

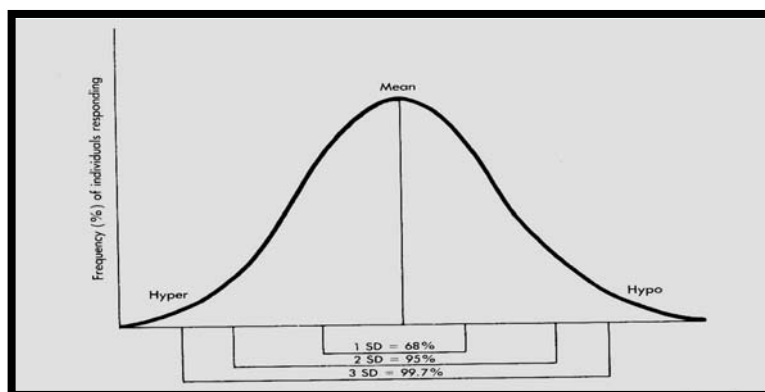
## Clinically-Useful Pharmacology

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:

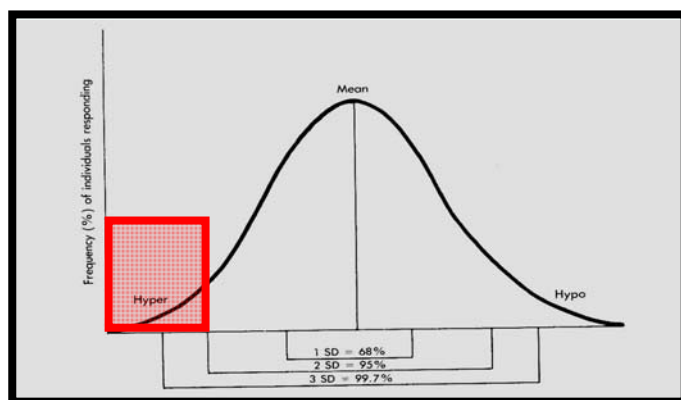
1. *Pharmacokinetics* deals specifically with the absorption of drugs from the outside environment, the distribution to their site of action within the body, their metabolism within the body, and finally their excretion.
2. *Pharmacodynamics* studies the interaction of the drug with the receptors at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



*Malamed SF, Robbins K. Medical Emergencies in the Dental Office. 5<sup>th</sup> ed. Philadelphia: Mosby;2000:346-348.*



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

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

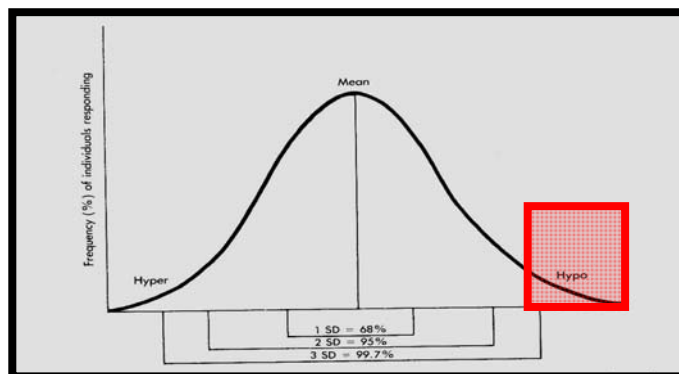
In the case of a sedation appointment, a preoperative protocol can account for this since a small amount of medication may be administered prior to the appointment. In general, always stick with the mantra: **“Go Low, Go Slow!”**

### **Other Notes or Questions to Ask:**

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


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

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



### **What is Pharmacogenomics? = Pharmacology + Genetics**

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



**Affymetrix  
GeneChip®  
Probe  
Array**




Image courtesy of Affymetrix  
1-888-DNA-CHIP

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

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

### **Other Notes or Questions to Ask:**

## Genetics and Dentistry?

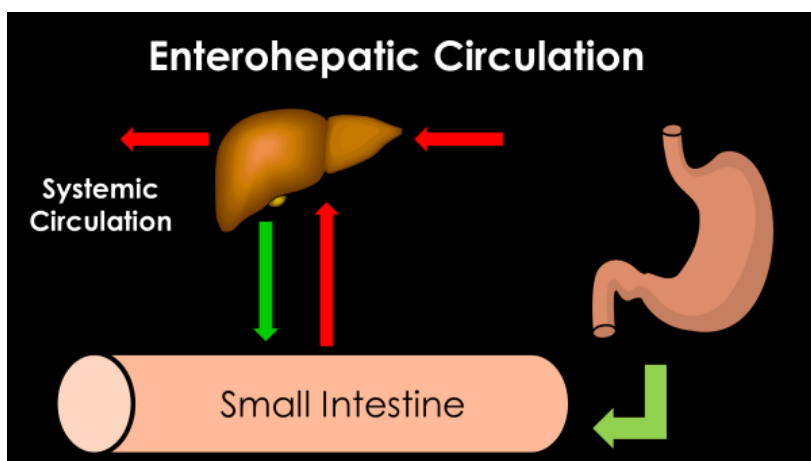
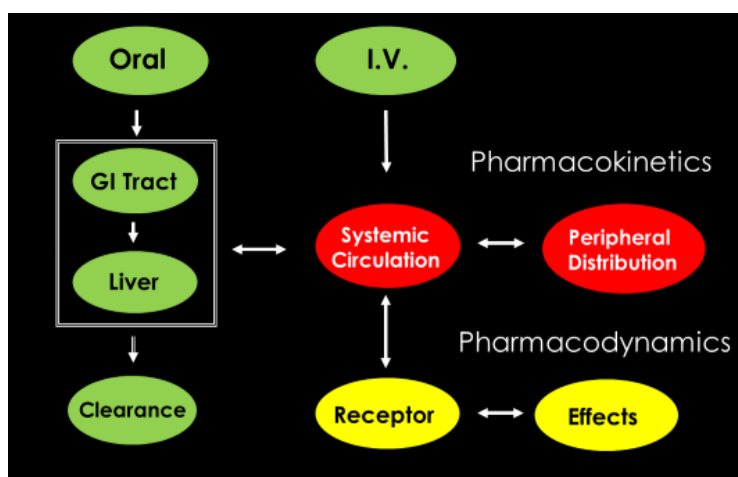
*Binkley CJ, Beacham A, Neace W, Gregg RG, Liem EB, Sessler DI. Genetic variations associated with red hair color and fear of dental pain, anxiety regarding dental care and avoidance of dental care. J Am Dent Assoc. 2009 Jul;140(7):896-905.*

*Randall CL, McNeil DW, Shaffer JR, Crout RJ, Weyant RJ, Marazita ML. Fear of Pain Mediates the Association between MC1R Genotype and Dental Fear. J Dent Res. 2016 Sep;95(10):1132-7.*

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:

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:

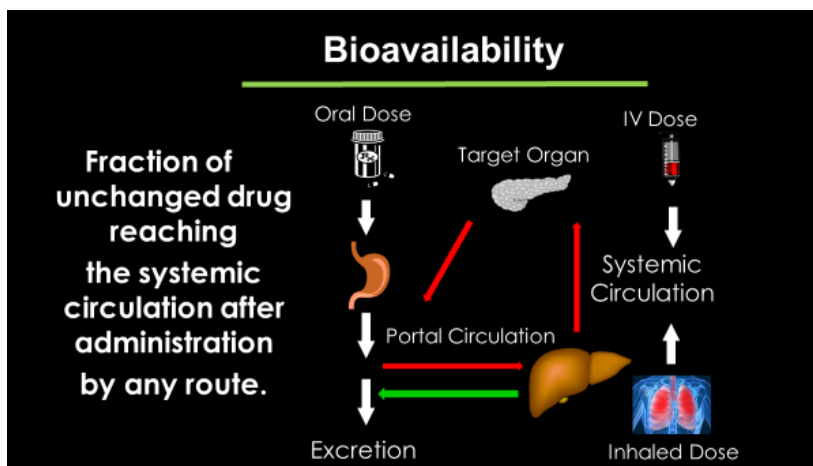
**A**bsorption, **D**istribution, **M**etabolism, **E**limination

## **Other Notes or Questions to Ask:**

## 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.



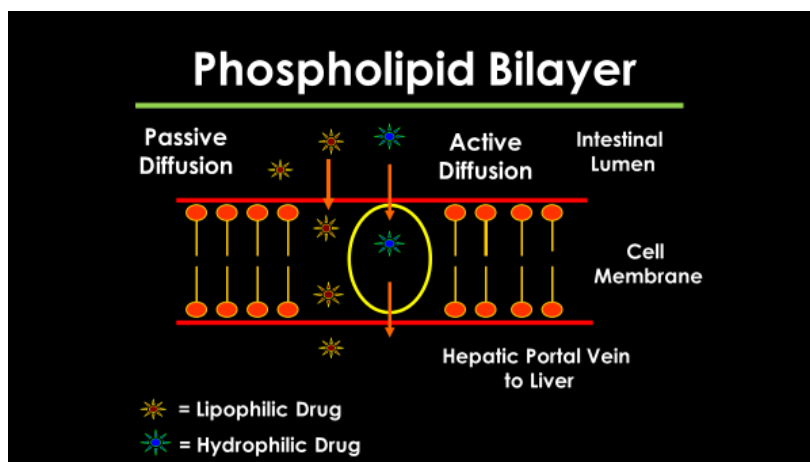
## Bioavailability

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:

<u>Route of Administration</u>	<u>Bioavailability</u>
Intravenous	100% by definition
Intramuscular	75 to ≤ 100%
Subcutaneous	75 to ≤ 100%
Oral	5 to ≤ 100%
Sublingual	more than oral
Rectal	30 to ≤ 100%
Inhalation	75 to ≤ 100%
Transdermal	80 to ≤ 100%

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

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



## **Other Notes or Questions to Ask:**

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

### 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.



### Principles of Local Anesthetics

#### $pK_a$

Lidocaine  $pK_a = 7.8$

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

Injected into an inflamed area with  $pH = 6.0$

98% Cationic species  
– IMPERMEABLE

2% Uncharged species



Hersh EV. Local Anesthetics. In: Fonseca RJ. Oral and Maxillofacial Surgery, 2000

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

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.  $CO_2$  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)
- 1/2 cc 28G x 1/2" 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.

#### Other Notes or Questions to Ask:

### Differences in Bicarbonate?

	Mean pH
50mL vial Sodium Bicarbonate	$8.12 \pm 0.13$
Onpharma Sodium Bicarbonate	$8.11 \pm 0.11$

pH testing of sodium bicarbonate used to buffer local anesthetic solution s: 50mL vial of 8.4% Sodium bicarbonate inj., USP (Hospira Inc, Lot# 41-14 3-EV) and Onpharma Sodium Bicarbonate inj., 8.4%, USP, Neutralizing Additive Solution (Irvine, CA, Lot# W0007328 and W0007361)

Goodchild JH, Donaldson M. *Compend Contin Educ Dent*. 2016 May;37(5):e6-e12



## Chairside Buffering of Local Anesthetics Study

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



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

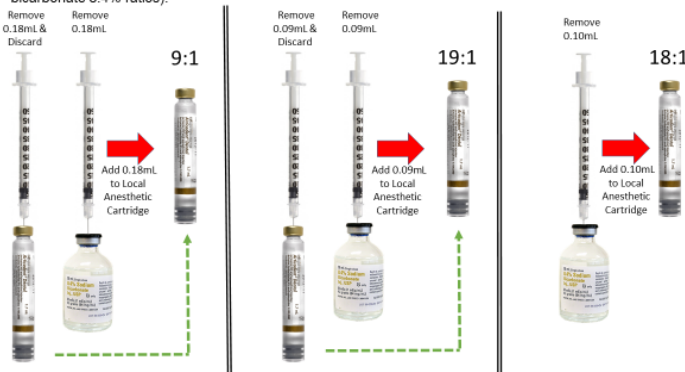
Goodchild JH, Donaldson M. *Compendium* 2015.

Goodchild JH, Donaldson M. Comparing the pH change of local anesthetic solutions using two chairside buffering techniques. *Compend Contin Educ Dent* 2016;37(5):e6-e12.

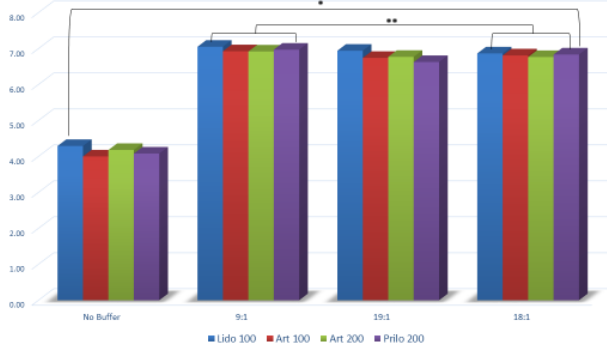
“Increasing the pH of lidocaine reduced pain and improved patient comfort and satisfaction. No adverse events were reported. Therefore, increasing the pH of commercial lidocaine solutions with bicarbonate immediately prior to their use should be considered.”

Goodchild JH, Donaldson M. Novel Direct Injection Chairside Buffering Technique for Local Anesthetic Use in Dentistry. *Compend Contin Educ Dent* 2019;40(7):e1-e12.

**Figure 1:** Buffering local anesthetics using two different chairside, handmixing techniques: remove and replace to achieve 9:1 and 19:1 and the direct injection technique to achieve 18:1 (local anesthetic to sodium bicarbonate 8:4 ratios).



**Figure 2:** Buffering Ratios per Concentration per Group



\*By two-tail T-TEST (p<.001), No Buffer is statistically different from the other 3 ratios

\*\*There is only a marginal significant difference between 9:1 vs 18:1 (p= 0.048) after Bonferroni correction for multiple comparisons

“The results of this systematic review show that buffered LAs are more effective than nonbuffered LAs when used for mandibular or maxillary anesthesia in pulpally involved teeth. Buffering LAs have 2.29 times greater likelihood of achieving successful anesthesia.”

## Other Notes or Questions to Ask:

Goodchild JH, Donaldson M. *Compend Contin Educ Dent*. 2019;40(7):e1-e12.

### Original Contributions

#### Cover Story

Do buffered local anesthetics provide more successful anesthesia than nonbuffered solutions in patients with pulpally involved teeth requiring dental therapy? A systematic review

Sreeni Kuttari, BDS, MSc, FRCD(C); Su-Min Lee, DDS, MS, DSD; Elliot V. Marsh, DMD, MS, PhD; Bekir Karabucak, DMD, MS

#### ABSTRACT

**Background:** The authors conducted a systematic review that addresses the following population, interventions, comparisons, outcome question: “In adults requiring dental therapy with pulpally involved teeth, what is the comparative efficacy of buffered local anesthetics (LBAs) compared with that of nonbuffered LAs in achieving anesthetic success?”

**Types of Studies Reviewed:** The authors searched MEDLINE, Scopus, Cochrane Library, CINAHL/Trisearch, World Health Organization International Trials Registry Platforms, Qeios, Google Scholar, and 2 textbooks to identify double-blind, randomized controlled trials in which researchers directly compared the efficacy of buffered and nonbuffered LAs in adult patients, as well as any associated side effects. Furthermore, they checked the reference lists of all included and excluded studies to identify any further trials. Weighted anesthetic success rates were estimated and compared by using a random-effects model.

**Results:** A total of 14,211 studies were initially identified from the search. 5 double-blind, randomized clinical trials met inclusion criteria. Buffered LAs were more likely to achieve successful anesthesia than nonbuffered LAs (odds ratio: 2.29, 95% confidence interval: 1.11 to 4.71,  $P = .0212$ ;  $I^2 = 68\%$ ).

**Conclusions and Practical Implications:** This investigation revealed that buffered LAs are more effective than nonbuffered LAs when used for mandibular or maxillary anesthesia in pulpally involved teeth. Buffering of LAs has 2.29 times greater likelihood of achieving successful anesthesia.

**Key Words:** Buffering, sodium bicarbonate, analgesics; adjusting pH, local anesthetic.

<https://doi.org/10.1016/j.cden.2019.05.001>

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<https://doi.org/10.1016/j.cden.2019.05.001>

**Local anesthetics (LAs)** form the backbone of pain control techniques and are the most used drugs in dentistry.<sup>1</sup> LA block nerve conduction by preventing the sodium ion membrane permeability to sodium ions that normally leads to a nerve impulse.<sup>2</sup> Two ionic forms of LAs exist in equilibrium within an anesthetic cartridge: the dissociated, active base form of the drug, which is a lipid soluble, and the unionized cationic form, which is not lipid soluble. The base form more readily penetrates the nerve membrane to enter the nerve axon. Once inside the nerve membrane, the base form of the LA re-equilibrates to the unionized cationic form, which binds the site of action within the sodium channel, causing conduction blockade.<sup>3</sup> The amount of the base form available compared with the amount of the unionized cationic form available is related to a particular compound's acid dissociation constant (pKa). The pKa of a compound is a measure of its affinity for hydrogen ions. When the pH of a solution has the same value as the pKa of a compound, 50% of the compound will exist in the unionized cationic state, and 50% will exist in the dissociated base form. The relationship of pH to pKa is determined by

*Kattan S, Lee SM, Hersh EV, Karabucak B. Do buffered local anesthetics provide more successful anesthesia than nonbuffered solutions in patients with pulpally involved teeth requiring dental therapy?: A systematic review. J Am Dent Assoc. 2019 Mar;150(3):165-177.*

### 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

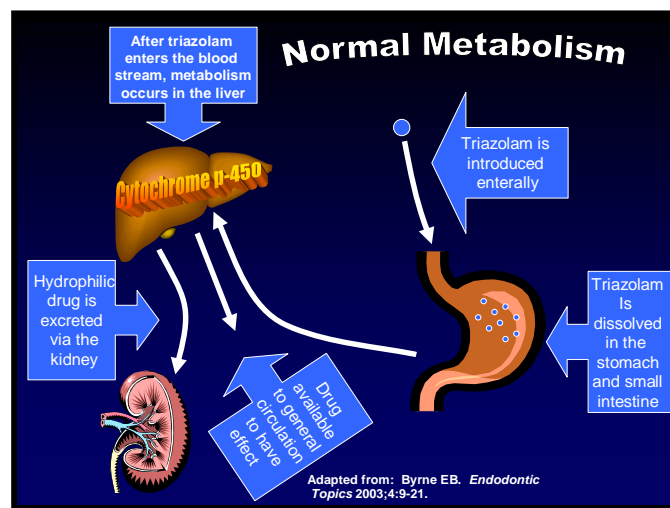
Drug distribution is often thought of in terms of compartments too, where highly lipophilic drugs cross readily from the plasma compartment to tissue compartments such as the brain. The *Blood-Brain Barrier* for example, is not a true “barrier”, but more like a selective gatekeeper for highly lipophilic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

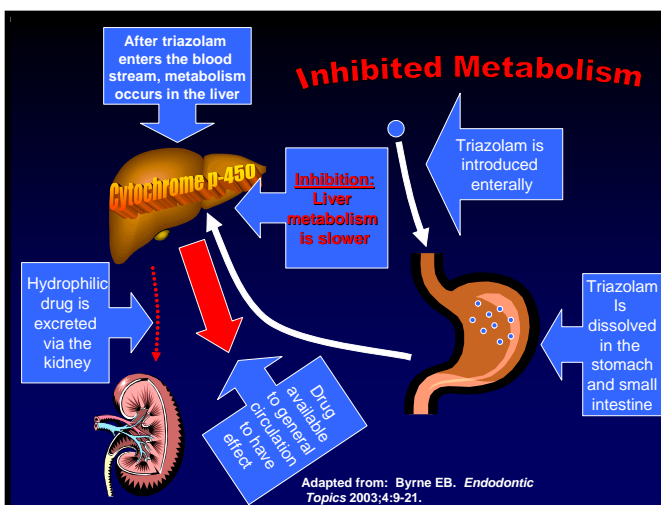
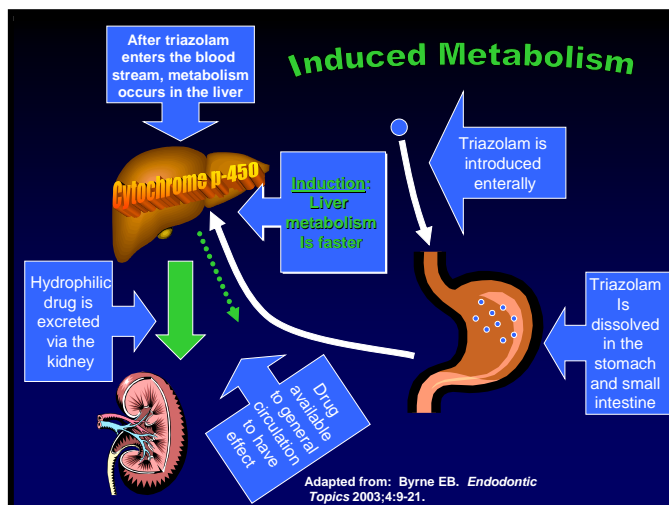
Drugs are chemically transformed by the body to make them more water soluble, and thus more easily excretable. The primary organ of metabolism for the oral sedative medications is the liver (although some similar enzymes exist in the cells of the gastrointestinal mucosa). The enzyme complexes in the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

### Other Notes or Questions to Ask:



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

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

#### Metabolism Effected By:

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

Substrate	Inducer	Inhibitor
Alprazolam	Barbiturates	CCBs
Astemizole	Cigarette Smoke	Clarithromycin
Atorvastatin	Cyclophosphamide	Corticosteroids
Barbiturates	Dexamethasone	Cyclosporine
CCBs	Lansoprazole	Erythromycin
Clarithromycin	Omeprazole	Fluconazole
Cyclosporine	Phenytoin	Fluoxetine
Erythromycin	Rifampin	Grapefruit Juice
Fentanyl	Sex Steroids	Itraconazole
Halothane		Ketoconazole
Loratidine		Lansoprazole
Lovastatin		Midazolam
Midazolam, SSRIs		Nefazodone
Simvastatin		Omeprazole
TCA's		Tamoxifen
Triazolam		

**Cytochrome  
P<sub>450</sub> 3A4**

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

#### Other Notes or Questions to Ask:



## Elimination:

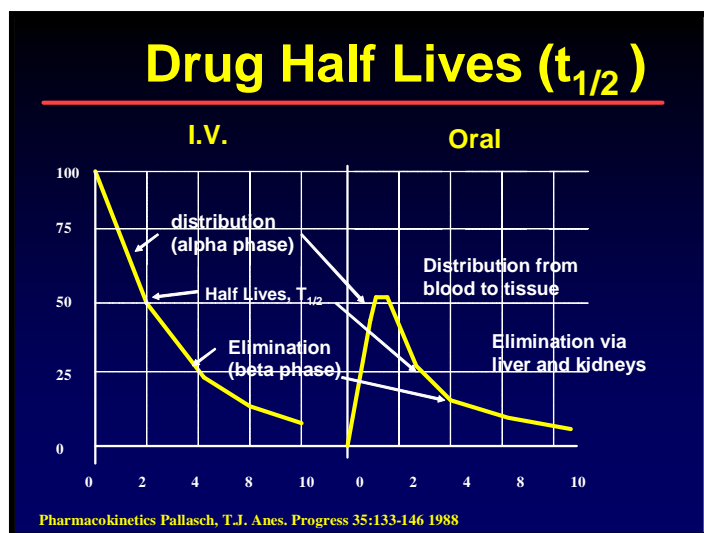
Renal clearance is the major pathway of **elimination** for most drugs and their metabolites. In fact, the role of the liver in metabolism is to generally convert lipophilic (fat-soluble) molecules into more hydrophilic (water-soluble) molecules for easier excretion via the kidneys. Elimination can also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

## Factors affecting elimination include:

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

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

100% divided by 2 = 50% (after one half life 50% of a drug has been cleared)  
 50% divided by 2 = 25% (after 2 half lives 75% of a drug has been cleared)  
 25% divided by 2 = 12.5% (after 3 half lives 87.5% of a drug has been cleared)  
 12.5% divided by 2 = 6.25% (after 4 half lives > 90% of a drug has been cleared)



## Therapeutic Levels

- Plasma level is a balance between dose per unit time and factors which will decrease the level of active drug (metabolism, excretion, dilution). Plasma levels of drugs are always changing.
- Steady state: If identical multiple doses of drug are given every half-life, relatively constant levels will be produced after 4 half-lives.  
 rate of elimination = rate of accumulation

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

## Other Notes or Questions to Ask:

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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.

*Donaldson M Goodchild JH. Pharmacological reversal agents in dental practice: keys to patient safety. Compend Contin Educ Dent 2016;37(10):1-8.*

### Agonists and Antagonists


Antagonists					
	5-HT <sub>3</sub> RAs	Promethazine	Atropine	Droperidol	NK-1 RA
Agonists					
	5-HT <sub>3</sub>	Histamine	Muscarinic	Dopamine (D <sub>2</sub> )	Substance P

Examples of some Neuro-Receptor Sites



### Pharmacodynamics

- As we age we may have enhanced sensitivity to drugs due to:
  - Changes in receptor numbers
  - Changes in receptor affinity
  - Alterations in the processes after a drug binds a receptor
- For example, the elderly are:
  - more sensitive to benzodiazepines
  - more sensitive to analgesic effects of narcotics
  - enhanced response to warfarin, heparin



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

### Other Notes or Questions to Ask: