# Introduction to Pathophysiology and Pharmacology I

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Updated Jan 2019

## Important Concepts

- Pathology: Study of Disease
- Pathophysiology
  - Patho: suffering, disease
  - Physiology: function of body
  - Normal
  - Disease

## Development of Disease

- Etiology
- Pathogenesis
- Manifestations

## Etiology

- Inherited or familial
- Congenital
- Toxic
- Infectious
- Traumatic
- Degenerative


## Pathogenesis

- Natural History

## Manifestations/Clinical Features

- Morphology
- Subclinical
- Symptoms
- Signs
  - Lesion
- Sequela(e)
- Complications
- Resolution

## Important Concepts Cont

- Drug, Prodrug
- Pharmacology
- Pharmacotherapeutics
- Effectiveness
- Safety: Therapeutic Range and Index
- Selectivity
- Reversible action
- Predictability
- Administration

## Important Concepts Cont

- Interactions
- Cost
- Chemical Stability
- Name: Generic, Trade, Chemical, Experimental
- Therapeutic Objective

## Intensity of Drug Response

- Administration
  - Route
  - Medication errors
  - Patient Compliance
- Pharmacokinetics
  - Absorption
  - Distribution
  - Metabolism
  - Excretion


## Intensity of Drug Response

- Pharmacodynamics
  - Drug-receptor interaction
  - Patient's functional state
  - Placebo effects
- Individual Variation
  - Physiologic variables
  - Pathologic Variables
  - Genetic variables
  - Drug interactions

## Nursing Responsibilities (the pitcher and the catcher)

- Pre-administration assessment
  - Baseline data
  - Stratification of risk
- Planning and Implementation: Dosage and Administration
  - Five (hundred) Rights
  - Understand the correct dosing range
  - Appropriate safety measures

## Nursing Responsibilities

- Evaluating and Promoting Therapeutic Effect
  - Evaluating Therapeutic Response
  - Promoting compliance/adherence
  - Implementing non-drug measures
- Minimize Adverse Effects
- Minimize Adverse Interactions
- PRN decisions
- Managing Toxicity
- Patient education

## Approval of Drugs: Drug Legislation

- 1906: A drug must be what it says it is
- 1938: Drugs must be tested for safety and approved by FDA
- 1962: Drugs must be effective for what they claim: testing procedures
- 1970: Controlled Substances Act
- 1992: Relaxed procedures for Cancer and AIDS drugs
- 1997: FDA Modernizing Act
  - Fast track for AIDS, cancer, and other life threatening conditions
  - Manufacturers must give 6 month notice before discontinuing a drug
  - FDA can require testing in children
  - Clinical trial database
  - Drug companies can provide physicians with articles on "off-label" uses

## Drug Approval: Process

- Preclinical testing
  - Toxicity
  - Pharmacokinetics
  - Possible Useful Effects
- Clinical Testing (in Humans)
  - Phase I: Normal subjects; metabolism and side effects
  - Phase II: Patients, therapeutic utility and dosage range
  - Phase III: Patients; safety and effectiveness
  - Conditional Approval
  - Phase IV: Postmarketing Surveillance
- Limitations of Process
  - Women and children
  - Failure to detect all adverse effects

## Drug Names

- Chemical (N-acetyl-para-aminophenol)
- Generic (acetaminophen)
- International name (paracetamol)
- Trade Name (Tylenol)

## Trade (Brand) Name Problems

- Easier to remember
- Frequent Emotional allusions
  - Viagra
  - Abilify
- Multiple trade names for one drug
- Same trade name with more than one product

## Availability

- OTC
- Legend
- Scheduled
  - V: Least dangerous & addictive (Lomotil)
  - IV: Less D&A (Ambien, Xanax)
  - III: D&A: hydrocodone, codeine
  - II: highly D&A: morphine, cocaine
  - I: dangers outweigh benefits: marijuana, heroin

## Ways to cross a cell membrane

- Channels and Pores
- Transport systems
- Direct penetration of membrane – must be lipid soluble
  - Polar molecules
  - Ions

## Pharmacokinetics

- Absorption – movement of drug from site of administration to blood
  - Rate of dissolution
  - Surface area
  - Blood flow
  - Lipid solubility
  - pH partitioning
- Distribution
- Metabolism
- Excretion

## Absorption: Routes of Administration

- Enteral – gastrointestinal (mouth, rectum, tubes)
- First Pass Effect
- Parenteral – injection (IM, IV, SC)
- Topical
- Transdermal
- Inhaled
- Vaginal

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## Drug Distribution

- Blood flow to tissues
- Exiting the Vascular system
  - Typical Capillary Beds
  - Blood-Brain Barrier
  - Placental Drug Transfer
  - Protein Binding
  - Entering Cells

## Metabolism

- Hepatic Drug-Metabolizing System
- P450 cytochrome system
  - hepatic microsomal enzyme system
- Therapeutic Consequences of Drug Metabolism
  - Accelerated Renal Drug Excretion
  - Drug Inactivation
  - Increased Therapeutic Action
  - Activation of prodrug
  - Increased or Decreased Toxicity

## Metabolism

- Considerations
  - Inductions of P450 system
  - Competition between drugs
  - First Pass Effect
  - Nutritional status

## Example P450 Drugs

| | Metabolization | Induction | Inhibition |
|---|---|---|---|
| Carbamazepine | CYP3A4 CYP2C8 | CYP2C9 CYP3A4 | |
| Clonazepam | CYP3A4 | | |
| Diazepam | CYP2C19 CYP3A | | |
| Ethosuximide | CYP3A4 CYP2E CYP2B CYP2C | | |
| Felbamate | CYP3A4 CYP2E1 | CYP3A4 | CYP2C19 β-oxidation |
| Lamotrigine | UGT | UGT (weak) | |
| Oxcarbazepine | | CYP3A4 CYP3A5 | CYP2C19 |
| Phenobarbital | CYP2C9 CYP2C19 CYP2E1 | CYP2C9 CYP3A4 UGT | |
| Phenytoin | CYP2C9 CYP2C19 | CYP2C9 CYP3A4 UGT | CYP2C9 |
| Primidone | | CYP2C9 CYP3A4 UGT | |
| Tiagabine | CYP3A4 | | |
| Topiramate | | β-oxidation | CYP2C19 |
| Valproic acid | CYP2C9 CYP2C19 β-oxidation UGT CYP2A6 | | CYP2C9 UGT |
| Zonisamide | CYP3A | | |

UGT, uridine diphosphate glucuronosyltransferase.

## Drug Excretion

- Removal of Drug from the body (urine, sweat, bile, saliva, breast milk, lungs)
  - Renal Drug Excretion
    - Glomerular Filtration
    - Passive Tubular Reabsorption
    - Active Tubular Secretion
  - Breast Milk
  - Bile

## Renal Function

- Serum Creatinine levels
  - Produced at constant rate by muscle
  - Excreted at constant rate by kidneys
  - Unreliable in “elderly”
- Creatinine Clearance
  - 24 hour urine
  - Estimated
    - Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72)
    - Sex: Male = 1;  Female = 0.85

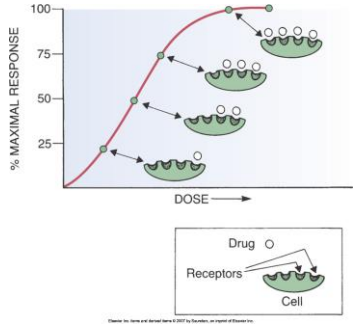
## Pharmacogenetic Testing (PGx)

- Predicting drug response based on patient’s genetic profile
- Largely determined by
  - P450 enzymes (metabolism)
  - Transporter Mechanisms
    - Absorption
    - Distribution
    - Excretion
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3791676/

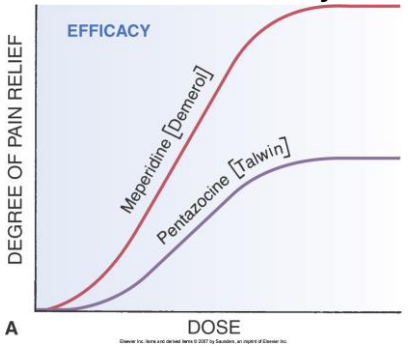
## Pharmacodynamics

- Dose – Response Relationships
  - Maximal Efficacy
  - Potency
- Drug – Receptor Interactions
  - Receptor-Types
  - Selectivity
  - Theories
  - Mode of Action

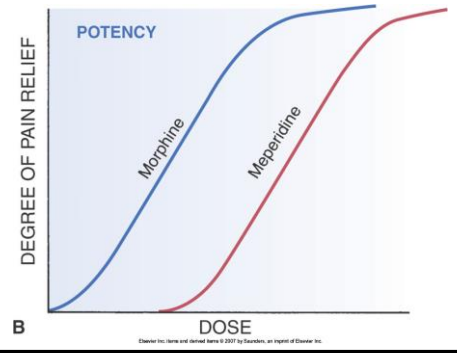
## Dose Response




## Maximal Efficacy



## Potency

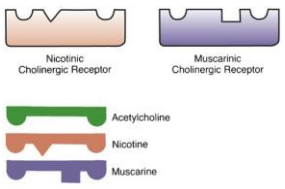



## Mode of Action

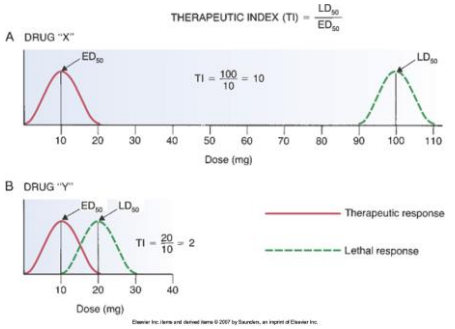
- Agonists
- Antagonists
- Partial Agonists
- Regulation of Sensitivity

- Selectivity
- Lock and key

## Example of Receptor Selectivity




## Therapeutic Index




## Drug Interactions

- Drug-Drug Interactions
  - Intensification: Effect and/or Adverse Effects
  - Reduction
- Food-Drug Interaction
  - Absorption
  - Metabolism
  - Toxicity
  - Action
- Food-Herb Interactions

## Adverse Effects

- Side Effect
- Toxicity
- Allergic Reaction
- Idiosyncratic
- Iatrogenic
- Withdrawal Syndrome
- Carcinogenic
- Teratogenic

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## Medication Errors

- Any preventable event that may cause or lead to inappropriate medication use or harm
- 13 types of errors (see Table 7-3, pg 67)
- Causes of Medication Errors (90%)
  - Human factors
    - Performance deficits (30%)
    - Knowledge deficits (14%)
    - Miscalculation of doses (13%)
  - Communication Mistakes (15%) – handwriting, confusing abbreviations, decimals, apothecary vs. metric units
  - Name Confusion