Advanced Pharmacology: Advanced Introductory Principles

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Drug Information Resources
Drug Information Resources & Literature Retrieval

- 60 million US adults use search engines daily
- 60% of adults search for health-related information
- Patients rely on the internet for health and drug information
- Skill of the researcher is essential in getting the best information

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Drug Information Resources & Literature Retrieval

- Technology has brought drug information to health care providers as well as patients
- Clinical decision should never be made from reading an abstract
- Critical evaluation of the literature is a prerequisite of providing evidence based care
- Many institutions and ambulatory care centers utilize clinical decision support to maximize patient care
Search Engines

- Do NOT rely on a single source of drug information
- Wikipedia is NOT peer reviewed and does not always provide valid/reliable drug information
- Search engines are “vastly” different and employ simple “logic” to search data
- Google Scholar not designed to be comprehensive
- More reliable databases (MEDLINE and PubMed) are preferred for researching drug information

Resources for Practitioners

<table>
<thead>
<tr>
<th>Resource</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed (<a href="http://www.ncbi.nlm.nih.gov">www.ncbi.nlm.nih.gov</a>)</td>
<td>Compilation of more than 21 million articles. Many articles are linked to full-text references.</td>
</tr>
<tr>
<td>Clinical Evidence (<a href="http://www.clinicalevidence.com">www.clinicalevidence.com</a>)</td>
<td>Evidence-based medicine database that provides grade levels to help put evidence into practice</td>
</tr>
<tr>
<td>US Food and Drug Administration (FDA) (<a href="http://www.fda.gov">www.fda.gov</a>)</td>
<td>Provides information on food, drugs, medical devices, vaccines, blood and biologics, animal and veterinary products, cosmetics, radiation-emitting products and tobacco products. Consumer and professional information. Safety recalls.</td>
</tr>
<tr>
<td>National Cancer Institute (<a href="http://www.cancer.gov">www.cancer.gov</a>)</td>
<td>Provides unbiased information on the treatment of cancer including clinical trials, cancer statistics, research and funding and patient information</td>
</tr>
</tbody>
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### Resources for Consumers

<table>
<thead>
<tr>
<th>Resource</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DailyMed</td>
<td>Provides high quality information about marketed drugs, including FDA-approved labeling. Provides easy-to-read product labeling.</td>
</tr>
<tr>
<td>(<a href="http://www.dailymed.nlm.nih.gov">www.dailymed.nlm.nih.gov</a>)</td>
<td></td>
</tr>
<tr>
<td>Drugs A to Z</td>
<td>Easily searched database to look up drugs, both generic and brand name, to find consumer information that can help patients understand their medications including risks and benefits.</td>
</tr>
<tr>
<td>(<a href="http://www.drugs.com/drug_information.html">www.drugs.com/drug_information.html</a>)</td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>High-quality health information written by professionals specifically for consumers. Provides a wealth of unbiased information.</td>
</tr>
<tr>
<td>(<a href="http://www.mayoclinic.com/">www.mayoclinic.com/</a>)</td>
<td></td>
</tr>
<tr>
<td>WebMD</td>
<td>Provides consumer health-related information written and edited by health care professionals. Allows users to create programs like vaccine trackers and food &amp; fitness planners.</td>
</tr>
<tr>
<td>(<a href="http://www.webmd.com">www.webmd.com</a>)</td>
<td></td>
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### Locating Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>Resource</th>
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<tbody>
<tr>
<td>Guideline.gov</td>
<td>National guideline clearinghouse of evidence-based guidelines. Large database of different guidelines form may professional organizations. Provides expert commentaries guideline synthesis, guideline resources, annotated bibliographies and comparative analysis of guidelines.</td>
</tr>
<tr>
<td>(<a href="http://www.guideline.gov">www.guideline.gov</a>)</td>
<td></td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>Provides current clinical guidelines as part of the American College of Physicians web site. Clearinghouse of clinically relevant guidelines.</td>
</tr>
<tr>
<td>(<a href="http://www.acponline.org/clinical_information/guidelines/">www.acponline.org/clinical_information/guidelines/</a>)</td>
<td></td>
</tr>
<tr>
<td>Open Clinical</td>
<td>International organization that created a Web site to promote clinical decision support tools, clinical workflow and advanced knowledge management technologies within patient care as well as clinical research.</td>
</tr>
<tr>
<td>(<a href="http://www.openclinical.org/guidelines.html">www.openclinical.org/guidelines.html</a>)</td>
<td></td>
</tr>
</tbody>
</table>
Electronic Drug Information Resources

<table>
<thead>
<tr>
<th>Facts and Comparisons</th>
<th>Lexicomp</th>
<th>Micromedex</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Abbreviated drug information is referenced</td>
<td>• Comprehensive drug information</td>
<td>• Provides a variety of information: drug info, poison info, compatibility info, drug-drug interaction info, acute care medicine and patient education</td>
</tr>
<tr>
<td>• Comparison charts</td>
<td>• Integrated with UpToDate</td>
<td>• Information is provided as full text and references throughout</td>
</tr>
<tr>
<td>• Information on patient assistance programs</td>
<td>• Includes current drug shortages, FDA recalls dangerous abbreviations therapeutic equivalent drugs</td>
<td>• Offers comprehensive, easy-to-read, extensively referenced data on drugs</td>
</tr>
<tr>
<td>• Look-alike and sound-alike drugs</td>
<td>• References are not provided for all information</td>
<td></td>
</tr>
<tr>
<td>• Manufacturer index</td>
<td>• Good source when quick retrieval of easy-to-read data is required</td>
<td></td>
</tr>
</tbody>
</table>

“Must Have” Resources

- Drug Information Handbook (text)
  - Adult/Pediatric/Geriatric/Dentistry/Psychiatry
  - Advanced Practice Nursing
- AHFS Drug Information (text)
- Drugs in Pregnancy and Lactation (text)
- Drug Information Center (where available)
- Poison Control Center: 1-800-222-1222
History can be traced to 3000 B.C., where the Babylonians recorded “prescriptions” on clay

Chinese recorded Pen Tsao (Great Herbal), a compilation of plant remedies ~2700 B.C.

PHARMACOLOGY is derived from two words:
- Pharmakon = “medicine”
- Logos = “study”

A. Paracelus: “All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing a poison…a lot kills, a little cures.”

Advanced Introductory Principles
Important History in Drug Regulation

- **1906: Pure Food and Drug Act**
  - Government given the power to control the labeling
  - Prohibited mislabeling, as well as adding extraneous, improper or inferior ingredients to drugs

- **1914: Harrison Narcotic Act**
  - Regulated importing, manufacturing, the sale and use of opium, cocaine and marijuana
  - Superceded by the Controlled Substances Act of 1970
Important History in Drug Regulation

1938: Food, Drug, and Cosmetic Act
- Passed by Congress; first law preventing marketing of drugs not thoroughly tested
- Yet, did not require proof of effectiveness

1952: Durham-Humphrey Amendments
- Separated drugs into prescription (legend) and nonprescription/over-the-counter (non-legend) categories.
- “Legend” must appear on every commercial container of legend drugs: “Caution Federal Law Prohibits Dispensing without Prescription”
- Additional legend rules

1962: Kefauver-Harris Amendments
- Required proof of efficacy and safety before any new drug could be placed on the market
- Included guidelines for conducting clinical trials

1970: Comprehensive Drug Abuse Prevention and Control Act (Controlled Substances Act)
- Established rehabilitation programs for drug users
- Established control (registration) and enforcement (DEA)
- Regulates export/import of controlled substances
Important History in Drug Regulation

1970: Poison Prevention Packaging Act
- Regulated that certain household products must be packaged in a manner to make it significantly difficult for children < 5 years of age to open
- Child-resistant containers apply to:
  - All controlled drugs
  - All legend drugs except:
    - SL nitroglycerin
    - Oral contraceptives in dispenser packs
    - Aspirin and most aspirin-containing preparations
    - Iron-containing drugs and most dietary supplements

1976: Medical Devices Act
- Required proof of both safety and efficacy before marketing of medical devices for human use

1984: Drug Price Competition and Patent Restoration Act
- Allowed patent protection to be extended for five years, yet not to exceed 14 years post-FDA approval
- Established Abbreviated New Drug Application (ANDA) procedures for generic copies of drugs
Important History in Drug Regulation

- **1987:** Prescription Drug Marketing Act
  - Prohibited sale, purchase or trade of drug samples
  - Intent was to curb *drug diversion* (i.e., use of prescription drugs for recreational purposes)

- **1988:** FDA officially established as an agency of the United States Department of Health and Human Services (USDHHS)

- **1990:** Omnibus Budget Reconciliation Act
  - New requirements/regulations:
    - States’ participation in the Medicaid program
    - Drug utilization review (DUR) development
    - Counseling of patients

- **1992:** Prescription Drug User Fee Act
  - Required non-generic and biologic manufacturers to pay fees for improved drug review processes

- **1994:** Dietary Supplement Health and Education Act
  - Required clear labeling of dietary supplements
  - FDA given power to remove supplements that cause significant risk
Important Healthcare Regulation

2010: Affordable Care Act
- Puts consumers back in charge of their health care
- “Patient’s Bill of Rights”
- Ends pre-existing condition exclusions for children
- Ends arbitrary withdrawals of insurance coverage
- Guarantees patient’s right to appeal
- Ends lifetime limits on coverage
- Insurance companies must now publicly justify any unreasonable rate hikes
- Covers preventive care at no cost to the patient

Stages of Drug Development and Approval
Stages of Drug Development and Approval

**Discovery**
- Chemical modification of known drugs
- Screening of natural products for activity
- Rational drug design based on known molecular mechanisms

**Preclinical Investigation: Safety and Toxicity Testing**
- *Always done in animals* – usually rodents – then data are extrapolated to humans
- Range: 1-3 years
- Investigates:
  - Acute, subacute and chronic toxicity
  - Reproductive function effects
  - Carcinogenicity
  - Mutagenicity
  - Teratogenicity

**Notice of Claim Investigational Exemption for New Drug (IND):**
- Three phases of clinical trials
  - Requires informed consent
  - Requires approval of FDA, organization sponsoring the IND and the Institutional Review Board (IRB) of trial site

**Phase 1**
- Healthy volunteers
- Establish dose range limits
- Observe for safety of tested doses
- Preliminary pharmacokinetic data
Stages of Drug Development and Approval

Phase 2
- Tests patients with disease states
- Safety and efficacy are examined

Phase 1 and 2 testing are usually conducted in White men.
- Female differences?
- Pregnant women?

Phase 3
- Evaluation in much larger numbers of patients
- Multi-center trials
- Actual use conditions
- Efficacy and broader range toxicity are explored

Stages of Drug Development and Approval

New Drug Application (NDA)
- Full reports of all preclinical and clinical data
- FDA review

Phase 4
- Approval for marketing
- Monitor safety under actual conditions of usage

Post-marketing Surveillance
- Adverse affects
- Reactions
- Reports
What’s in a name?

Drug Names

- **Chemical Name:** assigned by the International Union of Pure and Applied Chemistry (IUPAC) using standard nomenclature

- **Generic name:** assigned by the U.S. Adopted Name Council
  - Only one generic name for each drug!
  - Learn THIS one!!
  - Usually written lower case

- **Trade name:** assigned by a company for marketing
  - Usually, short and easy to remember
  - Caution: Many similar names + sound alike, etc.
  - Drug developers have 17 years of exclusive rights to name and market after being submitted to the FDA
  - After 17 years, a competing company may sale a generic equivalent (after FDA approval)
Federal Drug Classification and Schedules

Schedule I
- Abuse potential: Highest
- Limited or no accepted medical use in U.S.
- Investigational drugs
- Examples:
  - Opiates: heroin, many synthetic derivatives
  - Hallucinogens: lysergic acid diethylamide (LSD)
  - Marijuana
  - Methaqualone (Quaalude)
U.S. Drug Schedules - continued

- **Schedule II**
- Currently accepted medical use in U.S.
- Abuse potential: High
  - Physical dependence
  - Psychological dependence

**Examples:**
- **Opiates/narcotics:** opium, cocaine (topical anesthesia), codeine, hydrocodone (alone), meperidine (Demerol), methadone (Dolophine), morphine (MS Contin, Duramorph), pentazocine (Talwin Injection), oxycodone (OxyContin, Percocet, Tylox), hydromorphone (Dilaudid), fentanyl, others

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U.S. Drug Schedules - continued

- **Schedule II:** Examples (continued)
  - **Stimulants:** amphetamine (Benzedrine), dextroamphetamine (Dexedrine), methamphetamine (Ritalin)
    - Note: Schedule II stimulants may not be used as anorexiants in many states.
      - Valid uses: narcolepsy, hyperkinesis, brain dysfunction, severe depression, etc.
  - **Depressants:** intermediate-acting barbiturates [e.g., amobarbital (Amytal), pentobarbital (Nembutal), secobarbital (Seconal)], others
Rules for prescribing Schedule II drugs:

- Written prescription required with prescriber’s actual (legal) signature
- Must be dated the same day as signed
- *No refills allowed
- In some states for emergency situations, a verbal order may be given for a limited quantity of drug to treat the emergency condition
  - Must be followed by a written prescription within 72 hours

Schedule III
Abuse potential: Moderate

Rules for Schedule III prescriptions:

- Written or verbal prescriptions are allowed
- Valid for 6 months from the date written
- Refill limit: 5 times

Examples:
- Narcotic analgesics/antitussives: codeine and some derivatives in combination with non-narcotic analgesics
  - codeine/acetaminophen (Tylenol #3)
  - hydrocodone/acetaminophen (Lortab)
  - pentazocine/acetaminophen (Talacen)
  - Paregoric (camphorated opium tincture)
- Anabolic steroids
- Some non-barbiturate sedative-hypnotics
- Some stimulants used as anorexiants for obesity
U.S. Drug Schedules - continued

**Schedule IV**
- Abuse potential: Low
- Same prescription rules as Schedule III

**Examples:**
- Benzodiazepines
  - Diazepam (Valium)
  - Lorazepam (Ativan)
- Zolpidem (Ambien)
- Carisoprodol (Soma)

**Schedule V**
- Abuse potential: Lowest

**Examples:**
- Over-the-counter medications, including those with codeine
- Purchase subject to state regulations – may differ

**General Rule for Controlled Substances:** Classifications determined by the State Board of Health, but may not be classified in lower schedules than federal law permits
Prescription Writing

- **Date**
  - Controlled substances: valid for 6 months (most cases); DEA# required on prescription pad for controlled substances
  - Non-controlled: valid for one year (generally)

- **Name and address of patient**

- **Superscription**: The “heading” including the symbol Rx (Latin for take thou; recipe)

- **Inscription**: Drug name, strength, dosage form (tabs, capsule, suspension, etc.)

- **Subscription**: Directions to pharmacist

- **Signatura**: Also called “Sig”; Directions to the patient; transcribed by pharmacist onto the label

- “Dispense as written” or “product selection permitted” (generic)
# Joint Commission Official “Do not Use” List

<table>
<thead>
<tr>
<th>Do Not Use</th>
<th>Potential Problem</th>
<th>Use Instead</th>
</tr>
</thead>
<tbody>
<tr>
<td>U (unit)</td>
<td>Mistaken for “0”, the number “4” (four) or “cc”</td>
<td>Write “unit”</td>
</tr>
<tr>
<td>IU (International Unit)</td>
<td>Mistaken for IV (intravenous) and the number 10 (ten)</td>
<td>Write “International Unit”</td>
</tr>
<tr>
<td>Q.D., QD, q.d., qd (daily)</td>
<td>Period after the Q mistaken for “I” and the “O” mistaken for “I”</td>
<td>Write “daily”</td>
</tr>
<tr>
<td>Q.O.D., QOD, q.o.d., qod (every other day)</td>
<td>Mistaken for each other</td>
<td>Write “every other day”</td>
</tr>
<tr>
<td>Trailing zero (X.0 mg)</td>
<td>Lack of leading zero (.Xmg)</td>
<td>Write X mg</td>
</tr>
<tr>
<td>MS</td>
<td>Can mean morphine sulfate or magnesium sulfate</td>
<td>Write “morphine sulfate”</td>
</tr>
<tr>
<td>MSO₄ and MGSO₄</td>
<td>Confused for one another</td>
<td>Write “magnesium sulfate”</td>
</tr>
<tr>
<td>&gt; (greater than)</td>
<td>Misinterpreted as the number “7” (seven) or the letter “L”</td>
<td>Write “greater than”</td>
</tr>
<tr>
<td>&lt; (less than)</td>
<td>Confused for one another</td>
<td>Write “less than”</td>
</tr>
<tr>
<td>Abbreviations for drug names</td>
<td>Misinterpreted due to similar abbreviations for multiple drugs</td>
<td>Write drug names in full</td>
</tr>
<tr>
<td>Apothecary units</td>
<td>Unfamiliar to many practitioners</td>
<td>Use metric units</td>
</tr>
<tr>
<td>@</td>
<td>Mistaken for the number “2” (two)</td>
<td>Write “at”</td>
</tr>
<tr>
<td>Cc</td>
<td>Mistaken for U (units) when poorly written</td>
<td>Write “ml” or “milliliters”</td>
</tr>
<tr>
<td>mg</td>
<td>Mistaken for mg (milligrams) resulting in one thousand-fold overdose</td>
<td>Write “mcg” or “micrograms”</td>
</tr>
</tbody>
</table>
Phases of Drug Action

A. Pharmaceutical Phase
   - Pharmaceutics – physicochemical properties of drugs
   - Design and manufacture of dosage formulations

B. Pharmacokinetic Phase
   - Biopharmaceutics
     - Liberation
     - Absorption
     - Distribution
     - Metabolism (biotransformation)
     - Excretion
   - Pharmacokinetics
     - Physiological models
     - Design and individualization of dosage regimens
Phases of Drug Action

C. Pharmacodynamic Phase
   - Pharmacology: interaction of drugs with tissue and cells
   - Target sites of drugs: Receptors

D. Therapeutic Phase
   - Clinical pharmacology
   - Therapeutic and/or toxic effects of drugs

Pharmacokinetics

**Liberation** (of drug from dosage form)
   - Extends from the time of drug administration to the time the drug is dissolved in body fluids and ready for absorption

- Immediate liberation:
  - Parenteral
    - Exceptions:
      - Long-acting, slow-release suspension formulas for IM or SQ use (e.g., PCN G, insulins (except Regular), etc.
      - Solutions that may precipitate [(e.g., phenytoin (Dilantin)]

- Dosage-form dependent liberation:
  - Topical
  - Oral dosage forms (depend on the number of pharmaceutical barriers to drug release)
Liberation: Oral Dosage Forms (continued)

- **Solution, elixir, syrup**
  - Already dissolved; no barriers to release

- **Suspension**
  - Particles must completely dissolve for release to occur
  - Dissolution is the rate-limiting (slowest) step in drug liberation from solid oral forms

- **Capsule**
  - Disruption – outer gelatin capsule (rapid)
  - Dispersion – of a powder
  - Dissolution – of particles

- **Tablet**
  - Disintegration of granules to a powder
  - Dispersion – of a powder
  - Dissolution – of particles

- **Coated tablet**
  - Dissolution of the coat
  - Others same as tablets

Pharmacokinetics: Absorption

**Absorption**

- Process of drug movement from the absorption site across one or more cell membrane barriers in the circulation

**Mechanisms:**
- Passive diffusion
- Facilitated diffusion
- Active transport
- Pinocytosis
Absorption Mechanism: Passive Diffusion

**Passive Diffusion**
- The most common mechanism
- Involves the movement of drug from its absorption site across a cell membrane barrier in the direction of the **concentration gradient** (driving force)
- The drug moves from an area of higher concentration (e.g., GI lumen) to an area of lower concentration (e.g., the blood)
- Movement of drug across **lipid membranes** is favored for the non-ionized form of the drug
- The non-ionized form is the more lipid-soluble form and can more easily dissolve in and pass through biologic membranes
- Ability of drug molecules to pass through biologic membranes depends on the drug's **partition coefficient** (Kp), which is a measure of a drug's ability to dissolve in a lipid phase compared to an aqueous phase
  - In general, the higher the Kp for a drug, the better will be its extent and rate of absorption.

Absorption Mechanism: Facilitated Diffusion

**Facilitated Diffusion**
- Same principles as passive diffusion but, in addition...
  - A carrier molecule (usually a membrane protein) is required.
  - Drug at the absorption site combines with the carrier at the membrane surface, transported across the membrane, and then released.
    - This process does not require energy.
  - Drug movement occurs only in the direction of the concentration gradient and for only as long as a concentration gradient exists.
Absorption Mechanism: Active Transport

Active Transport
- Carrier-mediated transport process
- Requires energy
  - Movement of drug occurs against the concentration gradient
- The carrier system can become saturated so that the rate of drug transport reaches a maximum level.
- The carrier has specificity for certain drugs with proper chemical structures

Absorption Mechanism: Pinocytosis

Pinocytosis
- A portion of the cell membrane that surrounds the drug breaks off, and moves into the cell where drug is released
- May be significant for extremely large drug molecules
  - Polypeptides, proteins, etc.
Drug Absorption Sites

- **Enteral**
  - Oral
  - Rectal
  - Sublingual

- **Parenteral**
  - Intravenous
  - Intramuscular
  - Subcutaneous

- **Topical**
  - Percutaneous
  - Eye
  - Lung

Drug Absorption: Oral/Intestinal

- GI epithelial cell membrane barrier
- Small intestine – major site for drug absorption (huge surface area)
- Gastric emptying/intestinal motility (physiological factors) affecting drug absorption
  - Rate-limiting step in oral absorption

- Increased emptying:
  - Large fluid volumes
  - Cholinergics
  - GI pro-kinetics
  - Cathartics/laxatives

- Decreased emptying:
  - Solid foods – especially fatty, acidic or high in electrolytes
  - Alcohol
  - Antacids
  - Anticholinergics
  - Narcotics
  - Drugs with anticholinergic side effects (antidepressants, antihistamines)
Absorption Mechanism: First-pass Effect

**First-pass Effect**

- “Presystemic metabolism”
- During GI track drug absorption, there are two potential sites for metabolism to occur:
  - Gut wall
  - Liver

- If the drug is chemically altered as it passes through either of these sites (metabolized), it is said to undergo first-pass metabolism.
- Effectively, the drug has been metabolized before it ever reaches the systemic circulation.
  - Some drugs are so extensively metabolized when taken orally that therapeutic effects cannot be obtained (e.g., lidocaine)
  - Oral doses must be very large for some drugs compared to parenteral

Absorption Mechanisms (continued)

- **Rectal**
  - Epithelial cell membrane
  - Highly vascularized
  - Lower and middle hemorrhoidal veins drain directly into the inferior vena cava
  - First-pass effects may be partially avoided if a drug can be liberated and absorbed by the rectum

- **Sublingual**
  - Thin epithelial mucosal barrier
  - Eliminates first-pass effects
  - Requires rapid drug dissolution
Absorption Mechanisms (continued)

- **Intravenous**
  - No drug absorption barrier
  - Immediate absorption and drug availability

- **Intramuscular/Subcutaneous**
  - Capillary endothelial cell membrane barrier
  - Blood flow to the site: rate-limiting step

- **Percutaneous**
  - Thick epithelial barrier
  - Outer layer of epidermis (stratum corneum) is the rate-limiting step

Absorption Mechanisms (continued)

- **Eye**
  - Epithelial mucous membrane barrier
  - Absorption is greatly dependent on drop size

- **Lungs**
  - Thin epithelial mucous membrane barrier
  - Highly vascularized
  - Rapid absorption
  - Very large surface area
  - Aerosols/inhalers may not be used efficiently
  - As particle size decreases, absorption increases
Pharmacokinetics: Distribution

- Distribution Patterns:
  - Plasma
  - Uniform into body water
  - Tissue concentrations
  - Non-uniform: depending on plasma, affinity of binding sites, lipid solubility and perfusion

- Distribution Barriers:
  - Blood-brain barrier (BBB)
  - Placental barrier

Pharmacokinetics: Metabolism

- Metabolisms/Biotransformation:
  - Chemical alteration of a drug by enzymes in the body

- Purposes of drug metabolism:
  - Detoxification mechanism (defense)
  - Termination of drug action

- Major sites of drug metabolism:
  - Gut
  - Liver
  - Plasma
Pharmacokinetics: Excretion

- Major routes:
  - Kidney
  - Bile (via enterohepatic circulation) → fecal excretion
  - Pulmonary
  - Milk
  - Saliva

- Renal excretion involves three processes:
  - Glomerular filtration (only free drug is filtered)
  - Active tubular secretion (proximal tubule)
  - Passive tubular reabsorption (from the proximal tubule)

Pharmacodynamics:

How drugs interact IN the body…within cells, tissues and organs
Pharmacodynamics

Receptor Theory of Drug Action
- Receptor: portion of tissue or cell capable of interacting with a drug with resulting pharmacologic effects

- Chemical composition of receptors
  - Membrane macromolecules (mostly proteins, lipids)
  - Intracellular macromolecules (proteins, nucleic acids)
  - Enzymes

- Receptors evolved for the purpose of reacting with endogenous compounds
  - Drugs that resemble these endogenous compounds may also react with the receptor

Drug-Receptor Interactions

**Agonist** (full agonist)
- Drug which interacts with a receptor to produce a pharmacologic response that is the same response produced by the endogenous compound
  - Terbutaline (adrenergic agonist drug) reacts with adrenergic receptors in the bronchioles to produce bronchodilation (same effect as produced by the endogenous agonist, epinephrine)

**Partial Agonist**
- Drug which can interact with a receptor but produces a much weaker pharmacologic response than a full agonist

**Antagonist**
- Drug which interacts with a receptor to block the actions of the endogenous agonist
  - Phenoxybenzamine (adrenergic receptor antagonist) reacts with adrenergic receptors in blood vessels to block the actions of norepinephrine (endogenous agonist)
Properties of Drug-Receptor Interactions:

- **Affinity**
- **Efficacy**
- **Potency**

**Affinity**
- Measure of a drug’s ability to interact with a receptor

\[ \text{Drug} + \text{Receptor} \leftrightarrow \text{D-R complex} \]

- **Agonist**: high affinity
- **Antagonist**: high affinity
- **Partial agonist**: low affinity
Properties of Drug-Receptor Interactions

**Efficacy**
- Measure of a drug’s ability to produce a pharmacologic response after interacting with a receptor

  \[ \text{D-R complex} \to \text{Response} \]

  - **Agonist**: high efficacy
  - **Antagonist**: zero efficacy
  - **Partial agonist**: low efficacy

**Potency**
- Measure of the dose of a full agonist required to produce the maximum pharmacologic response.

  - If drugs A and B are both agonists, and drug A produces the maximum response at a lower dose than drug B, then drug A is more potent than drug B.
Toxicology Principles

Definitions:

- **Effective dose 50 (ED<sub>50</sub>)**: Dose which produces a desired therapeutic effect in 50% of test subjects.

- **Lethal dose 50 (LD<sub>50</sub>)**: Dose which is lethal to 50% of test subject.

- **Therapeutic index (TI)**: Ratio of the LD<sub>50</sub> to the ED<sub>50</sub>
  \[ TI = \frac{LD_{50}}{ED_{50}} \]
  A very low value of TI means that there is small difference between the doses of a drug which produce therapeutic vs. lethal effects.

Adverse Drug Reactions (ADRs)

**Drug Allergies**
- Generally not dose-related
- Four types of allergic responses
  - **Type I**: Allergic reactions to stings and drugs
    - Symptoms range from mild rash to life-threatening anaphylaxis
    - Onset is immediate
  - **Type II**: Autoimmune reactions to drugs
  - **Type III**: Serum sickness, vasculitis
  - **Type IV**: Contact dermatitis from topical application
Adverse Drug Reactions (ADRs)

- **Side effects**
  - Unwanted effects of drugs that appear at normal doses required for a therapeutic response

- **Toxicity**
  - Unwanted effects of drugs that appear as drug dosage is increased beyond the dose required for a therapeutic response

Pharmacology: Practical Principles for Clinical Use
Pharmacokinetics

- The study of drug movements within an organism, particularly the rate of such movements, as affected by absorption, distribution, metabolism, and excretion (ADME); “the art of pharmacotherapeutics”
- “What the body does to the drug”
- Clinically, pharmacokinetics influences how much drug to give a patient, and how often to dose.

Standard Parameters of Pharmacokinetics

1. Clearance (CL)
2. Volume of Distribution (Vd)
3. Half-life

**Clearance (CL):**
- The volume of fluid cleared of drug per unit of time.
- Total clearance is the sum of renal and non-renal (primarily hepatic) routes of elimination.

**Volume of Distribution (Vd):**
- Fictitious proportionality constant between the total amount of drug in the body and the concentration of the drug in the plasma
  - A low volume of distribution indicates that a drug remains mostly within the circulatory system.
  - A high volume of distribution indicates that the drug is widely disseminated to various compartments, although it provides no information concerning the specific tissues in which a drug may be concentrated.
- Vd is highly dependent on certain properties of the drug, particularly protein binding.
Half-life (t1/2):

- If a drug follows so-called first order elimination processes, the half-life (t1/2) represents the time required for 50% of the drug dose to be removed from the body.

- If the drug is being administered on a routine basis and steady state, a relatively constant plasma concentration occurs after approximately 4-5 half-lives have elapsed.

- For most drugs, once administration is discontinued, the drug is eliminated in about 7 half-lives.

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The Plasma Concentration- Time Curve and AUC

Single Dosing Regimens:

- Typical plasma concentration-time curves after intravenous administration of a single dose show that upon infusion, drug concentration in the serum increases rapidly to peak, then gradually declines as the drug is distributed to peripheral tissues and is removed from the body.

- The area under the curve (AUC) is a pharmacodynamic parameter that represents the exposure of receptor to the drug.

- The AUC is the single best predictor of clinical efficacy.

  - This is particularly the case (and best documented) for the anti-infective drugs.
Pharmacology: Practical Principles for Clinical Use

**For effective drug levels:**
- A larger dose of the drug could be given at the same dosing interval
- The same dose could be administered more frequently or
- A similar drug with longer half-life could be used
  - The second or third options are the most favorable as increasing dose may increase side effects.
  - If the second option is used, consideration should be given as to whether increasing dosing frequency may decrease compliance.

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**Multiple Dosing Regimens:**
- Used to maintain drug serum concentration levels at a steady state.
- As the drug is distributed to tissues or is metabolized and excreted, its levels decrease in the serum.
- To maintain efficacy, the drug must be dosed again in the appropriate time interval (determined by the half-life of the drug).
Bioavailability and Bioequivalence

**Bioequivalence:**
- Compares different dosage forms of the same drug to determine if these reach the same AUC.
- Particularly important when comparing generic versus “trade name” drugs
- **Bioavailability** describes how much of the drug is available to interact with it receptor after dosing.
- With I.V. dosing, bioavailability is 100%.
  - Bioavailability shifts markedly in PO forms of drugs.
  - In this case, the drug is first absorbed via the portal circulation into the liver where a large fraction of it may be metabolized before it reaches the systemic circulation.
  - This “first-pass” effect determines the amount of drug per dose.
  - For several drugs, the first-pass effect is significant enough to markedly increase the oral dose versus the IV dose.

Pharmacology:
**Practical Principles for Clinical Use**

- **Protein Binding**
  - A highly (90%) protein bound drug can have three different outcomes:
    - decreased drug activity
    - effects on tissue distribution
    - effects on elimination
  - A highly bound drug is usually clinically ineffective, as only unbound drug can diffuse from the capillaries into the interstitial space of tissues where it works.
  - Only unbound drug can interact with receptors due to the “lock and key” fit drug molecules have with their specific receptors.
  - Protein binding also may affect elimination. Only unbound drug is filtered at the glomerulus, so protein binding slows elimination and prolongs half-life. Some protein bound drugs are actively secreted off of their plasma proteins into the proximal tubule. This effect usually negates the slowing of filtration of these drugs at the glomerulus.
Pharmacodynamics

Pharmacodynamics:
- The study of drug action at the receptor level
  - “What the drug does to the body”
  - A drug needs to bind to receptor molecules on or in a cell with sufficient avidity to disrupt normal cellular functions.

Drug receptors on or in cells are linked to biochemical processes in that particular cell.
- Four types:
  - Receptor-operated ion channels
  - G Protein-linked receptors
  - Enzyme receptors
  - DNA-linked receptors

Pharmacodynamics: Drug Receptors

- Receptor-operated ion channels:
  - Binding of an agonist opens these channels, and antagonists prevent opening.
  - Receptors include those for ACH (nicotinic), GABA, Glycine, 5 Hydroxytryptamine (5-HT) and Purine.
  - Effects at these receptors are seen within milliseconds.

- G Protein-linked receptors:
  - At rest, these receptors exist, linked in a complex fashion, to guanosine diphosphate (GDP).
  - When an agonist binds to the receptor, GDP is converted to GTP, which activates the G protein complex.
  - The result is a change in enzyme systems, including those that make cyclic nucleotides (including cAMP), inositol phosphate or diacylglycerol.
  - Cyclic AMP formation results in increased lipolysis, decreased glycogen synthesis, increased glycogen breakdown and increased calcium currents and release from the SR of cardiac cells.
  - Agonists at these receptors include autonomic agents such as epinephrine, norepinephrine, isoproterenol, etc.
  - Inositol phosphate and DAG formation result in a number of cellular processes.
  - Effects at these receptors are seen within seconds.
Pharmacodynamics: Drug Receptors

- **Enzyme receptors:**
  - One of the most common is tyrosine kinase.
  - When an agent binds to this enzyme, growth and metabolism are affected.
  - Guanylyl cyclase is another enzyme receptor found in cardiac atria.
  - Effects at these receptors are seen within minutes.

- **DNA-linked receptors:**
  - These are nuclear proteins that are intracellular.
  - Agonists must be lipid soluble to get across the cell membrane to interact with these receptors.
  - Once in the nucleus, they may regulate protein expression.
  - These agents take longer to work because of this mechanism—effects are seen over a period of hours.

Homework: Important Trivia

- What are “red flag” drugs in relation to therapeutic index? Provide examples.
- Why specifically do some drugs potentially work differently based on one’s race/ethnicity?
- What is the difference between a drug and a medication?
- Do generic drugs work the same as all others? Discuss.
- Describe the CYP450 system. Define polymorphisms, inhibition and induction.
- Locate the Top 100 (Medicare) drug list and the Top 200 drug list. Identify specific agents, and note similarities of each list.
- What is the Wal-Mart $4 drug list? How does it work? Give examples.
Homework: Important Trivia

- What is the difference between side effects and adverse effects? Give two examples.
- Differentiate between the four types of Medicare benefits. Contrast differences in Medicare and Medicaid. Identify how much Medicare reimbursement a nurse practitioner may receive in collaboration with a supervising physician?
- What does “highly protein bound” mean clinically? Give two examples.
- What are the top prescribed drugs in the United States? How many are there? Name at least 10.
- What is the difference between prescribing and furnishing medications?
- In California, how does a nurse practitioner obtain the privilege to furnish medications? What are the requirements? Outline the procedure.

The End