

PHARMACODYNAMICS II

QUANTITATIVE ASPECTS OF DRUGS

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

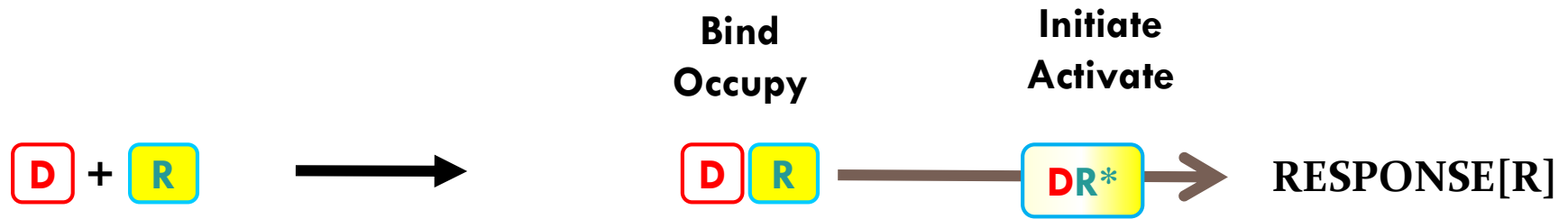
Quantitative aspects of drugs



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)

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

A Concentration-Binding Curve

Dose Response Curves

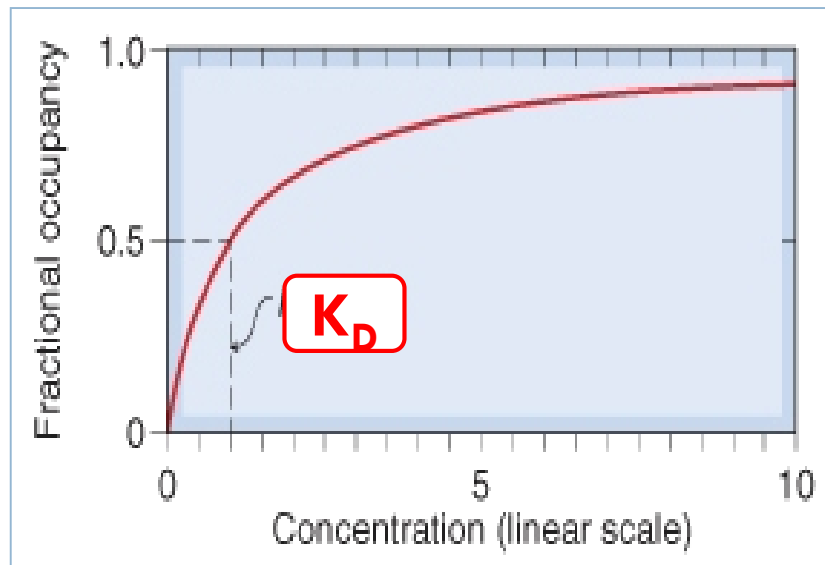
AFFINITY

EFFICACY

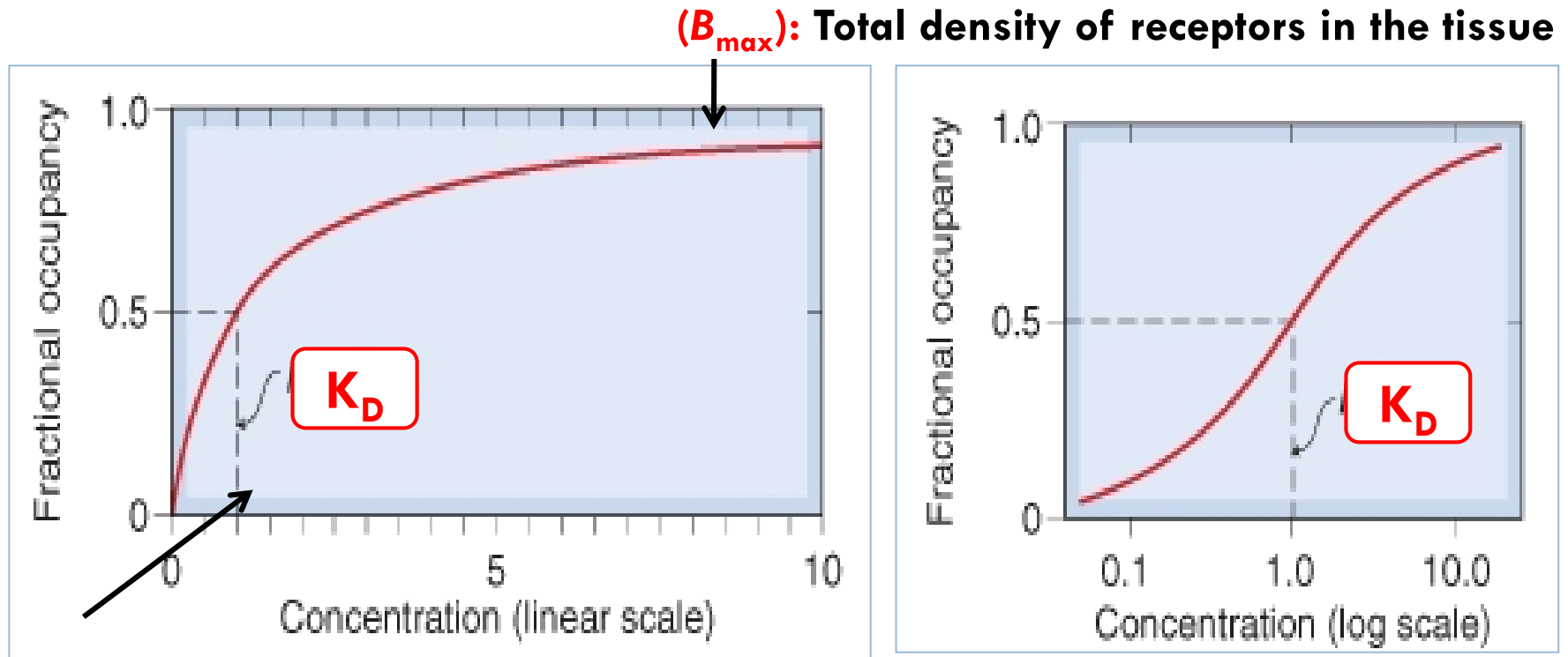
POTENCY

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



$(k_D) = [C]$ 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

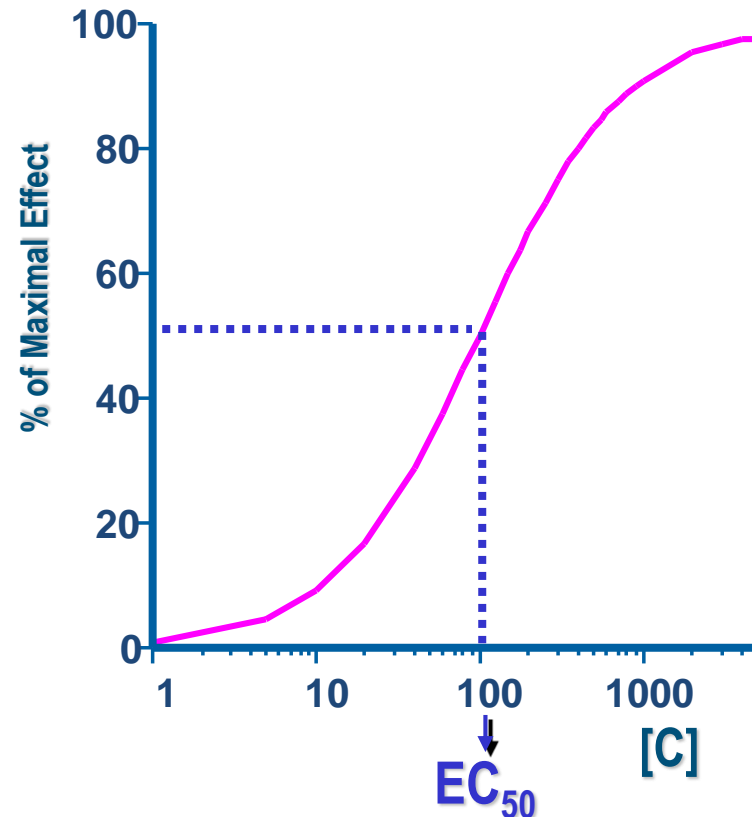
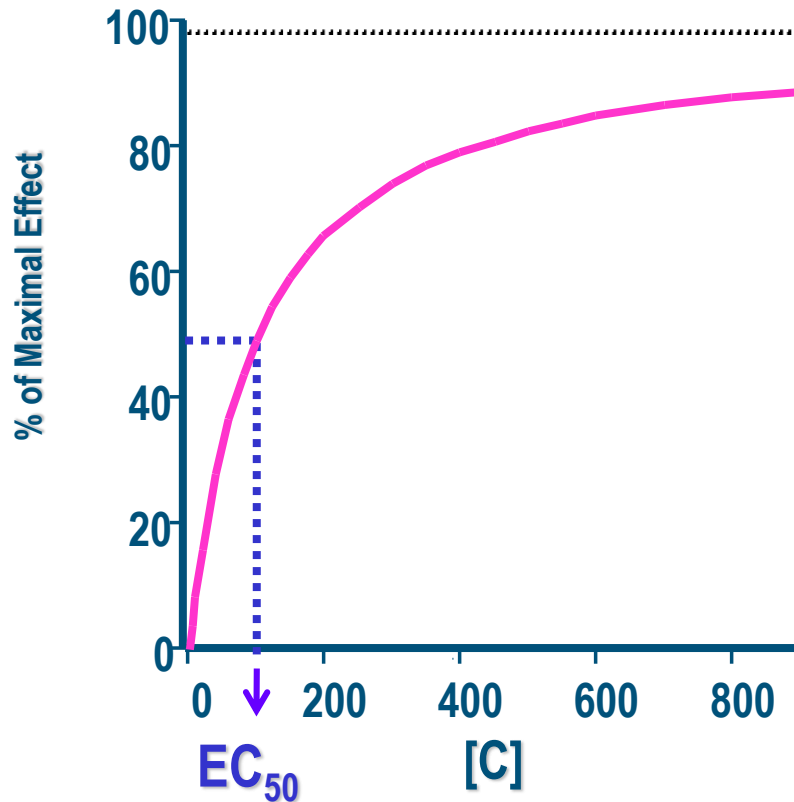
- Type of Dose-response curves
 - ▣ Graded dose-response curve
 - Response is gradual
 - Gradual increase in response by increasing the dose (continuous response).
 - e.g. ↓blood pressure, heart rate, blood glucose level, cholesterol,...

Dose -response curves

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

Dose -response curves- Graded

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



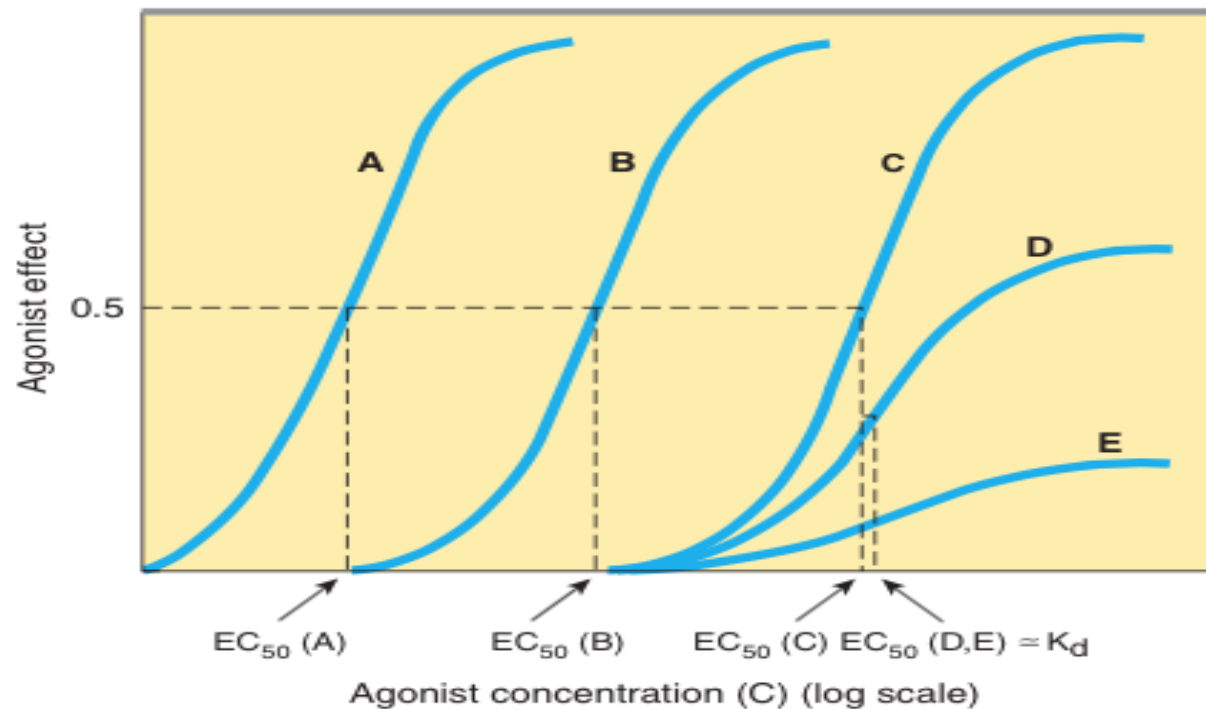
$EC_{50} = C$ that gives the half-maximal effect

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



Question

- Is it possible for a drug to be potent and have a low efficacy?

Yes/ No How?

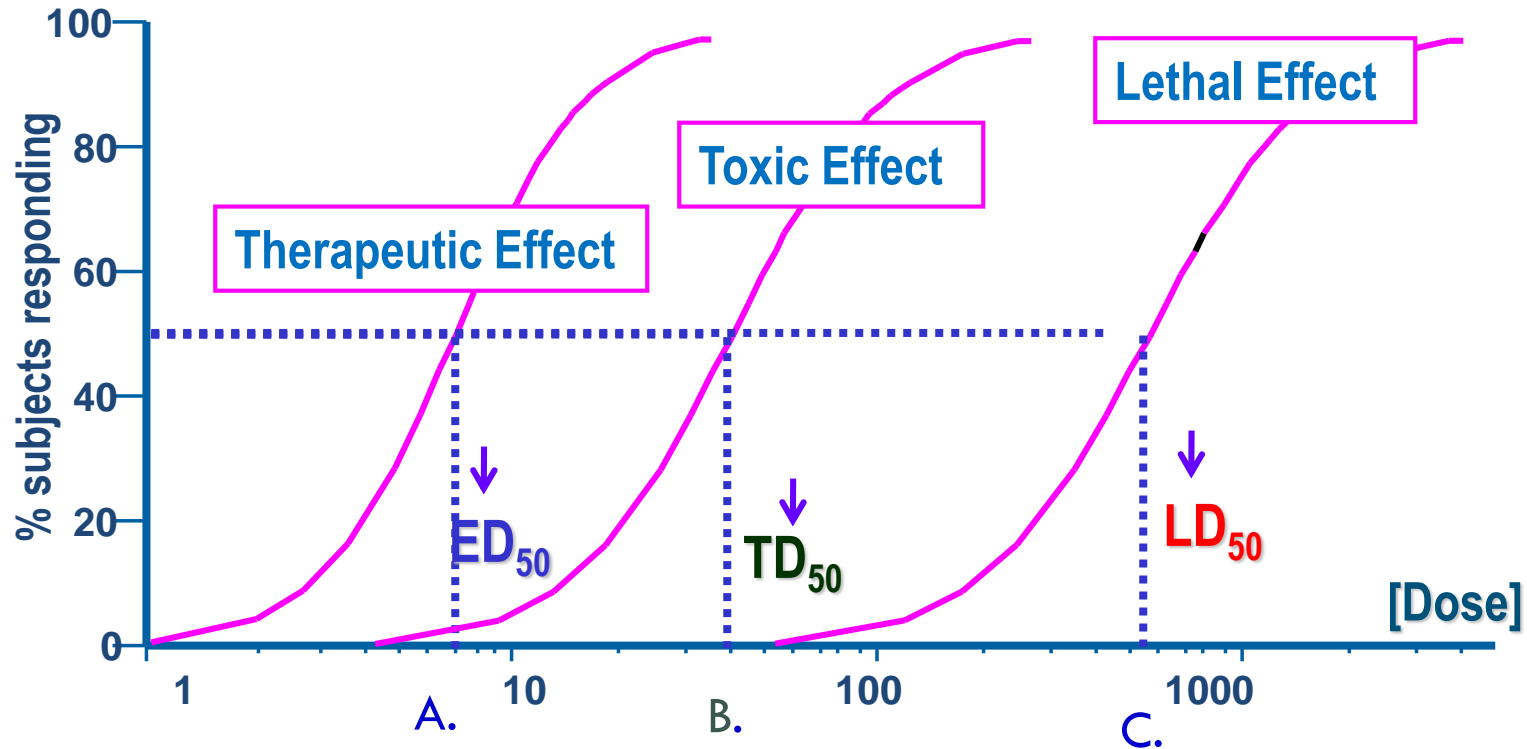
Dose -response curves

□ 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



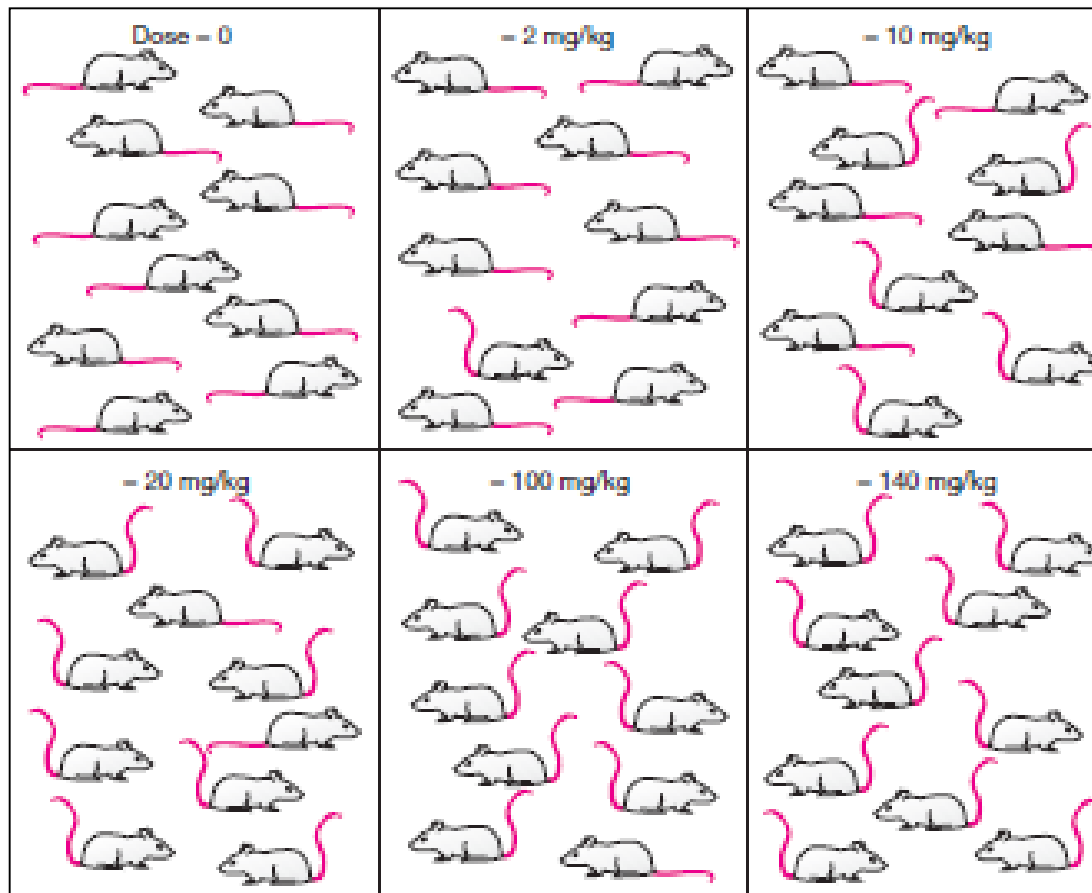
- A. 50% of individuals exhibit the specified therapeutic response
- B. “ “ “ toxic effects
- C. “ “ “ death

Predict the safety profile

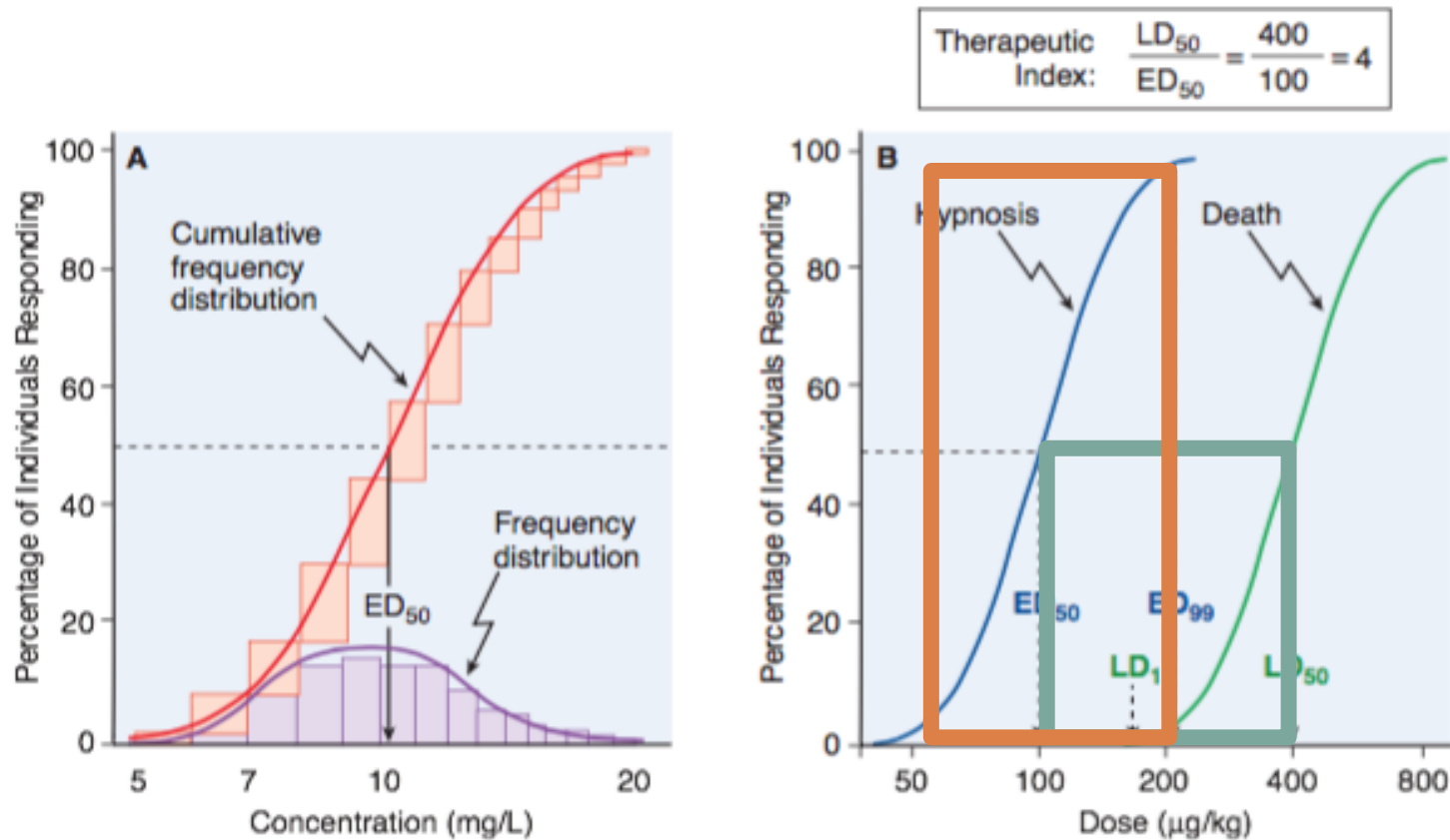
Therapeutic Index (T.I.)

- 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.)

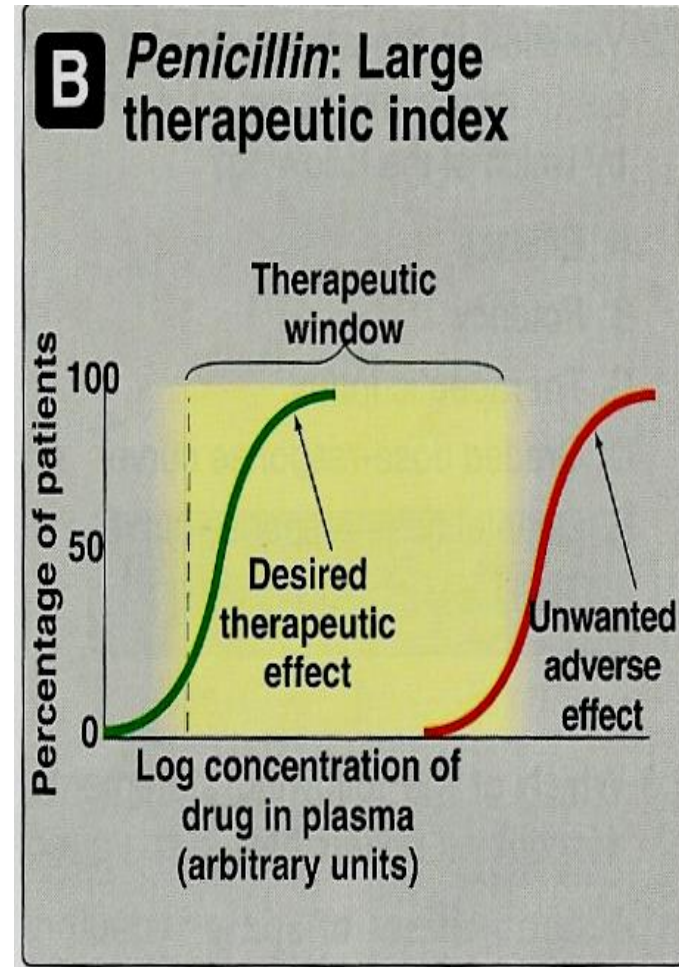
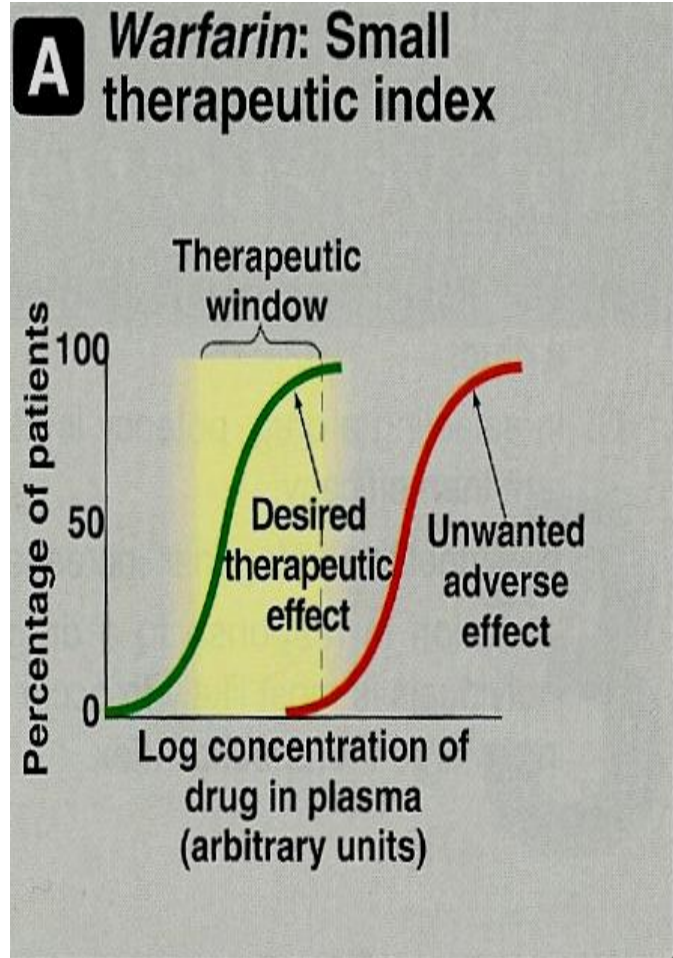


Therapeutic Window



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 (\uparrow BP) & bronchodilation.

□ **Histamine** → vasodilatation (\downarrow 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

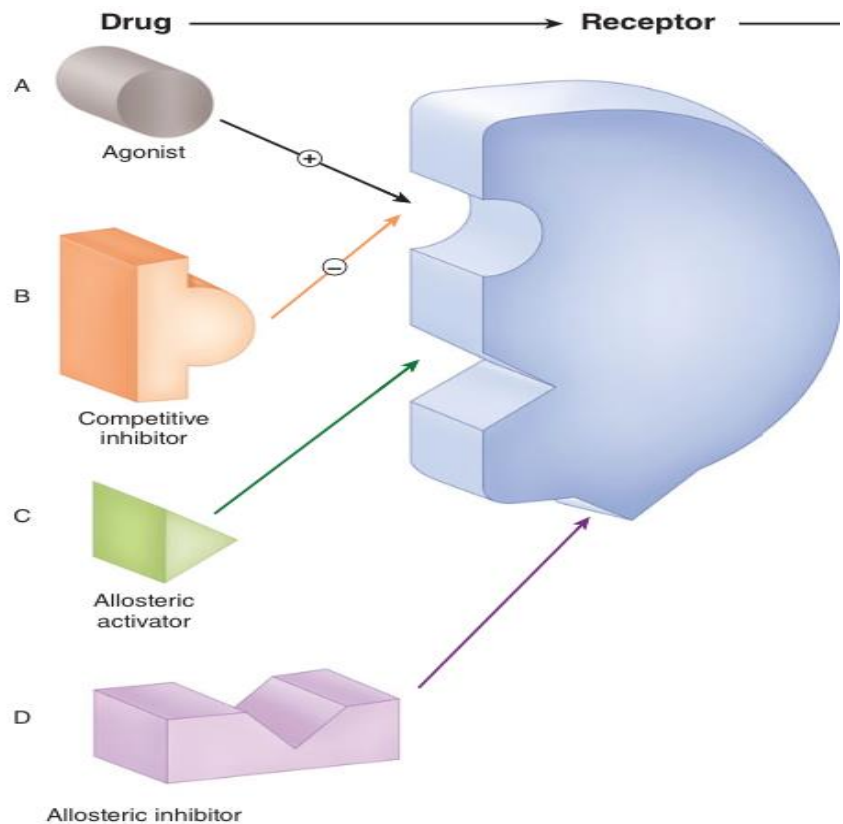
▣ Pharmacodynamic antagonism (Receptor-blockade antagonism).

■ Competitive

■ Reversible

■ Irreversible

■ Non-Competitive



Antagonism

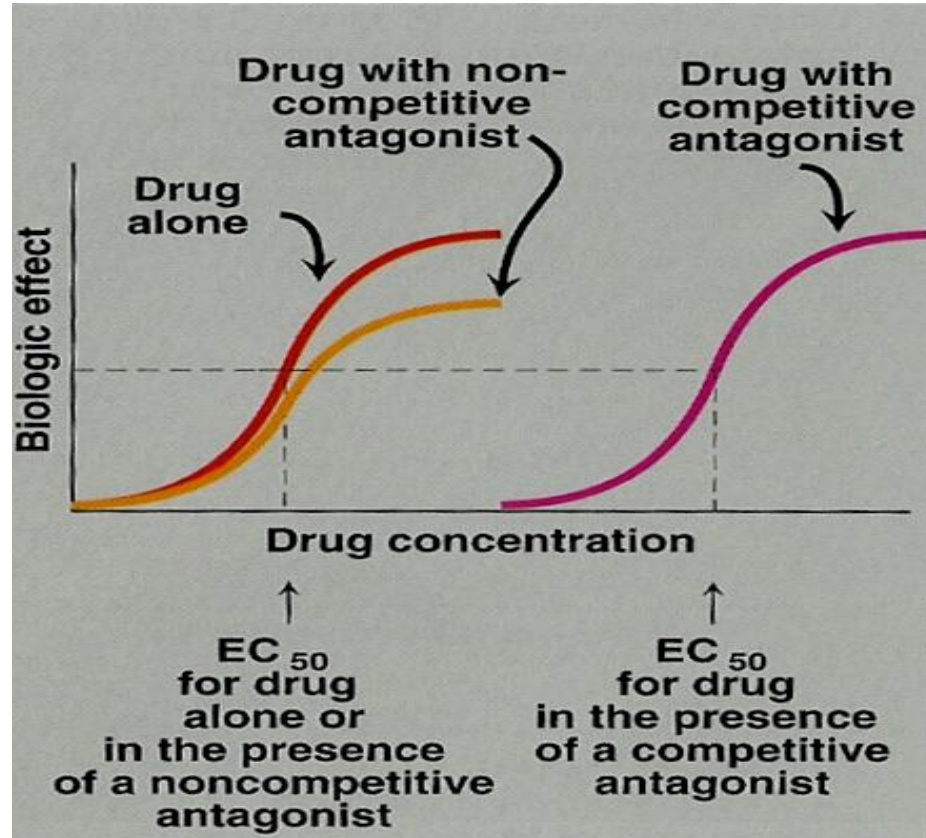
- **Types**
 - Pharmacodynamic antagonism (Receptor-blockade antagonism).
 - Competitive
 - Reversible
- Two drugs compete for the same receptor.
- The antagonist partially or completely prevents the pharmacological effect of agonist.
- Antagonist dissociate rapidly from receptor.
- Antagonism can be 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

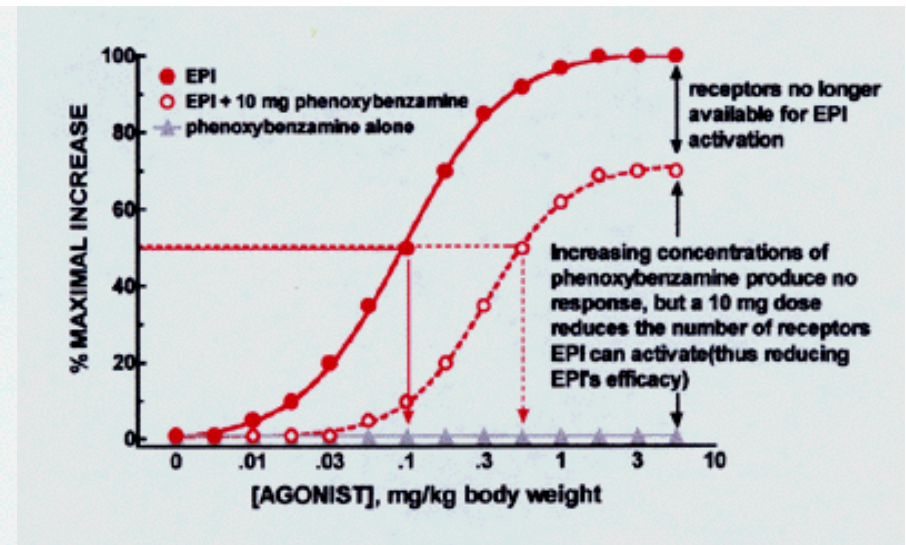
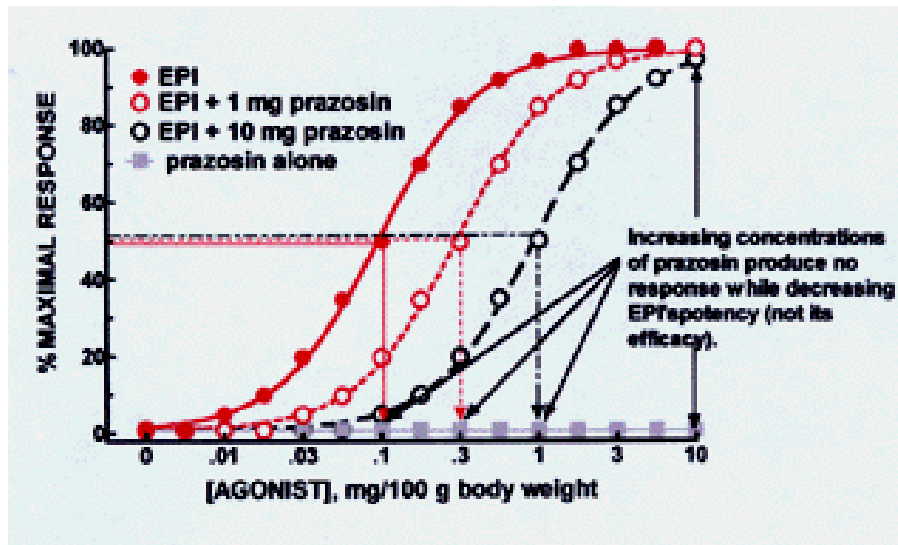
- Pharmacodynamic antagonism (Receptor-blockade antagonism).
 - Competitive
 - Irreversible
- Two drugs compete for the same receptor.
- **Antagonist** forms stable, permanent chemical bond with receptor.
- The original response can not be overcome even by increasing the dose of the agonist.
- No parallel 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

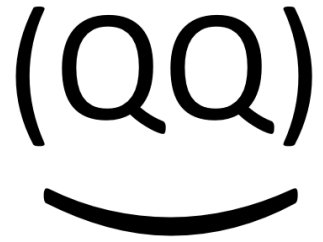
□ Types

- 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 dissociation 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.

Questions/Quote (QQ)



“It always seems impossible until it's done.”

Nelson Mandela

Read more at: https://www.brainyquote.com/quotes/nelson_mandela_378967?img=2&src=t_motivational