General Pharmacology

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Introduction to Pharmacology

- **The Drug**

  A drug is any chemical agent used in the treatment, prevention, or diagnosis of disease (biologically active substance) because of it's interaction with living processes.

- **Treatment might be:**
  - Curative (e.g. antibiotics treating bacterial infections)
  - Suppressive (e.g. treatment of diabetes or hypertension)

Introduction to Pharmacology

- **Prevention or prophylaxis:**

  e.g. malaria, aspirin after myocardial infarction

- **Diagnosis:**

  e.g. edrophonium (short-acting anticholinesterase) in the diagnosis of myasthenia gravis

Sources of Drugs

1. Natural sources

- From animals (e.g. Insulin)
- From plants (e.g. morphine from opium)

2. Semi-synthetic

e.g. aspirin from salicylates

3. Synthetic

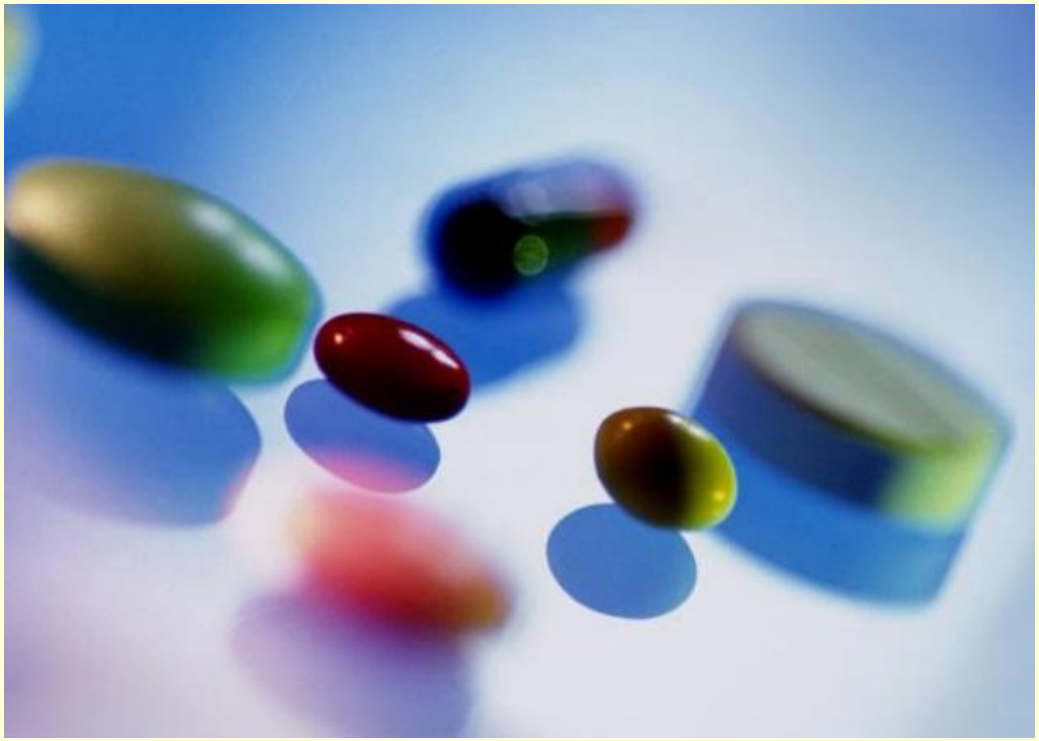
e.g. Most of recent drugs

IDEAL DRUG PROPERTIES

Characteristics of ideal drug:

Three most important:

- Effectiveness
- Safety
- Selectivity



IDEAL DRUG PROPERTIES

Other important properties:

- Reversible action
- Ease of Administration
- Predictability
- Freedom from drug interactions
- Low cost
- Generic Name ease

THERAPEUTIC OBJECTIVE

- Maximum Benefit
- Minimum Harm

INTENSITY OF DRUG RESPONSES

Depends on:

- Administration
- Pharmacokinetics
- Pharmacodynamics
- Individual variations

PHARMACOKINETICS

Body's impact on the drug.

How much of the dose gets to the site of action.

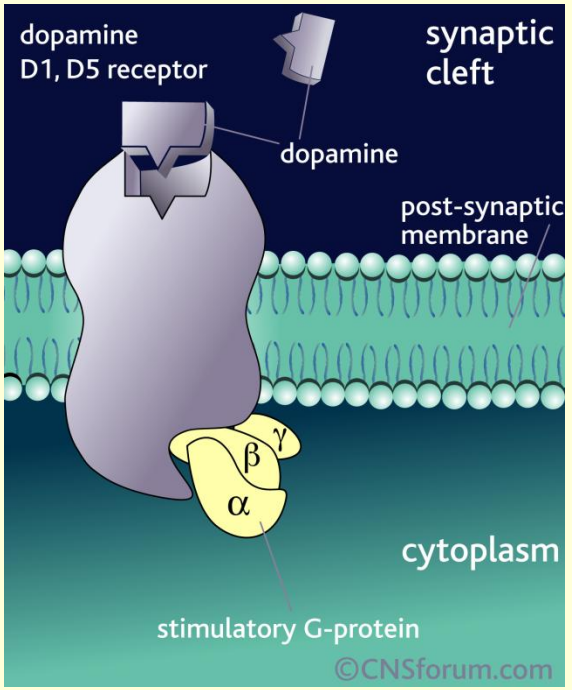
Depends on:

- Absorption
- Distribution
- Metabolism
- Excretion

PHARMACODYNAMICS

Impact of drug on the body:

- At site of action
- Influenced by patient's functional state



INDIVIDUAL VARIATION

Sources of Individual Variation Include

- Age
- Gender
- Weight
- Genetic Factors

The Life Cycle of a Drug (pharmacokinetics)

– The process by which a drug is absorbed, distributed, metabolized and eliminated by the body

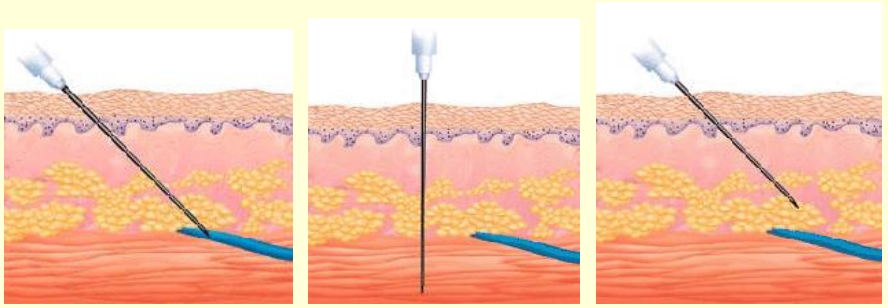
- Absorption
- Distribution
- Metabolism
- Excretion

Slow Absorption

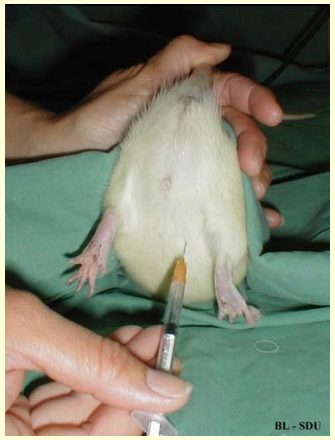
- Orally (swallowed)
- through Mucus Membranes
  - Oral Mucosa (e.g. sublingual)
  - Nasal Mucosa (e.g. sniffed)
- Topical/Transdermal (through skin)
- Rectally (suppository)

Faster Absorption

- Parenterally (injection)
  - Intravenous (IV)
  - Intramuscular (IM)
  - Subcutaneous (SC)
  - Intraperitoneal (IP)



- Inhaled (through lungs)



Fastest Absorption

- Directly into brain
  - Intracerebral (into brain tissue)
  - Intracerebroventricular (into brain ventricles)

General Principle: **The faster the absorption, the quicker the onset, the higher the addictiveness, but the shorter the duration**

Absorption: Solubility

- Water- soluble
  - Ionized (have electrical charge)
  - Crosses through pores in capillaries, but not cell membranes
- Lipid (fat) - soluble
  - Non-ionized (no electrical charge)
  - Crosses pores, cell membranes, blood-brain-barrier

Dissociation constant or pKa → indicates the pH where 50% of the drug is ionized (water soluble) and 50% non-ionized (lipid soluble);

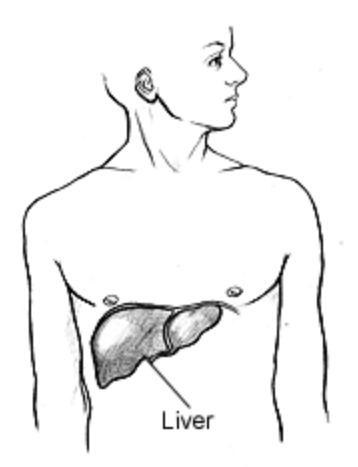
$$pKeq = pH + \log [X]_{ionized}/[X]_{non\text{-}ionized}$$

This affects a drug's solubility, permeability, binding, and other characteristics.

Bioavailability

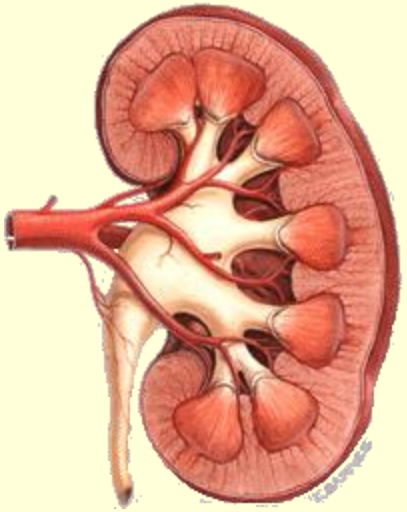
- The fraction of an administered dose of drug that reaches the blood stream.
- What determines bioavailability?
  - Physical properties of the drug (hydrophobicity, pKa, solubility)
  - The drug formulation (immediate release, delayed release, etc.)
  - If the drug is administered in a fed or fasted state
  - Gastric emptying rate
  - Circadian differences
  - Interactions with other drugs
  - Age
  - Diet
  - Gender
  - Disease state

Degradation & Excretion



- **Liver**
  - Enzymes(cytochrome P-450) transform drugs into more water-soluble metabolites
  - Repeated drug exposure increases efficiency → tolerance

- **Kidneys**
  - Traps water-soluble (ionized) compounds for elimination via urine (primarily), feces, air, sweat



Excretion: Other routes

- Lungs
  - alcohol breath
- Breast milk
  - acidic ---> ion traps alkaloids
  - alcohol: same concentration as blood
  - antibiotics
- Also bile, skin, saliva ~~

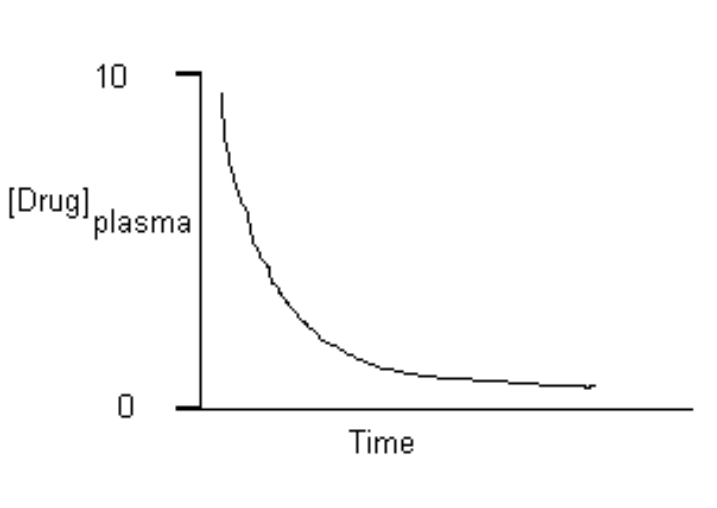
Metabolism and Elimination

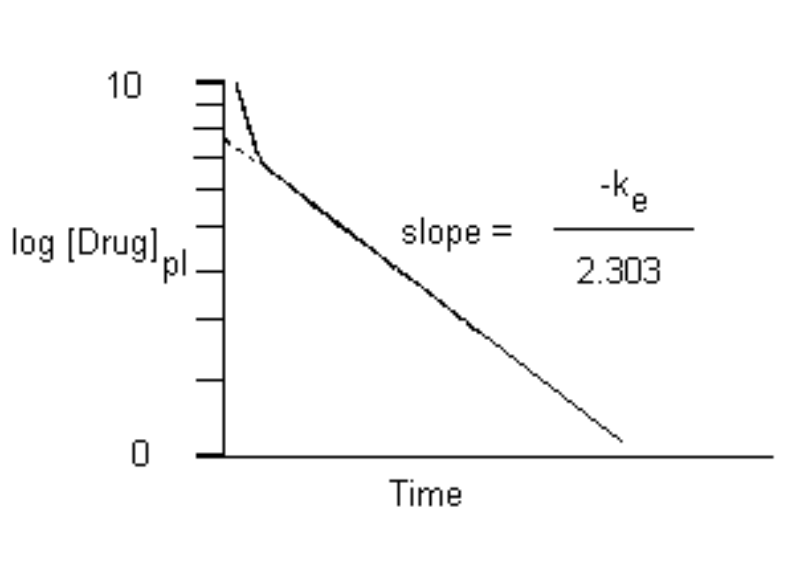
- Half-lives and Kinetics
  - Half-life:
    - Plasma half-life: Time it takes for plasma concentration of a drug to drop to 50% of initial level.
    - Whole body half-life: Time it takes to eliminate half of the body content of a drug.
  - Factors affecting half-life
    - age
    - renal excretion
    - liver metabolism
    - protein binding

First order kinetics

A constant *fraction* of drug is eliminated per unit of time.

When drug concentration is high, rate of disappearance is high.





Zero order kinetics

Rate of elimination is constant.

Rate of elimination is independent of drug concentration.

Constant *amount* eliminated per unit of time.

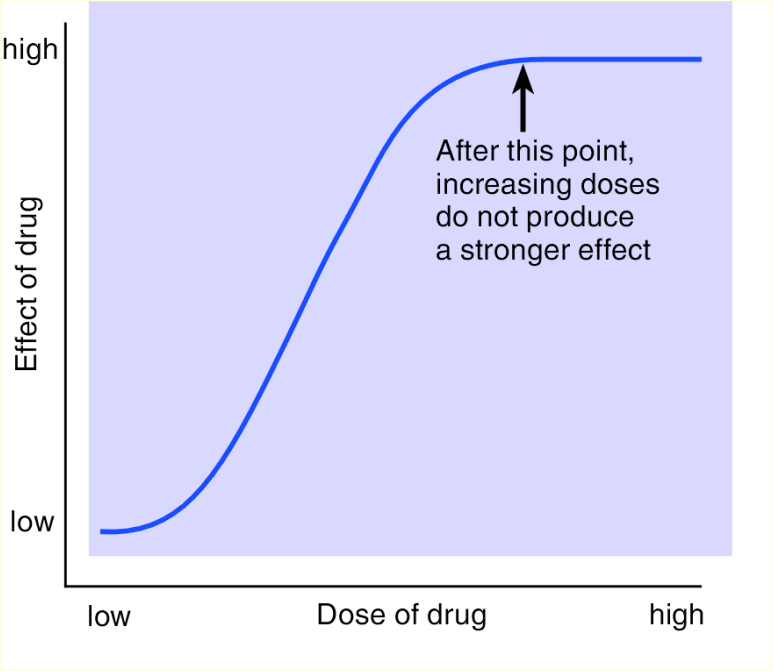
Example: Alcohol

Comparison

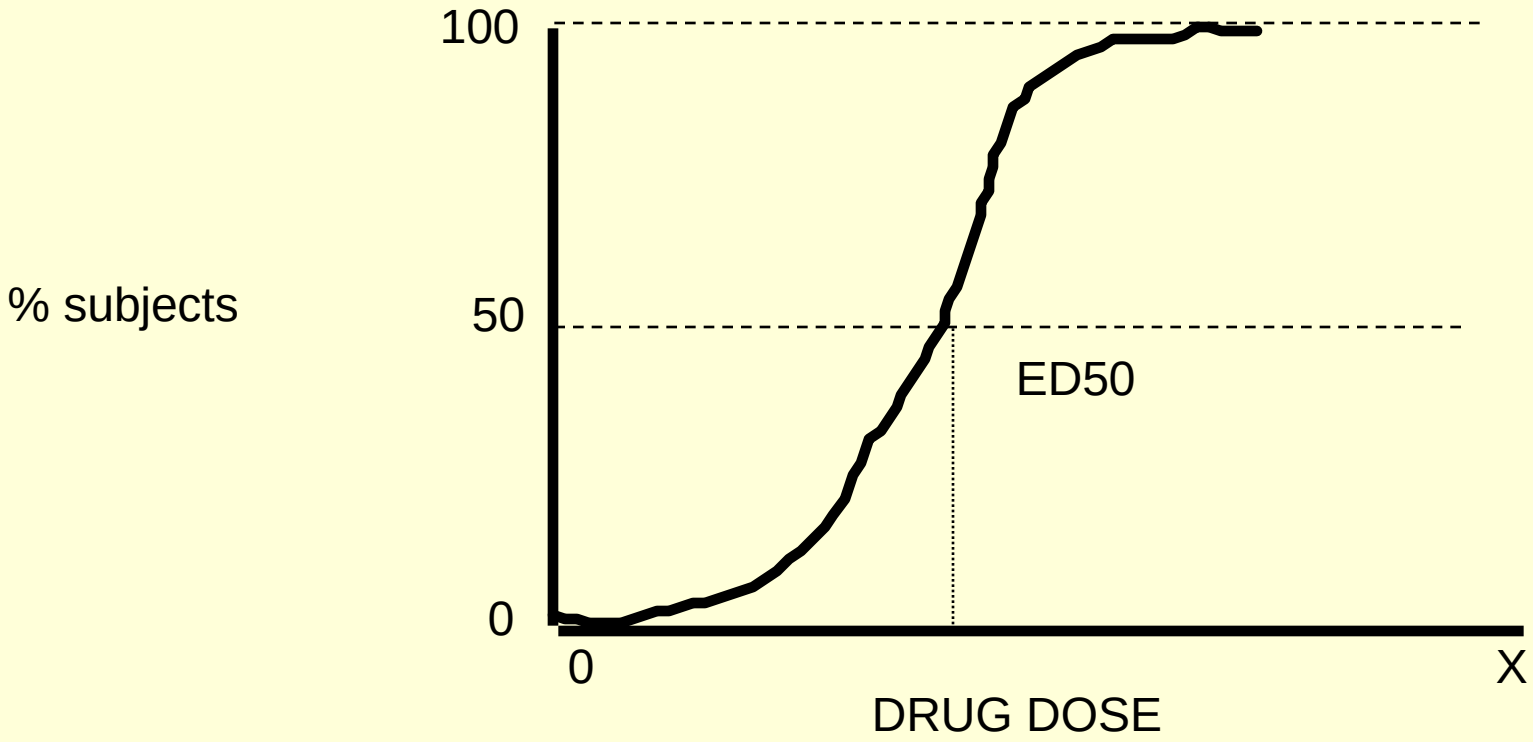
- First Order Elimination
  - [drug] decreases exponentially with time
  - Rate of elimination is proportional to [drug]
  - Plot of log [drug] or ln[drug] vs. time are linear
  - $t_{1/2}$ is constant regardless of [drug]
- Zero Order Elimination
  - [drug] decreases linearly with time
  - Rate of elimination is constant
  - Rate of elimination is independent of [drug]
  - No true $t_{1/2}$

Drug Effectiveness

- Dose-response (DR) curve
  - Depicts the relation between drug dose and magnitude of drug effect
- Drugs can have more than one effect
- Drugs vary in effectiveness
  - Different sites of action
  - Different affinities for receptors
- The effectiveness of a drug is considered relative to its safety (therapeutic index)

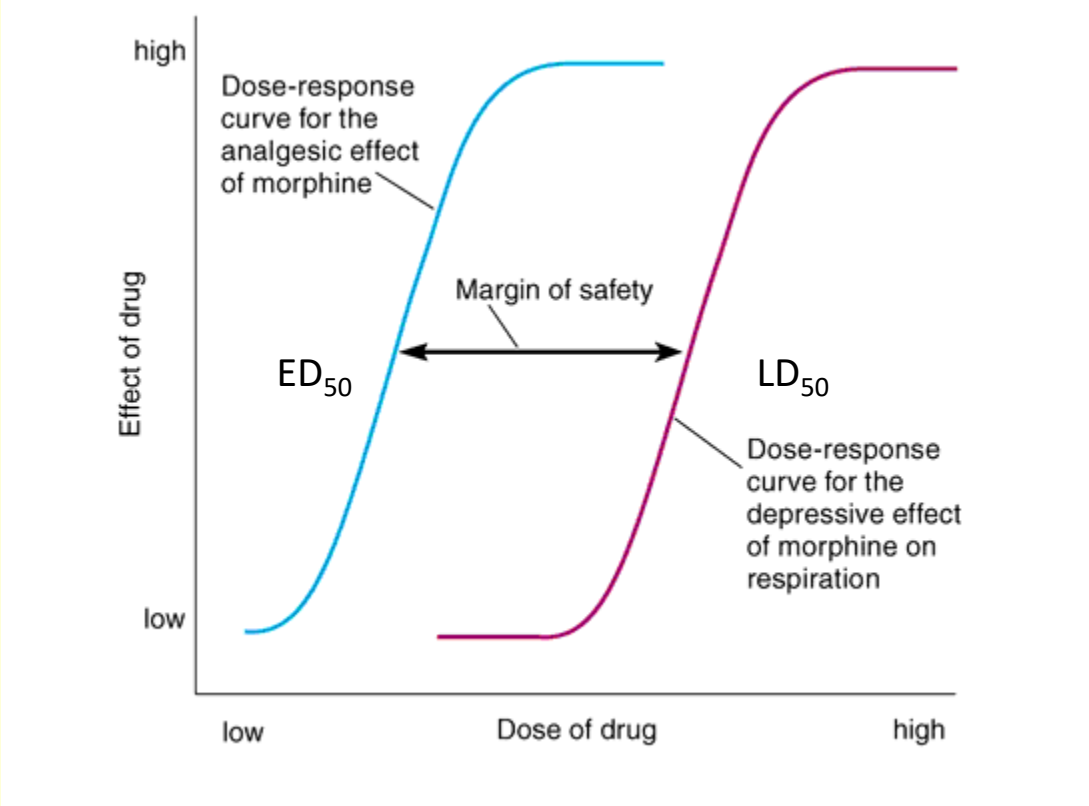


ED_{50} = effective dose in 50% of population



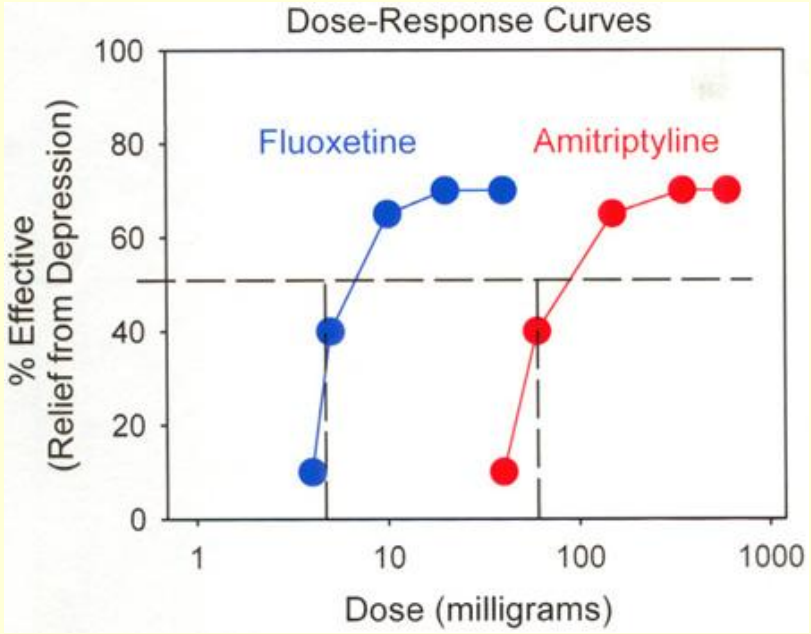
Therapeutic Index

- Effective dose (ED_{50}) = dose at which 50% population shows response
- Lethal dose (LD_{50}) =dose at which 50% population dies
- TI = LD_{50}/ED_{50}, an indication of safety of a drug (higher is better)

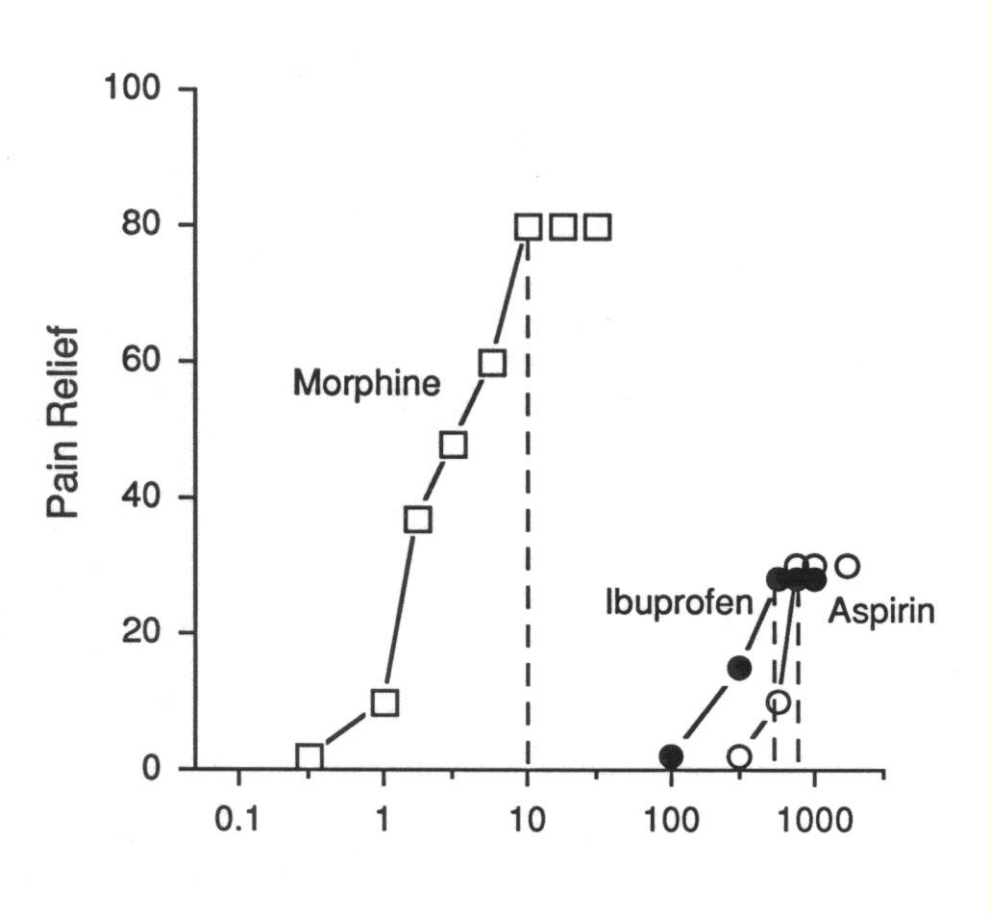


Potency

- Relative strength of response for a given dose
  - Effective concentration (EC_{50}) is the concentration of an agonist needed to elicit half of the maximum biological response of the agonist
  - The potency of an agonist is inversely related to its EC_{50} value
- D-R curve shifts left with greater potency

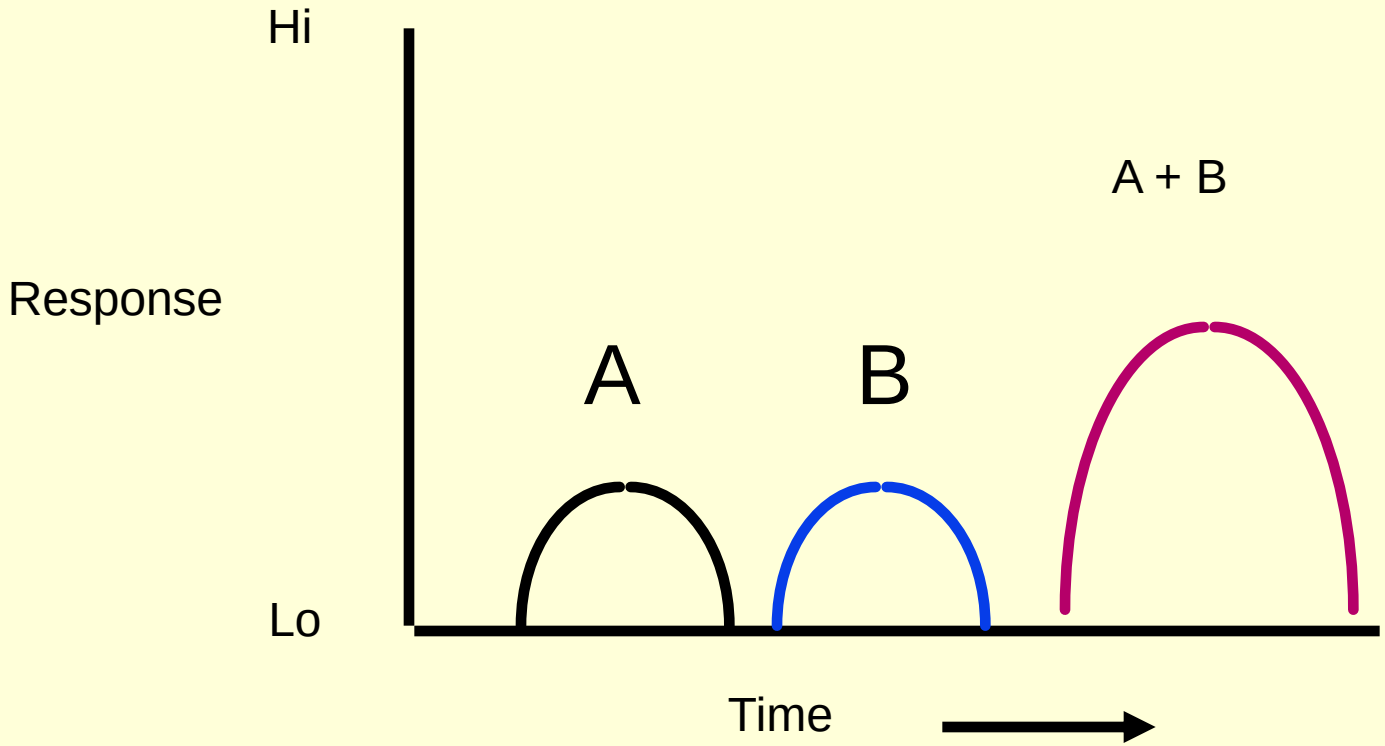


Efficacy



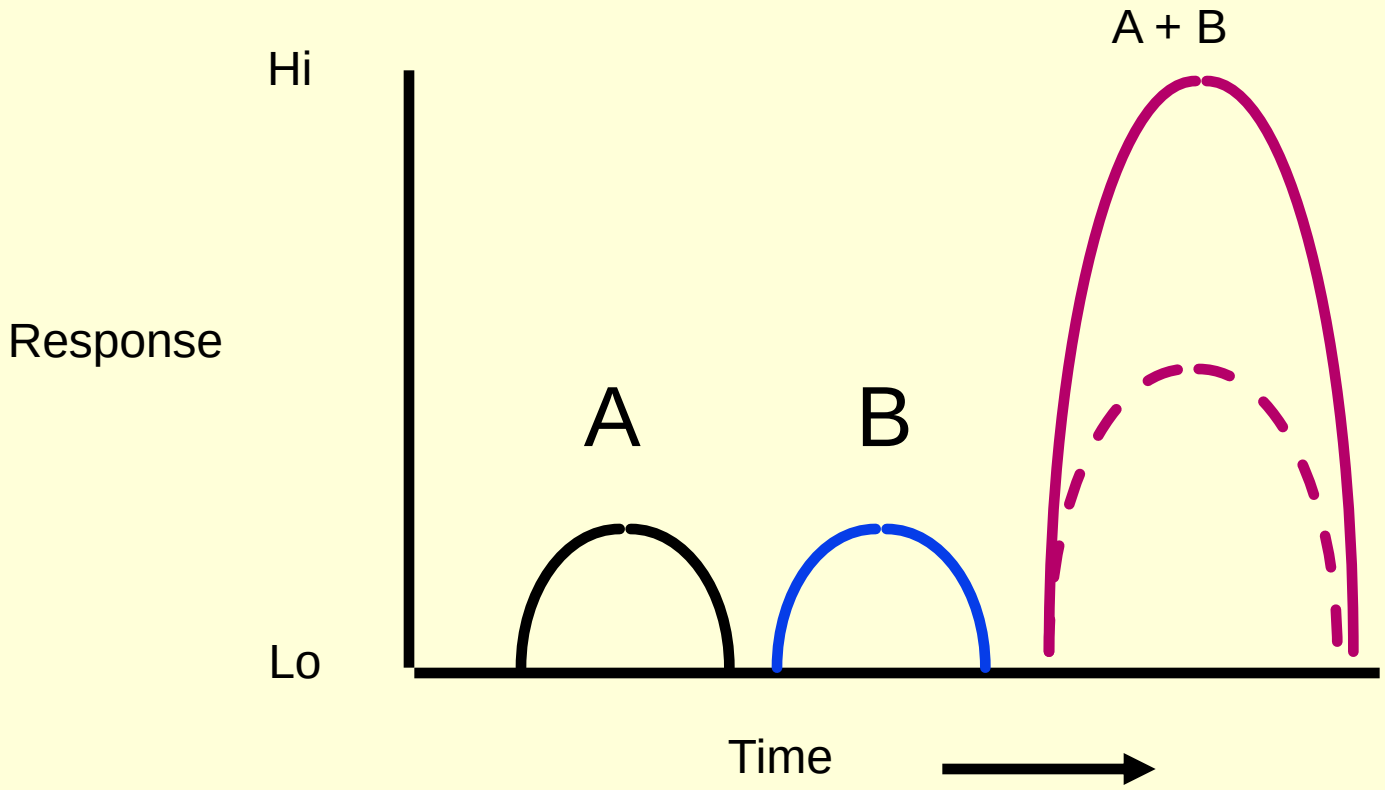
- Maximum possible effect relative to other agents
- Indicated by peak of D-R curve
- Full agonist = 100% efficacy
- Partial agonist = 50% efficacy
- Antagonist = 0% efficacy

Additive Effects



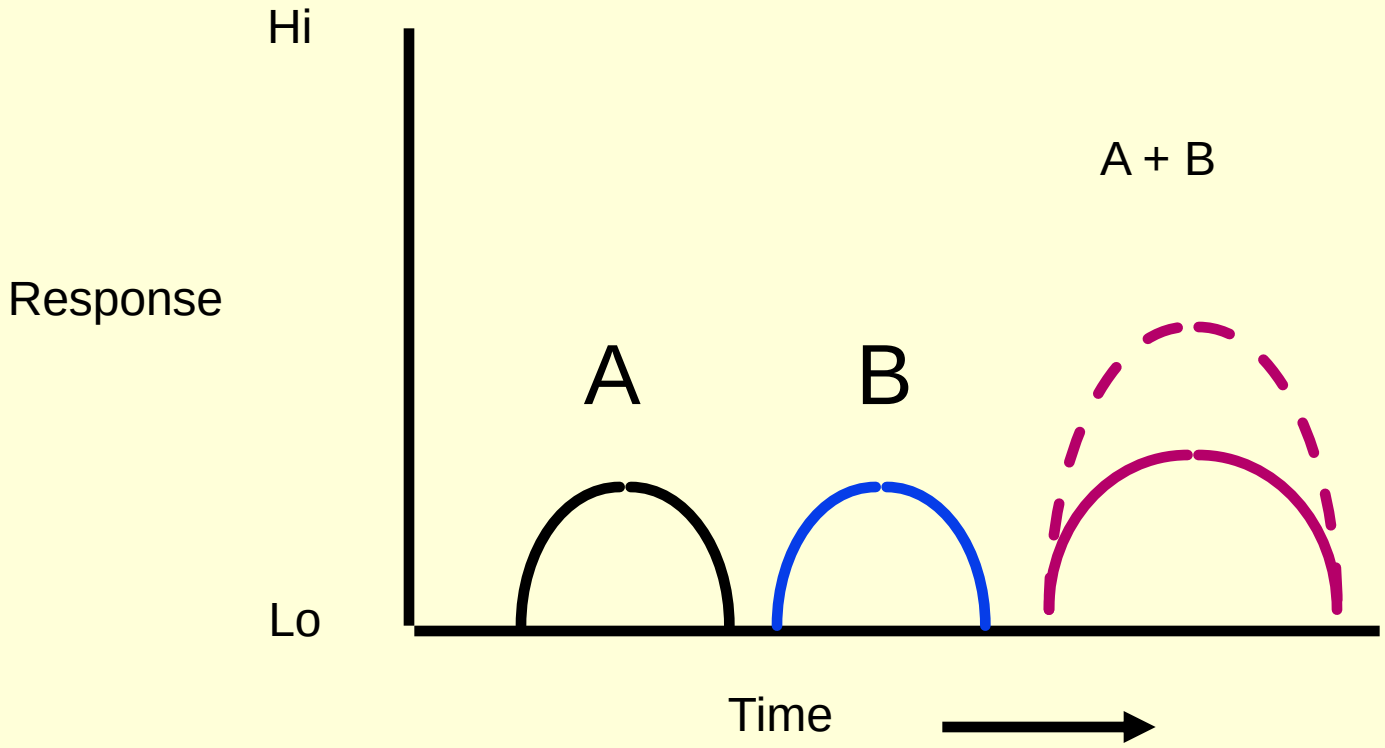
The effect of two chemicals is equal to the sum of the effect of the two chemicals taken separately, eg., Aspirin and Motrin.

Synergistic Effects



The effect of two chemicals taken together is greater than the sum of their separate effect at the same doses, e.g., alcohol and other drugs

Antagonistic Effects



The effect of two chemicals taken together is less than the sum of their separate effect at the same doses

Pharmacodynamics

- Receptor
  - target/site of drug action (e.g. genetically-coded proteins embedded in neural membrane)

- Lock and key or induced-fit models
  - drug acts as key, receptor as lock, combination yields response
  - dynamic and flexible interaction