

# General Principles

## Terminology

- Study of biochemical and physical aspects of drug effects (absorption, distribution, metabolism, elimination, toxicity) and specific drug actions
  - o Pharmacotherapeutics – cure/treatment/prevention of disease and pain relief
  - o Toxicology – poisons and environmental toxicity
  - o Abuse – abused substances
- Pharmacodynamics (drug action to body)
  - o Biochemical, physiologic, behavioral effect and mechanisms of action
- Pharmacokinetics (body action to drug)
  - o Drug function over time
  - o ADME – drug disposition – Absorption, Distribution, Metabolism, Excretion
  - o Intensity of drug effects by concentration
  - o Clinical decisions – dosage and intervals dependent on complete knowledge

## Nomenclature

- Chemical name – ID's chemical structure (ex:// 2-diethylamino-2,6-acetoxylidide)
- Generic (official) name – assigned by US Adopted Name Council (ex:// lidocaine)
- Trade (proprietary) name – assigned by company (Xylocaine, ultracaine, etc)

## Drug Info Sources

- US Pharmacopeia (USP) and National Formulary (NF) – authoritative, unbiased, general medical and clinical info
- Physician's Desk Reference (PDR) – only FDA approved indications/contraindications, only info provided by companies
- Accepted Dental Therapeutics (ADT) – by Council of Dental Therapeutics (CDT) intended for selection of drugs to treat oral diseases
- FDA – approve or reject applications from companies to market new drugs. Old drugs may be removed
  - o Prime concern is drug safety
- DEA – make legitimate balance between medical needs and availability for drug abuse
  - o Regulates all drugs for abuse except ^OH and tobacco

## Controlled Substances

Classification	Medical Use	Potential Abuse	Addictive
Schedule I	No	Yes	Yes
Schedule II	Yes	Yes	Yes
Schedule III	Yes	Yes	< Schedule I or II
Schedule IV	Yes	Yes	< Schedule III
Schedule V	Yes	Yes	< Schedule IV
Unscheduled	Ex:// Aspirin, Tylenol		

# Drug Abuse and Disposition

## Terminology

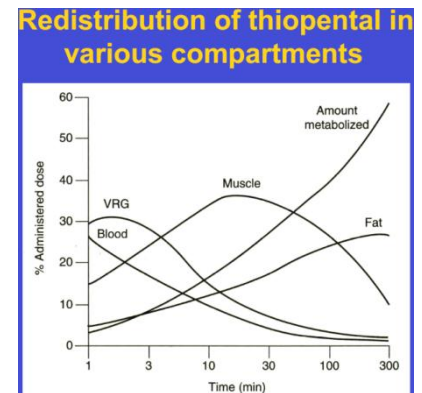
- Passage across lipid bilayer semipermeable membranes is primary step in absorption
- Filtration occurs through
  - o Intracellular process
  - o Intercellular process (ex:// movement through fenestrations between endothelial cells)
- Passive diffusion
  - o Down concentration gradient
  - o Dependent on lipid-water partition coefficient (higher lipid solubility = faster diffusion)
  - o Directly proportional to concentration, membrane SA, temperature
  - o Inversely proportional to particle size
- Passive Absorption
  - o % ionization if pH dependent
    - High ionization of weak acids at high pH
    - High ionization of weak bases at low pH
    - H-H equation to determine relative ratio of ionized drug (**drugs must be non-ionized to pass through the lipid bilayer!!!**)
      - $pK_a = pH + \log[A/B]$
- Active Transport
  - o Against concentration gradient, especially notable in kidneys and CNS
  - o Exhibits carrier protein transport saturation
- Facilitated Diffusion
  - o Down a concentration gradient, but with a carrier protein, may be unidirectional
  - o Exhibits carrier protein transport saturation
- Ion channels
  - o Allow passage of charged ions through a protein channel, may be bidirectional
- Pinocytosis
  - o Small engulfment of substances into cytoplasm via encapsulation into intracellular vesicle from the cell membrane

## Administration

Alimentary Routes – oral, rectal, sublingual, buccal	
Advantages	Disadvantages
<ul style="list-style-type: none"><li>- Most common</li><li>- Convenient, economical, fast</li></ul>	<ul style="list-style-type: none"><li>- First-pass metabolism (liver)</li><li>- Irregular absorption (pH, gastric emptying time, complex formation with stomach contents)</li><li>- Gastrointestinal irritation</li><li>- Inactivation from low pH (ex:// penicillin)</li></ul>
Parenteral routes – intravenous, intramuscular, subcutaneous, intraperitoneal, intra-arterial, intrathecal, transdermal	
Advantages	Disadvantages
<ul style="list-style-type: none"><li>- Precise, accurate, immediate</li><li>- Local – at sight of action</li><li>- Rapid dilution – limits [ ] necrotic material</li><li>- Can be used on unconscious patient</li><li>- Delivery of large volumes</li></ul>	<ul style="list-style-type: none"><li>- Adverse effects difficult to counteract</li><li>- Sterile formulation/technique vital</li><li>- Risk of embolisms</li></ul>
Topical – mucous membranes, skin (transdermal), eye	

## Distribution after IV administration

- Initial phase – cardiac output and regional blood flow dependent
  - o Initially heart, liver, kidneys, other highly perfused organs receive majority of drug
- Second phase – distribution to tissues with greater mass but less blood flow
- Diffusion across membranes – dependent on same factors as absorption
  - o UNIQUE CASE – blood brain barrier
    - No intercellular gaps – most lipophilic substances can cross, ionized substances cannot cross
- Placenta – not a barrier
  - o Low MW pass easily, high MW less easy to pass
  - o Exhibits ion trapping
- Plasma binding – limits drug availability, often point at which drug interactions occur
- Binding to other tissues
  - o Thiopental (adipose)
  - o Lead, tetracycline (bone)
  - o Heavy metals (kidneys, bone)
- Redistribution – drug passes from blood to organs, muscles, targets, etc



## Drug Metabolism and Excretion

- Metabolism (biotransformation) can change ionization state, deactivating drug or activating prodrug
  - o More polar – less lipid soluble
  - o Less renal re-absorption
  - o More metabolized drug excreted
- Relative tissue metabolic activity
  - o Liver 100
  - o Lung 10-20
  - o Kidney 8
  - o Intestine 6
  - o Placenta 5
  - o Adrenal 2
  - o Skin 1

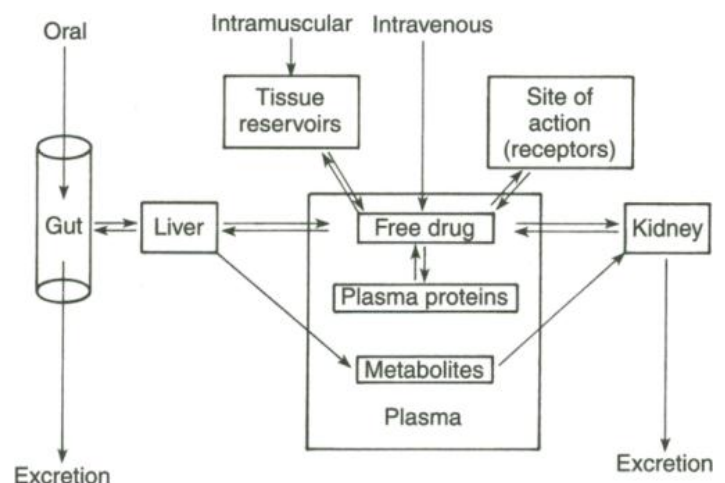
## 2 Different Types of Metabolism

- Phase I – alter chemical reactivity and increase aqueous solubility
  - o Oxidation
    - Enzyme system – mixed function oxidase (MFO)
    - In sER
    - Cytochrome P450 (superfamily of enzymes)
    - Subject to induction (increase metabolism in vivo) or inhibition
    - Non-microsomal oxidation = alcohol dehydrogenase
  - o Reduction
  - o Hydrolysis
- Phase II – further increase solubility promoting excretion
  - o Glucuronidation
    - Common conjugation reaction pathway (enterohepatic recirculation)
    - Occurs primarily in liver (for detox)
    - Converts toxic substances (steroids, drugs, enzymes, toxins, etc) for urinary excretion
  - o Sulfation
  - o Acetylation
- Metabolic Order
  - o Phase I
  - o Phase II
  - o Phase I followed by Phase II
  - o NEVER Phase II followed by Phase I

## Pharmacokinetics

- Rates of change
  - o Zero order – drug concentration decreases at a linear rate in the body
    - Rate limiting step is at saturation (enzyme or secretory processes)
    - Constant amount is being eliminated
  - o First order – drug concentration decreases in an exponential rate
    - Constant fraction of the drug is being eliminated (similar to half-lives)

- Apparent Volume of Distribution ( $V_d$ ) – ( $V_d = \text{dose} / \text{plasma concentration}$ )
  - Estimating drug concentration in a specific tissue as related to drug concentration in blood plasma
    - Assumes:
      - Instantaneous distribution, no metabolism
      - No excretion
      - No sequestration (ex:// no binding to albumin)
- Elimination is a function of clearance rate (renal clearance, liver clearance/detox)
  - Half-life – time it takes for concentration of a drug to decrease by half
  - Clearance – drug elimination from body relative to drug concentration in plasma
    - $\text{Clearance} = (\text{metabolism} + \text{excretion}) / [\text{drug}] \text{ in plasma}$ 
      - $\text{L/hr} = (\text{mg/hr} + \text{mg/hr}) / (\text{mg/L})$
- Excretion
  - Renal excretion dependent on 3 factors
    - Glomerular filtration
    - Tubular secretion
    - Tubular reabsorption
- Dosage, infusion, and steady state
  - The goal is to achieve a drug dosage given to the patient to maintain a concentration where the rate of the drug's metabolism is equal to its intake, and to maintain this concentration in the therapeutic range.
  - Steady state
    - Achieved after ~4 half lives
    - Independent of dosage
  - Fluctuations
    - Proportional to dosage given
    - Infusion < small doses < large doses
  - Steady state concentration
    - Proportional to dose/dosage interval
  - Therapeutic range
    - Rate in = rate out
    - $\text{Steady state } [ ] = (\text{fraction absorbed} \times \text{dose}) / (\text{dosing interval} \times \text{clearance})$
  - Loading Dose
    - $\text{Initial concentration} = \text{loading dose} / \text{body volume}$
- Factors affecting therapeutic or toxic drug dosages
  - Age
  - Genetics
  - Health
  - Drug interactions



## Pharmacodynamics

- There are a variety of detriments during the ingestion of a drug before it reaches its target site
- Once absorbed into the body, drugs can be bound (ex:// by albumin), sequestered in tissues, or excreted. All these processes compete with the target organ for drug distribution
- Drug receptor interaction assumptions
  - Law of mass action – reversible reaction between single receptor unit and single drug unit
    - Hill-Langmuir Equation =  $\frac{[DR]}{R_T} \frac{[D]}{K_d + [D]} = \frac{effect}{max\ effect}$ 
      - DR = drug-receptor complex
      - D = drug
      - K<sub>d</sub> = dissociation constant
      - R<sub>T</sub> = total number of receptors
        - Similar to Lineweaver Burke plot, when [D] = K<sub>d</sub>, [DR]/R<sub>T</sub> = 0.5
    - All receptors are identical and equally accessible
    - Drug response intensity directly proportional to how many receptors react with drug
    - Effective drug concentration doesn't change – number of receptors is negligible

## Differences affecting Dose-Response curve

- Different drugs will require different concentrations to reach the max effect
  - Stronger potency = smaller X-axis range to reach maximum effect
- Some drugs (partial agonists) have different maximum effects, even if they occupy same number of receptors
- Competitive Inhibition – antagonist binds to same active site as drug
  - Increases amount needed to reach maximum effect
- Non-competitive inhibition – antagonist binds to different active as drug
  - Decreases maximum effect

## Quantal Dose Response

- Curve that shows the % of individuals that fall within the normal drug response range
  - Has a Gaussian distribution
- ED<sub>50</sub> – dose where center of the distribution = 50% of individuals fall into the center of the therapeutic range
- TD<sub>50</sub> – dose where center of the distribution = 50% of individuals fall into the center of the toxic range
- LD<sub>50</sub> – dose where center of the distribution = 50% of individuals fall into the center of the lethal range
- Therapeutic index = LD<sub>50</sub> / ED<sub>50</sub>
  - Usually, the higher the TI, the better
- Certainty Safety Factor (CSF) = LD<sub>1</sub> / ED<sub>50</sub>
  - <1.0 = overlap of LD and ED for population
  - >1.0 = better
  - Therapeutic index is not [always] a good indicator for drug dosage safety
- Standard Safety Margin = (LD<sub>1</sub> – ED<sub>99</sub>) / ED<sub>99</sub>
  - The percentage by which ED<sub>99</sub> must be raised to reach LD<sub>1</sub>

## Drug Specificity

- Highly specific drugs have an effect if they interact with only 1 type of receptor
  - That single type of receptor may be in many locations, so drug may still have many effects
    - Non-selective drugs act (have an effect) on many locations
  - Atropine (anticholinergic) – acts on cholinergic receptors
    - Stomach – reduces acid secretion
    - Mouth – reduces salivary flow
    - Eye – causes pupil dilation
- Non-specific drugs can interact with multiple receptors
  - Can have multiple mechanisms of action
  - Diphenhydramine (antihistamine and anticholinergic) – acts on histamine and CNS
    - Histamine – reduces vasodilation, reduced smooth muscle contraction
    - Cholinergic receptors – causes sedation, dry mouth

## Drug Interactions

- Pharmacological effect altered by at least one other substance
  - o Pharmacokinetic interactions – alteration in final blood plasma level
  - o Pharmacodynamics interactions – alteration in drug effect
- >750K patients die per year from dosing errors
- Between 1.5-5.5B is spent in reparations per year

## Pharmacokinetics

- Absorption
  - o Drug preparations
    - Incompatibility with infusion fluids
    - Incompatibility with  $\geq 2$  drugs – problems with solubility
    - Drug complex formation
  - o Altered enteric absorption
    - Complex formations – cations and tetracyclines
      - Chemical antagonism – tetracycline + antacid ( $\text{Ca}^{++}$ ) decreases tetracycline effect
    - Intestinal motility – opioids
    - Dietary influences – fatty meals, hydrolysis of penicillin by acidic fruit juice
    - Gastric pH – buffering affects weak acid absorption
- Distribution
  - o Plasma protein binding – sequesters drugs, makes them inactive
    - Competition for the same binding sites affects concentration of free drug in bloodstream
    - Affects activity and half-life
      - Dopamine's peripheral systemic effects limited by presence of and binding to carbidopa
        - o Carbidopa cannot cross blood brain barrier – greater amount of DOPA crosses blood brain barrier
  - o Altered parental distribution – administration of vasoconstrictors with anesthetics
- Metabolism
  - o Biotransformation rate – induction of microsomal enzymes (mixed function oxygenases) can lead to rapid metabolism of other drugs (alters pharmacokinetic properties of the second drug)
  - o Rate of First Pass Metabolism – altered hepatic blood flow inhibits clearance of other drugs already metabolized by liver enzymes (increases other drug half-lives)
- Excretion
  - o Reduction in renal excretion – competition between drugs for the active transport system (active sites) can affect half life
  - o Urinary pH – alkalization of urine with bicarbonate increases ionization of weak acids, enhancing their excretion. Acidification with ammonium chloride enhances weak base excretion.
  - o Changes in urinary volume – diuretics reduce concentration of toxins/metabolites in renal tubules

## Pharmacodynamics

- Receptor interactions – antagonistic action of one drug to counteract the action of another drug
- Physiologic interactions – the action of one drug can be counteracted by the effect of another drug through an entirely different mechanism



## Drug Interaction Classifications

- Biochemical antagonism – phenytoin (induces CYP3A4) increases metabolism of gleevec, decreases its biological effect (decreases biological inhibition)
- Synergism – monoamine oxidase inhibitors increase tyramine effect, increasing catecholamine release from synaptic vesicles (for treatment of depression)
- Pharmacological antagonism – two drugs using the same active site, but have opposing biological effects
- Physiological antagonism – two drugs using different active sites, and have opposing biological effects
- Addition – two drugs using the same active site have the same effect (aspirin and acetaminophen)
- Summation – two drugs using different active sites have the same effect (codeine and aspirin)
- Antagonism
  - Pharmacologic
  - Physiologic
  - Biochemical
  - Chemical
- Addition – combined effects of  $\geq 2$  drugs that have same pharmacologic effect
- Summation – effects of a drug enhanced by another drug though their pharmacologic effects are different
- Novel drug effects – combination of 2 drugs gives new response different than if each drug is given individually

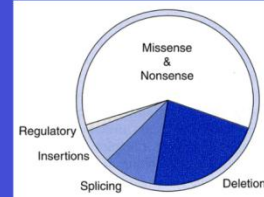
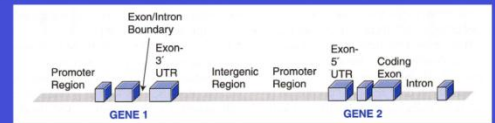
## Things that change drug effects

- Physiologic condition (health)
  - Liver disease (clearance rate)
  - Kidney disease (clearance rate)
  - Tolerance
  - Dehydration
  - Pregnancy
- Body weight
- Administration route
- Sex
- Patient compliance
- Placebo effect – roughly 1/3 of patients show a positive placebo effect
  - Patient's confidence in prescriber
  - Trivial factors (taste, color, price)
- Age – relates to metabolic rate, and therefore metabolism of drug
  - Neonates may have a low metabolism [low levels of cytochrome P450]
  - Older patients have increased fat, decreased muscle and plasma protein, etc – decreases drug clearance
    - Histamines – make adults sedate, but makes kids hyper

## Pharmacogenetics

- The study of how [and to what degree] genetic polymorphism (genetic diversity) impacts drug responsiveness
  - o Idiosyncratic responses
    - Pharmacokinetic – drug metabolism
    - Pharmacodynamics – drug target sites
  - o Drug response varies inside a population (shows a Gaussian distribution)
- Drug metabolism can be severely affected by genetic mutations
  - o Shown in maternal and fraternal twin studies of analgesic metabolism of a drug requiring multiple enzymes for metabolism
- Genetic variation affects individual expression of different enzymes, therefore affecting target site [active sites]
  - o Individualized therapy based on genotype could, theoretically, decrease adverse effects of drugs, tailoring treatment for the individual to maximize therapeutic effect

### Genomic regions & types of genetic variability



- 27,027 DNA variations studied
- 1,222 linked to disease
- Sorted into functional groups

## Autonomic Drugs

### 1. Cholinomimetic Agents (agents that can mimic some or all of the effects of ACh)

- M1 Receptors: gastric parietal cells (CAMP/ Phospho)
- M2 Receptors: cardiac cells and smooth muscle (K<sup>+</sup>)
- M3 Receptors: bladder, exocrine glands, and smooth muscle (CAMP/ Phospho)
- - a. **Muscarinic Agonist** (aka *Parasympathomimetics*)
    - o unselective for various subtypes of M receptors
    - o exert same effects that are caused by ACh on tissues innervated by parasympathetic nerves
    - o cause vasodilation indirectly via stimulation of nitric oxide synthesis and release from vascular endothelial cells
    - o cause sweating (sympathetic N.S. response)
    - o will cause peripheral effects DUMBELS:
      - Diarrhea
      - Urination
      - Miosis (constriction of pupils)
      - Bradycardia
      - Bronchoconstriction
      - Excitation of Skeletal Muscle & CNS
      - Lacrimation
      - Salivation
      - Sweating

**Pilocarpine:** stimulate salivary flow

**Cevimeline:** stimulate salivary flow

#### b. Indirectly Acting Cholinomimetics (AChEI will elevate [ACh] at all sites where ACh is released from cholinergic nerves)

- o AChEI can stimulate skeletal muscle contraction
- o Stimulate ganglionic transmission (ie: depolarize postganglionic nerves of both PNS and SNS)
- o Cause release of epi and norepi from adrenal medulla
- o Accentuate muscarinic effects due to buildup of ACh at the effector cell

**Donepezil:**

- can be distributed to the CNS
- side-effects include accompany donepezil therapy include nausea, vomiting, diarrhea, cough, hypotension and bradycardia

**Neostigmine:**

- quaternary N-containing compound with obligatory positive charge
- treats myasthenia gravis

**Physostigmine:**

- tertiary nitrogen and uncharged at physiological pH (can get into CNS)
- used to treat poisoning by muscarinic antagonists like atropine in the CNS
- causes buildup of endogenous ACh levels wherever it is released

**Organophosphate AChEI:**

- alkylate the AChE enzyme, thus inhibit its action irreversibly
- primarily of toxicological interest, but can be used locally (ie: eyedrops, to treat glaucoma)

### 2. Cholinergic Blocking Agents (cholinergic blockers, parasympatholytics or anticholinergic drugs)

#### a. Muscarinic Antagonists (block muscarinic receptors causing inhibition of all muscarinic functions)

- o Blocks ACh action on muscarinic receptors that reside on:
  - Cells receiving postganglionic parasympathetic nerves
  - Sweat glands that are innervated by postganglionic sympathetic nerves
  - Vascular endothelial cells
  - Absence of effect normally associated with tonic (increase) influence of ACh on these tissues
  - Muscarinic antagonists will also block the vasodilator effect of muscarinic agonists
  - Causes xerostomia – poor dental health
  - Patients can be photophobic due to mydriasis

**Atropine:** used for CNS effect in tx of Parkinson's, control drooling

**Scopolamine:** used for CNS effect in tx of Parkinson's, reduce motion sickness

**Ipratropium:** used by some patients w/ COPD

**Glycopyrrolate:** useful during surgery to decrease secretions

**Tolterodine:** used chronically by some patients w/ incontinence due to "overactive bladder"

**Diphenhydramine:** used in OTC sleep-aid preparations, as an anti-histamine, tx of motion sickness, and antiemetic (used to tx cancer chemotherapy-induced vomiting)

**NOTE:** this agent not classified as a muscarinic antagonist, but it readily blocks muscarinic receptors when used in common doses!

#### b. NMJ Blocking Agents (blocks ACh effect on skeletal muscle)

#### c. Ganglionic Agents (specifically act on nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia)

**Nicotine:** effects include increase blood pressure, cardiac rate, peristalsis, and secretions (at higher doses, bp falls b/c of ganglionic blockade and activity both in the GI tract and bladder musculature ceases)

**Mecamylamine:** blocks ganglionic transmission (part of smoking cessation programs)

- Might exhibit photophobia, orthostatic hypotension and xerostomia

## Sympathomimetic Agents

Alpha 1	Alpha 2	Beta 1	Beta 2
Vasoconstriction	Inhibition of NorEpi release	Tachycardia	Vasodilation
Increase peripheral resistance	Inhibition of ACh release	Increase lipolysis	Slightly decreased peripheral resistance
Increase blood pressure	Inhibition of insulin release	Increased myocardial contractility	Bronchodilation
Mydriasis		Increased release of renin	Increased muscle & liver glycogenolysis
Increase closure of internal sphincter of bladder			Increased release of glucagon
			Relaxed uterine smooth muscle

**Epinephrine:** agonist at alpha 1, alpha 2, beta 1, beta 2 receptors

**Norepinephrine:** agonist at alpha 1, alpha 2, beta 1 receptors

**Isoproterenol:** agonist at beta 1, beta 2 receptors

**Dopamine:** agonist at dopamine receptors (DA 1 and DA 2), alpha 1 and beta 1 receptors (w/ higher doses of DA)

### 1. Sympathomimetic Agents

#### a. Prototype Agent

##### i. Alpha 1: **Phenylephrine**

- Vasoconstriction
- Dilation of pupil

##### ii. Alpha 2: **Clonidine** & **Alphamethyl Norepinephrine (Levonordefrin)**

- Decreases sympathetic outflow from the vasomotor center to heart and vessels → hypotension
- CNS effect also causes sedation
- Reduce transmitter release on presynaptic membrane of autonomic nerves
- Vasoconstriction on peripheral blood vessels
- **NOTE:** Levonordefrin will still be effective in pts treated with alpha 1 blockers

##### iii. Beta 1 (mainly cardiovascular effects): **Dobutamine**

- Stimulate cardiac tissues
- Increase HR, conduction velocity & contractility

##### iv. Beta 2: **Albuterol**

- Relaxation of vascular, bronchiolar and uterine smooth muscle
- Breakdown of glycogen to glucose

##### **Salmeterol**

- Slow-acting, long-acting cmpd used for chronic tx of asthma, not for termination of acute attacks
- Side-effects are minimal: tachycardia & skeletal muscle tremor

##### v. **Dopamine**

- Vasodilation of kidney arterioles
- Can be used to stimulate cardiac output (via its beta 1 activity)
- Can cause vasoconstriction w/ higher doses

#### b. Indirectly Acting Agents (act via release of NE from nerve ending stores; intact neuronal stores of NE are needed for these drugs to act)

##### i. **Amphetamine**

##### ii. **Tyramine**

##### iii. **Pseudoephedrine**

##### iv. **Cocaine**

- **Prevent uptake of released NE into sympathetic nerve ending**

### 2. Sympatholytics

#### a. Agents Acting as Pharmacological Antagonists (occupy postjunctional receptors, lack efficacy, compete w/ endogenous NE, EPI and DA for adrenoceptors)

#### b. Alpha Adrenoceptor Antagonists

- Block those effects of endogenous NE and EPI that are exerted via alpha receptors:
  - Alpha blockers will decrease NE-induced tonic arteriolar and venous constriction
  - Decrease load on heart by decreasing vascular resistance
  - May cause reflex tachycardia
  - Decrease resistance to urinary outflow
  - Cause miosis
- i. **Prazosin:** (*see above?*)
- ii. **Tamsulosin:** (*see above?*)
- iii. **Phentolamine:** (*see above?*)

#### c. Beta Adrenoceptor Antagonists

- Block cardiac and metabolic effects of sympathomimetics w/ beta agonist activity
- Decrease blood pressure (after chronic use)
- Decrease work load on heart
- Unselective beta blockers reduce beta 2-mediated relaxation of smooth muscle and thus can aggravate asthma
  - i. **Propranolol:** (unselected blockade of beta receptors)
  - ii. **Metoprolol** (selective beta 1 aka cardioselective blockade)
  - iii. **Carvedilol** (block of alpha 1 and beta receptors)

**d. Agents Acting at the Sympathetic Nerve Ending**

- **NOTE:** these agents can be EITHER sympatholytics or sympathomimetics
  - i. **Guanadrel:** inhibit nerve AP – induced release of NE → sympatholytic effect
  - ii. **Reserpine:** inhibits storage of NE in the vesicle - depletion of NE stores → sympatholytic effect
    - Will also have CNS effects (depressants)
  - iii. **Cocaine:** blocks uptake I (re-uptake of NE into nerve ending) → sympathomimetic effect

**e. MAO Inhibitors**

- Can cause decreased NE biosynthesis and formation of a low-efficacy “false transmitter” → decr sympathetic funct
- Chronic tx can cause orthostatic hypotension
- Ingestion of tyramine-containing foods/injections of an indirectly acting sympathomimetic (causing sudden release of remaining, stored NE) can cause dangerous elevation in BP!



## General Anesthesia

- Complete Anesthesia has 3 components:
  - o Unconscious
  - o Muscle relaxation
  - o Analgesia
- Balanced anesthesia – using more than 1 anesthetic
- Stages of Anesthesia
  - o Stage I – analgesia
  - o Stage II – delirium, retching, amnesia
  - o Stage III – surgical
    - Plane 1 – dental and thoracic procedures
    - Plane 2 – abdominal surgeries
    - Plane 3 – deep abdominal surgeries
    - Plane 4 – danger zone
  - o Stage IV – medullary depression

## Mechanisms

1. Anesthesia commences when any substance obtains a certain concentration in membrane
2. Anesthesia results when agents alter function of specific proteins critical for neuronal communication
3. Anesthetics target selected neuronal centers and/or certain aspects of synaptic transmissions (or both)

## Procedural Sedation in Dentistry

1. Inhalation Sedation ( $N_2O/O_2$ ) – technique of choice
  - a. Titratable, easy, rapid onset, well tolerated, controlled duration
  - b. Moderate efficacy, patient cooperation needed
2. Oral sedation (benzodiazepine, chloral hydrate, antihistamine)
  - a. Very easy, well tolerated
  - b. Not titratable, difficult to reverse, prolonged duration
3. IM Sedation (benzodiazepines, antihistamines)
  - a. Easy, faster than oral
  - b. Pain of injection, prolonged duration, local tissue damage
4. IV sedation (benzodiazepines, opioids, propofol)
  - a. Titratable, rapid onset, high efficacy
  - b. More difficult, prolonged duration, not as well accepted

## Local Anesthetics

- Local factors
  - o Diameter – smaller fibers have shorter inter-nodal distances (need to block at least 3 to be effective)
  - o Pattern of impulse traffic – rapid conduction fibers more sensitive to LA
    - Painful/noxious stimuli evoke frequent firing
  - o Inflammation – lowers pH, shifts more LA to ionized form
- Usually block voltage gated sodium channels (phase 0)
  - o Phase 1 – inactivation
  - o Phase 2 – plateau
  - o Phase 3 – repolarization
  - o Phase 4 – slow depolarization

## Structure

- Lipophilic/aromatic – facilitates passing through membrane
- Linker – spatial separation, distinct metabolism, allergenicity
- Hydrophilic/amine – water solubility and channel blocking

Esters – procaine/novocaine, tetracaine/pontocaine, cocaine/generic

- Inactivated by hydrolysis (pseudocholinesterase)
- Short halflife
- Minimal excretion of unmetabolized agent

Amides – lidocaine/xylocaine, mepivacaine/carbocaine, bupivacaine/Marcaine, prilocaine/citanest

- Liver metabolism (P450)
  - o Amide toxicity for liver damaged patients
- Hepatic blood flow = limiting factor
  - o Slower halflife
- Minimal excretion of unmetabolized agent

## Absorption

- Drug dosage
- Administration site
  - o Vary widely in topical administration
  - o Fastest induction at highly vascular sites (fast into blood = fast into brain)
- Vasodilation/vasoconstriction
  - o All LA cause vasodilation (except cocaine)
    - Bupivacaine > procaine > lidocaine > prilocaine > mepivacaine
  - o Vasoconstrictors are added to increased duration of LA
- Unbound LA effectively cross B-B barrier and placenta (severe cardiac depression in fetus)
- Amide and slow metabolized esters distribute to highly perfused areas (heart, brain, liver)
  - o Reduces systemic LA levels

## Adverse Effects

- Moderate systemic absorption – LA = CNS stimulants
  - o Tingling, lightheadedness, tinnitus, convulsions
- High systemic absorption – LA = CNS depressants
  - o Profound hypotension, respiratory depression, coma
- Some LA's are anti-arrhythmic drugs (ex:// lidocaine) – target overactive cardiac regions ( $\text{Na}^+$ )
  - o High systemic levels may decrease cardiac  $\text{Na}^+$  excitability
- Cardiotoxic – bupivacaine, etidocaine
- Not cardiotoxic – ropivacaine



## Intravenous Drugs – used to induce anesthesia

Drug	Chemistry	Mechanism	Kinetics	Analgesia	Cardio	Respiratory	Side Effects
Barbiturates	High lipid soluble	GABA(A) receptor agonist Hyperpolarizes Cl <sup>-</sup> channels	Unconscious <30s Regain 10-20min	Hyperalgesia	Decreased BP Increased rate	Depression	Vasospasm Elderly Asthmatics
Benzodiazepines	Prefer to use midazolam	GABA(A) receptor agonist	Unconscious <60s Long lasting (1h)	NONE	Minimal	Minimal	Long $t^{1/2}$ = 20-70h Drowsiness
Opioids	Potency 100x morphine	Mu receptor agonist		Excellent	Insignificant	Profound depression	Nausea, constipation COPD, asthma
Ketamine/Ketalar	“Angel Dust”	NMDA receptor antagonist  Given IV, IM, oral, rectal	Rapid onset 5-20min duration	Dissociative Anesthesia - Analgesia - Amnesia - Catalepsy - Protective reflexes maintained	Increased rate, output, and BP	Minimal	Hallucinations, nausea, vomiting  Given with benzodiazepines
Propofol	Unique structure		Rapid onset, action <10min	For intensive care  No analgesia	none	depression	Faster recovery than barbiturates  Seizures, pain on injection

## Inhalation Anesthetics

- Surgery conducted at 1.4\*MAC
  - o MAC = minimal alveolar concentration for 50% of patients anesthetized

Drug	MAC	Analgesia	Muscle Rel.	Cardio	Respiratory	Side Effects
N <sub>2</sub> O	105%, rapid	Good	Minimal	None	COPD, asthma hypoxia warning	Dysphoria, nausea, addiction, abortion, infert.
Desflurane	7%, rapid	Moderate	Good	Increased rate Decreased BP	Depression	Resp irritant, malignant hyperthermia
Isoflurane	1.2%, rapid	Moderate	Moderate	Increase rate Decrease contract. Decreased BP	Depression	Malignant hyperthermia

## NSAIDS

- Anti-inflammatories
  - o Runs risk of blocking normal response – can do more harm than good
  - o Inflammation mediated by
    - Histamines
    - Serotonin
    - Complement
    - Bradykinin
    - Prostaglandins – lowers activation threshold for pain response
      - NSAIDs block prostaglandin formation
    - Leukotrienes
- Analgesics
- Antipyretics

## Mechanism

- Trauma → PLA2 causes arachidonic acid release from phospholipid storage → converted to eicosanoids → metabolized → pain, headache, fever, inflammation
  - o Prostaglandins cause
    - Sensitize nerve endings
    - Inflammation
    - Fever
    - Inhibit platelet aggregation
    - Uterine contractions
- NSAIDs block COX pathway → block prostaglandin formation
- Leukotrienes – only produced in lungs, leukocytes, blood vessels and epicardium
  - o Inflammation
    - Induce chemotaxis
    - Vasoconstrictors of bronchial smooth muscle
    - Increase capillary permeability
    - Important in asthma and hyperalgesia
- Leukotriene inhibitors are usually used for mild/moderate asthma

## NSAID Use

- o COX1 – constitutively expressed
- o COX2 – trauma expressed
- Inhibit COX2 = antipyretic, anti-inflammatory, analgesic
- $IC_{50}$  = [drug] that inhibits enzyme by 50%
  - o  $IC_{50}$  COX2/COX1
    - $>1$  = more selective for COX1
    - $<1$  = more selective for COX2

## Therapeutics

- All comes from blocking COX pathway – symptom alleviation, not curative
- Blocks mild/moderate pain, inhibits preoptic hypothalamic region (antipyretic)
- Superior to opioids for some post-op pain
- Does not have opioid narcotic side effects, but has ceiling effects (600mg/6h)

- Used for inflammatory diseases, vascular headache, platelet inhibition, prevent colon cancer and Alzheimer's
  - o Aspirin irreversibly inhibits COX1, other NSAIDs transiently (reversibly) inhibit COX1
    - Aspirin may increase bleeding time, Ibuprofen shown to counter this effect
    - Other NSAIDs do NOT significantly affect platelets
  - o Appropriate use of NSAIDs is empirical – adequate symptom relief, patient history and preference
- Chronic NSAID Use
  - o Loss of prostaglandin protection to stomach – ulceration
    - Misoprostol – prostaglandin analog that may help with side effects

## Side Effects

- Uterine contraction inhibition – prolongation of gestation
- Inhibit prostaglandin mediated renal functions (chronic use)
  - o  $\text{Na}^+$  and  $\text{H}_2\text{O}$  retention can reduce effectiveness of some antihypertensives
  - o NSAIDs block compensatory vasodilation by renal prostaglandins
- Hypersensitivity
  - o Acetylation of COX1 produces abnormal antigen – may be antibody target

## Other NSAIDs

- Kinetics
  - o Rapid and complete absorption via passive diffusion
  - o Elimination via hepatic transformation to soluble product
  - o Most can cross B-B barrier
- Dynamics
  - o Similar to Aspirin
    - Exception – reversible inhibition of platelets
  - o No accepted guidelines for NSAIDs – based on clinical experience and side effects
- COX2 Inhibitors
  - o Efficacy approximates conventional NSAIDs
  - o GI ulcerations reduced compared to COX1
  - o No antithrombotic activity
  - o Renal complications AT LEAST the same
  - o Cardiovascular complications
- Nitric Oxide (NO)
  - o Increase mucosal blood flow, bicarb secretion, mucus secretion
    - Effects similar to cytoprotective prostaglandins
  - o Combining NO with NSAIDs decreases GI side effects (similar to COX2)
- Combinations
  - o Aspirin and acetaminophen – no increased analgesia or antipyretics, ceiling at 1g
  - o NSAIDs and caffeine – no increased analgesia
  - o NSAIDs and opioids – works very well

## Aspirin

- Low dose (COX1 inhibition)
  - o Blocks TXA2 – TXA2 causes platelet aggregation and vasoconstriction
- High dose (COX2 inhibition)
  - o Blocks PGI2 – PGI2 inhibits platelet aggregation, causes vasodilation
- GI distress – bleeding reduced when taken with food and water
- Hepatic effects – Reyes syndrome for kids with chicken pox or influenza
- Hypersensitivity – usually history of asthma and nasal polyps, spillover of excess arachidonic acid to leukotrienes
  - o 50% cross reactivity with other NSAIDs
- Drug interactions
  - o  $\text{^OH}$  – GI ulcerations
  - o Warfarin – increased bleeding time
- Contraindications
  - o Peptic ulcers
  - o Hemophilia
  - o Aspirin hypersensitivity
- Mild toxicity – Tinnitus, headache, nausea, dizziness
- Lethal toxicity – treat with gastric lavage, charcoal, IV (restore pH), fluids and electrolytes
- Dosage
  - o 650mg ceiling (more effective than 60mg codeine for post-op dental)
  - o 80-160mg for antiplatelets
  - o 6-8 tablets/12h for anti-inflammatory

## Acetaminophen

- Dosage
  - o 325-650mg/4h as needed
    - Ceiling effect at 1g/day
    - Lethal at 4g/day
  - o Acceptable alternative if patient cannot take NSAIDs
- Indications
  - o Post-op dental pain (analgesic effect same as aspirin)

Drug	IC <sub>50</sub> (COX-2) /IC <sub>50</sub> (COX-1)	Use/Dosage	Side Effects	Notes
Aspirin	166	<p>650mg ceiling</p> <ul style="list-style-type: none"> <li>- More effective than 60mg codeine for post-op dental</li> </ul> <p>80-160mg for antiplatelets</p> <p>Low dose (COX1 inhibition)</p> <ul style="list-style-type: none"> <li>- Blocks TXA<sub>2</sub> – TXA<sub>2</sub> causes platelet aggregation and vasoconstriction</li> </ul> <p>High dose (COX2 inhibition)</p> <ul style="list-style-type: none"> <li>- Blocks PGI<sub>2</sub> – PGI<sub>2</sub> inhibits platelet aggregation, causes vasodilation</li> </ul> <p>6-8 tablets/12h for anti-inflammatory</p> <ul style="list-style-type: none"> <li>- Anti-inflammatory requires 5g/day</li> </ul> <p>Blocks platelet aggregation – may prevent stroke and SECOND heart attack, increased risk of GI bleeding</p> <p>Contraindications – Peptic ulcers, hemophilia, aspirin hypersensitivity</p>	<p>GI distress – bleeding reduced when taken with food and water</p> <p>Hepatic effects – Reyes syndrome for kids with chicken pox or influenza</p> <p>Hypersensitivity – usually history of asthma and nasal polyps, spillover of excess arachidonic acid to leukotrienes</p> <ul style="list-style-type: none"> <li>- 50% cross reactivity with other NSAIDs</li> </ul> <p>Drug interactions</p> <ul style="list-style-type: none"> <li>- ^OH – GI ulcerations</li> <li>- Warfarin – increased bleeding time</li> </ul> <p>Mild toxicity – Tinnitus, headache, nausea, dizziness</p> <p>Lethal toxicity – treat with gastric lavage, charcoal, IV (restore pH), fluids and electrolytes</p>	<p>Irreversible COX1 inhibitor</p> <p>Detectable after 30min</p> <p>Peak at 2h (<math>t^{1/2} = 3h</math>)</p> <p>Metabolized to salicylic acid (90% protein bound)</p> <p>Glucuronidation metabolism in liver</p>
Acetaminophen	Not an NSAID	<p>325-650mg/4h as needed</p> <ul style="list-style-type: none"> <li>- Ceiling effect at 1g/day</li> <li>- Lethal at 4g/day</li> </ul> <p>Acceptable alternative to NSAIDs for analgesia</p> <p>Better at blocking CNS than peripheral COX</p>	<p>Weak anti-inflammatory</p> <p>Little effect on platelet aggregation, low GI irritation, few renal effects</p> <p>P450 produces toxic metabolite (4%)</p> <ul style="list-style-type: none"> <li>- Detox by conjugation to glutathione</li> <li>- Liver damage if glutathione is depleted</li> <li>- Caution for ^OH abusers</li> </ul>	<p>Peak at ½h-2h (<math>t^{1/2} = 3h</math>)</p> <p>Glucuronidation metabolism by liver</p> <p>Barbituates, rifampin, carbamazepine, hydantoins – increase hepatic P450</p>
Ibuprofen (Propionic acid derivative)	15	<p>200-400mg/4-6h, 3.2g/day max</p> <p>First choice – safe, effective, cheap</p> <p>Better tolerated than aspirin</p>		<p>May counter aspirin's anti-thyombolytic effect</p>

Misoprostol				Prostaglandin analog – helps reduce stomach ulcerations
Indomethacin (Acetic acid derivative)	60	Suppress uterine contraction (pre-term labour)  Closure of ductus arteriosus after birth	Not routine analgesia  Not for <14y/o	
Ketorolac		10mg/4-6h, 40mg/day max Therapy does NOT exceed 5 days  For moderate/severe post-op pain (not for arthritis) - analgesia potency similar to narcotics	Not anti-inflammatory	Oral rinse decreases perio inflammation (animals)  Prescription only, oral dose only after initial IV/IM use
Diflunisal				Doesn't cross B-B barrier (not anti-pyretic)
Narproxen	0.6	500mg loading dose, 250mg/6h, 1250mg/day max	Associated with increased cardio risk and Alzheimer's disease	
Diclofenac	0.7			Liquid filled gel
Arthrotec				Misoprostol/diclofenac combination (NSAID/misoprostol combination)
Etodolac	0.1	1dose post-op analgesia for 6-8h  200-400mg/6-8h, 1200mg/day max	Less GI irritation	Selective COX2 inhibitor
Nabumetone	0.2	Better tolerated than other NSAIDs  One per day dosing		Selective COX2 inhibitor
Celecoxib (COXIBs)	<0.001	Osteoarthritis (100-200mg/day) and rheumatoid arthritis (200-400mg/day)	Chronic use – increased cardio risk  Well tolerated, low GI effects	Selective COX2 inhibitor

Drug Name	Mechanism of Action	Uses	Side Effects	Distinguishing Features
<b>Triazolam</b> - 2-6h <b>Alprazolam</b> - 6-20h <b>Diazepam</b> - 14-90h	Oral benzodiazepine Short half life Generalized CNS depressant - GABA receptor agonist	Short term presurgical sedation Anxiety, insomnia	No major respiratory or cardiac depression No anesthetic action Psychological dependence in long term use	Rebound anxiety and insomnia in short half-life type (triazolam)
<b>Midazolam</b>	IV benzodiazepine Short acting, water soluble Generalized CNS depressant - GABA receptor agonist	Dental pre-anesthetic sedation Reduce pre-op anxiety and apprehension/tension	No major respiratory or cardiac depression No anesthetic action	Rebound anxiety and insomnia once drug wears off
<b>Flumazenil</b>	IV benzo/gaba receptor antagonist	Brings dental patient out of benzo sedation after visit Used to treat benzo overdoses	Any prior anxiety state of patient is restored/aggravated	Benzo/GABA receptor antagonist
<b>Thiopental</b>	IV barbiturate Ultra short acting Generalized CNS depressant - GABA receptor agonist Rapidly enters brain – quick anesthesia Very lipid soluble – anesthetic state quickly wears off as it redistributes from brain to fat stores	Short term surgical anesthesia	Major respiratory and cardiac depression in overdoses Hangover intoxication from slow leaching out from fat stores (of redistributed drug)	
<b>Secobarbital &amp; pentobarbital</b>	Oral barbiturate Intermediate acting Generalized CNS depressant - GABA receptor agonist Liver metabolism – slow enough to permit use for insomnia	Short term prescription for insomnia (tolerance to sedating dose, but not to lethal dose) - Diminishing therapeutic index (accidental suicide risk) develops with continued use	Major respiratory and cardiac depression in overdose (lethal) Drug hangover effect Physical dependence or withdrawal from long term use/abuse	
<b>Phenobarbital</b>	Oral barbiturate Long acting Generalized CNS depressant Slow liver metabolism – lasts in body for a long time	Low dose for epileptic seizure prevention without tolerance developing to antiseizure effect	Major respiratory and cardiac depression in overdose (lethal)	

<b>Diphenhydramine &amp; Hydroxyzine</b>	Oral Anticholinergic action of antihistamine causing mild sedation	Insomnia with/without runny nose Good for people who need quick presurgical calming drug but can't tolerate benzos anymore	None Some decongestants accompany them Can elevate blood pressure	Avoid such cocktails when taking MAO antidepressants
<b>Meprobamate</b>	Oral Barbiturate-like action Cannot produce surgical anesthesia	To treat anxiety and insomnia Prescribed to zombify wives Rarely used today	Low therapeutic index Anxiolytic doses are also sedating (Stepford wives)	Zombify and Stepford Wives
<b>Chloral hydrate</b>	Liquid sedative Anesthetic like mechanism of action Used only in low doses for sedation Rapid onset, short duration	Liquid form – convenient to sedate unruly kids for dentistry	Low therapeutic index	Liquid form
<b>Nitrous oxide</b>	Laughing gas Early gas anesthetic	Inhalation anesthesia used for euphoric sedation, preanesthesia, and dental anesthesia Patient becomes unconcerned and giggly with low doses	No cardiac or respiratory suppression in appropriate dosage Risk of bone marrow suppression Risk of abuse	
<b>Melatonin</b>	Neurohormone made by pineal gland Can be a dietary supplement Mild hypnotic effect Can shift circadian/sleep patterns	Insomnia in jet lag NOT for dentistry	Dietary preps can be uncontrolled in dose and not certified pure (can't extract pure form)	Considered a sedative
<b>Buspirone</b>	Serotonin 5-HT <sub>1A</sub> antagonist Used to reduce 5-HT neurotransmission to reduce brain hyperactivity	Anxiolytic effect only, no sedation occurs Takes a few weeks to work (not useful in dentistry)	No major side effects	This is considered a non-sedating anxiolytic
<b>Zolpidem</b>	Not benzochemical, but still acts on the benzo site of the GABA receptor	Insomnia Not anxiolytic at non-sedating doses Not used for dentistry	Mild psychologic dependence possible	This is considered a non-sedating anxiolytic



## Antihistamines and GI

- H1 receptors – allergy suppression and sedation
- H2 receptors – gastric reflux block
- Synthesized from histidine (histidine decarboxylase), then inactivated and excreted
  - o Histamine-N-methyl-transferase (Monoamine oxidases) – methylates (inactivates) histamine
  - o Diamine oxidase – further metabolism for excretion
- Histamine – highest in barriers tissues (lungs, skin, intestinal)
  - o Exocytotic release from granules in Mast cells and basophils
  - o Possible in hypothalamus as neural transmitter
  - o Stimulates gastric acid secretion (parietal cells)
  - o Important for tissue growth and injury repair
- Histamine release
  - o IgE mediated – immediate hypersensitivity
  - o Non-IgE mediated – cholinergic/adrenergic agents, basic drugs/peptides, bee venoms, plasma expanders, cytotoxic agents
- Degranulation Inhibitors – block release of histamine
  - o B-adrenergic agents
  - o Cromolyn sodium – only works if given before histamine release (no effect if given after)
- H1 blockers – block pharmacologic effect of histamine
- Physiologic effects

H1	H2
<ul style="list-style-type: none"> <li>- Contraction (GI, respiratory)</li> <li>- Vasodilation</li> <li>- Increased permeability</li> <li>- Localized edema, skin erythema               <ul style="list-style-type: none"> <li>o Triple response of Lewis (flush, flare, wheal)</li> </ul> </li> <li>- Peripheral nerve stimulation               <ul style="list-style-type: none"> <li>o Pain, itch</li> </ul> </li> <li>- CNS stimulation               <ul style="list-style-type: none"> <li>o Increase wakefulness, inhibits appetite, mediates motion sickness</li> </ul> </li> <li>- Rapid and transient vascular effects               <ul style="list-style-type: none"> <li>o Decreased BP, lower peripheral resistance</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Vasodilation</li> <li>- Gastric acid release stimulation</li> <li>- Slow, sustained vascular effects               <ul style="list-style-type: none"> <li>o Decreased BP, lower peripheral resistance</li> <li>o Increased cardiac rate and output</li> </ul> </li> </ul> <p><i>Vasodilation, gastric acid, and heart rate/force. Everything else is H1</i></p>

- Block H1 receptors – slow but steady and long decrease in BP after histamine release
- Block H2 receptors – fast spike decrease in BP, fast recovery after histamine release

- H1 Antagonists
  - Blocks itching, vaso/bronchodilation, smooth muscle contraction, motion sickness
  - Rapid digestion (oral admin), onset in 30min, duration depends on generation
    - 1<sup>st</sup> gen = 4-6h
    - 2<sup>nd</sup> gen = <24h
  - Metabolized in liver (hydroxylation)
  - Sedative effect in 1<sup>st</sup> generation (crosses BB barrier), no correlation with antihistamine effect
    - Sedative effect enlarged by CNS depressants and ^OH
  - Can affect local anesthetics – decrease pain/swelling
  - Used to treat
    - Allergies, motion sickness, vertigo, sleep, anxiety, anti-parkinson's disease, etc
    - DOES NOT treat bronchial asthma

First gen – crosses BBB – acts centrally and peripherally <ul style="list-style-type: none"> <li>- Diphenhydramine (Benadryl), promethazine (Phenergan), clemastine (Tavist), chlorpheniramine (chlor-trimetron), hydroxyzine (atarax, vistaril), dimenhydrinate (Dramamine), etc</li> <li>- High antihistamine, high anticholinergic, sedation</li> </ul>	2 <sup>nd</sup> Gen – doesn't cross BBB – non-sedating, acts peripherally <ul style="list-style-type: none"> <li>- Fexofenadine (Allerga) – terfenadine metabolite</li> <li>- Loratadine (Claritin) – 24h duration</li> <li>- Cetirizine (zyrtec) – kids</li> <li>- Terfenadine (seldane) and astemizole (Hismanal) – withdrawn due to cardiac concerns</li> <li>- High antihistamine, no anticholinergic or sedation</li> </ul>
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- Adverse effects
  - Overdose [especially in kids – different metabolism]
    - Hallucinations, excitement, ataxia, convulsions
  - Sedation – first gen, can interfere with daily activities
  - CNS effects – tinnitus, nervousness, lassitude (weariness)
  - Gastric distress
  - Atropine-like effects – xerostomia, blurred vision, dysuria, etc
  - Allergic reactions
- H2 Antagonists
  - Block gastric acid secretion (all pathways)
    - Primary – Inhibits histamine
    - Secondary – inhibits gastrin and cholinergic pathways
    - Secondary – promotes healing via inducing endogenous prostaglandin synthesis
  - Hydrophilic – some CNS effects
  - Rapid GI absorption, peak 1-2hrs, duration 4-12hrs
  - Liver metabolism, lots excreted in urine (caution for renal impaired patients)
  - Used to treat gastric/duodenal ulcers, GERD, hypersecretory states (Zollinger-Ellison syndrome)

- Proton Pump Inhibitors – irreversibly bind to Parietal cells ( $H^+/K^+$  ATPase) and inhibits secretion
  - More effective than H<sub>2</sub> inhibitors for GERD and PUD (peptic ulcers)
  - Prodrug, activated by acidic environment
  - Only way to reverse is to make new proton pumps
  - If treating H. pylori, use either H<sub>2</sub> or PPI with antibiotics
  - Side effects = headache, diarrhea, nausea, altered absorption of other drugs (pH change)
- Antacids (weak bases)
  - Rapid onset, induces prostaglandin synthesis (healing)
    - $NaHCO_3$
    - $Mg^{++}$  (milk of magnesia)
    - $Al^{+++}$  (reaction resulting in constipation when given with  $Mg^{++}$ )
    - $CaCO_3$
  - Sucralfate
    - Binds to ulcerated sites (Forms protective barrier)
    - Not absorbed by GI tract (very safe)
  - Misoprostol
    - Not for pregnant women (causes uterine contractions)
    - Binds to parietal cells, inhibits anenyl cyclase (decrease cAMP → less acid secretion)
- Anti-diarrheals
  - Opioids – slow gastric motility – increased time for water absorption
    - Diphenoxylate – similar to meperidine (addiction potential like cocaine)
      - Combined with atropine to block abuse
    - Loperamide – OTC, very selective (Very effective)
      - Remains concentrated in GI tract, does not distribute to CNS
    - Bismuth suspension (peptol-bismol)
      - Anti-secretory, antibacterial, anti-inflammatory
      - Good for treating E.coli traveler's diarrhea
    - Kaolin-pectin mixtures
      - Absorbent of bacteria, toxins, irritating foods
      - Adverse effects limited to absorption interference of other drugs in GI tract
- Anti-emetics – inhibits CTZ (treat nausea and motion sickness)
  - Dopamine antagonists – major side effect of xerostomia
  - 1<sup>st</sup> Gen H<sub>1</sub>s – side effects of xerostomia and drowsiness
  - Cannabinoids – for patients undergoing cytotoxic chem
  - Drug combination for chemo patients as effects are usually synergistic

## Dental Implications

- Biggest caution for drug interactions for GERD and PUD patients
  - Antacids – alter gastro pH, changes drug absorption
  - H<sub>2</sub> antihistamines – induction of hepatic enzymes by cimetidine
  - NSAIDs – contribute to GI irritation – avoid salicylates, prefer acetaminophen or COX-2 inhibitors

## Anticonvulsants

- You see a *convulsion* in someone experiencing a *seizure* because they have *epilepsy*
  - o Causes – congenital development/genetics, injury, infection, high body temp, toxins, drug side effect, past seizure history

## History

- Described in Mesopotamia (5000BC) – thought to be communion with gods
- Correlated to brain by Hippocrates (400BC)
- Discharge of neural electricity by John Jackson (1850AD)
- Phenobarbital first used (1922AD)

## Presentation

- Petite-Mal (Absence)
  - o Conscious changes in quality (zone out), most common in KIDS
- Partial
  - o Focal, no spread or “kindling”
  - o LIMB JERKS, NO UNCONSCIOUSNESS
- Grand-Mal
  - o Generalized “tonic clonic” convulsions, loss of consciousness
- Status epilepticus (continual)
- Temporal lobe epilepsy (limbic areas) – mood/emotional/behavioural changes
  
- No age correlation, but can be progressive (neuropotentiation via past seizures)
- Hypermnesia, amnesia, smells, visions
- Abnormal EEG activity in cortex or amygdala

## Drugs

Name	Mechanism	Used to treat	Side Effect
Phenobarbital	Low dose barbiturate Generalized CNS depressant (GABA agonist) Prevents initial seizure and spread (kindling)	All seizures	Anesthetic-level sedation Depressed respiration Elevated hepatic metabolism of other drugs
Carbamazepine	Block V-gated "fast" Na <sup>+</sup> channels Prevents spread (kindling)	General tonic clonic Partial <i>Neuralgia (neuropathic pain)</i> <i>Bipolar depression</i>	Nystagmus Ataxia Vertigo (getting up from chair caution)
Clonazepam	Benzodiazepines Generalized CNS depressant (GABA agonist) Prevents initial seizure and spread (kindling)	General tonic clonic Partial	Sedation (milder than barbiturates) Slight respiratory depression
Lorazepam	Benzodiazepines Generalized CNS depressant (GABA agonist) Prevents initial seizure and spread (kindling)	Status epilepticus	Sedation (milder than barbiturates) Slight respiratory depression
Ethosuximide	Blocks low-threshold (T-type) Ca <sup>++</sup> channels - These selectively cause absence seizures	Absence seizures	GI distress Drowsiness (caution – synergistic with sedatives)

# Antidepressants

## History/Epidemiology

- Biblical "Job" – situational depression
- Coke (with cocaine) – first antidepressant (1886)
- MAO-Is, tricyclics, iproniazid – first modern antidepressant drugs (1950s)
  
- All ages
- 20% of population
- 15% of depressed people suicide

## Signs

- Classic Depression (unipolar)
  - o Anhedonia (no happiness)
  - o Intense sadness and pessimistic worry
  - o Loss of energy/drive
  - o Insomnia
  - o Loss of (or excess) food ingestion and sex
- Bipolar Depression
  - o Swings between depression and mania (abnormal elation/foolishness)

## Neural Hypotheses

- Amine receptor hypothesis – 2 weeks of amine receptor desensitization (amine overdose) = better mood
- Amine hypothesis – more amines = better mood

## Drugs (roughly 2 weeks to work)

Name	Mechanism	Used to treat	Side Effect
Clomipramine	Tricyclic – NE reuptake inhibitor <ul style="list-style-type: none"> <li>- Blocks NE removal, increases in [CNS]</li> <li>- Desensitize NE receptors</li> </ul>	Unipolar depression OCD Trichotillomania (hair plucking)	Orthostatic hypotension SLUD (anticholinergic) effects CV Coma/death from OD Xerostomia CNS synergistic effects with other sedatives
Sertraline	SSRI – 5HT reuptake inhibitor <ul style="list-style-type: none"> <li>- Blocks 5HT removal, increase in [CNS]</li> <li>- Desensitize 5HT receptors</li> </ul>	Unipolar depression	No major side effects – cannot OD Safest antidepressant No drug interactions
Phenelzine	MAO-A inhibitor <ul style="list-style-type: none"> <li>- Blocks CNS breakdown of NE, DA, 5HT</li> <li>- Elevates all of them in CNS</li> <li>- Desensitize NE, DA, 5HT receptors</li> </ul>	Unipolar depression	Convulsions if OD Cannot intake tyramine or cause HTN crisis (red wine, beer, sour cream, chocolate, bananas, etc) Synergistic effects with other sedatives HTN crisis with other decongestants/antihistamines
Bupropion	DA and 5HT reuptake inhibitor <ul style="list-style-type: none"> <li>- Blocks CNS reuptake of 5HT and DA, increase in [CNS]</li> <li>- Desensitize 5HT and DA receptors</li> </ul>	Unipolar depression with psychomotor retardation Nicotine addiction	Nervousness Insomnia Convulsions if OD Drug interactions with sedatives
Venlafaxine	SNRI – 5HT and NE reuptake inhibitor <ul style="list-style-type: none"> <li>- Blocks CNS removal of NE and 5HT, increase in [CNS]</li> <li>- Desensitize 5HT and NE receptors</li> </ul>	Unipolar depression <ul style="list-style-type: none"> <li>- Must be taken 2-3x daily</li> </ul>	HTN Safer than most other tricyclics
Carbamazepine	Block V-gated “fast” Na <sup>+</sup> channels	Bipolar depression <ul style="list-style-type: none"> <li>- Low doses to stabilize mood</li> </ul>	Nystagmus Ataxia Vertigo (getting up from chair caution)
Lithium	Modifies NE and 5HT transmission, or IP3 inside neurons <ul style="list-style-type: none"> <li>- Mechanism is uncertain</li> </ul>	Bipolar disorder Mania	Fatigue Muscle weakness Ataxia Xerostomia and thirst Coma in OD NSAIDs block Li excretion – toxicity after several days combined use

Category	Drug	Mechanism of Action	Uses	Side Effects	Other
DA Replacement	Levodopa ** (L-Dopa)	<ul style="list-style-type: none"> <li>Crosses B-B barrier and metabolized to DA</li> </ul>	<ul style="list-style-type: none"> <li>Parkinsons</li> <li>Bradykinesia/akinesia reduced</li> <li>Tremor reduced less consistently</li> </ul>	<ul style="list-style-type: none"> <li>DA &amp; NE toxicity (orthostatic hypotension, nausea)**</li> <li>Only 5% get into brain before peripheral conversion to DA and later NE (hence side-effect)**</li> <li>Peripheral side effects less with Sinemet: <ul style="list-style-type: none"> <li>Orthostatic hypotension</li> <li>Nausea/vomiting</li> </ul> </li> <li>Central side effects (peak dose): <ul style="list-style-type: none"> <li>Dyskinesias, including bruxism (kinda like "reverse" of PD)</li> <li>Psychiatric effects, including PSYCHOSIS</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Can be in diff ratios (quick-release for late PD or controlled release for early PD)</li> <li>No resistance to meds but duration of benefit per dose shortens as disease progresses → motor fluctuations</li> </ul>
	L-Dopa + Carbidopa (Sinemet®)	<ul style="list-style-type: none"> <li>Addition of carbidopa inhibit peripheral decarboxylation of L-Dopa to DA, allowing more L-Dopa to get into brain</li> <li>Carbidopa ↑ L-Dopa effectiveness at lower doses</li> </ul>	<ul style="list-style-type: none"> <li>Parkinsons</li> <li>Bradykinesia/akinesia reduced</li> <li>Tremor reduced less consistently</li> </ul>		
	Entacapone (Comtan®)	<ul style="list-style-type: none"> <li>Peripheral COMT inhibitor</li> <li>Blocks synthesis of inactive L-Dopa metabolite that competes w/ L-Dopa at the B-B barrier</li> <li>↓ L-Dopa elimination &amp; ↑ half-life &amp; bioavailability</li> </ul>	<ul style="list-style-type: none"> <li>Parkinsons (extend Sinemet duration of action &amp; decrease "on/off" and "wearing off" effects)</li> </ul>		
Anticholinergics	Benzatropine (Cogentin®)	<ul style="list-style-type: none"> <li>ACH stimulates motion suppression – so anti-ACh enhance motion</li> </ul>	<ul style="list-style-type: none"> <li>Early stage PD</li> <li>Tremor often responds better than to L-Dopa</li> </ul>	<ul style="list-style-type: none"> <li>Low therapeutic index</li> <li>SLUD → decay</li> <li>Side effects more troubling in elderly (sedation, delirium, tachycardia, SLUDs)</li> </ul>	<ul style="list-style-type: none"> <li>Scopolamine: 1<sup>st</sup> PD drug but not used for vertigo (has SLUD side effects)</li> </ul>
DA Receptor Agonists	Bromocriptine (Parlodel®)	<ul style="list-style-type: none"> <li>D2 DA receptor agonist</li> </ul>	<ul style="list-style-type: none"> <li>Early PD monotherapy, later PD adjunct therapy</li> <li>PD-associated hyperprolactinemia (DA needs to act on D2 receptors in pituitary to block prolactin secretion)</li> </ul>	<ul style="list-style-type: none"> <li>Fibrosis</li> <li>Dyskinesias</li> <li>Hallucination</li> </ul>	<ul style="list-style-type: none"> <li>Side effects typical of DA or other DA receptor agonists</li> </ul>



Category	Drug	Mechanism of Action	Uses	Side Effects	Other
Miscellaneous Drugs	Amantidine (Symmetrel®)	<ul style="list-style-type: none"> <li>Enhances DA release from SNc (substantia nigra)</li> <li>Blocks GLU (GLU &amp; ACH may have similar roles in caudate)</li> </ul>	<ul style="list-style-type: none"> <li>Early PD monotherapy, later PD adjunct therapy</li> </ul>		<ul style="list-style-type: none"> <li>Antiviral drug (PD therapeutic effect 1<sup>st</sup> noted on elderly flu patients)</li> </ul>
	Selegiline (Deprenyl® or Eldepryl®)	<ul style="list-style-type: none"> <li>Inhibits metabolism of brain DA to DOPAC via MAO-B inhibition</li> </ul>	<ul style="list-style-type: none"> <li>DA-like effects</li> <li>Early PD monotherapy, later PD adjunct therapy, <i>but</i> only mild benefit &amp; expensive</li> </ul>	<ul style="list-style-type: none"> <li>Interact w/ tricyclic and SSRIs antidepressants → serotonin syndrome (↑ bp)</li> </ul>	
“OFF” State Emergency Rescue Drug	Apomorphine	<ul style="list-style-type: none"> <li>Powerful mixed D1/D2 agonist</li> </ul>	<ul style="list-style-type: none"> <li>Rescues PD patients rapidly from an “off” (immobile) state</li> </ul>		<ul style="list-style-type: none"> <li>Admin s.c, i.v, sublingually, rectally, or intranasally (Europe avail as pen-injection)</li> </ul>
	Benzodiazepines		<ul style="list-style-type: none"> <li>Temporarily reduce tremors</li> </ul>		

PD Drug of Choice? Depends on....

**AGE:** Old? Simpler L-Dopa  
Young? Delay or use other drugs?

**STAGE:** Early? Use other drugs?  
Late? Sinemet

**WEARAGE (SYMPTOMS):** Wears off? More L-dopa or add DA agonist or COMT blocker  
Tremor only? Anticholinergics  
Mild? DA agonist or amantadine,  
Night-time off? CR sinemet  
On/off or biphasic dyskinesia? Lower peak/increase through L-dopa w/ controlled form + add DA agonist or COMT inhibitor

**TEARAGE (SIDE EFFECTS):** Nausea? More carbidopa  
DA-excess or other med side effects?  
Reduce meds in order of least importance: anticholinergics, amantadine, selegiline, DA agonists, COMPT inhibitors, Sinemet

Category	Mechanism of Action	Drug	Side Effects	Other
<b>"Typical"</b> Antipsychotics (D2 Antagonists)	<ul style="list-style-type: none"> <li>Antiadrenergic/ anticholinergic properties</li> </ul>	Chlorpromazine (Thorazine®)	<ul style="list-style-type: none"> <li>High sedative, moderate hypotensive &amp; motor side effects</li> </ul>	<ul style="list-style-type: none"> <li>200 Ti</li> </ul>
	<ul style="list-style-type: none"> <li>Antiadrenergic/ <b>high anticholinergic properties</b></li> </ul>	Thioridazine (Mellaril®)	<ul style="list-style-type: none"> <li><b>High sedative</b>, moderate hypotensive &amp; <b>low motor side effects</b></li> <li>Xerostomia</li> </ul>	<ul style="list-style-type: none"> <li>70 Ti</li> </ul>
	<ul style="list-style-type: none"> <li><b>Low anticholinergic properties</b></li> </ul>	Haloperidol (Haldol®)	<ul style="list-style-type: none"> <li><b>Low sedative</b>, moderate hypotensive &amp; <b>high motor side effect</b></li> </ul>	<ul style="list-style-type: none"> <li>&gt;1000 Ti</li> </ul>
<b>"Atypical"</b> Antipsychotics (5-HT <sub>2</sub> Antagonists)	<ul style="list-style-type: none"> <li>May act via mild D<sub>2</sub> receptor antagonist activity</li> <li>Strong antagonist of BOTH 5-HT &amp; D<sub>2</sub> receptors</li> </ul>	Risperidone (Risperdal®)	<ul style="list-style-type: none"> <li><b>Less</b> motor side effects than typicals</li> <li>May increase anxiety/ depression</li> </ul>	
	<ul style="list-style-type: none"> <li>Strong 5-HT (and D<sub>4</sub>?), weak D<sub>2</sub> antagonist</li> <li>Strong anticholinergic</li> </ul>	Clozapine (Clozaril®)	<ul style="list-style-type: none"> <li>NO motor side effects due to 5-HT action</li> <li>Potentially fatal agranulocytosis</li> </ul>	
	<ul style="list-style-type: none"> <li>Strong 5-HT<sub>2</sub> (and D<sub>4</sub>?), weak D<sub>2</sub> antagonist</li> </ul>	Olanzapine (Zyprexa®)	<ul style="list-style-type: none"> <li>NO motor side effects</li> <li>Same benefits as clozapine, but with NO agranulocytosis</li> <li>NEW SE: diabetes!!!</li> </ul>	<ul style="list-style-type: none"> <li>May require higher doses than clozapine</li> </ul>
<b>"Atypical"</b> Antipsychotics ( <b>NOT</b> 5-HT <sub>2</sub> Antagonists)	<ul style="list-style-type: none"> <li>Mild reduction of DA release and mild action on post-syn striatal D<sub>2</sub> receptors</li> </ul>	Aripiprazole (Abilify®)	<ul style="list-style-type: none"> <li>NO motor side effects</li> <li>No weight gain</li> </ul>	<ul style="list-style-type: none"> <li>Try when typical D<sub>2</sub> antagonist cause motor side effects &amp; atypical 5-HT antagonists are ineffective</li> </ul>

Drug of Choice? Depends on....

**COMPLIANCE:** Paranoid out-patient? Use a longer-acting drug (fluphenazine) – less daily regimentation for drug administration

**CV DISEASE:** Heart trouble? Thioridazine can change cardiac rhythms  
Chlorpromazine is a myocardial depressant

Orthostatic hypotension? Could try haloperidol or some atypicals

**AGE:** Old? Sedation & hypotension less tolerable, so use haloperidol or atypicals

**SEDATION:** Don't like sedation? Usually tolerance develops, but could use haloperidol

**EPS's:** Motor symptoms? Use anticholinergic antipsychotic (thioridazine) or atypicals (the likeliest class to be used nowadays)

Uses	Category	Mechanism of Action	Side Effects	Advantages
<ul style="list-style-type: none"> <li>Psychotic symptoms (hallucinations, paranoia, disordered thinking)</li> <li>Agitated</li> <li>Restless</li> <li>Aggressive</li> <li>Impulsive</li> <li>Unresponsive</li> <li>Uncommunicative</li> </ul>	"Typical" Antipsychotics (D2 Antagonists)	Blocks excess DA function in non-motor areas of brain (cortex/ limbic)	<ul style="list-style-type: none"> <li>Drug induced Parkinsonism</li> <li>Tardive Dyskinesia</li> <li>Xerostomia (anticholinergic antipsychotics)</li> <li>Neuroleptic malignant syndrome (NMS) – high temp, muscle rigidity, autonomic deregulation, impaired consciousness <ul style="list-style-type: none"> <li>Treat by stopping D2 antagonist and giving muscle relaxer &amp; D2 agonist (bromocriptine)</li> </ul> </li> </ul>	Efficacy in ameliorating psychosis due to cortical-limbic D2 antagonism of excess DA function
	"Atypical" Antipsychotics (5-HT2 Antagonists)	Blocks excess 5-HT function in non-motor areas of brain (cortex/limbic)	<ul style="list-style-type: none"> <li>Potentially FATAL but reversible agranulocytosis</li> <li>Agranulocytosis: low WBC count can cause immune deficiency and oral candidiasis, among other infections</li> </ul>	No drug-induced parkinsonism & tardive dyskinesia due to less inhibition of motor D2 receptors vs more inhibition of 5-HT receptors not involved in motion
	BOTH	Cortical glutamatergic neurons do coexpress DA & 5-HT receptors, that is why both work	<ul style="list-style-type: none"> <li>Orthostatic Hypotension</li> <li>SLUDs</li> <li>Sedation</li> <li>Tachycardia, palpitations, dizziness</li> <li>Hyperprolactinemia</li> <li>Weight gain</li> <li>Potential of other CNS depressants (opioids, barb booze)</li> </ul>	

**ADVANTAGES for ALL ANTIPSYCHOTICS:**

- 1) High therapeutic index (TI) → relatively safe; a wide range of doses can be used
- 2) No tolerance develops to drug → can use uninterrupted, indefinitely, at same dose
- 3) Only mild dependence → withdrawal is only muscle discomfort, rebound nausea, headache, restlessness

# Diabetes Mellitus

- Pancrease
  - o Endocrine – regulate metabolism
    - Synthesis and secretion of involved hormones – directly into blood capillaries
    - Islets of Langerhans – each has ~3K cells, make up 1% of pancreatic weight
  - o Exocrine – digestive enzymes
    - Synthesis and secretion via duct system
- Islet of Langerhans cells
  - o  $\alpha$  – glucagon
    - Raises blood glucose, promotes glucose production
    -
  - o  $\beta$  – insulin, islet amyloid polypeptide
    - Lowers blood glucose, promotes glucose utilization and suppresses glucose production
  - o  $\delta$  – somatostatin
  - o F/PP – pancreatic polypeptide
- Proinsulin – A, B, and C peptides
- Insulin – A and B peptides
  - o Insulin half life = 5min
  - o C peptide half life = 30 minutes
    - Use C peptide to measure insulin levels in blood
- Serious complications (cardiovascular, renal, eye and nervous) onset years after diabetes
  - o Controlled metabolism can minimize complications
    - Short term – relieve and prevent acute metabolic symptoms – hyperglycemia and ketoacidosis
    - Long term – prevent long term complications associated with organ [systems]
  - o Diet, weight, exercise, hypoglycemic agents, insulin to mimic physiological insulin levels
- IDDM (Type 1)
  - o Juvenile onset, 0.5% prevalence
  - o Skinny, polygenic, genetic prevalence (50% in twins)
  - o Ketoacidosis, frequent complications
  - o Complete loss of Islet  $\beta$ -cells – unknown cause/autoimmune
    - Requires insulin therapy – no circulating insulin/C-peptide
- NIDDM (Type 2)
  - o Adult onset, 6-10% prevalence
  - o 80% obese, polygenic, genetic prevalence (100% in twins)
  - o Ketoacidosis rare, frequent complications
  - o No apparent change in  $\beta$ -cells, insulin, or C-peptide – unknown cause, strong genetic correlation
    - Treat diet, exercise, oral hypoglycemic agents (sulfonylureas, biguanides, thiazolidinediones,  $\alpha$ -glucosidase inhibitors), insulin
    - Possible defects from insufficient glucose-induced insulin secretion/peripheral insulin resistance

- Diabetes
  - Fast blood glucose > 126mg/dl
  - Casual blood glucose > 200mg/dl
  - Oral glucose tolerance test value > 200mg/dl @ 2h
  - Impaired fasting glucose – blood glucose >110mg/dl, <126mg/dl
  - Impaired glucose tolerance – blood glucose >140mg/dl, <200mg/dl @ 2h
- EDUCATION
- Diet, exercise, oral hypoglycemic agents (sulfonylureas, biguanides, thiazolidinediones,  $\alpha$ -glucosidase inhibitors)
- Type 1 – ONLY insulin
  - Insulin = safest for managing surgery, high stress, pregnancy

Seconds	Minutes	Hours
Insulin binds to $\alpha$ -subunit of receptor Activates tyrosine kinase $\beta$ subunits Receptor autophosphorylation	Gene transcription changes Stimulates hexose transport Alters enzyme activity Receptor internalization	Synthesis of protein, lipid, DNA Cell growth/changes Down regulation of receptor

- Insulin Analogs
  - Short Acting Insulins
    - **Regular insulin**
      - Soluble crystalline zinc
      - Only form that can be used IV or in SQ infusion
    - Semilente insulin
      - Amorphous suspension with zinc in acetate
    - **Lispro (Humalog) and Aspart (Novolog)**
      - Twice as fast as regular insulin – rapid onset, short duration
      - Little variation in action when injected at different sites
      - Action is not delayed when mixed with long acting insulin
  - Long acting insulins
    - Ultralente insulin
      - Poorly soluble zinc insulin
    - Protamine zinc insulin
      - Protamine/insulin/zinc complex
    - **Glargine (Lantus)**
      - Long acting – relatively constant time profile over 24h
      - Cannot be mixed with any other insulin
      - Soluble at pH 4, microprecipitate at pH 7
  - Intermediate acting insulins – combinations of short and long acting
    - Lente insulin
      - Semilente and ultralente (70/30)
    - NPH (neutrapi protamine hagedorn) insulin
      - Regular insulin and protamine zinc insulin (2:1)

- Insulin reaction (hypoglycemic reaction)
  - Causes – insulin overdose, failure to eat, spontaneous lowering of insulin needed (exercise)
  - Symptoms – weakness, sweating, pallor, anxiety
  - Treatment – oral glucose, glucagon injection
  - Complications – seizures, coma, death when untreated
- Insulin resistance
  - Frequently associated with Type 2 diabetes and obesity
- New insulin delivery – deliver insulin in a manner accurately reflecting physiological secretion
  - Pancreas transplantation
  - Islet transplantation
  - Insulin pumps
  - Inhalation
    - Nasal spray – absorption through nasal mucosa
    - Inhaler – pulmonary administration through aerosolized insulin
  - Needleless injectors
- Hyperglycemia inducing drugs – corticosteroids, diuretics, phenytoin, diazoxide, clonidine,  $\text{Ca}^{++}$  channel blockers, CNS stimulants,  $\beta$ -adrenergic agonists,  $\text{H}_2$  receptor blockers, morphine
- Hypoglycemia inducing drugs – anabolic steroids, ethanol, salicylates, clofibrate, sulfonamides, disopyramide,  $\beta$  blockers, ACE inhibitors,  $\text{Ca}^{++}$ ,  $\text{Li}^+$ , theophylline
- Hypoglycemic Agents (Type 2)
  - Sulfonylureas (**glyburide**)
    - Mechanism – direct stimulation of insulin secretion from  $\beta$ -cells
    - Metabolism – circulating are 90% protein bound
      - Metabolism is by liver and metabolites are excreted
    - Absorption – well absorbed, slowly peaks at 2-4h, administered 30min before meals
    - Side effects – weight gain, hypoglycemia, GI upset,
      - Disulfiram reactions with 1<sup>st</sup> generation sulfonylureas
      - Allergies are rare, CV risk is controversial
      - **Tolbutamide** and chlorpropamide stimulates vasopressin release
      - **Glimeperide** – causes pancreas to produce insulin
    - Drug Interactions
      - Displacement from plasma binding proteins by other drugs
        - NSAIDS, oral anticoagulants (dicumarol), probenecid, miconazole
      - Inhibition of sulfonylureas' hepatic metabolism by other drugs
        - Sulfonamide antibiotics
      - Reduction of renal excretion of sulfonylureas
        - Chloramphenicol, clofibrate
      - Drugs with intrinsic hypoglycemic activity
        - Ethanol,  $\beta$ -blockers, etc
      - Drugs with intrinsic hyperglycemic activity
        - Glucocorticoids, thiazide diuretics, etc

- Non-sulfonylurea insulin secretagogues (similar to sulfonylureas, but chemically distinct)
  - **Repaglinide (Prandin, Novoform)**
    - Recently approved – 4mg, effect similar to 15mg glyburide
    - Regulates ATP-sensitive  $K^+$  channel, binding to different receptor site
    - Rapidly absorbed, has plasma  $t^{1/2} < 1h$
    - Risk of hypoglycemia diminished (short  $t^{1/2}$ )
    - Ideal for use before meals, diabetics with kidney dysfunction
    - Metabolites not active, excreted via bile
- Biguanides
  - **Metformin (Glucophage)**
    - Usually given in divided doses (1-3g), duration 10-12h
      - Can be used alone, or combined with glyburide
  - Mechanism – unknown, increases anaerobic glycolysis and glucose uptake
    - Decreases GI absorption of glucose, decreases hepatic gluconeogenesis
      - Contraindicated for those with renal and liver disease
    - Doesn't promote hypoglycemia or promote weight gain
- Insulin sensitizers
  - **Thiazolidinediones (Glitazones)**
    - **Rosiglitazone (Avandia), pioglitazone (Actos)**
    - Approved for monotherapy or in combination with sulfonylurease, metformin, or insulin
  - Mechanism – sensitize cell to insulin via PPAR $\gamma$  nuclear receptors – control expression of lipogenesis genes
  - Side effects – minimal, but liver function should be checked
- Oral  $\alpha$ -glucosidase inhibitors
  - **Acarbose (precose)**
  - Mechanism – glucose competitive inhibitor at GI  $\alpha$ -glucosidase (slows glucose conversion and absorption)
    - Reduces blood sugar rise after meal, does not cause hypoglycemia [directly]
    - Can be used in combination with other hypoglycemic agents
  - Side effects – GI symptoms (flatulence, diarrhea), no systemic side effects (not absorbed)

## - NIDDM Management

- Diet and exercise → monotherapy ( $\alpha$ -glucosidase inhibitor, sulfonylurea, metformin, thiazolidinedione) → combination therapy → insulin
  - Go directly to insulin if:
    - Severe hyperglycemia
    - Ketosis
    - Unrecognized IDDM
    - Pregnant

## Adrenal Steroids

- Ligands – lipid soluble, cross membranes, have a direct effect on gene expression
  - o Nuclear receptor recognition/binding of specific DNA sequences [mostly] ligand dependent
- Endogenous ligands act on receptors:
  - o Corticosteroids
  - o Sex steroids
  - o Vitamin D
  - o Thyroid hormone
  - o Retinoids
- Ligand dissociated from carrier protein, crosses membrane, binds to intracellular receptor protein, moves into nucleus, binds to receptor sequence
  - o Nuclear receptors vary in length, but have characteristic domains (sequences are conserved)
  - o Binding causes conformational change of the nuclear receptor
- First response (primary) – immediate induced synthesis of primary response proteins
- Secondary (delayed) – primary response proteins suppress primary response genes, induce secondary response genes → synthesis of secondary response proteins
- Drug
  - Tamoxifen – ER antagonists (cancer treatment)
  - Thiazolidiones – PPAR $\gamma$  agonist (type 2, reduce insulin resistance)
  - Fenofibrate – PPAR $\alpha$  agonist (CV disease, reduce cholesterol)
  - Progestin and estrogen – ER and PR agonists (oral contraceptives)
  - Anabolic steroids – AR agonists (performance enhancement)
  - o Drug discovery with a focus on Orphan Nuclear Receptors
- Adrenal steroids
  - 90% bound to plasma proteins – albumin and corticosteroid binding globulin (**transcortin**)
  - o Corticosteroids
    - Mineral corticosteroids (aldosterone) – salt and water. Angiotensin causes secretion
    - Glucocorticoids (cortisol) – sugars, proteins, lipid metabolism. Stress causes secretion
- Metabolic effects
  - o Increased blood glucose
  - o Increase breakdown of protein and lipid
  - o Normal levels help maintain normal glucose levels
- Anti-inflammatory and immunosuppressive effects
  - o Decrease expression of proteins involved in inflammation and immune response
  - o Nonspecifically block inflammation from numerous stimuli
- Therapeutic uses
  - o Hormone replacement (Addison's disease, acute crisis, etc), allergies (asthma, bee sting, etc), arthritis, bursitis, immunosuppressant, lung maturation of preterm fetus, collagen vascular disorders, eye diseases, GI disease, bronchial asthma, skin diseases, cerebral edema, hematological disorders



- Glucocorticoid analogs
  - Short Acting
    - Cortisol hydrocortisone
      - Mainly used for replacement therapy and emergencies – adrenal crisis
      - Major glucocorticoid in body – normally 10mg/day
    - Cortisone
      - Inactive until converted
      - Contraindicated for abnormal liver function
      - Local injection of derivatives relieves inflammation but NOT pain
      - Biologic  $t^{1/2}$  = 8-12h
  - Intermediate acting
    - Prednisone
      - Most common, oral
      - Anti-inflammatory disorders, immunosuppression for organ transplants
      - 4x more potent than cortisol
      - Contraindicated for abnormal liver function
    - Prednisolone – active metabolite of prednisone
      - Biologic  $t^{1/2}$  = 18-36h
  - Long acting
    - Dexamethasone
      - 25-50x more potent than cortisol (anti-inflammatory)
      - Growth retardation potential
      - Restricted from Olympic games
      - Biologic  $t^{1/2}$  = 36-54h
  - Adverse effects
    - Withdrawal
      - prolonged use suppresses HPA – natural hormone production inhibition
        - adrenal insufficiency
      - 2-3 months for pituitary to return to normal responsiveness
      - 6-9 months for normal cortisol levels to return
        - Dosage should be tapered, not cold turkey
      - <25mg/day prednisone @ 8am for <10days does not suppress HPA
      - Alternate day steroid therapy recommended for kids
    - Continued use/supraphysiological doses
      - Diabetes (hyperglycemia), muscle wasting (antianabolic effect), suppressed immunity
      - Negative nitrogen balance
      - Osteoporosis (enhanced bone resorption), growth retardation
      - HTN and edema (hypokalemia,  $\text{Na}^+$  retention)
      - Cataracts, glaucoma, psychotic symptoms, emotional lability
- Dentistry Implications
  - Large dose and long duration = suppressed immunity, poor healing
    - Carious teeth, inflamed gingiva
    - Signs/symptoms of adrenal insufficiency
  - Inject 100mg cortisone 8h before dental surgery, taper off over 2-3 day period after surgery

## Sex Hormones

- Female hormones
  - Estrogen and progesterone synthesized in multiple tissues
    - Circulating estrogens – ovaries (non-pregnant, pre-menopausal)
      - Also fat cells, adrenal glands
    - Progesterone – ovary, testis, adrenal glands, placenta
    - Fetal placenta – large amounts of both
  - Estrogen
    - Sex characteristics, growth/support XX reproductive structures
    - Regulates menstruation, libido, mood
    - Decreases bone resorption, cholesterol, LDL
    - Increases HDL, better blood coagulation
  - Progestins
    - Slow mitotic growth of estrogen stimulated uterus
    - Breast development
    - Decreases triglycerides, HDL
    - Increases LDL, lipoprotein lipase, fat storage, basal and insulin secretion
    - Suppresses menstruation and uterine contractility (maintain pregnancy)
    - Increases body temperature  $\sim 0.5^{\circ}\text{C}$
  - Metabolism of Estrogen and Progestin drugs
    - Liver
    - Synthetics modified to avoid first-pass metabolism (increases  $t^{1/2}$ )
    - Estrogens – oral, parenteral, transdermal, topical (rapidly absorbed)
    - Both extensively bound to sex steroid binding globulin and albumin
  - Adverse Effects
    - Weight gain, fluid retention, depression, withdrawal bleeding, abdominal cramps, anxiety, irritability, decrease insulin sensitivity, decrease glucose tolerance, acne
  - Therapeutic uses
    - **Peri and post-menopausal hormone replacement therapy**
      - Medroxyprogesterone acetate – mixture conjugated horse estrogens with progestin
        - Most desirable effects due to estrogen
      - Benefits
        - Vasomotor effects – relief of hot flashes and sweating, improved sleep
        - Improved wellbeing feeling
        - Reduced atherosclerosis, risk of osteoporosis
      - Risks
        - Slight increased risk of thromboembolic disease (stroke, pulmonary embolism)
        - Increase risk of breast and ovarian cancer
          - Reduced risk of colon cancer post-menopausal
    - **Oral contraception (very effective)**
      - Not appropriate to extrapolate side effects between HRTs and contraceptives
      - Benefits – reduced incidence of
        - Anemia, benign breast disease, osteoporosis
        - Uterine and ovarian cancer, ovarian cysts
    - Hypogonadism, infertility, hormone sensitive breast cancer tamoxifen, endometriosis, androgen dependent prostate tumors, dysmenorrhea or uterine bleeding

- Mechanisms
  - Estrogens
    - Suppress FSH
    - Inhibits follicle development and ovulation
    - Stabilize endometrium, prevent irregular shedding and breakthrough bleeding
    - Increase progesterone receptors – potentiate progestin action
  - Progestins
    - Suppress LH secretion and ovulation
    - Prevent uterine overgrowth stimulated by estrogens
    - Produce endometrium not receptive to ovum implantation
    - Thick, viscous cervical mucus – inhibits sperm transport
- Oral contraceptive options
  - Combination oral contraceptives (99.9% effective)
    - Pill has both estrogen and progestins (variable ratios)
    - Usually take pill for 21 days, then inert pills for 7 days
    - Side effects
      - CV – venous thrombus
      - Cancer – 50% decrease endometrial cancer
        - Decrease ovarian cancer, increased breast cancer risk
        - Hepatic adenoma and hepatocellular carcinomas
      - Other – nausea, edema, headache, menstrual irregularities, weight gain, acne
  - Progestin only (99% effective)
    - Single daily oral small dose (mini pill)
    - Effect uterus and cervical mucus, associated with irregular menses
    - Can be used by nursing mothers
    - Safer for older women with HTN, overweight, or history of blood clots
    - Side effects – menstrual irregularities, acne, headache
  - Contraindications (use physical contraceptives instead)
    - Thromboembolic disease, coronary artery disease, cerebral vascular disease, etc
    - >35y/o who smoke heavily
    - Breast cancer, GU cancer, hormone dependent responsive neoplasms
    - Abnormal undiagnosed vaginal bleeding
    - Liver tumors, impaired liver function
    - Individual basis – migraines, HTN, diabetes mellitus, gall bladder disease
  - Dental Implications
    - High dose – gingival hyperplasia
    - Drug interactions – induction P450 enzymes, potentiation of corticosteroids

- Male Hormones
  - Testosterone – 98% protein bound, 2% circulate
    - Oral = rapid absorption and metabolism by liver (synthetics used clinically)
    - More active in skeletal muscles (little DHT produced, degrades DHT)
  - DHT – major active metabolite of testosterone (dominant androgen in most tissues), >affinity
  - Sex characteristics, support male reproductive structures
  - Therapeutic use
    - Male hypogonadism
    - Male senescence
    - AIDS related muscle wasting
    - Angioedema
    - Anti-aging and athletic performance enhancement
  - Used to treat
    - Benign prostate hypertrophy
    - Prostate cancer
    - Acne, hirsutism, precocious puberty
  - Dental Implications
    - Excessive androgens – gingival disease
    - Lower estrogens – osteoporosis
    - Estrogens potentiate corticosteroids – careful mixing drugs

## Thyroid Hormones

- TSH from anterior pituitary – regulates thyroid hormone production
- Thyroglobulin  $\xrightarrow{\text{proteolysis}}$  thyroid hormones
  - o Hormones eliminated via hepatic metabolism
- 99.5% circulating  $T_3$  and  $T_4$  bound to plasma proteins (prolonged  $t^{1/2}$ )
  - o  $T_3$  = 1.5 days
  - o  $T_4$  = 1 week
- Hypothyroidism
  - o Can occur at any age
  - o Usually chronic autoimmune thyroiditis
    - Other causes = insufficient iodine, surgical removal, destruction from radioactive iodine, etc
    - May result from altered TSH secretion
  - o Therapeutics
    - Pure synthetics and animal extract – all quantitatively similar effects
      - Synthetics – more stable and standardized = better
        - o Levothyroxine ( $T_4$ )
        - o Levothyroxine ( $T_4$ ) and liothyronine ( $T_3$ )
- Hyperthyroidism
  - o Caused from
    - Toxic diffuse goiter (Grave's disease), toxic multinodular goiter (Plummer's disease)
    - Toxic adenoma
    - Painful subacute thyroiditis
    - Iodine induced hyperthyroidism
    - Excessive TSH or trophoblastic disease, excessive ingestion of TH
  - o Therapeutics (decrease TH production)
    - Surgical removal
    - Radioactive iodine ( $^{131}\text{I}$ )
      - Preferred for older patients, Grave's disease
      - Ablative therapy – quick solution
        - o Causes hypothyroidism, require TH replacement therapy
          - May start partial replacement doses @ 2months
      - No risk of infertility, congenital malformations, or cancer
      - Contraindicated
        - o Pregnancy – may ablate fetal thyroid
        - o Breast feeding – appears in breast milk
    - Anti-thyroid drugs (**propylthiouracil, methimazole**) – suppress TH synthesis
      - Preferred for younger patients

- Dental implications
  - Subclinical hypothyroidism
    - Delayed tooth eruption, malocclusion, skeletal retardation
    - Tongue enlargement, increased capillary fragility
    - Exaggerated response to sedatives and opioids
  - Hyperthyroidism
    - Osteoporosis of alveolar bone
    - Dental caries, perio disease
    - Gingival changes (ill-fitting dentures)
  - Pediatric hyperthyroidism
    - Rapid tooth/jaw development
    - Early loss of deciduous teeth, early permanent teeth eruption

## Respiratory Drugs

- COPD – irreversible tracheobronchial and alveolar tissue damage
  - Edema, inflammation, sputum, lowered forced respiratory volume
  - Bronchitis – chronic cough and sputum production
  - Emphysema – destruction of lung parenchyma and loss of alveoli elasticity
    - Less responsive to treatment
- Clinical Caution
  - Signs of cardiac disease
  - Upright chair position
  - Use O<sub>2</sub> with care
- Avoid
  - Long appointments, sedatives (benzodiazepines), narcotics (cause respiratory depression)
- Sedation
  - Hydroxyzine (vistaril), first generation H<sub>1</sub> antihistamine
- Asthma – acute episodic hypersensitive response of tracheobronchial tree, airway obstruction, mucus hypersecretion, with no inherent tissue damage in most cases
  - Early phase – mast cell degranulation – histamine, platelet activating factor, prostaglandins, leukotrienes
  - Late phase – broncho-constrictive reaction and development of bronchial hyperreactivity
    - Symptoms may develop as response to both allergic and nonallergic stimuli
- Treatment – best to avoid precipitating factors
  - **First choice = glucocorticoids (anti-inflammatories)**
    - Oral - prednisone
    - Inhaled – beclomethasone, budesonide, fluticasone
- Sedation – hydroxyzine (atarax, vistaril)
- Analgesia – acetaminophen
- Prophylaxis –  $\beta$ 2 selective adrenergic agents (bronchodilators) – (terbutaline, metaproterenol, albuterol)
- Epinephrine – reserved for severe cases
- Avoid
  - Long appointments
  - Opioids, aspirin, ibuprofen
  - Erythromycin (interacts with theophylline – metabolized by same P450 enzyme)

- Drugs

- Theophylline (xanthine) – related to caffeine and theobromine
  - Natural plant alkaloid, bronchodilator, flexible administration
  - **Increases cAMP** (blocks phosphodiesterase)
  - Oral for bronchial asthma
    - Individual dosing – want serum [ ] at 10-20mg/ml
  - Interactions – smoking, phenytoin, phenobarbital, rifampin, erythromycin (P450)
  - Toxicity – anorexia, nausea, vomit, abdominal discomfort
- Non-selective adrenergic agents
  - **Increase cAMP**, bronchial dilation, cardiac stimulation
- Drugs acting on  $\alpha$  and  $\beta$  receptors
  - **Epinephrine – acute asthmatic attack or bronchospasm**
    - Parenteral epi (IV, IM), may be administered with inhaler
    - Excessive use = drying/irritation of bronchial mucosa, anxiety, dizziness
    - Dental consideration – CV side effects
  - **Ephedrine** – oral admin, often combined with theophylline, sedative, expectorants
    - Side effects = xerostomia, convulsions, CNS depression, dizziness
    - Dental considerations – CV side effects, xerostomia
  - **Isoproterenol** (prototype  $\beta$  agonist) – largely superseded by selective  $\beta_2$  agonists
    - $\beta_2$  bronchodilation
    - Rapid onset, short duration
    - Excessive use = nervousness, headache, arrhythmia, tolerance, etc
    - Side effects = xerostomia, dizziness, cardiac arrest, vomiting
    - Dental considerations – CV side effects, xerostomia
- Selective  $\beta_2$  agonists – decrease bronchial smooth muscle contraction
  - **Metaproterenol** – isoproterenol derivative, long duration, inhaled > oral
    - Side effects = xerostomia, dizziness, tachycardia, tremor
    - Dental considerations – xerostomia
  - **Terbutaline and Albuterol** – longer duration, inhaled > oral, less side effects
  - **Bitolterol** – prodrug (activated by ester hydrolysis), rapid onset, long duration (5h)
    - Side effects – headache, nervousness, palpitations, tremor

- Prophylaxis

- **Cromolyn and nedocromil** - inhalation
  - Inhibit  $\text{Ca}^{++}$  influx into mast cells – inhibit degranulation
    - No bronchodilation or anti-inflammatory action
    - Not effective for acute asthma attacks
    - Least toxic asthma medication
    - Highly charged – largely excreted unmetabolized
    - Side effects – burning mouth
- **Ketotifen (zaditen)** – cromolyn-like
  - Both anti-anaphylactic (blocks  $\text{Ca}^{++}$  influx) and strong  $\text{H}_1$  antihistamine
    - Side effects – drowsiness



- New Drugs
  - **5-lipoxygenase inhibitor (Zileuton)**
    - Inhibit leukotriene formation from arachidonic acid
      - Maintenance therapy for chronic asthma
    - Oral, rapid liver metabolism = multiple daily doses
    - Side effects – headache, GI irritation, liver toxicity, multiple drug interactions
  - **Anti-IgE omalizumab (Xolair)**
    - Block mast cell activation
      - Persistent allergic asthma
    - Injection only, not for severe acute asthma attacks
    - May cause allergic reactions at injection site
    - May prevent manifestation of other allergic reactions

# ANTIBIOTICS

## Penicillin V (similar to Pen G but better)

MOA: inhibit transpeptidase (beta-lactams)

PK: oral absorption, excreted in urine

RMR: penicillinase (altered penicillin binding proteins which decrease drug affinity)

SE: ash, anaphylactic shock, seizures at high doses, GI-nausea vomiting, diarrhea

SOA: effective against Gr+/- cocci, but not Gr- rods & anaerobes, penicillinase microbes, MRSA, multi-drug resistant Strep

## Ampicillin

MOA: extended spectrum penicillin

PK: oral absorption (reduced by food)

RMR: not a substitute for Pen G/V, resistance increasing

SE: rash

SOA: effective against non-lactamase Gr+/- bacilli, including Staph, Strep species (E. coli, H. influenza, Salmonella, Shigella)

## Clavulanic Acid

MOA: beta-lactamase suicide inhibitor

PK: weakly effective alone but synergistic when used w/ Amoxicillin to tx beta-lactamase producers

RMR: n/a

SE: n/a

SOA: beta-lactamase producers

## Cephalexin

MOA: same as penicillin (structure similar to penicillin)

PK: parentally/ orally; doesn't penetrate CNS

RMR: bacterial resistance if forms cephalosporinase, penicillinase

SE: generally well tolerated, allergy 5% of patients are hypersensitive cross-sensitivity to penicillin

SOA: effective against Gr+ and some community-acquired Gr- organisms

## Erythromycin

MOA: interfere with bacterial protein synthesis (bacteriostatic); can be bactericidal at therapeutic doses  
protein synthesis inhibitor binds to bacterial ribosome (50S) – inhibits translocation

PK: orally as free base, salt or insoluble ester; IV for serious infections

hydrolyzes in stomach – enteric coated tablet, capsule or insoluble ester used

enters cells, most body sites except brain & CSF

secreted in breast milk – crosses placenta

excreted (in active form) in bile, little renal elimination

RMR: approx. 50% of clinic Staph are resistant

SE: rarely serious – perhaps safest antibiotic to take

GI effects less common with azithromycin (azithro) & clarithromycin

cholestatic jaundice – not seen with free base usually spontaneously reversible

allergy – infrequent

drug interaxn: reduced elimination of theophylline, warfarin, cyclosporine, etc; not seen with azithro

SOA: Gr+/- aerobes and some anaerobes:

Mycoplasma pneumoniae, Legionella, Bordetella pertussis, Corynebacteria diptheriae

often used in penicillin-allergic patients

not effective against MRSA

\*azithromycin & clarithromycin are macrolides with structural similarities to erythromycin: broader spectrum of action and more desirable pharmacokinetics

## Clindamycin

MOA: bacteriostatic

PK: well absorbed following oral; IM/ IV, topical available; biliary excretion follows hepatic metabolism

Enterohepatic cycling occurs-drug stays in gut for long time which can cause AAC

RMR: similar resistance seen with erythromycin

SE: diarrhea pseudomembranous colitis (AAC, CDAD) - symptoms can appear after tx completed, skin rash, thrombophlebitis may follow IV administration

SOA: alternative therapy for Bacteriodes fragilis, serious Gr+ infections in penicillin-allergic pts, intra-abdominal infection or abscess; infections of femal pelvis or genital tract

## Metronidazole

MOA: activated in protozoa & anaerobic bacteria to produce reactive group – damage DNA

PK: oral admin, hepatic metabolism, renal elimination (reduced in hepatic failure)

RMR: n/a

SE: headache, nausea & vomiting, xerostomia, CNS effects (dizziness, vertigo, convulsions), disulfiram-like rxn if co-admin w. EtOH

SOA: anti-parasitic (Giardiasis, T vaginalis, intestinal & extra-intestinal ameba), anaerobic bacteria (Bacterioides fragilis & Clostridium difficile)

## Tetracycline

MOA: inhibits bacterial protein synthesis binds 30S ribosomal particle; bacteriostatic

PK: absorption from gut is incomplete; antacids reduce absorption

co-ingestion of dairy products also reduces uptake (maybe not for doxycycline);

widely distributed in body crosses BB barrier even in absence of infection (doxy penetrate well);

crosses placenta-secreted in breast milk

excretion is primarily via kidney (contraindicated in renal insufficiency; doxycycline is excreted by liver, and can use in renal insufficiency)

oral, parenteral & topical (ophthalmic) admin avail

RMR: frequently involves cross-resistance to other tetracyclines

SE: GI irritation – not in all individuals, pseudomembranous colitis (AAC, CDAD) rare, photosensitivity

permanent discoloration of growing teeth (avoid during mid preg and btwn 2mo to 8 yrs old)

super infection: vagina, oral, and systemic yeast infections (C. albicans)

drug interxn: barbiturates, phenytoin induce reduced levels of tetracycline in serum;

oral contraceptives: efficacy may be reduced

reduce elimination of warfarin (enhance anti-coagulant effect of warfarin)

SOA: community acquired respiratory infections: broad spec, Gr+/-, ameba

(lyme disease, rocky mountain spotted fever, Q fever, mycoplasma pneumoniae, chlamydiae)

MOA: mechanism of action

PK: pharmacokinetics

RMR: relevant mechanism of resistance

SE: side-effects

SOA: spectrum of action

# NEED TO KNOW

## ANTIBIOTICS con't

### **Vancomycin**

MOA: inhibit synthesis of bacterial cell wall; blocks cell wall precursor formation  
(diff part of pathway from penicillin)

MCI: active against most Gr+ cocci & bacilli; not effective against Gr- bugs  
Effective against most MRSA, penicillin-resistant Strep pneumoniae coagulase

### **Daptomycin**

MOA: depolarizes Gr+ bacteria, rapidly bactericidal

MCI: treat complicated skin & soft tissue infections caused by susceptible Gr+ organisms  
(MRSA & Strep species, vancomycin-sensitive Enterococcus faecalis)

### **Streptogramins**

MOA: interfere w/ protein synthesis

MCI: tx for vancomycin resistant Enterococcus (VRE) and  
methicillin-susceptible strains of S. aureus and S. pyogenes

### **Linezolid**

MOA: protein synthesis inhibitor novel ribosomal binding site;  
no cross-resistance w/ other protein synthesis inhibitors

MCI: vancomycin-resistant enterococcus faecium (VRE); MRSA, MSSA, penicillin resistant S pneumoniae

### **Folic Acid Synthesis Inhibitors**

#### **(Trimethoprim - TMP)**

MOA: inhibitor of bacterial dihydrofolate reductase (DHFR)

MCI: UTI, acute otitis media, Shigellosis, Pneumocystis carinii pneumonia

#### **(Sulfadiazine)**

MOA: inhibits bacterial enzyme dihydropteroate synthase (toxic against bacteria that synthesize folate)

MCI: combination therapy with TMP

### **Fluoroquinolones**

#### **(Ciprofloxacin)**

MOA: inhibits bacterial enzymes gyrase & topoisomerase IV

MCI: uses vary with type: UTI, acute uncomplicated cystitis in females, chronic bacterial prostatitis,  
lower resp tract infection, acute sinusitis, skin/skin structure infections, etc  
(not first drug choice)

### **Urinary Antiseptics**

#### **(Nitrofurantoin)**

MOA: bacterial enzymes metabolize drug to produce reactive intermediate which damage DNA

MCI: UTI caused by E coli, enterococci, S aureus, Klebsiella & Enterobacter species

#### **(Methenamine)**

MOA: releases formaldehyde in acidic urine (slow rxn); will only work if urine is acidic

MCI: chronic suppressive therapy, not effective in catheterized pt; drug must accumulate in bladder

#### **(Fosfomycin)**

MOA: cell wall biosynthesis inhibitor

MCI: single-dose oral tx of uncomplicated UTIs in women caused by E faecalis & E coli

### **Anti-Tuberculosis Agents**

#### **(Isoniazid)**

MOA: unknown

MCI: combo therapy to tx active TB, used in mono therapy as prophylactic

#### **(Rifampin)**

MOA: inhibits bacterial DNA dependent RNA polymerase

MCI: combo therapy to tx active TB & nasopharyngeal carriers of Neisseria meningitidis  
(not used to tx active meningococcal disease)

#### **(Ethambutol)**

MOA: interferes w/ incorporation of mycolic acid into cell wall

MOA: mechanism of action

MCI: major clinical indications

# BE FAMILIAR ONLY

# ANTIVIRAL

## Oseltamivir

MOA: inhibits viral neuraminidase

PK: pill & liquid availability, well absorbed orally (admin as esterified pro-drug), renal elim

RMR: observed lab settings, clinical impact unclear

SE: nausea & vomiting, RARE cases of Stevens-Johnson syndrome or anaphylaxis

SOA: effective against influenza A & B, prophylaxis (not substitute for vaccination),

acute therapy in pts >1 yr old w/ uncomplicated flu symptoms of <2 days duration

## Foscarnet

MOA: inhibits DNA polymerase of HSV, CMV, and others

PK: oral not effective

RMR: emerges during long term therapy

SE: renal impairment, nausea, vomiting

SOA: CMV retinitis (inclu Ganciclovir-resistant strains), acyclovir-resistant HSV or VZV, other CMV infect.

## Acyclovir

MOA: prodrug selectively inhibits viral DNA polymerase (activated by viral thymidine kinase)

PK: systemic absorption min w/ topical application; low but satisfactory oral bioavailability, penetrate most tissues (reduced conc in CNS)

RMR: emerges during long term therapy

SE: generally well tolerated

SOA: primary & 2ndary HSV, varicella zoster in immunocompromised pts, prophylaxis in BMT, organ transplant, HSV encephalitis

\*Valciclovir: L-valyl ester prodrug of acyclovir has improved oral bioavailability

Famciclovir: diacetate ester pro-drug version of penciclovir (structural analog of acyclovir), used to tx shingles & recurrent genital herpes in immunocomp pts

## Ganciclovir

MOA: prodrug preferentially phosphorylated by CMV;

activated drug inhibits DNA polymerase & suppress chain elongation

PK: low but satisfactory oral bioavail; IV delivery leads to effective intraocular concentration

RMR: emerges during therapy

SE: toxicity limits dosage & duration of tx

effects includes: leukopenia, neutropenia, thrombocytopenia, renal impairment

MOA: mechanism of action

PK: pharmacokinetics

RMR: relevant mechanism of resistance

SE: side-effects

SOA: spectrum of action

## AZT

MOA: nucleoside analog reverse transcriptase inhibitor (NRTI)

MCI: tx/ control of HIV infections; reduce maternal-neonate HIV transmission; post exposure prophylaxis

## Nevirapine

MOA: non-nucleoside reverse transcriptase inhibitors (NNRTI)

MCI: combo therapy to tx HIV-1 (not 2) infections; reduce maternal-neonate transmission

## Indinavir

MOA: inhibits maturation of HIV polypeptide via HIV protease

MCI: combo therapy w/ other anti-retroviral drugs

## Enfuvirtide

MOA: binds to gp41 of HIV-1 (not 2); prevents conformational change necessary for fusion of virus & cell

MCI: tx for HIV-1 → experience pt w/ evidence of HIV-1 rep despite ongoing retroviral therapy

## Raltegravir

MOA: inhibits catalytic activity of HIV-1 integrase

MCI: tx of HIV-1 →

experienced pt w/ evidence of viral rep & HIV-1 strains resistant to mult anti-retroviral agents

## Maraviroc

MOA: CCR5 co-receptor antagonist (not effective vs CXCR4 tropic strains)

MCI: tx of adults w/ CCR5-tropic HIV-1 infection →

experienced pts w/ evidence of viral rep & resistance to mult anti-retroviral agents

MOA: mechanism of action

MCI: major clinical indications

# BE FAMILIAR ONLY

# NEED TO KNOW

# ANTICANCER

## **Cyclophosphamide**

MOA: DNA damaging via alkylation – nitrogen mustard alkylating agent, bis-electrophile  
PK: well absorbed orally, cyp450 –mediated activation penetrates BBB, excretes in urine (keep pt hydrated)

SE: myelosuppression (dose-limiting); nausea & vomiting, bladder toxicity; alopecia, cardiac toxicity (high dose), amenorrhea w/ ovarian failure, potential sterility

## **Etoposide**

MOA: topoisomerase II inhibitor, semi-synthetic derivative of camptothecin  
PK: oral (50% absorption), IV; mostly urinary elimination, min hepatic metabolism  
SE: myelosuppression (dose-limiting); nausea & vomiting; anorexia; alopecia; mucositis

## **Methotrexate**

MOA: folic acid analog; S-phase acting agent; inhibit dihydrofolate reductase, polyglutamated forms inhibit thymidylate synthase (incorp of dUTP into DNA)  
PK: oral/ IV; undergoes enterohepatic cycling; primarily urinary elim  
SE: myelosuppression (dose-limiting); mucositis (can be dose-limiting); acute renal failure; CNS effects; reproductive toxicity at high dose

## **Mercaptopurine**

MOA: purine analog; S-phase acting agent, prodrug activated to 6-MP ribose phosphate by HGPRT (inhibits PRPP & blocks purine synthesis) and to 6-thioguanine nucleotides (incorporated into DNA & RNA)  
PK: oral admin, hepatic metab, primarily urinary elim  
SE: myelosuppression; mucositis and/or diarrhea; hepatotoxicity, nausea & vomiting; mutagenic, teratogenic & carcinogenic

## **Paclitaxel**

MOA: enhance microtubule polymerization  
PK: IV only, ext hepatic metab & biliary elim  
SE: myelosuppression (dose limiting); hypersensitivity rxn; neurotoxicity-peripheral neuropathy; alopecia; mucositis; hepatic toxicity

## **Tamoxifen**

MOA: selective estrogen receptor modulator  
PK: oral dose, ext hepatic CYP450 metabolism produce more potent metabolite endoxifen, parent drug & metabolites primarily excreted in feces  
SE: menopausal symptoms; myelosuppression (rare); thromboembolic complications; elevated serum triglycerides; increased incidence of endometrial hyperplasia polyps & endometrial cancer

## **Anastrozole**

MOA: nonsteroidal aromatase inhibitor, blocks final step in conversion of androgens to estrogen & estradiol  
PK: oral dose, ext metab in liver, excreted in feces  
SE: asthenia; mild nausea & vomiting; hot flashes; arthralgia; headache; peripheral edema

## **Imatinib**

MOA: protein tyrosine kinase inhibitor; binds to ATP-binding site of BCR-ABL protein (& other kinases) and inhibit substrate phosphorylation  
PK: oral dose, hepatic metab, primarily excreted in feces  
SE: nausea & vomiting; diarrhea; edema-fluid retention w/ pleural effusion, ascites, pulmonary edema & (rarely) chronic heart failure, occasional myalgia (dose limiting); myelosuppression; skin toxicity

## **Cetuximab**

MOA: monoclonal antibody, anti-EGFR specificity, blocks endogenous ligand-mediated activation of \ critical mitogenic & anti-apoptotic signals  
PK: IV admin, long ½ life  
SE: elevated blood press (esp in pt w/ underlying HTN); pruritis, dry skin; elevated liver enzymes; asthenia & anorexia; mild nausea/vomiting & mucositis; rare incidence of hemoptysis & GI bleeding

MOA: mechanism of action  
PK: pharmacokinetics  
SE: side-effects

# NEED TO KNOW

# ANTIFUNGAL

## **Amphotericin B**

MOA: disrupts fungal plasma membrane—forms pores which K<sup>+</sup> are lost (doesn't kill bact b/c lack sterols)

PK: poorly absorbed following ingestion; can be used to tx bowel Candida infection

RMR: relatively rare

SE: acute- fever, chills, rigors, aches, nausea vomiting

chronic-nephrotoxicity, anemia, thrombopenia, leukopenia

SOA: IV intrathecal for meningitis (soln); also for disseminated fungal systemic infections (however toxic)

## **Fluconazole**

MOA: fungistatic inhibitor of ergosterol biosynthesis

PK: oral dose well absorbed; excreted unchanged in urine; distributes well including CNS

RMR: n/a

SE: GI – nausea, vomiting & bloating, reversible alopecia; rare reversible thrombocytopenia

drug intxn: increase lvl of P450 metabolism of cyclosporine, warfarin, etc

SOA: oropharyngeal & esophageal candidiasis

## **Caspofungin**

MOA: fungicidal; blocks fungal cell wall biosynthesis; inhibits fungal enzyme beta (1,3)-D-glucan synthase

PK: not absorbed orally, IV only, renal & hepatic elimination

(adjust dosage for hepatic but not renal insufficiency)

RMR: none clinically but exists experimentally

SE: possible histamine-mediated symptoms; better tolerated than amphotericin B

SOA: effective against Aspergillus & Candida species

Candida: intra-ab abscesses, peritonitis, pleural space infections, esophageal candidiasis

Aspergillus: invasive aspergillosis in pt who are refractory to or intolerant of other therapies

## **Nystatin**

MOA: same as amphotericin

PK: mouthwash, tablet, suspension, topical powder ointment (not absorbed orally)

RMR: n/a

SE: too toxic for parenteral admin

SOA: appropriate for bowel infection (doesn't absorbed well),

applied topically on skin/ mucous membrane (tx candida infections)

## **Clotrimazole**

MOA: similar to other azoles

PK: not absorbed orally; lozenges, creams, suspensions, topical uses

SE: n/a

SOA: tx athlete's foot, jock itch, ringworm, oropharyngeal candidiasis,

prophy to reduce incidence of oropharyngeal candidiasis in immunocompromised pts

MOA: mechanism of action

PK: pharmacokinetics

RMR: relevant mechanism of resistance

SE: side-effects

SOA: spectrum of action

# NEED TO KNOW