Course: *Toxicology, Path-438*

# Pharmacology Basics:

## *Biological Half Life, Potency, Efficacy, Effectiveness, Therapeutic Index*

## Learning Objectives:

- List the phases of the life cycle of a drug in human body.
- Describe the routes of administration of drugs.
- Define the terms: Bioavailability, half life, drug effectiveness, tolerance, efficacy, therapeutic index, potency, agonist, antagonist.
- List the factors affecting bioavailability.
- List the routes of drug excretion.
- List the factors affecting drug half life.

## Definitions:

- **Toxicology**: is the study of the adverse effects of chemical or physical agents on living organisms.

- **Pharmacology:** is the branch of medicine and biology concerned with the study of drug action.

- **Pharmacokinetics**: The process by which a drug is ***absorbed, distributed, metabolized*** and ***eliminated*** by the body.

- **Pharmacodynamics**: The ***interactions*** of a drug and the receptors responsible for its action in the body.

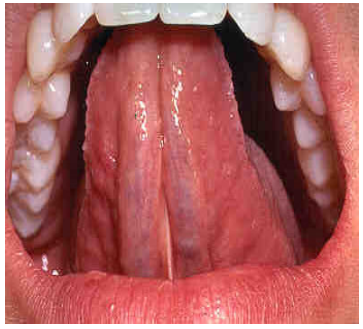
## The Life Cycle of a Drug (pharmacokinetics):

- Absorption
- Distribution
- Degradation/Metabolism
- Excretion

# Slow Absorption:

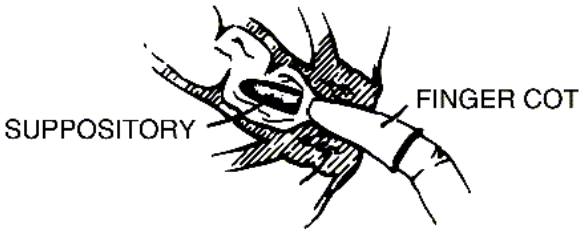
- **Orally (swallowed)**


- **Through Mucus Membranes**
  - Oral Mucosa (e.g. sublingual)
  - Nasal Mucosa (e.g. insufflated)



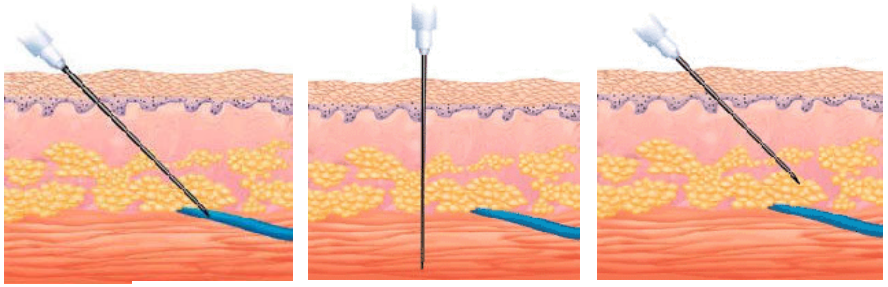
- **Topical/Transdermal**
  (through skin)

- **Rectally** (suppository)



# Fast Absorption:

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



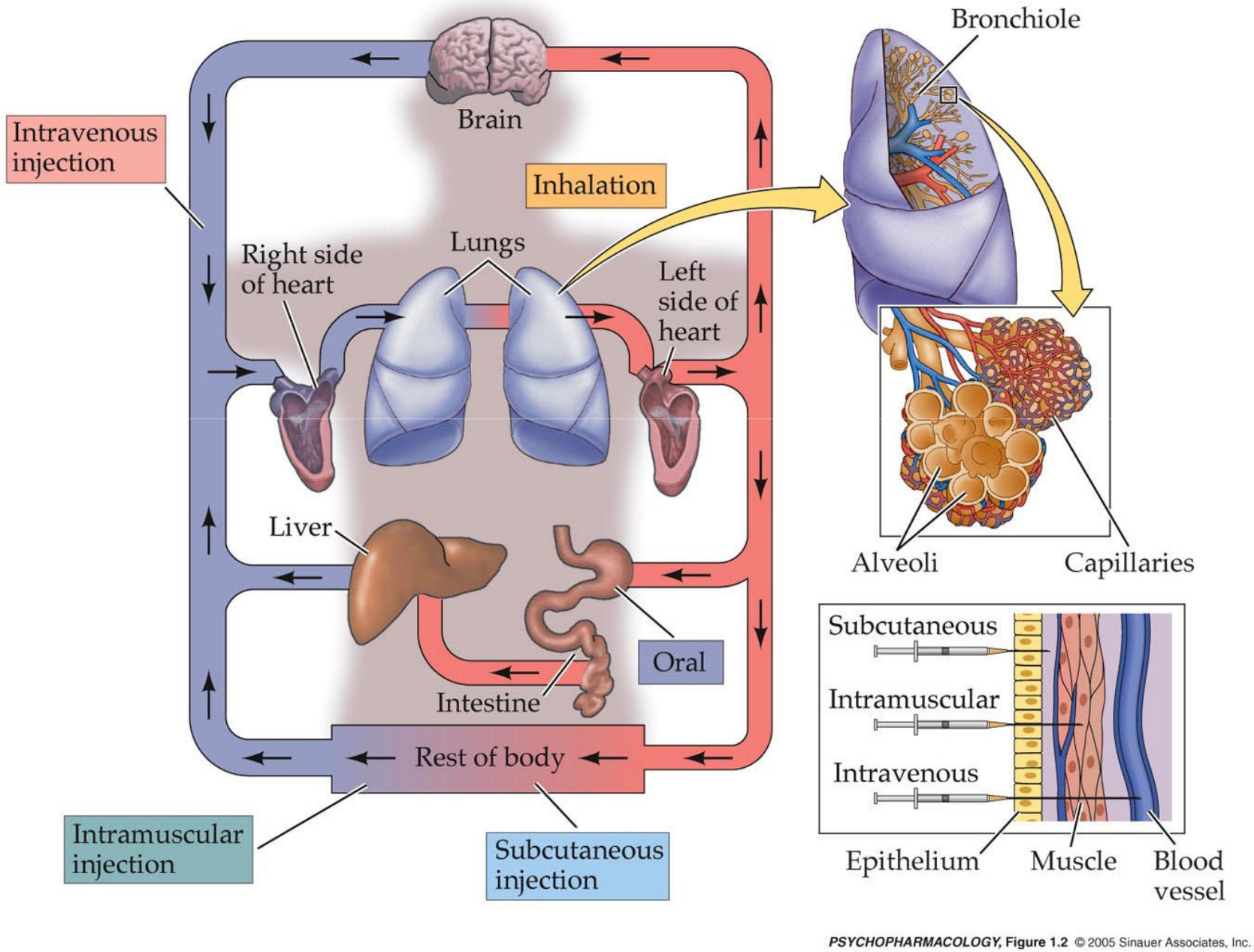
- **Inhaled (through lungs)**

- **Directly into brain:**
  - **Intracerebral (into brain tissue)**


  - **Intracerebroventricular (into brain ventricles)**

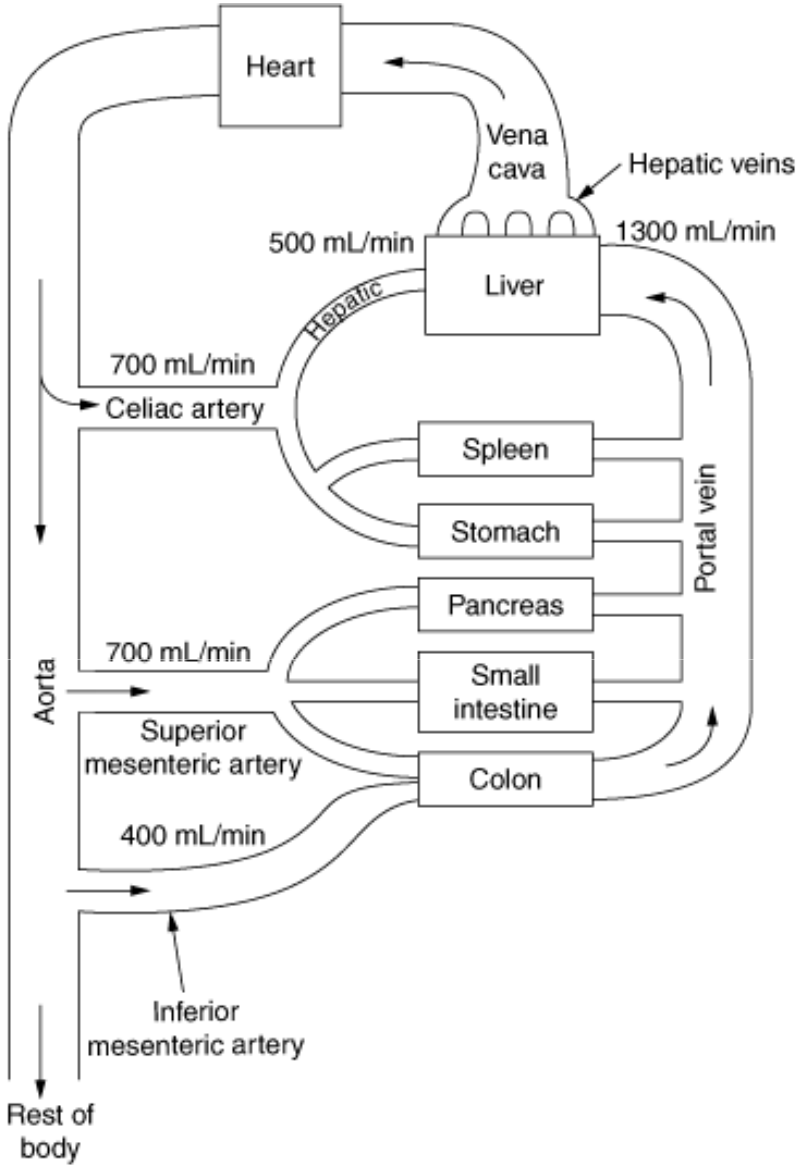
***General Principle:*** ***The faster the absorption, the quicker the onset, the higher the addictiveness, but the shorter the duration***

# Routes of Administration:




*PSYCHOPHARMACOLOGY*, Figure 1.2 © 2005 Sinauer Associates, Inc.

# GIT Circulation:




*Branches of the hepatic artery also supply the stomach, pancreas and small intestine

## Bioavailability & Bioequivalence:

- ***Bioavailability is the fraction of an administered dose of drug that reaches the blood stream.***

- **Factors that influence bioavailability:** In contrast to IV administration (100% bioavailability), oral administration of a drug often involves ***first-pass metabolism***. This biotransformation, in addition to the ***drug's chemical and physical characteristics***, determines the amount of the agent that reaches the circulation and a what rate.

- ***Bioequivalence: Two related drugs are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.***

## Bioavailability - *Factors that influence bioavailability:*

- **First-pass hepatic metabolism:** After absorption of the drug through GIT it enters portal circulation and then it is rapidly metabolized in the liver or gut wall during this initial passage. So the amount of unchanged drug gaining access to the circulation is decreased. e.g. 90% of Nitroglycerine is cleared by this mechanism if it is given orally and thus it should be given sublingually.

- **Solubility of the drug:** Very hydrophilic drugs are poorly absorbed (they cannot cross lipid rich membranes), also extremely hydrophobic drugs are totally insoluble in aqueous fluids and are poorly absorbed. The drug must be largely hydrophobic, yet have some solubility in aqueous solutions (that is why many drugs are either weak acids or weak bases).

- **Chemical instability:** Some drugs, such as penicillin G, are unstable in the pH of the gastric contents. Others, such as Insulin are destroyed in the GIT by the digestive enzymes.

- **Nature of drug formulation:** Particle size, salt form, crystal polymorphism, enteric coatings..etc can alter the rate of absorption.

# Depot Binding (accumulation in fatty tissue):

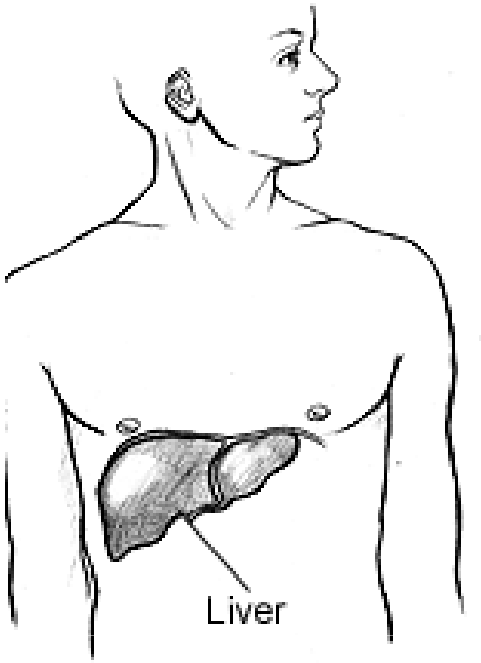
- Drugs bind to "***depot sites***" or "***silent receptors***" (fat, muscle, bones, etc).

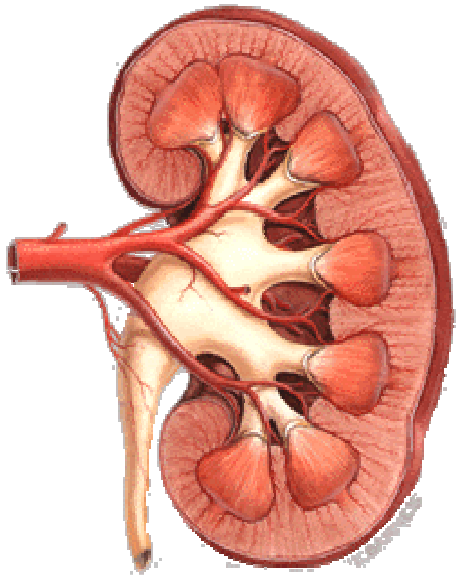
- Depot binding ***reduces bioavailability, slows elimination, can increase drug detection window***.

- Depot-bound drugs can be ***released during sudden weight loss*** – may account for ***flashback experiences***.

# Degradation & Excretion

- **Liver:**
  - Enzymes(cytochrome P-450) transform drugs into more water-soluble metabolites.
  - Repeated drug exposure increases efficiency → ***tolerance*** *(Tolerance is a reduced response to repeated administration of the same dose or increase in the dose are required to produce the same magnitude of response).*
- **Kidneys:**
  - Traps water-soluble (ionized) compounds for elimination via urine (primarily).
- **Clearance by other routs**: feces, air, bile, sweat, breast milk.



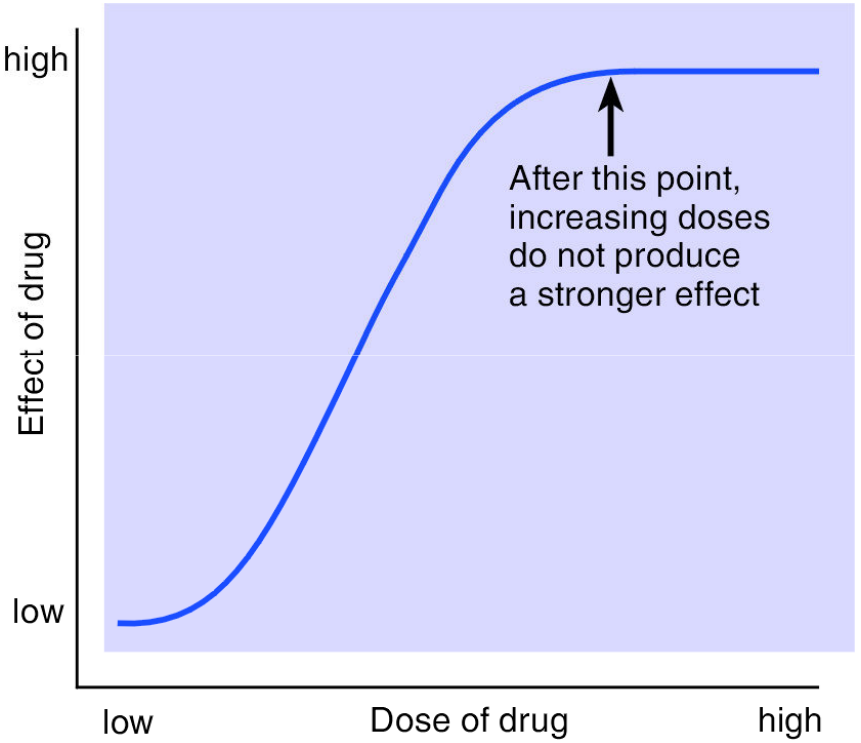
## Half-lives and Kinetics:

- **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 (increased half life in infants and elderly).
  - Renal excretion.
  - Liver metabolism.
  - Protein binding.

# Drug Effectiveness:

- **Dose-Response (DR) curve:**
  - Depicts the relation between drug dose and magnitude of drug effect.

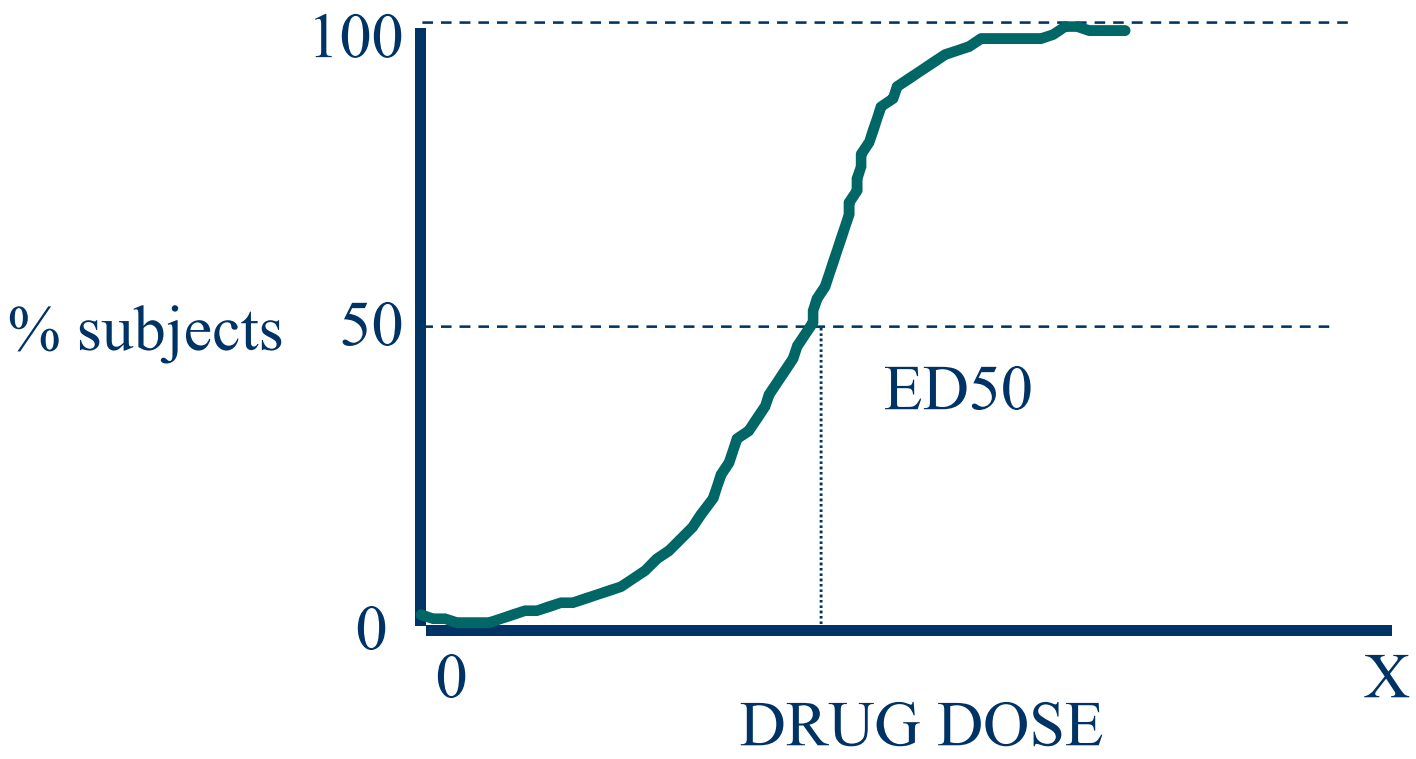



- Drugs can have more than one effect.
- Drugs vary in effectiveness:
  - Different sites of action.
  - Different affinities for receptors.
- The effectiveness of a drug is considered relative to its safety (***therapeutic index***).

# Drug Effectiveness:

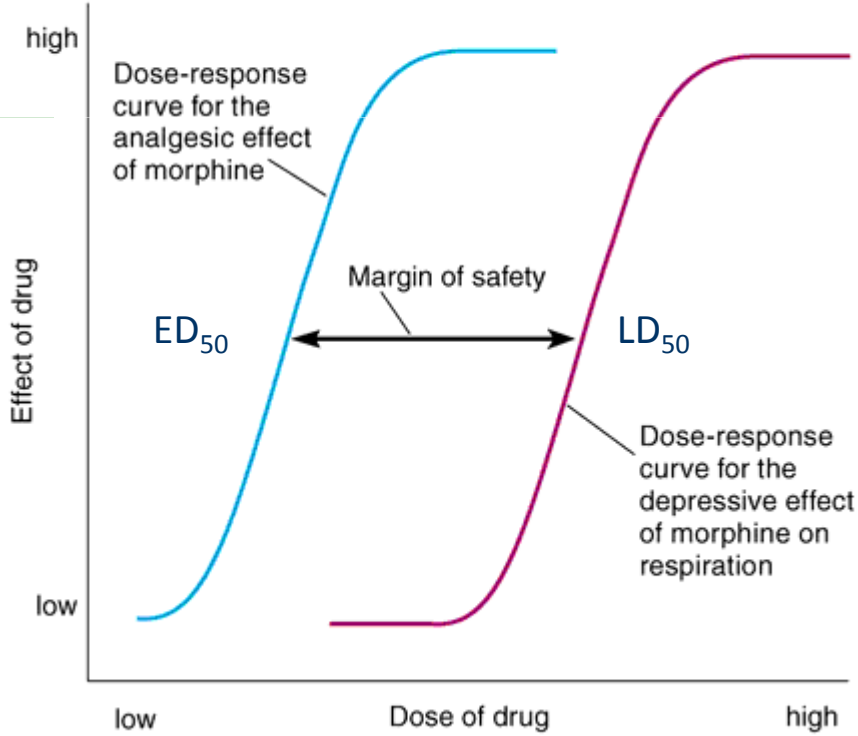
**Drug effectiveness:** Refers to the ability of a drug to produce a beneficial effect.

**Effective dose ($ED_{50}$) = effective dose in 50% of population**



# Therapeutic Index (TI):

- **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**).*




- **Therapeutic index = toxic dose/effective dose.**
- **This is a measure of a drug's safety:**
  - **A large number = *a wide margin of safety.***
  - **A small number = *a small margin of safety .***

# Potency:

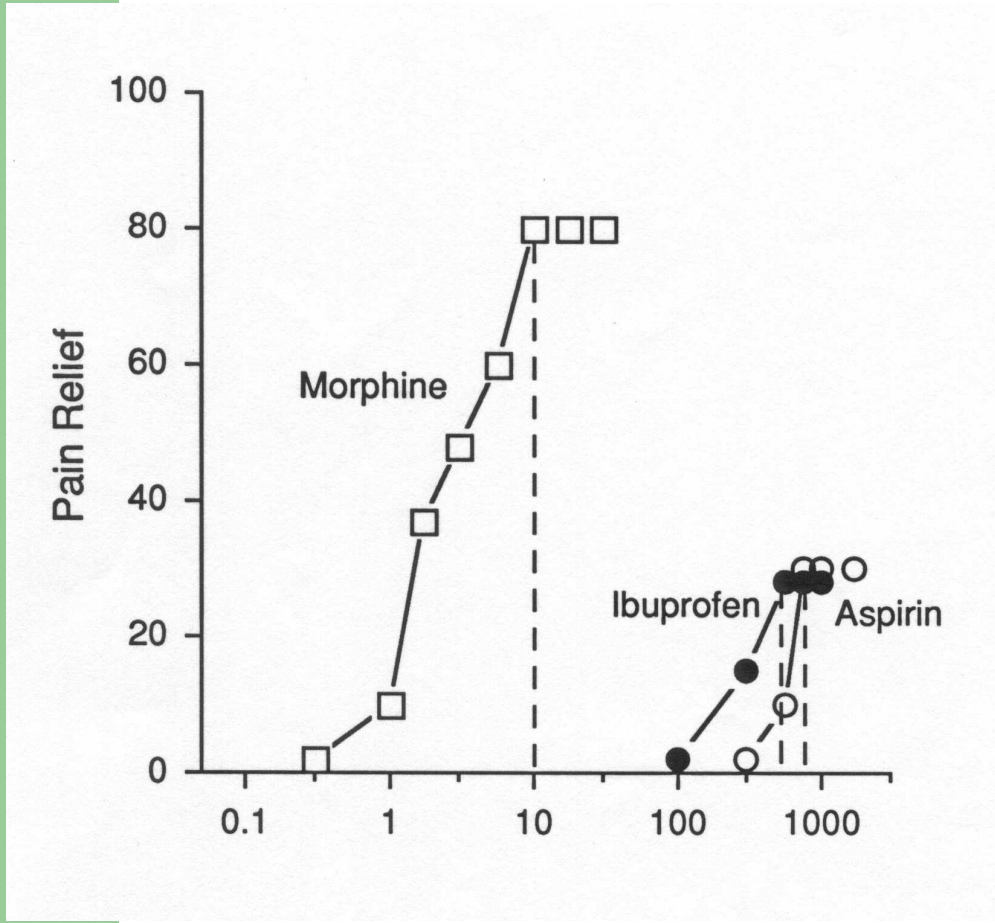
- **Potency** is the relative strength of response for a given dose ( **potency** is a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity. A highly potent drug (e.g., morphine) evokes a larger response at low concentrations, while a drug of lower potency (e.g. ibuprofen) evokes a small response at low concentrations:

  - **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***

***Agonist:*** A drug which binds a receptor & produces a biologic response. It may mimic the response of the endogenous ligand on the receptor or elicit a different response.

***Antagonist:*** A drug that decreases or opposes the action of another drug or endogenous ligand. Antagonist has no effect if the agonist is not present.

# Efficacy:




- **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
- Inverse agonist = -100% efficacy