PHARMACODYNAMICS II
QUANTITATIVE ASPECTS OF DRUGS

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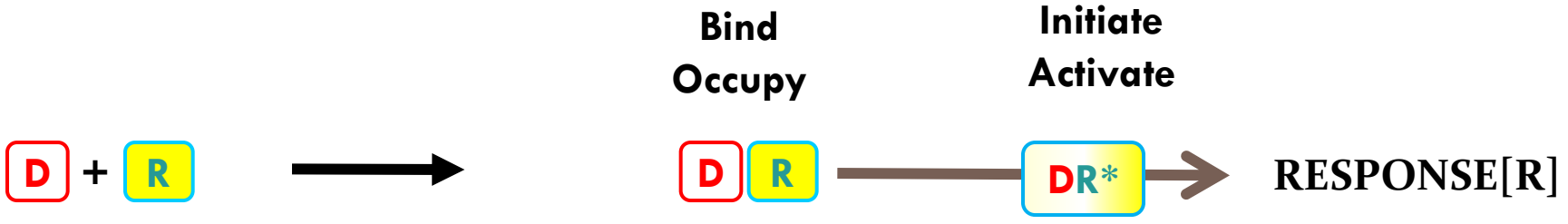
(Slides are adopted and modified from Prof. Hanan Hajar)

Quantitative aspects of drugs

By the end of this lecture, you should:

- Determine quantitative aspects of drug receptor binding.
- Recognize concentration binding curves.
- Identify dose response curves and the therapeutic utility of these curves.
- Classify different types of antagonism.

QUANTIFY ASPECTS OF DRUG ACTION



Relate concentration [C] of D used (x- axis) to the binding capacity at receptors (y-axis)

A Concentration-Binding Curve

Relate concentration [C] of D used (x- axis) to response produced (y-axis)

Dose Response Curves

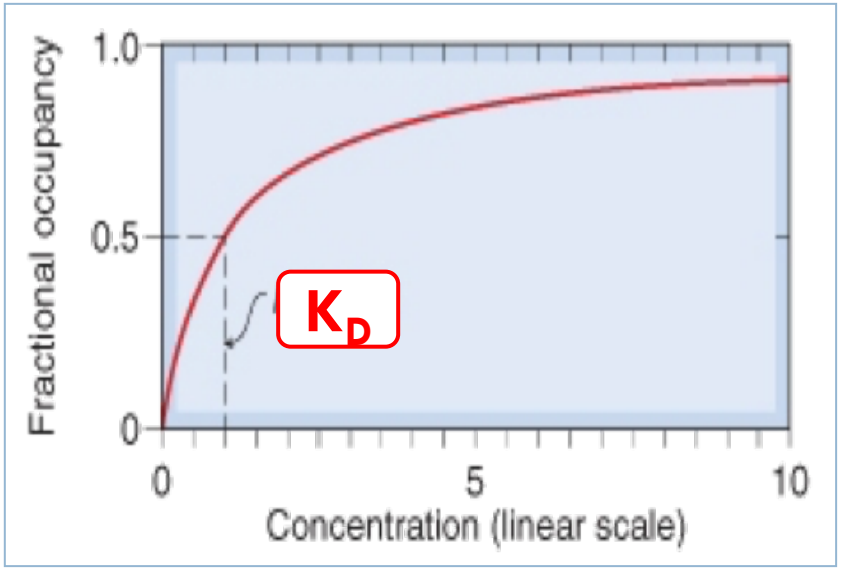
AFFINITY

EFFICACY

POTENCY

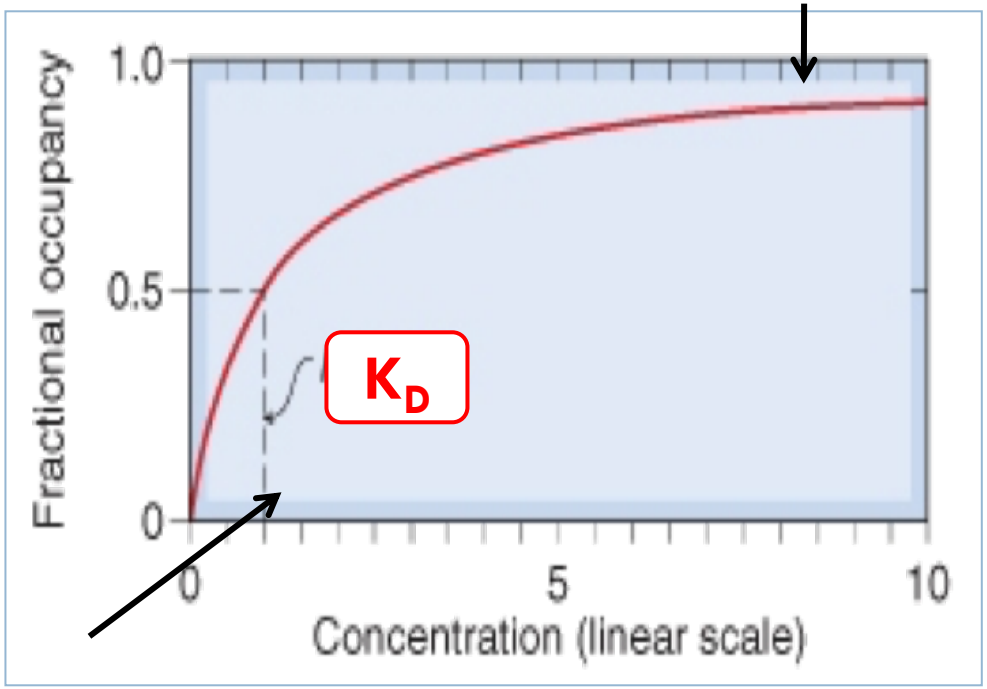
Concentration binding curves

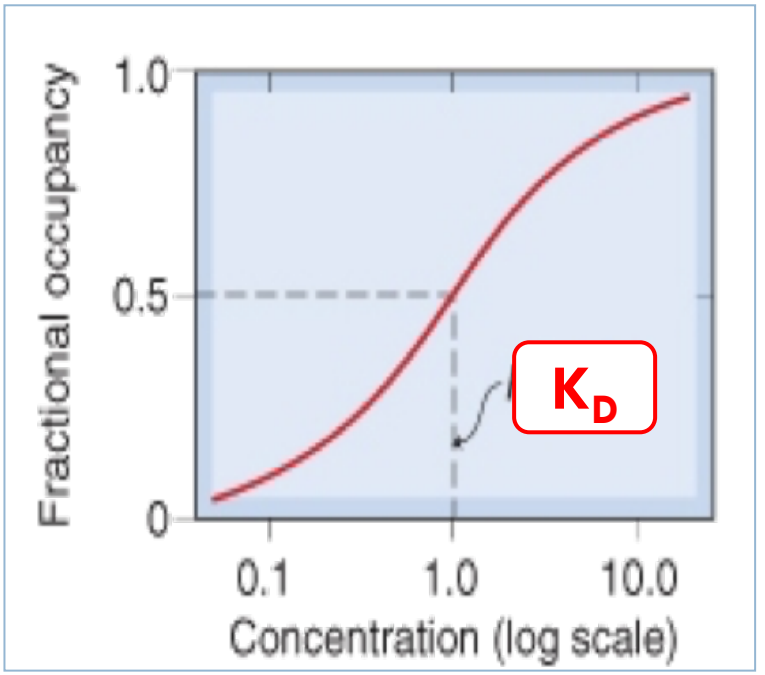
- Is a correlation between drug concentration [C] used (x- axis) and drug binding capacity at receptors [B] (y-axis). i.e. relation between concentration & drug binding



Concentration binding curves

(B_{max}): **Total density of receptors in the tissue**





(k_D)= [C] of **D** required to occupy 50% of receptors at equilibrium

Concentration binding curves

- B_{max} (the binding capacity)
  - is the total density of receptors in the tissues
- K_{D50}
  - is the concentration of drug required to occupy 50% of receptors at equilibrium.
- The affinity of drug for receptor
  - The higher the affinity of D for receptor the lower is the K_D i.e. inverse relation (Binding Potential= B_{max}/K_D)

Dose -response curves

- Used to study how response varies with the concentration or dose.
- Is a correlation between drug concentration [D] used (x- axis) and drug response [R] (y-axis).
- i.e. relation between concentration & Response

Dose -response curves

- Type of Dose-response curves
  - Graded dose-response curve
  - Quantal dose-response curve (all or none).

Dose -response curves

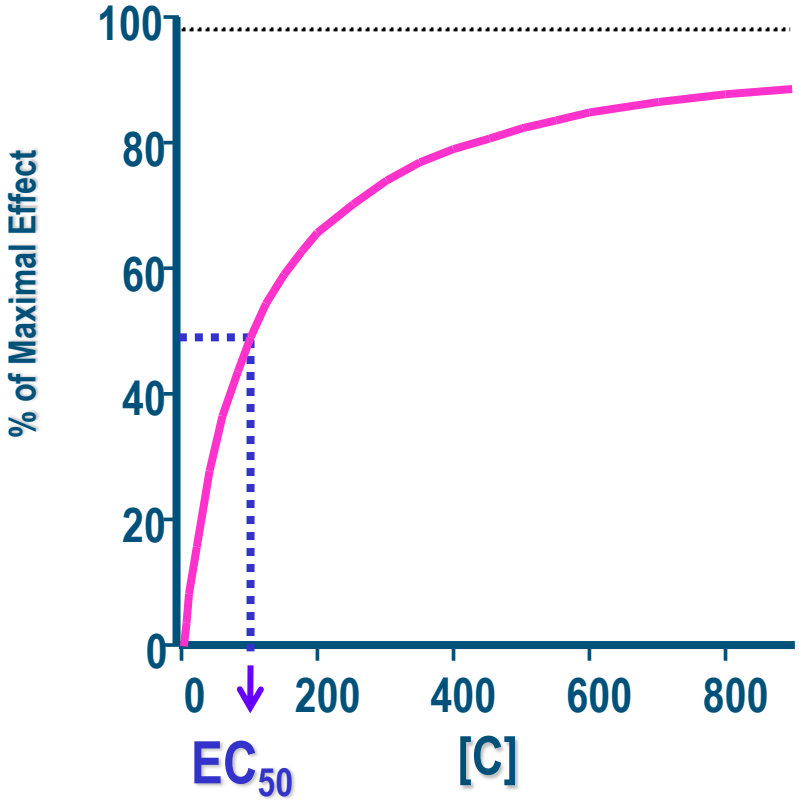
- Type of Dose-response curves
  - Graded dose-response curve
    - Response is gradual
    - Gradual increase in response by increasing the dose (continuous response).
    - e.g. ↓blood pressure, heart rate, blood glucose level, cholesterol,…

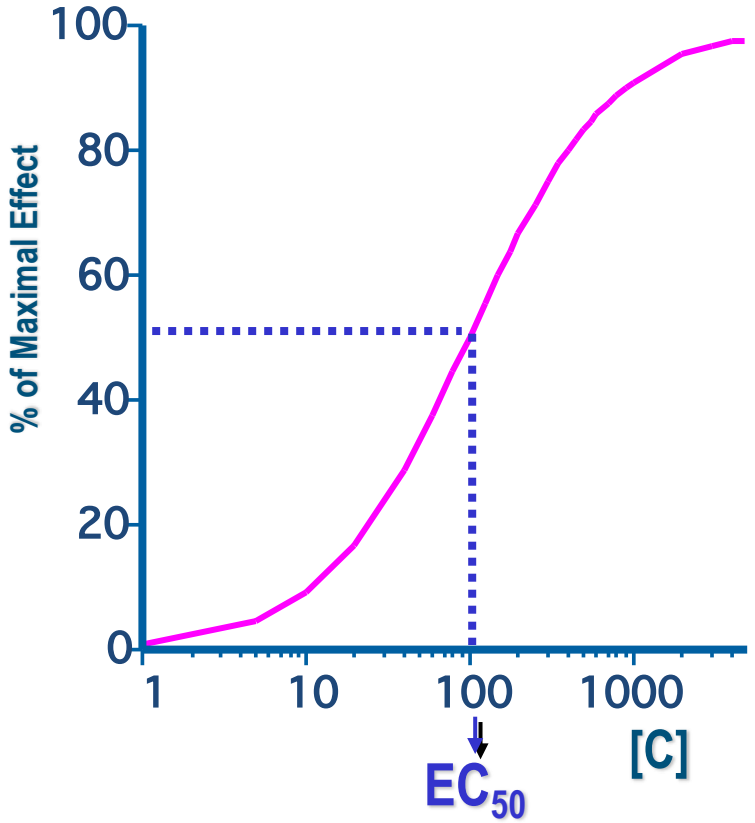
Dose -response curves

- Type of Dose-response curves
  - Graded dose-response curve
    - Curve is usually sigmoid in shape
    - Used to calculate
      - Emax
      - EC_{50}
      - Potency
      - Efficacy

Dose -response curves- Graded

Max effect = E_{max} Effect when all the receptors are occupied by D





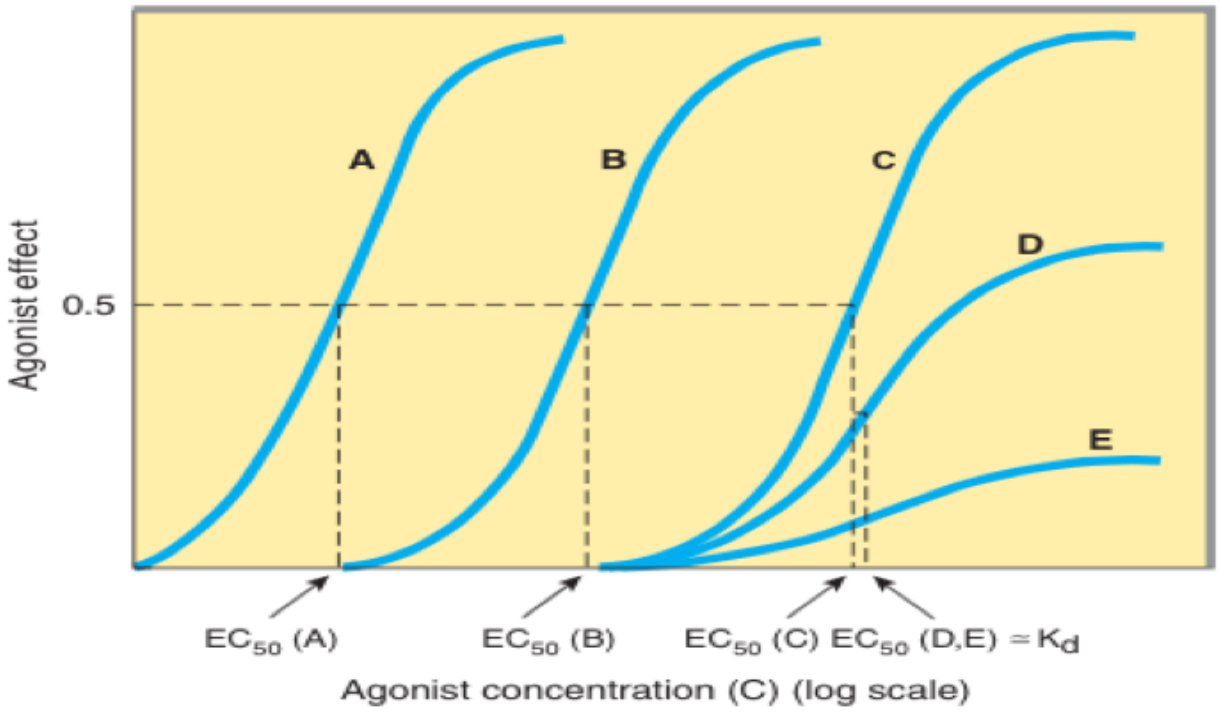
EC_{50} =C that gives the half-maximal effect

Dose -response curves

- Dose -response curves- Graded
  - Used to determine
- Maximum Efficacy (Emax): is the maximal biological response produced by a drug.
- Median Effective concentration (EC50): is the concentration of the drug that gives 50% of the maximal response (Emax).
- Potency: the concentration of drug required to produce a specified response (50% of the maximal response = EC50).
- Potency: is inversely proportional to EC 50.

Dose -response curves

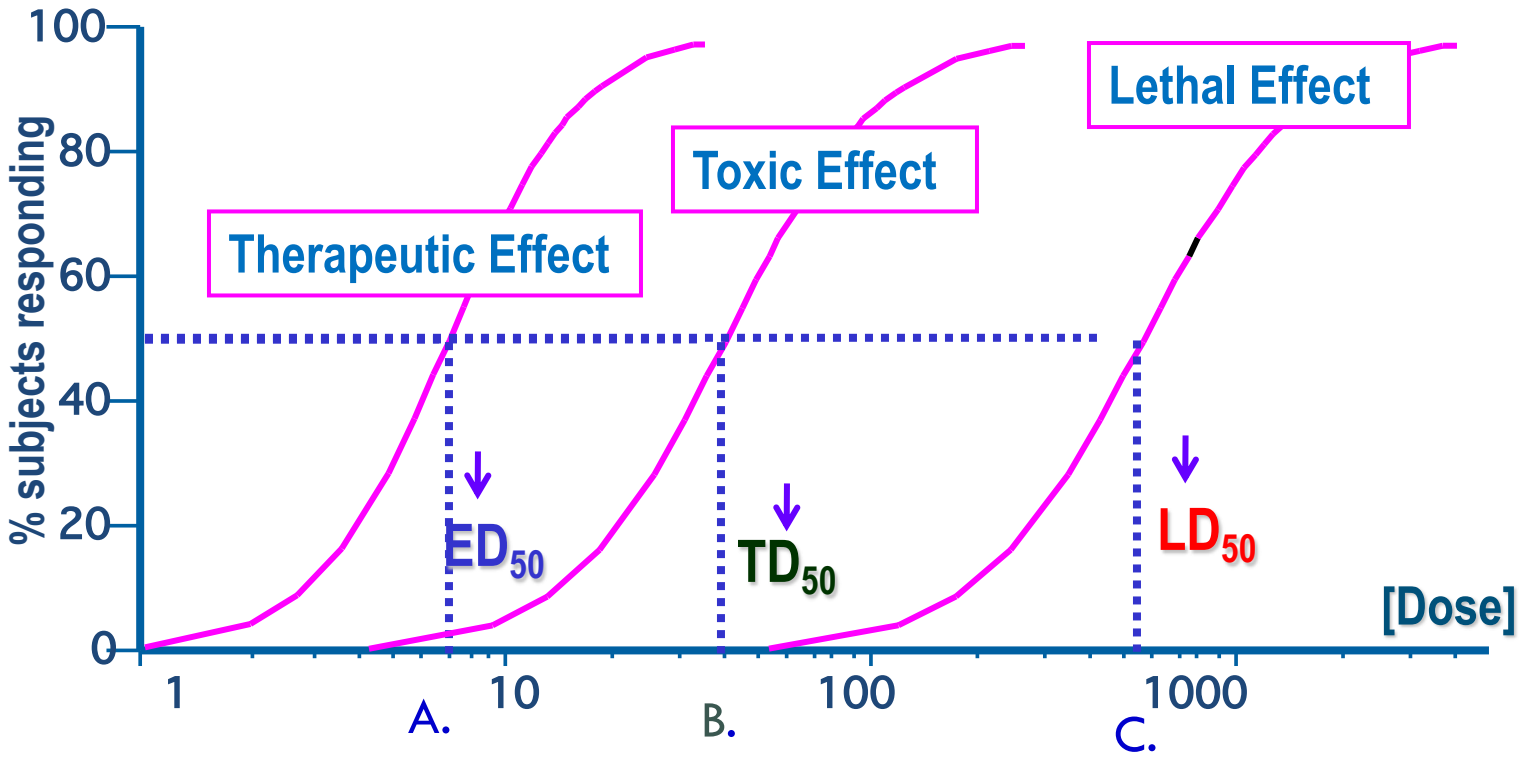
- Dose -response curves- Graded



Dose -response curves

- Type of Dose-response curves
  - Quantal dose-response curve
    - Relate drug concentration to % percentage of patients responding (all or none response).
    - The response may be therapeutic response, adverse effect or lethal effect.
    - e.g. prevention of convulsion, arrhythmias or death.
    - Used to determine
      - ED50
      - TD50 & LD50
      - Therapeutic index.

Dose -response curves-Quantal



A. 50% of individuals exhibit the specified therapeutic response

B. " " " toxic effects

C. " " " death

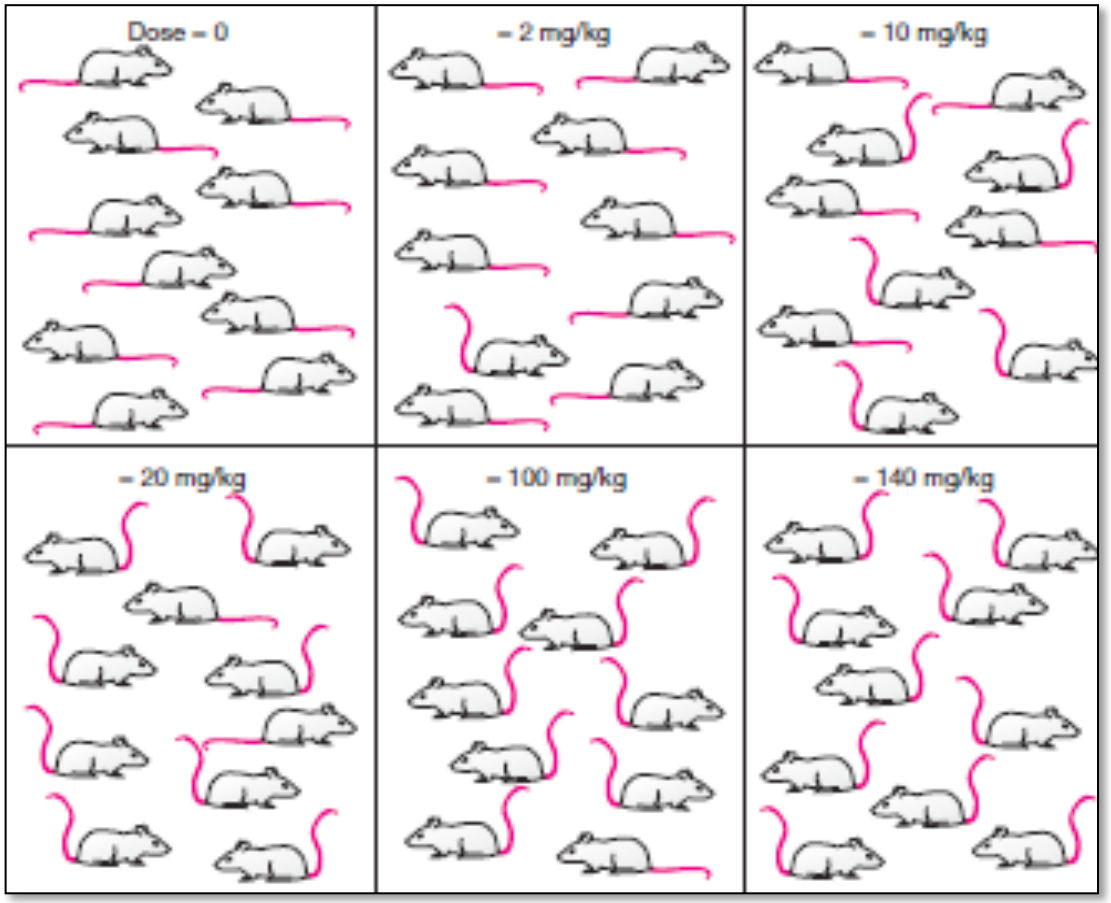
Predict the safety profile

Therapeutic Index (T.I.)

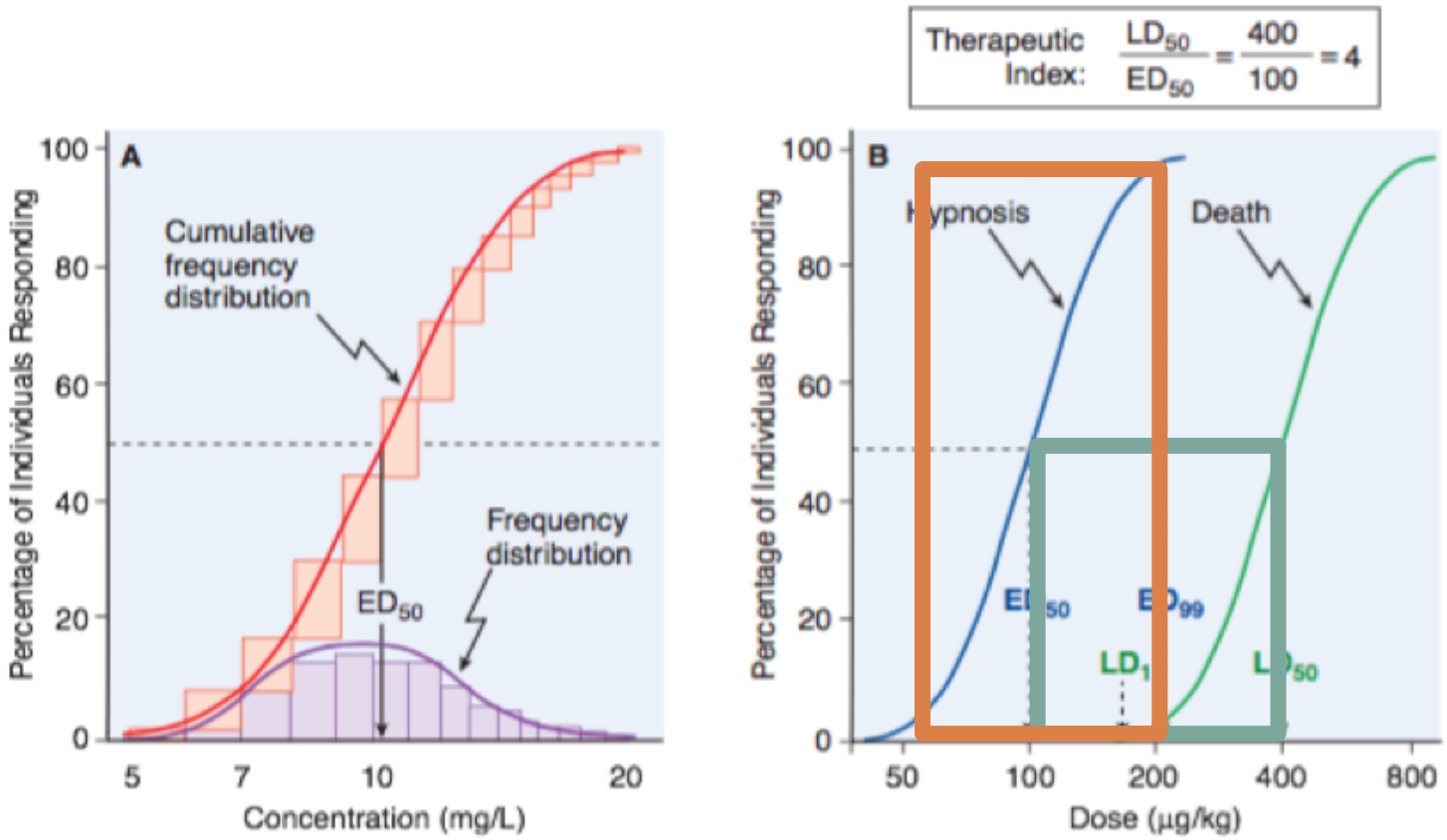
- A measure of drug safety
- "The ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals"
- Therapeutic Index = TD_{50}/ED_{50} or LD_{50}/ED_{50}
  - TD_{50} is the dose that produces a toxic effect in 50% of the population.
  - LD_{50} is the dose that is lethal in 50% of the population
  - ED_{50} is the dose that produces therapeutic response in 50% of the population

- Large value = drug has wide margin of safety e.g. diazepam
- Small value = a narrow margin of safety e.g. digoxin

Dose -response curves-Quantal



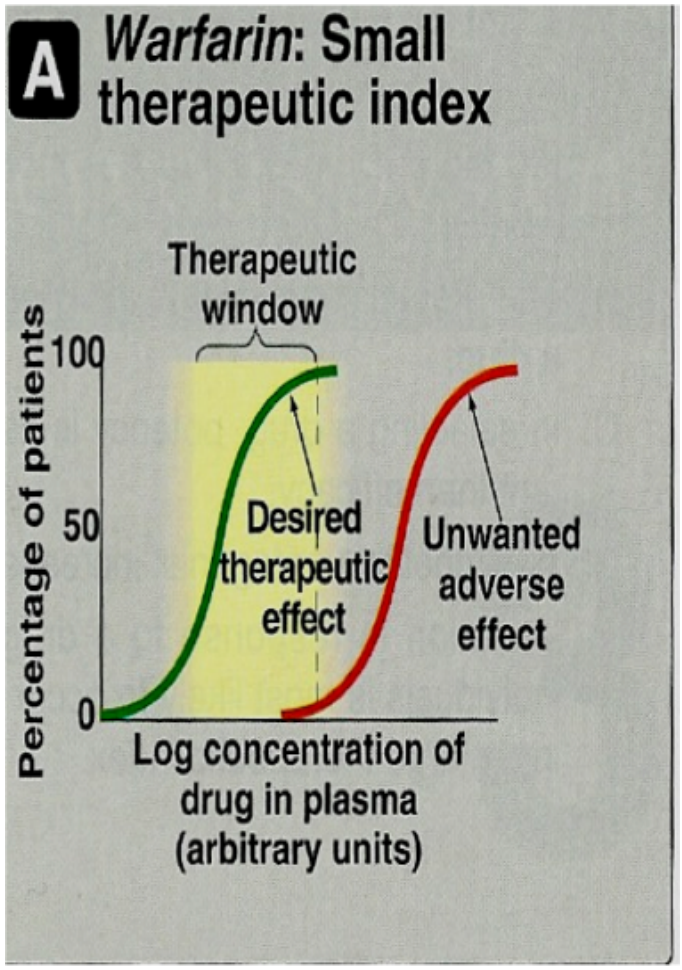
Therapeutic Index (T.I.)

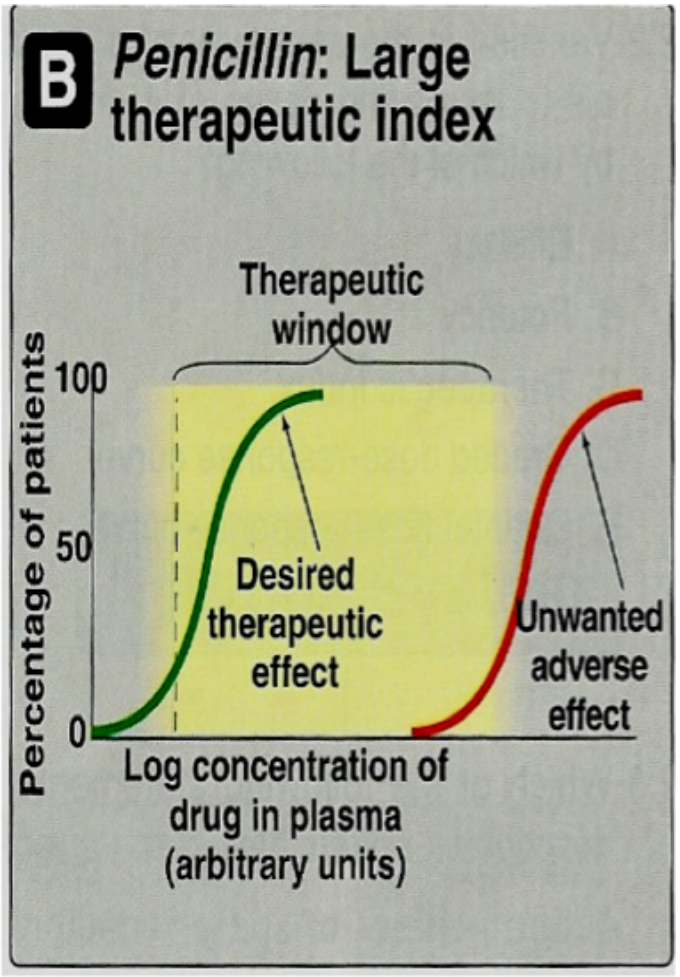


Therapeutic Window

Therapeutic Index

Therapeutic Index (T.I.)





Antagonism

- It is the decrease or the complete abolishment of the effect of one drug in the presence of another.
- Types
  - Physiological antagonism
  - Chemical antagonism
  - Pharmacokinetic
  - Pharmacodynamic antagonism (Receptor-blockade antagonism).
    - Competitive
      - Reversible
      - Irreversible
    - Non-competitive

Antagonism

- Types
  - Physiological antagonism

Two drugs act on different receptors to produce different physiological effects. e.g. Histamine & Adrenaline

- Adrenaline → Vasoconstriction (↑ BP) & bronchodilation.
- Histamine → vasodilatation (↓BP) & bronchoconstriction

Antagonism

- Types
  - Chemical antagonism
    - Simple chemical reaction & loss of activity
    - No receptor.
    - e.g. Dimercaprol reduces heavy metal toxicity (as in lead toxicity).

Antagonism

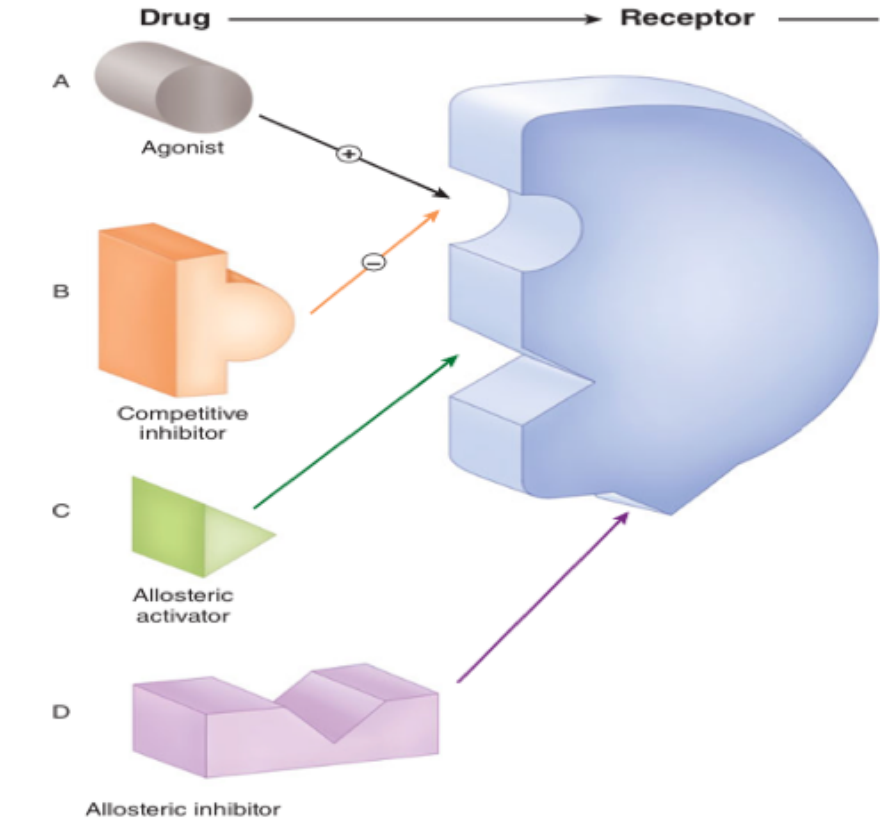
- Types
  - Pharmacokinetic

  The antagonist effectively reduces the concentration of the active drug at the site of action.

    - e.g. Phenobarbitone accelerates hepatic metabolism of warfarin

Antagonism

- Types
  - Pharmacodynamic antagonism (Receptor-blockade antagonism).
    - Competitive
      - Reversible
      - Irreversible
    - Non-Competitive

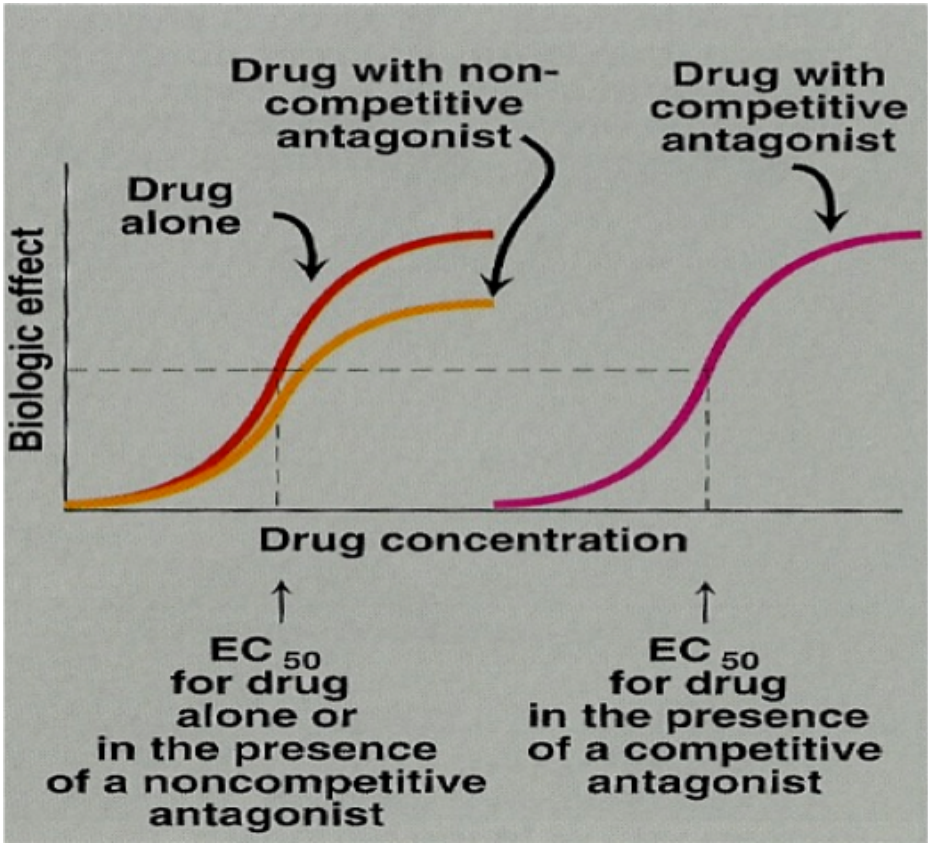


Antagonism

- Types
  - Pharmacodynamic antagonism (Receptor-blockade antagonism).
    - Competitive
      - Reversible
- Two drugs compete for the same receptor.
- The antagonist partially or completely prevents the pharmacological effect of agonist.
- Antagonist dissociate rapidly from receptor.
- Antagonism can be overcome by increasing the concentration of the agonist.
- Parallel shift of the curve to the right, without any change in slope or maximum
- e.g. acetylcholine and atropine

Antagonism

- Types
  - Pharmacodynamic antagonism (Receptor-blockade antagonism).
    - Competitive
      - Reversible

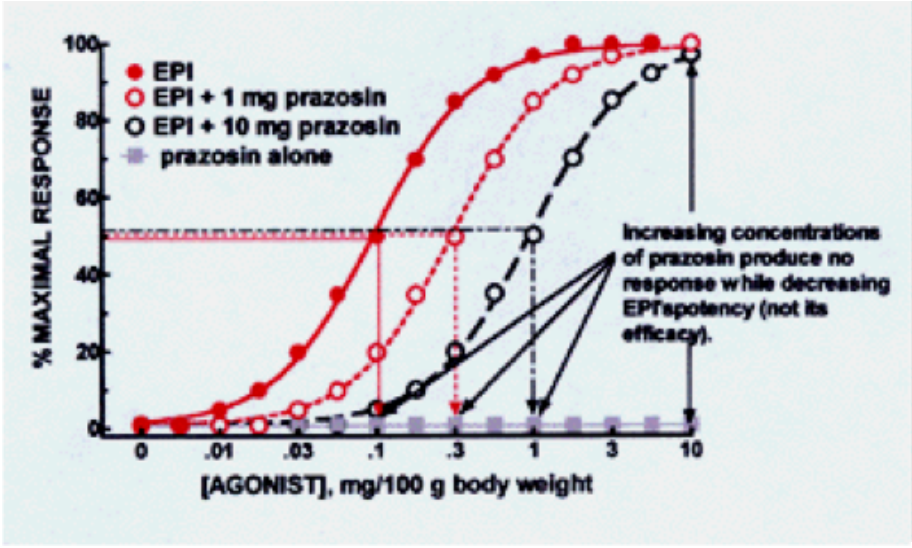


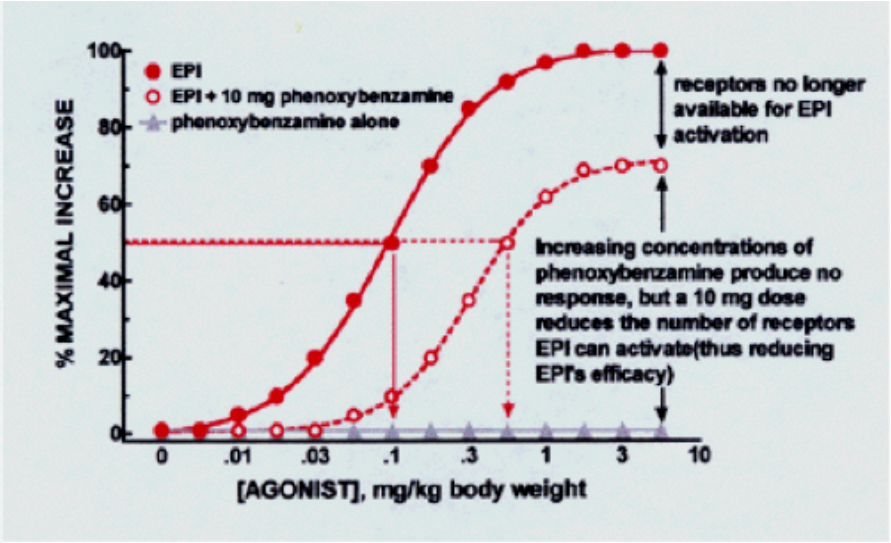
Antagonism

- Types
  - Pharmacodynamic antagonism (Receptor-blockade antagonism).
    - Competitive
      - Irreversible
- Two drugs compete for the same receptor.
- Antagonist forms stable, permanent chemical bond with receptor.
- The original response can not be overcome even by increasing the dose of the agonist.
- No parallel shift
- A decrease in slope and a reduced maximum are obtained.
- e.g. phenoxybenzamine and noradrenaline.

Antagonism

Competitive reversible antagonist vs Competitive irreversible antagonist





EPI, Epinephrine

Antagonism

- Types
  - Pharmacodynamic antagonism (Receptor-blockade antagonism).
    - Non-Competitive
- Antagonist block at some point the chain of events that stimulate the response of agonist.
- Agonist and Antagonist can be bound simultaneously.
- Antagonism cannot be overcome by increasing concentration of agonist e.g. verapamil and noradrenaline.

What about EC100?

- As the concentration (X) goes up, the dose-response equation computes the response (Y) as getting closer and closer to the Top plateau. But it never reaches it. When a drug binds to a receptor with mass action rules, the fraction occupancy equals $D/(D+K)$, where D is the concentration of drug (that you vary) and K is the equilibrium binding dissiociation constant, which is a fixed property of the drug and receptor. As D gets higher and higher, the fractional occupancy gets closer and closer to 1.0, but never reaches it. Therefore, there can be no EC100. And no EC0.