Introduction and general pharmacological principles

Dr. Khetam Alhilali

What is pharmacology

Pharmacology is a branch of science that deals with the study of drugs and their actions on living systems - that is, the study of how drugs work in the body (sometimes referred to as 'drug actions'). To understand this we need to consider what a drug is, how it affects our physical, emotional and psychological wellbeing, the type of drug being used, the modes of administration, how the drug is absorbed and the characteristics of the person taking the drug.

What is pharmacology?

• Pharmacology (from pharmakon, the Greek word for drug) is the study of drugs (substances that produce changes in the body) and the characterization of their:

• Structure, targets, and mechanisms of action

• Distribution in and handling by the body

• Effects on the body, including desirable responses (efficacy) and undesirable side-effects (toxicity).

Important “pharmaco” terminology

- Pharmacoepidemiology investigates the effects of drugs on populations.
- Pharmacoeconomics examines the cost-effectiveness of drug treatments.
- Pharmacogenetics and pharmacogenomics study the influence of genetic variation on pharmacodynamic and pharmacokinetic properties of drugs

What is pharmacology

- Clinical pharmacology is the study of drugs in human patients.
- Toxicology is the study of harmful rather than therapeutic effects.
- Pharmacy involves manufacture, preparation, and dispensing of drugs.
- Pharmacotherapy is the use of drugs to treat disease requires knowledge of drugs, physiology, and pathology

History of Pharmacology

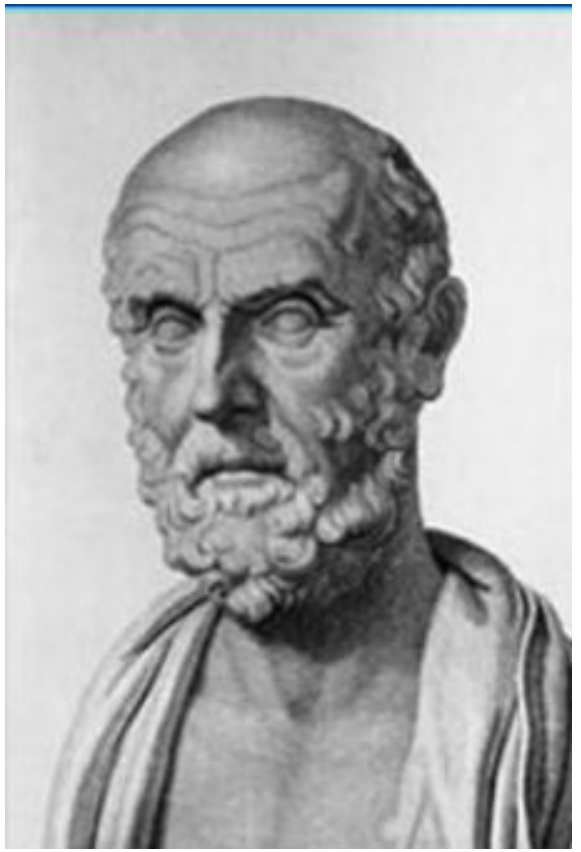
Ancient Times A series of scattered facts exists that speak of the early history of humankind's efforts to harness the healing properties of natural compounds. However, what we know for certain is that ancient peoples made extensive use of plant, animal and mineral sources for this purpose.

History of Pharmacology

- The Ebers papyrus, written in Egypt in the 16th century B.C., lists the extensive pharmacopea of that civilization. Included in this are: beer, turpentine, myrrh, juniper berries, poppy, lead, salt etc. Also included were products derived from animals, including lizard's blood, swine teeth, goose grease, donkey hooves and the excreta from various animals. The effects of many of these drugs on patients of antiquity can only be imagined.

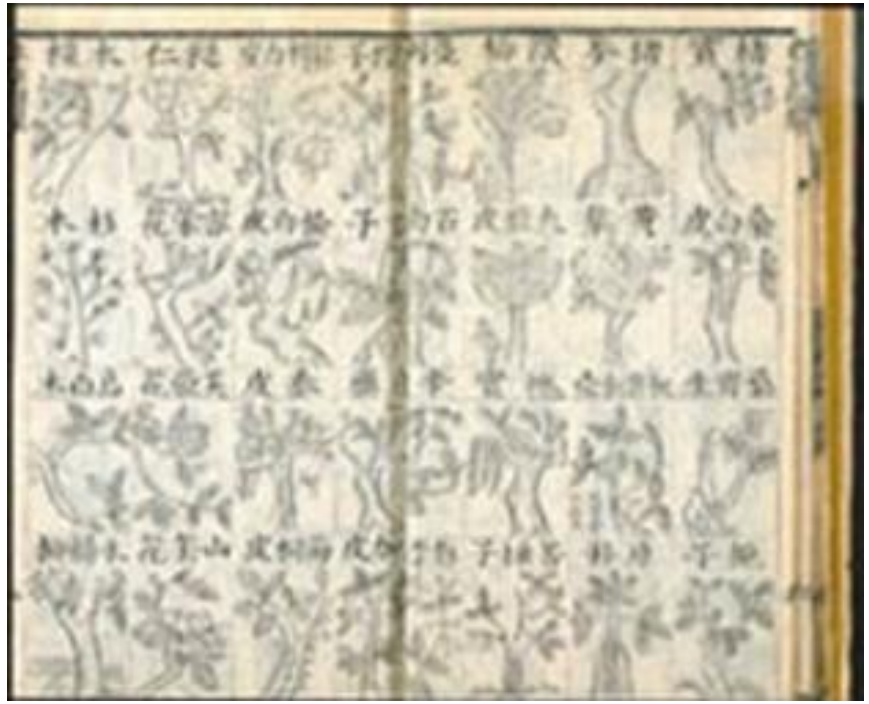
History of Pharmacology

- Ancient Greek medicine
- Hippocrates (460-370 B.C.) “Father” of western medicine (Born at Cos)
- Illness had a natural cause First to use observation of symptoms for clinical diagnosis; “observe patients” No dissection Used diet to counteract disease
- Four Humours - Illness was caused by natural factors inside the patient. Yellow bile, black bile, blood, and phlegm.



History of Pharmacology From ancient China

- History of Pharmacology From ancient China comes evidence of that culture's extensive efforts to heal through the use of natural products. The Pen Tsao, or Great Herbal, comprised forty volumes describing several thousands of prescriptions.



History of Pharmacology

- History of Pharmacology Interestingly, the eastern herb Artemisia annua L. (wormwood), used in China since antiquity to treat fevers, is the source of the modern drug artemisinin, which shows great promise as a modern anti-malarial compound.

Medicine in the Middle Ages

- Ibn Sina (Avicenna, 980-1037 AD)
- The cannon of medicine
- Medical standard text until the mid-1600's
  Significant advances in pharmacology
- Compilation of Greek, Roman, & Persian medical knowledge;

History of Pharmacology

- Antiquity to the modern era The ancients considered disease a consequence of demonic possession, or the wrath of god.

- Thus, in ancient times, the treatment of illness with natural products was invariably accompanied by religious rituals deemed essential to the healing process.

- With time, the thoughts returned to the appreciation that the natural products themselves held the power to cure.

History of Pharmacology

- For example,
- The purple foxglove, Digitalis purpurea, was one of twenty herbs used in a folk remedy to treat dropsy in 18th century England.

- From the leaves of this plant was isolated the cardiac glycoside digitalis, a drug still used today to treat heart failure.

- Over time, as a more sophisticated view of illness evolved, an increasingly scientific approach to the isolation of drugs from natural products was taken. In the early 19 th century, morphine was isolated from the opium poppy (Papaver somniferum)
- The anti-malarial compound quinine from the bark of the cinchona tree (Cinchona officinalis).

- Felix Hoffman, a research chemist synthesized acetylsalicylic acid. On February 1, 1899, Aspirin® was registered as a trademark.

What is drug

- Drug, any chemical substance that affects the functioning of living things and the organisms (such as bacteria, fungi, and viruses) that infect them. Drugs produce harmful as well as beneficial effects, and decisions about when and how to use them therapeutically always involve the balancing of benefits and risks.

- Medicine - in the past was plant or animal substances a drug or a mixture of drugs combined with other substances to make it stable, palatable and useful for therapy
- Agent - a collective noun (antihypertensive, anticancer agents).

- Compound - is a chemical used for pharmacological purpose, but not as a therapeutic agent

Drug names / Drug nomenclature

A single drug have a variety of names.

Drug nomenclature is the systematic naming of drugs, especially pharmaceutical drugs.

In the majority of circumstances, drugs have 3 types of names:

- ❖A chemical nomenclature is a set of rules to generate systematic names for chemical compounds. The nomenclature used most frequently worldwide is the one created and developed by the International Union of Pure and Applied Chemistry (IUPAC).
- ❖A generic name. This is the drug's medical name, describing the active chemical in the drug. There will only be one generic name for a specific drug.
- ❖A trade or brand name. These are names given to a drug by companies which manufacture the drug. Individual drugs can have several different trade names.
- For example, the antidepressant with the generic name fluoxetine is also known by the trade names Olena, Oxactin, Prozac and Prozep. These are all names for the same medicine, containing the same active ingredient.

Drugs

- Drug Antagonism : Drug Opposition An interaction between two or more drugs that have opposite effects on the body. Drug antagonism may block or reduce the effectiveness of one or more of the drugs.

- Drug Concentration : Concentration The amount of a drug in a given volume of blood plasma, measured as the number of micrograms per milliliter.

- Drug Resistance : Resistance When a bacteria, virus, or other microorganism mutates (changes form) and becomes insensitive to (resistant to) a drug that was previously effective.

- Drug Synergism: Synergism, Synergy An interaction between two or more drugs that causes the total effect of the drugs to be greater than the sum of the individual effects of each drug. A synergistic effect can be beneficial or harmful.

- Drug-Drug Interaction : A change in a drug's effect on the body when the drug is taken together with a second drug. A drug-drug interaction can delay, decrease, or enhance absorption of either drug. This can decrease or increase the action of either or both drugs or cause adverse effects.

Dose

- Dose The quantity of a medication to be given at one time, or the total quantity of a medication administered during a specified period of time. For example, a patient might receive an initial medication dose of 50 mg, and, during the entire course of treatment, receive a total medication dose of 500 mg.

- Dose-Ranging Trial A type of clinical trial. In dose-ranging trials, different doses of a drug are tested. Trial results are compared to determine which dose is most safe and effective.

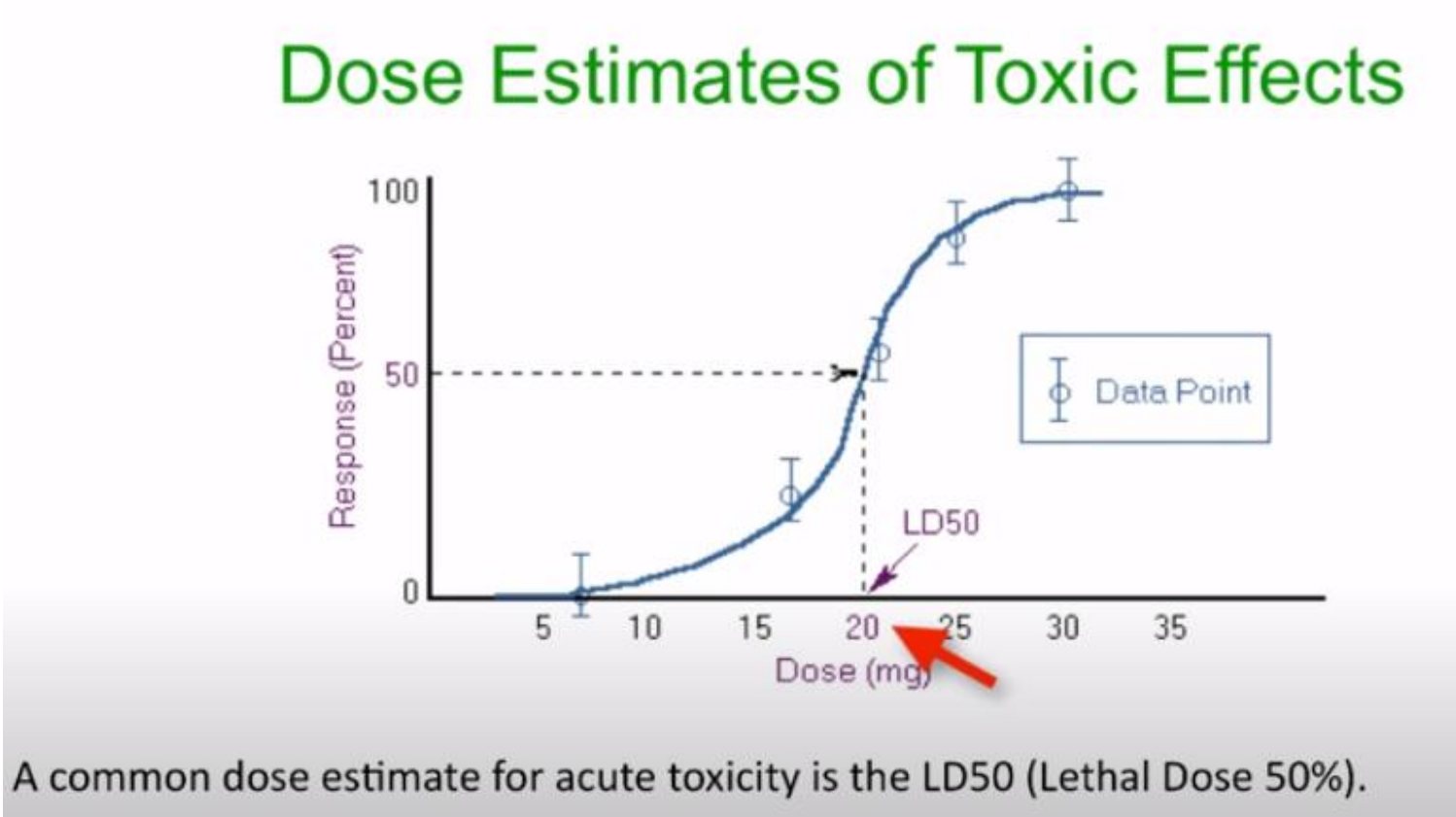
- Dose-Response Relationship The association between the dose of a drug and the body's corresponding response to that dose.

- Potency: A comparative measure, refers to the different doses of two drugs that are needed to produced the same degree of effect. These two drugs have similar chemical structure and mechanisms of action. The lower the dose of drug effect, the higher the potency of drug.

- Efficacy: The maximum effect of drug, Emax is a measure of drug efficacy. Efficacy is also called intrinsic activity.

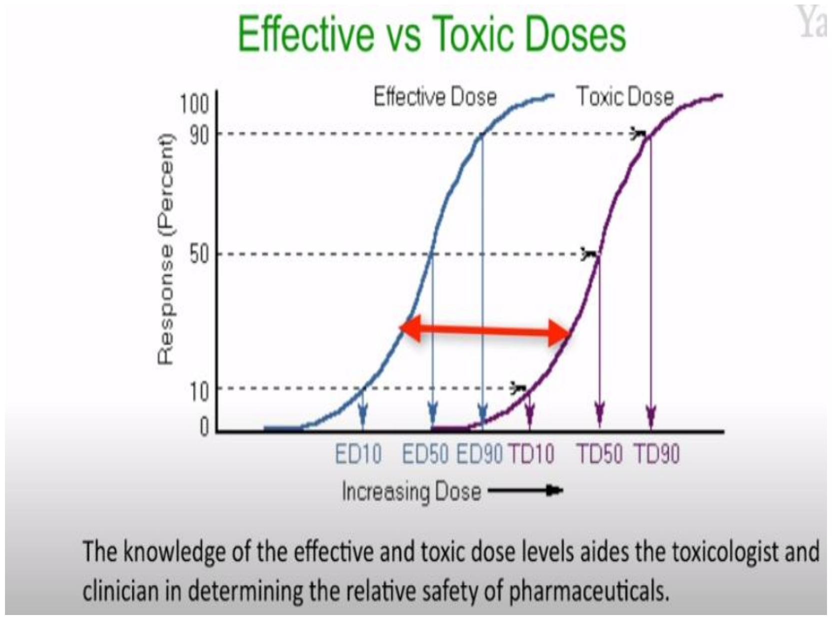
Dose

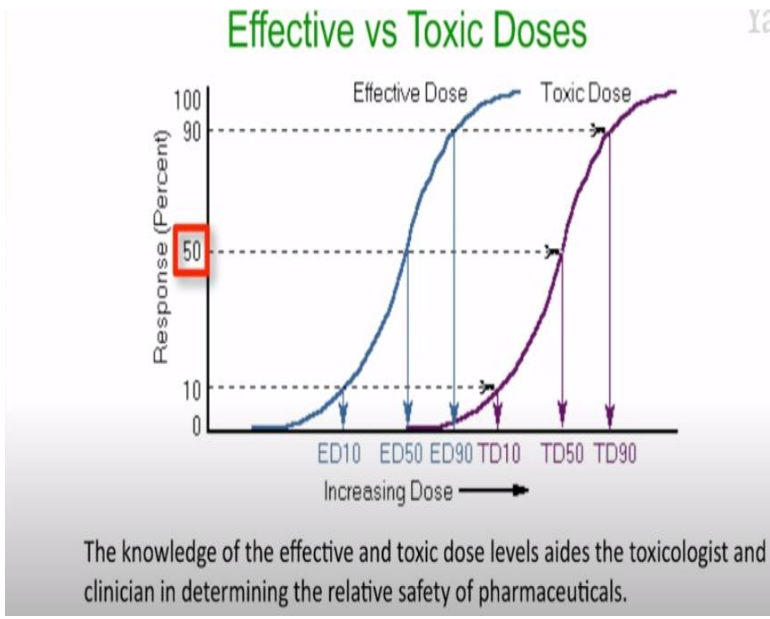
Lethal Dose(LD_{50}) : LD stands for "Lethal Dose". LD_{50} is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals. The LD_{50} is one way to measure the short-term poisoning potential (acute toxicity) of a material.

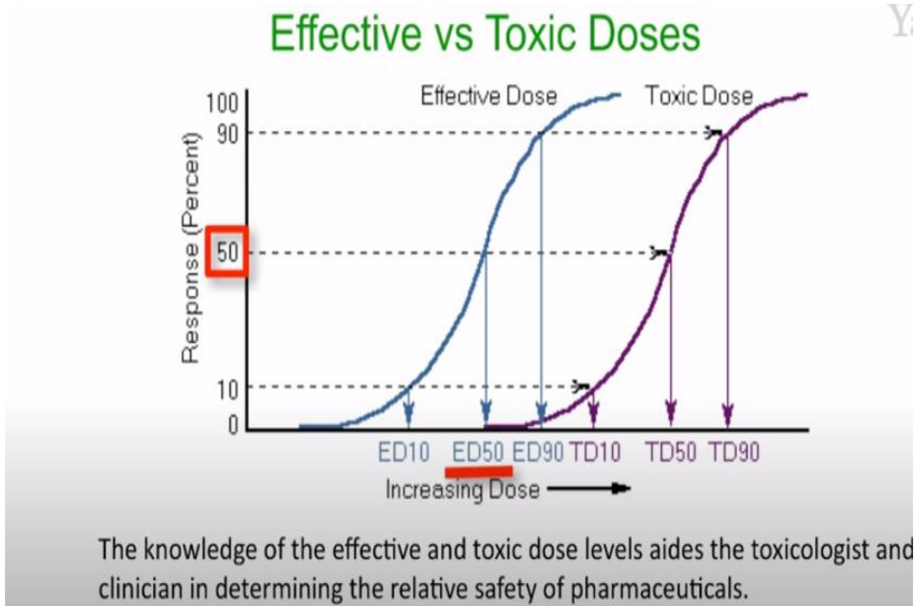


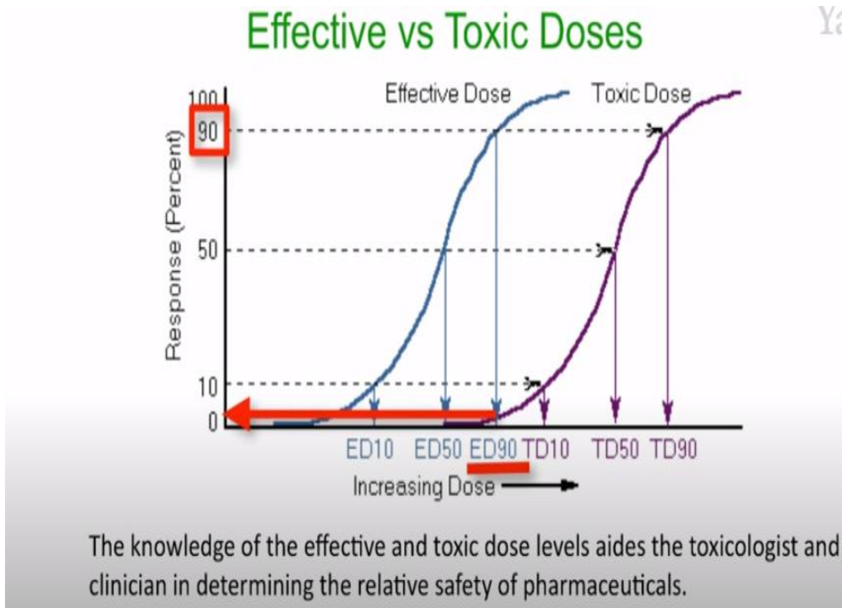
Effective dose 50 (ED50)

is a pharmacological term for the dose or amount of drug that produces a therapeutic response or desired effect in 50% of the subjects taking it. ED50 is dependent upon the patient and can vary according to their age and health, although the dose administered by a physician should fall into the drug's predetermined therapeutic window.







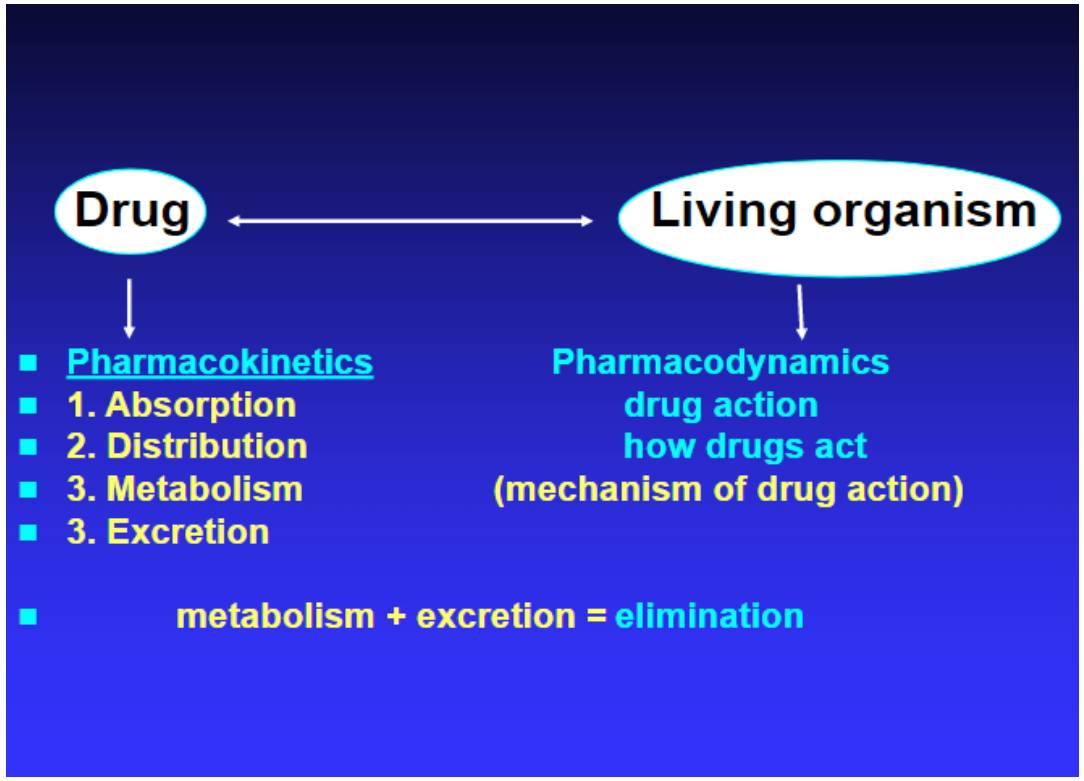


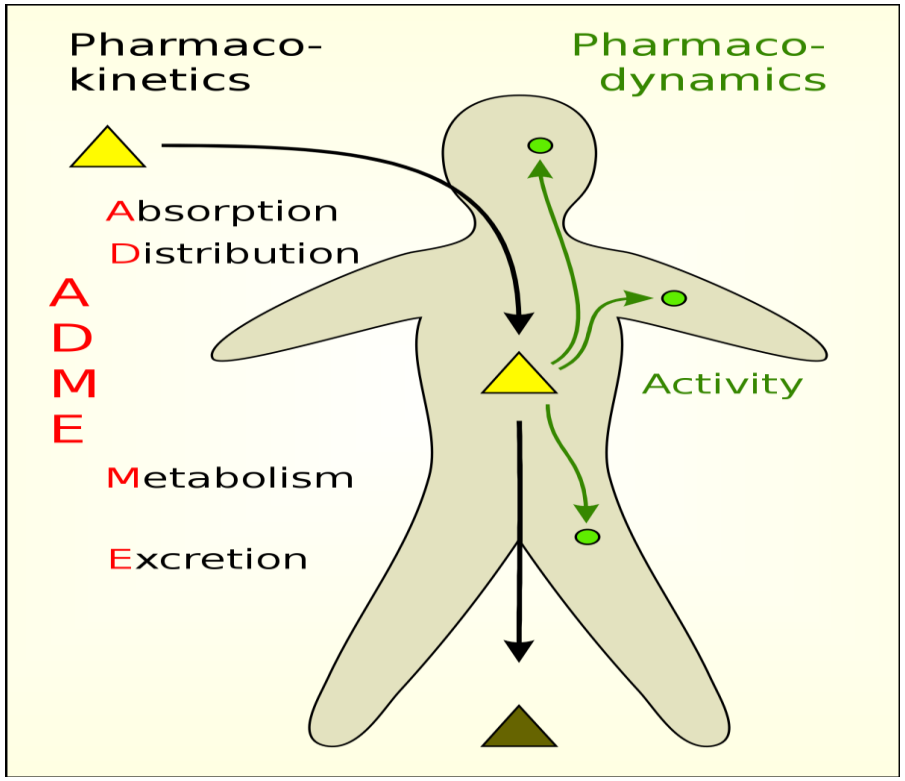
Tolerance, Dependence and Addiction

- **Tolerance**
- Tolerance happens when a person no longer responds to a drug in the way they did at first. So it takes a higher dose of the drug to achieve the same effect as when the person first used it. This is why people with substance use disorders use more and more of a drug to get the "high" they seek.
- **Dependence**
- Dependence means that when a person stops using a drug, their body goes through "withdrawal": a group of physical and mental symptoms that can range from mild (if the drug is caffeine) to life-threatening (such as alcohol or opioids, including heroin and prescription pain relievers). Many people who take a prescription medicine every day over a long period of time can become dependent; when they go off the drug, they need to do it gradually, to avoid withdrawal discomfort. But people who are dependent on a drug or medicine aren't necessarily addicted.
- **Addiction**
- Unlike tolerance and dependence, addiction is a disease; but like tolerance and dependence, addiction can result from taking drugs or alcohol repeatedly. If a person keeps using a drug and can't stop, despite negative consequences from using the drug, they have an addiction (also called a severe substance use disorder). But again, a person can be dependent on a drug, or have a high tolerance to it, *without* being addicted to it.

Pharmacokinetics (PK) and Pharmacodynamics (PD)

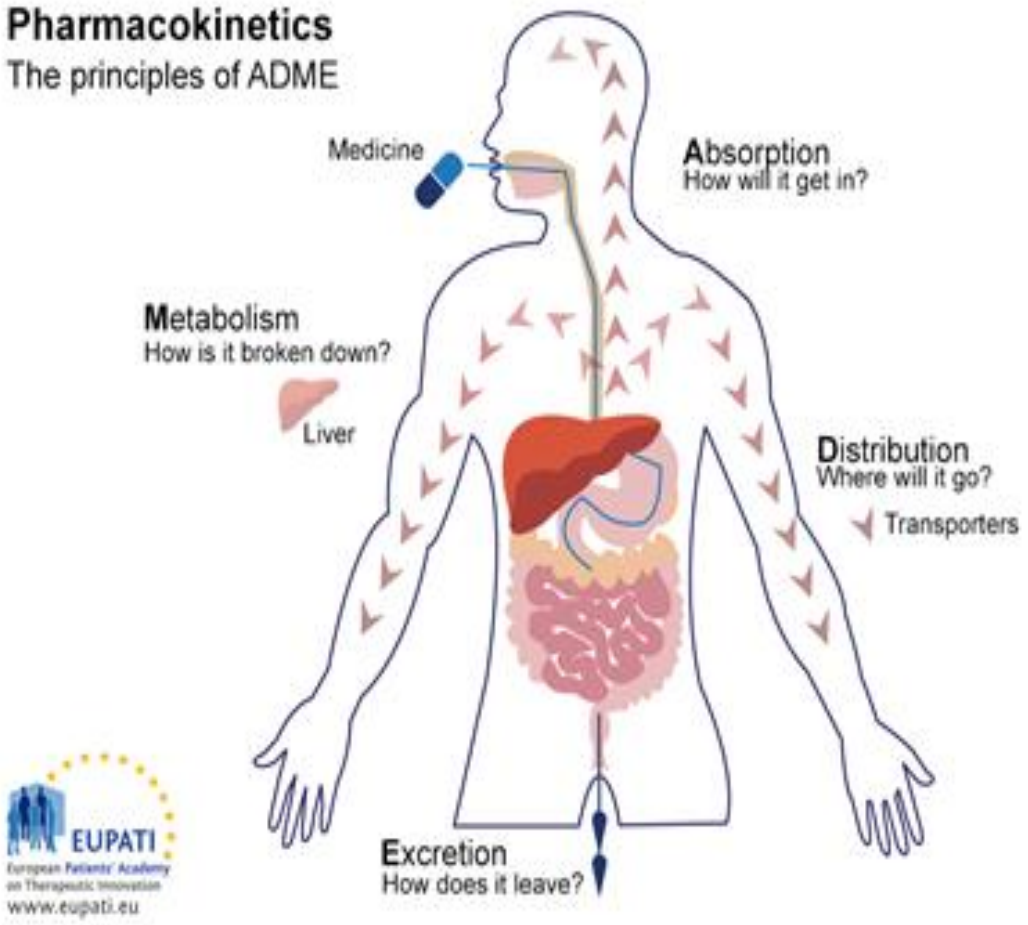
Pharmacodynamics (PD) is the study of how the drug affects the organism, while pharmacokinetics (PK) is the study of how an organism affects a drug; they are the two main branches of pharmacology.





Clinical Pharmacokinetics (PK)

- Introduction to Pharmacokinetics: Four Steps in a Drug's Journey Through the Body. Pharmacokinetics : what the body does to the drug.
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- The magnitud of the pharmacological effect of a drug depends on its concentration at the site of action.
- Drug concentration at sites of action influenced by several factors, such as:
  - Route of administration
  - Dose
  - Characteristics of drug molecules (e. g. , lipid solubility)



Absorption

- Absorption is the movement of a drug from its site of administration to the bloodstream.

❑The rate and extent of drug absorption depend on multiple factors, such as:

➢Route of administration.

➢The formulation and chemical properties of a drug.

➢Drug-food interactions.

➢The administration (e.g., oral, intravenous, inhalation) of a drug influences bioavailability, the fraction of the active form of a drug that enters the bloodstream and successfully reaches its target site.

- When a drug is given intravenously, absorption is not required, and bioavailability is 100% because the active form of the medicine is delivered immediately to the systemic circulation. However, orally administered medications have incomplete absorption and result in less drug delivery to the site of action. For example, many orally administered drugs are metabolized within the gut wall or the liver before reaching the systemic circulation. This is referred to as first-pass metabolism, which reduces drug absorption.

Drug Absorption

- **Drug absorption is determined by the drug's physicochemical properties, formulation, and route of administration. Dosage forms (eg, tablets, capsules, solutions),**
- consisting of the drug plus other ingredients, are formulated to be given by various routes (eg, oral, buccal, sublingual, rectal, parenteral, topical, inhalational). Regardless of the route of administration, drugs must be in solution to be absorbed. Thus, solid forms (eg, tablets) must be able to disintegrate and deaggregate.
- Unless given IV, a drug must cross several semipermeable cell membranes before it reaches the systemic circulation. Cell membranes are biologic barriers that selectively inhibit passage of drug molecules. The membranes are composed primarily of a bimolecular lipid matrix, which determines membrane permeability characteristics. Drugs may cross cell membranes by
- **Passive diffusion**
- **Facilitated passive diffusion**
- **Active transport**
- **Pinocytosis**
- **Sometimes various globular proteins embedded in the matrix function as receptors and help transport molecules across the membrane.**

Drug Absorption n Routes of Drug Administration

❖Oral (per os, p. o.)

❖Inhalation (vapors, gases, smoke)

❖Mucous membranes

- intranasal (sniffing)
- sublingual
- rectal suppositories

❖ Injection (parenteral)

- intravenous (IV)
- intramuscular (IM)
- subcutaneous (SC)
- intraperitoneal (IP; nonhumans only)

❖Transdermal

Bioavailability

- Bioavailability of drugs complex of pharmacokinetic processes that maintenance active concentration of drug in the area of specific receptors (part of administered drug that reaches the systemic circulation and effects specific receptors)
- PRESYSTEMIC ELIMINATION (first pass metabolism) presystemic elimination - extraction of the drug form blood circulatory system during it's first passage through the liver-it leads to decreasing of bioavailability (and therefore, decreasing of biological activity) of drugs propranolol (anaprilin), labetolol, aminazin, acetylsalicylic acid,
- ONSET - the period between the moment of drug introduction to the organism and the beginning of its action
- DURATION OF DRUG ACTION - the period then specific effects of the drug are maintained
- WIDENESS of therapeutic action (therapeutic window) - the distance between minimum therapeutic and minimum toxic doses of drug

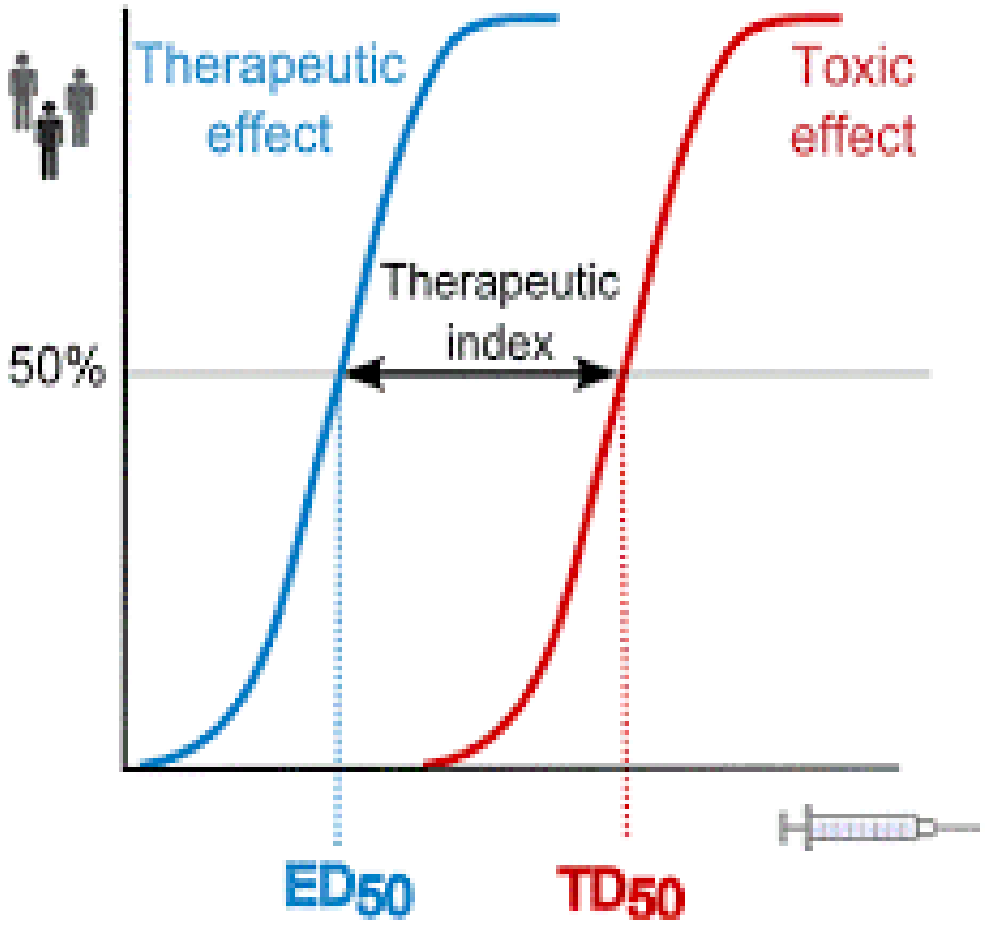
DRUG ABSORPTIO

- Ionization of Drugs
- Most drugs are weakly acidic or basic substances and are thus ionized at physiologic pH. Passive diffusion across lipophilic membranes depends on the degree of ionization. Based on the passive diffusion barrier concept, only the nonionized (lipophilic) portion of the drug is assumed to pass readily through the lipoid barriers. In contrast, the ionized form carries a charge and is polar, so it cannot pass through the membranes.
- Lipid solubility
- pKa = pH at which 50% of drug molecules are ionized (charged)

- Only uncharged molecules are lipid soluble.
- The pKa (Calculate the acid dissociation constant (pKa))of a molecule influences its rate of absorption through tissues into the bloodstream.
- p H varies among tissue sites e. g. , stomach: 3 -4, intestines: 8 -9

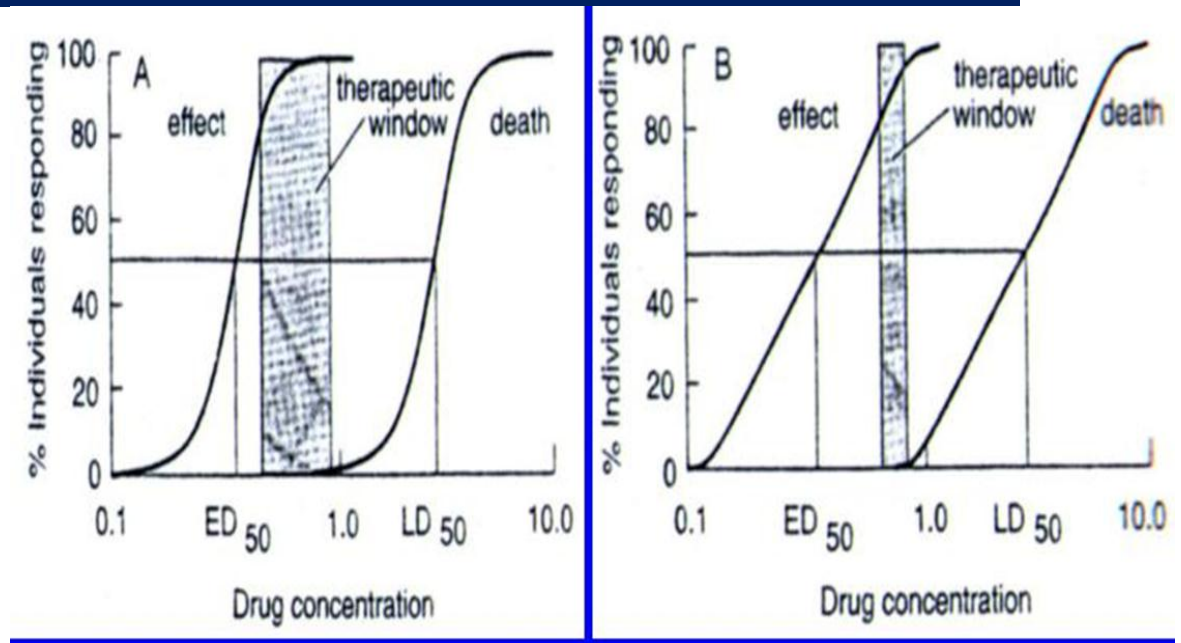
Therapeutic Index (TI)

- **Therapeutic Index (TI)**
- A ratio that compares the blood concentration at which a drug becomes toxic and the concentration at which the drug is effective. The larger the therapeutic index (TI), the safer the drug is. If the TI is small (the difference between the two concentrations is very small), the drug must be dosed carefully and the person receiving the drug should be monitored closely for any signs of drug toxicity.
- **Therapeutic index (TI) = LD50 / ED50**



Therapeutic window

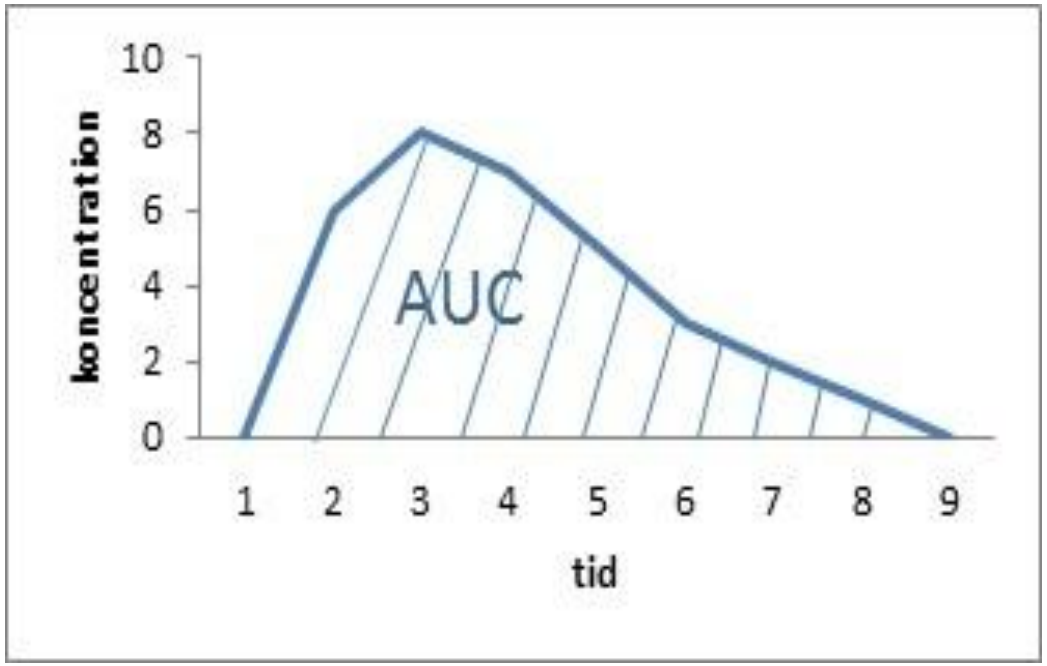
- Therapeutic window
- The *therapeutic window* (or pharmaceutical window) of a drug is the range of drug dosages which can treat disease effectively without having toxic effects. Medication with a small therapeutic window must be administered with care and control, frequently measuring blood concentration of the drug, to avoid harm. Medications with narrow therapeutic windows include theophylline, digoxin, lithium, and warfarin.



A and B: to have same TI, difference slope

Area Under Curve (AUC)

- **Area Under Curve** (AUC): Area under the plasma concentration curve is a measure of drug exposure, where the plasma concentration is plotted at different times . AUC is used to determine the bioavailability.



Area under the curve (AUC) is a measure of drug exposure and depends on dose, absorption, metabolism, and clearance etc.