it is necessary to determine the ability of the individual to understand the sedation procedure. If that level of understanding is not present or the practitioner is unable to determine it, nitrous oxide and oxygen should not be used. The same rational is appropriate for persons with Alzheimer’s disease or autism. N₂O/O₂ sedation can be used as long as the level of understanding is present and there are no other conditions present that would be relative contraindications.

N₂O/O₂ use should be avoided in patients under the influence of drugs or alcohol. Although alcohol is initially a stimulant, it and other classes of drugs such as barbiturates, opiates, and benzodiazipines are potent CNS depressants. They should never be present when a healthcare provider is administering N₂O/O₂ unless prescribed for a legitimate medical purpose.

Patients under psychiatric and/or psychological care should be carefully assessed before N₂O/O₂ use. Many patients are treated with antidepressants or other psychotropic drugs. It is important to understand the pharmacology of these drugs and be aware of any synergistic effects. Medical consultation should be considered before N₂O/O₂ administration.

N₂O may enhance drugs that are used directly to induce sleep or that have drowsiness as a side effect. Again, seek medical consultation to determine the extent of the underlying condition. Ensure that the patient has not just recently taken these drugs before N₂O/O₂ administration.

 Severely phobic individuals may not benefit from N₂O/O₂ administration, as N₂O/O₂ may not be able to provide adequate relief to accomplish the intended procedure. Deeper levels of sedation that can be accomplished with N₂O/O₂ alone, may be the procedure of choice in these situations.

In some cases, patients with claustrophobic tendencies may feel uncomfortable with the use of a nasal hood. Usually, these patients relax enough during N₂O/O₂ sedation that this is overcome.

**Middle Ear Disturbances**

Because N₂O infiltrates the rigid, noncompliant cavity of the middle ear, increased pressure and resulting discomfort results. In some cases, significant damage such as tympanic membrane rupture, graft displacement, and other complications have been observed. Also, the negative pressure that results from the rapid departure of N₂O after general anesthesia can cause other side effects, especially after recent ear, nose, and throat complications utilizing higher concentrations than used for minimal sedation.
Eye Surgery

Patients should be questioned about recent ophthalmic surgery before N₂O/O₂ sedation is used. In patients undergoing vitreo-retinal procedures, a gas bubble is typically placed in the eye to assist with the healing process. This gas bubble could expand with N₂O use and complicate healing or promote injury.

Other
N₂O should not be used on patients who have been scuba diving in the last 24 hours to avoid decompression sickness.