Lecture (6)

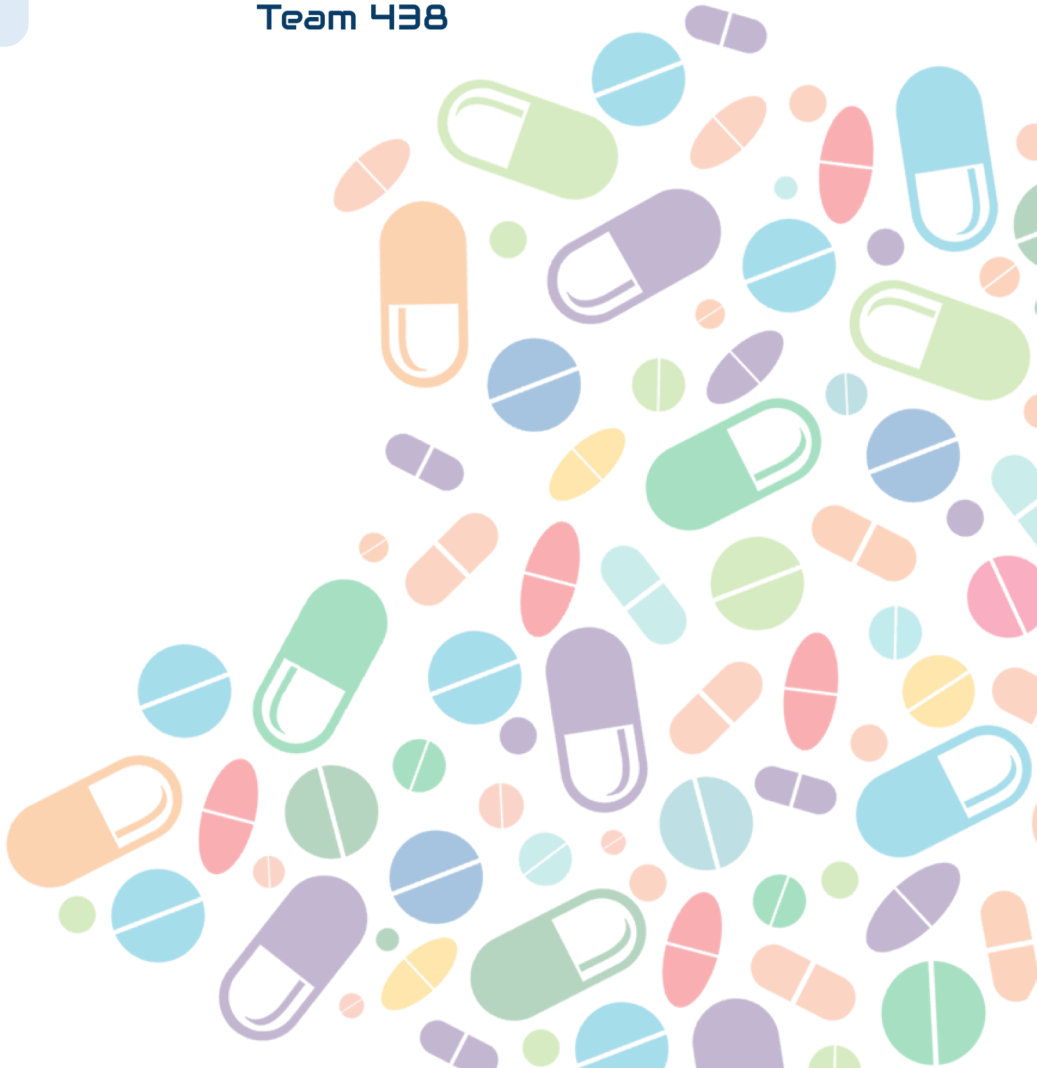
QUANTITATIVE ASPECTS OF DRUGS

pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

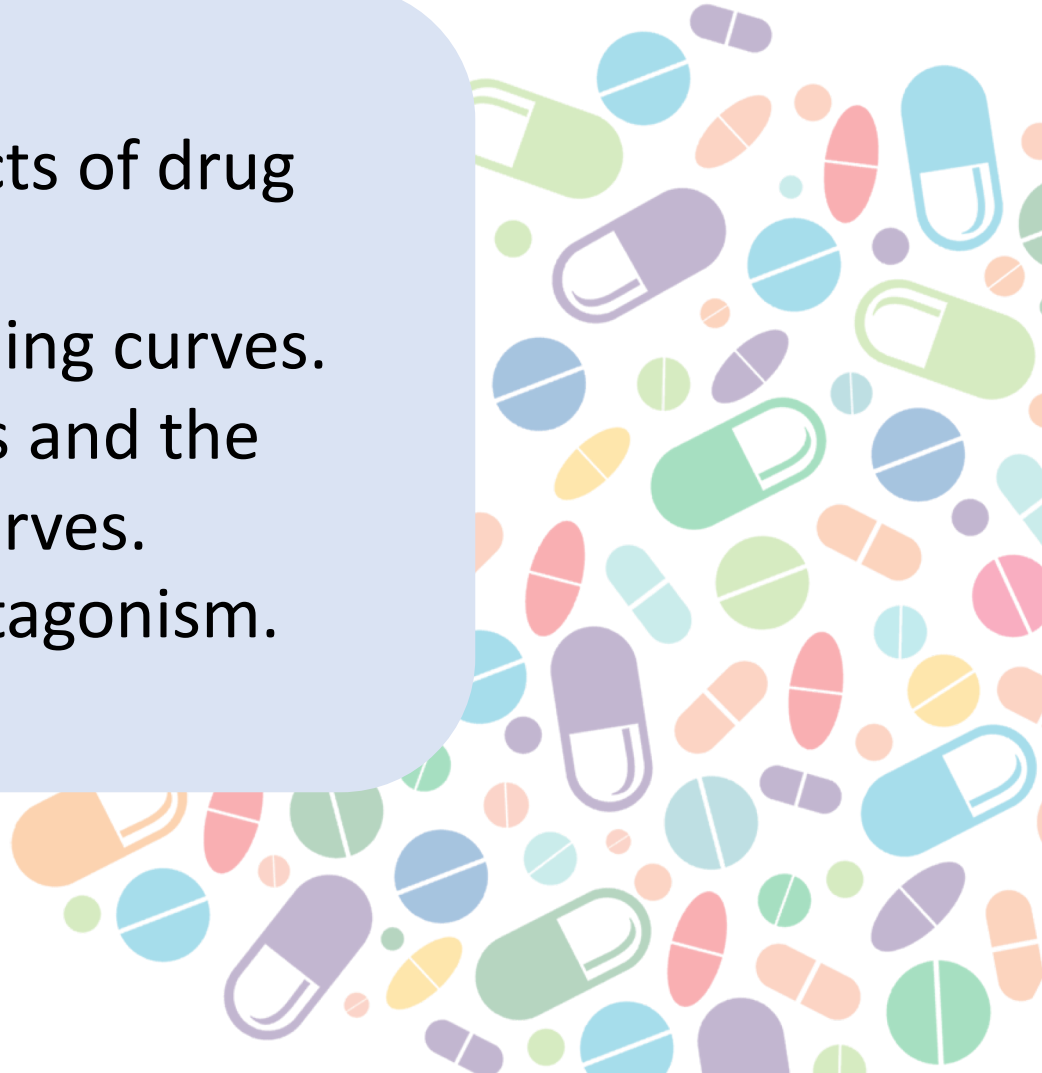
- Red : important
- Black : in male / female slides
- Pink : in girls slides only
- Blue : in male slides only
- Green : notes, Extra

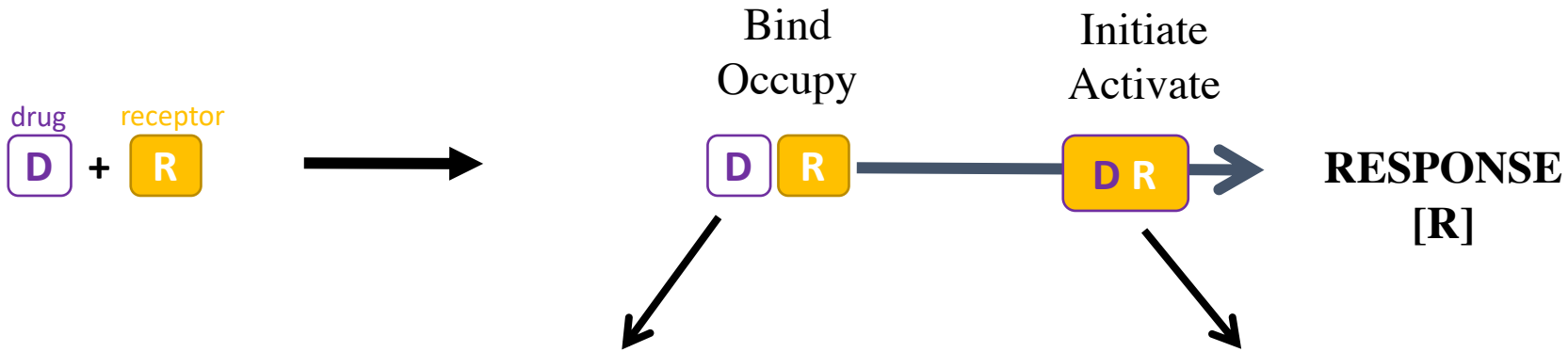
Reviewed by Razan AlRabah & Khalid Alkhani



Objectives:

- 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.





Relate concentration of D used (x- axis) to **binding capacity** at receptors (y-axis)

Concentration-Binding Curve

Affinity

The tendency of a drug to bind to the receptors

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

Dose-Response Curve

Efficacy

The ability for the drug, once bound, to activate the receptor

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. Affinity

The concentration binding curve is used to determine:

B_{max} (binding capacity):
Is the total density of receptors in the tissue.

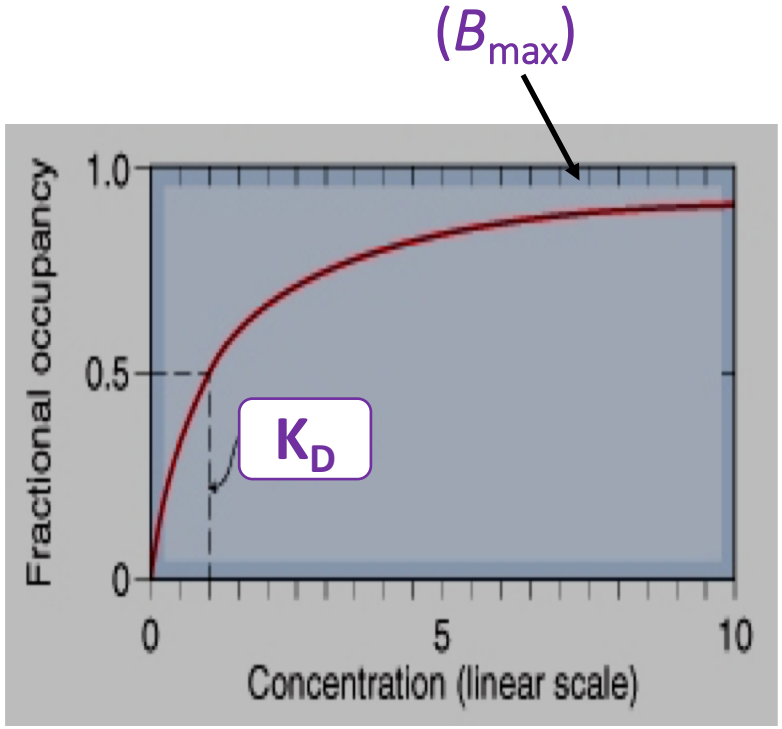
k_{D50} : concentration of drug required to occupy 50% of receptors at equilibrium.

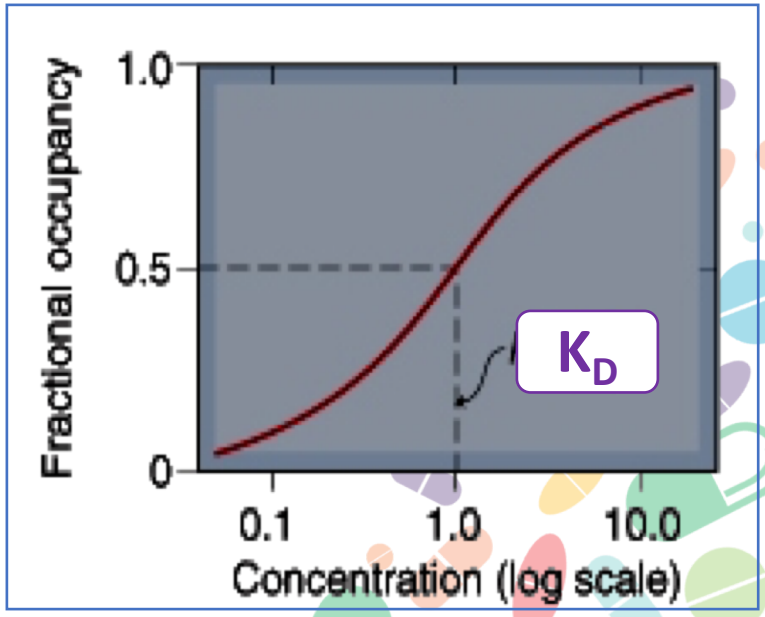
The affinity of drug for receptor:

The higher the affinity of drug for receptor, **the lower is the K_D**

i.e. inverse relation

(Binding Potential= B_{max} / k_D)





Dose-response curves: Is a correlation between **drug concentration** "C" (x-axis) and **drug response** "R" (y-axis).

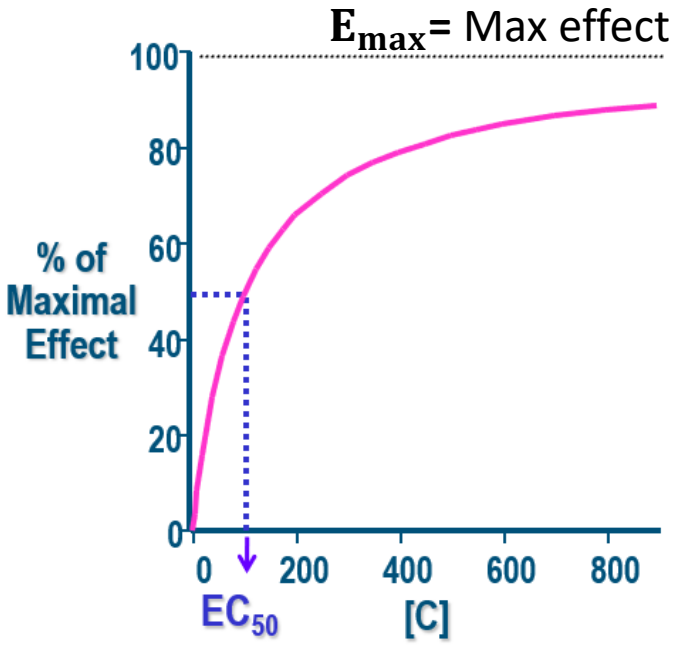
Used to study how response changes with the concentration of the drug or dose.

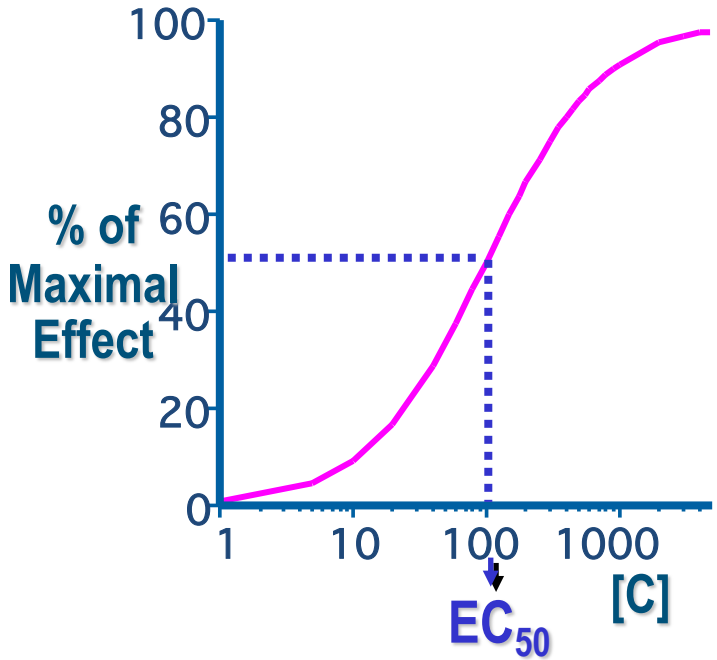
Types of **Dose-response curves:**

- **Graded Dose-response curve**
- **Quantal Dose-response curves** (All or None)

1- Graded Dose-Response Curve:

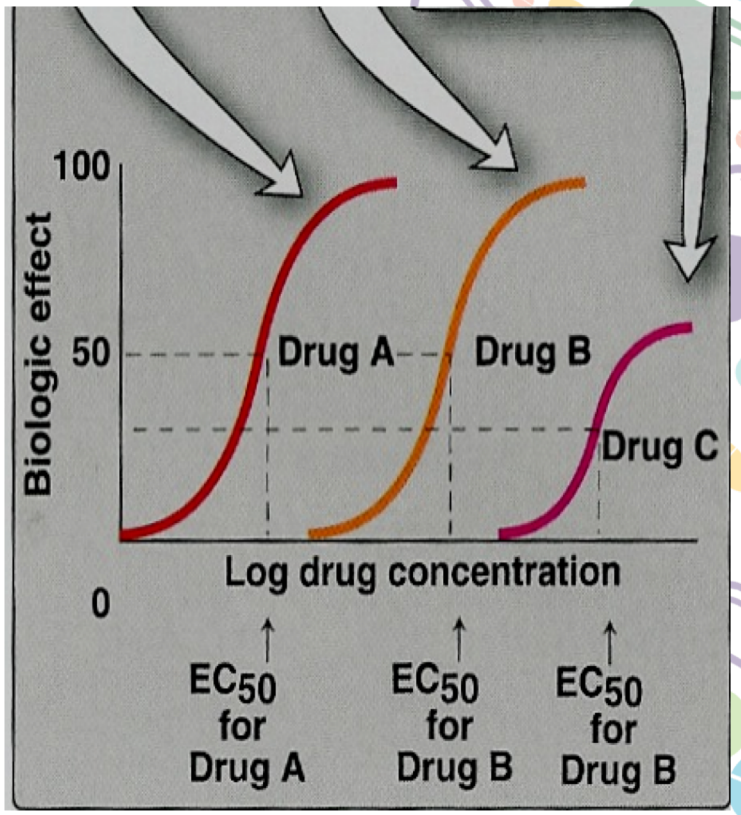
- Relate drug concentration to response
- Response is **gradual**
- Gradual increase in response by increasing the dose **(continuous)**
- Examples:↓blood pressure, heart rate, blood glucose level, cholesterol,…
- usually **sigmoid** in shape





Graded dose-response curves are used to determine:

- **Efficacy**
- **E_{max} (maximum efficacy):** is the **maximal** biological **response** produced by a drug.
- **EC_{50} (median effective conc.):** is the concentration of the drug that produces a response equal to **50%** of **(E_{max})**.
- **Potency**: the concentration of the drug required to produce a specified response
  (50% of the maximal response = **EC_{50}**)
- **Potency** is inversely proportional to EC_{50}
  (The smaller the **EC_{50}**, the more potent the drug is)



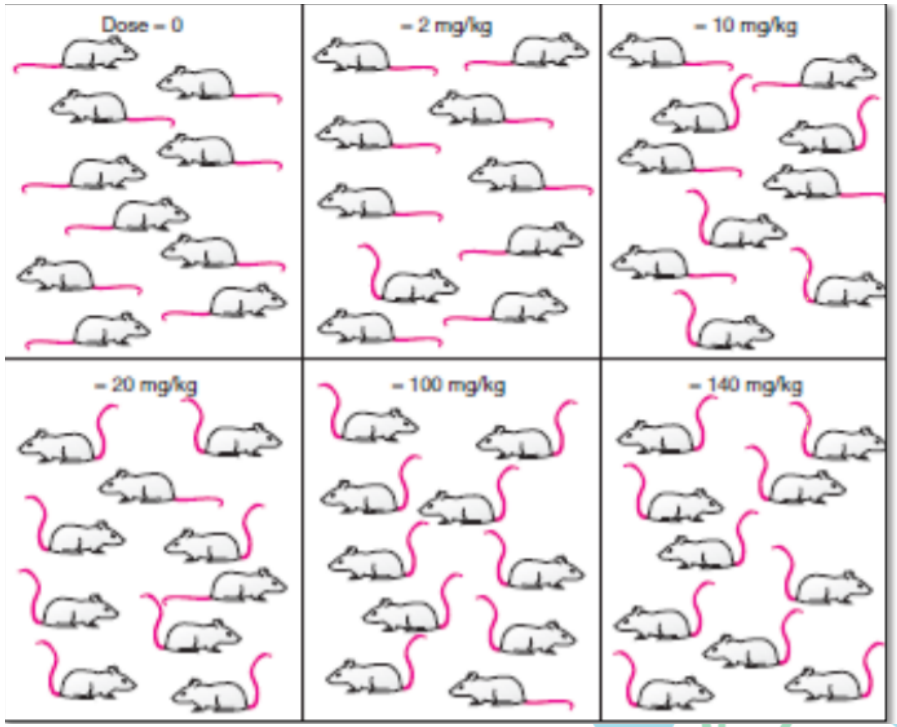
Drug A is more potent than **Drug B.**
Drug B is more potent than **Drug C.**
so **Drug C** has the least potency.

PS: **Drug C** has also the lowest efficacy (measured by the height).

In case we want to know about the **potency** we compare the **EC50** for all the drugs. And if we want to know about the **Efficacy** we compare the **Emax** for all the drugs.

2- 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.
    - Examples: prevention of convulsion, arrhythmias or death.



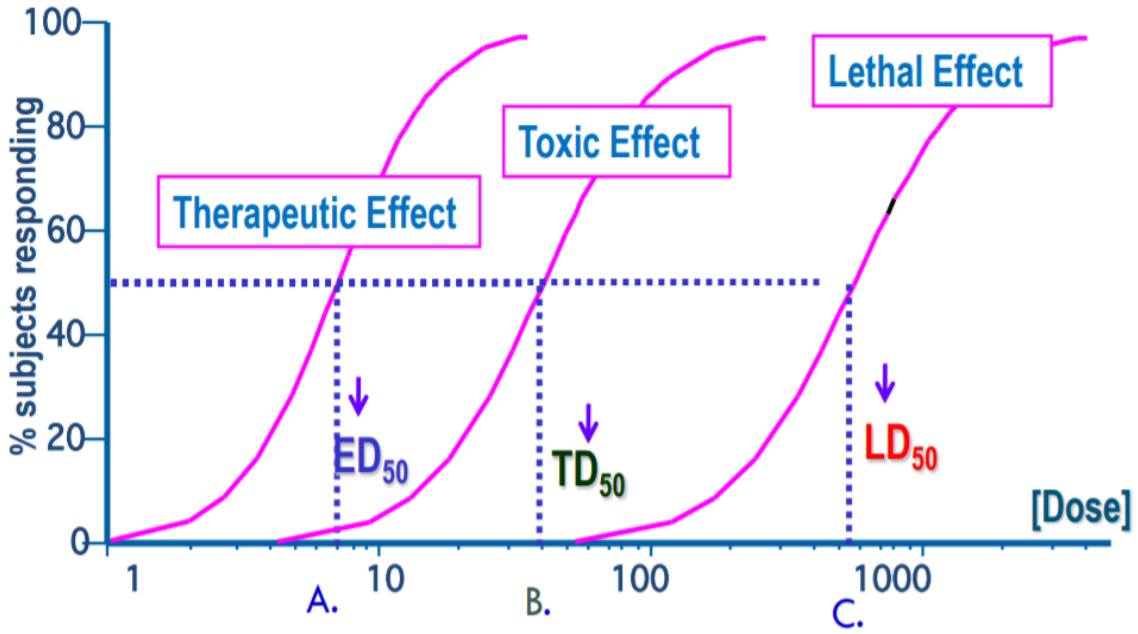
Quantal Dose-response Curve is used to determine:

1- **(ED_{50}) Median Effective Dose :** is a dose of the drug required to produce a **therapeutic effect** in **50%** of **individuals**. (arrhythmia prevention)

2- **(TD_{50}) Median Toxic Dose :** is the dose of a drug required to produce **toxic effects** in **50%** of **individuals**. (e.g. kidney failure)

3- **(LD_{50}) Median Lethal Dose :** is the dose of a drug required to produce **death** in **50%** of **individuals**.

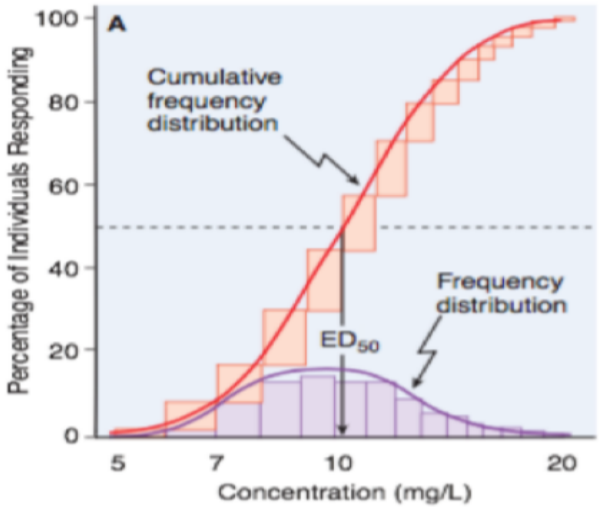
4-**Therapeutic index (TI) :** is the range of doses that produces therapeutic response without causing any significant adverse effect in patients.

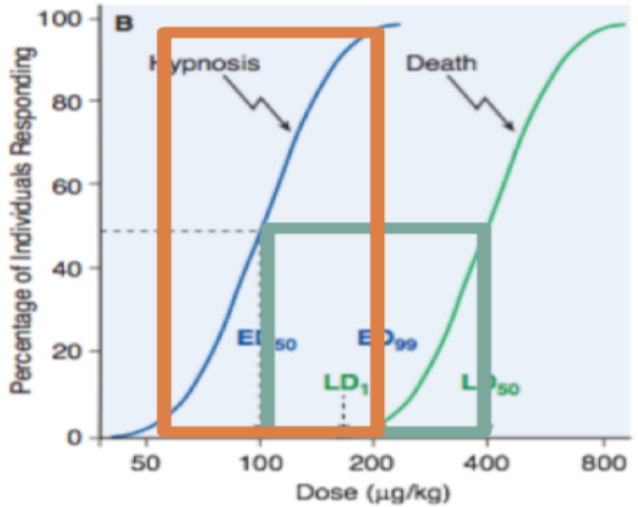


Therapeutic Index (TI):

- Therapeutic index = TD_{50}/ED_{50} or LD_{50}/ED_{50}
- Is a measure of safety profile
- **High value**= drug with **wide margin of safety**.
  Examples: diazepam, penicillin
- **Small value** = a **narrow margin of safety**.
  Examples: digoxin, warfarin

Therapeutic Index: $\frac{LD_{50}}{ED_{50}} = \frac{400}{100} = 4$



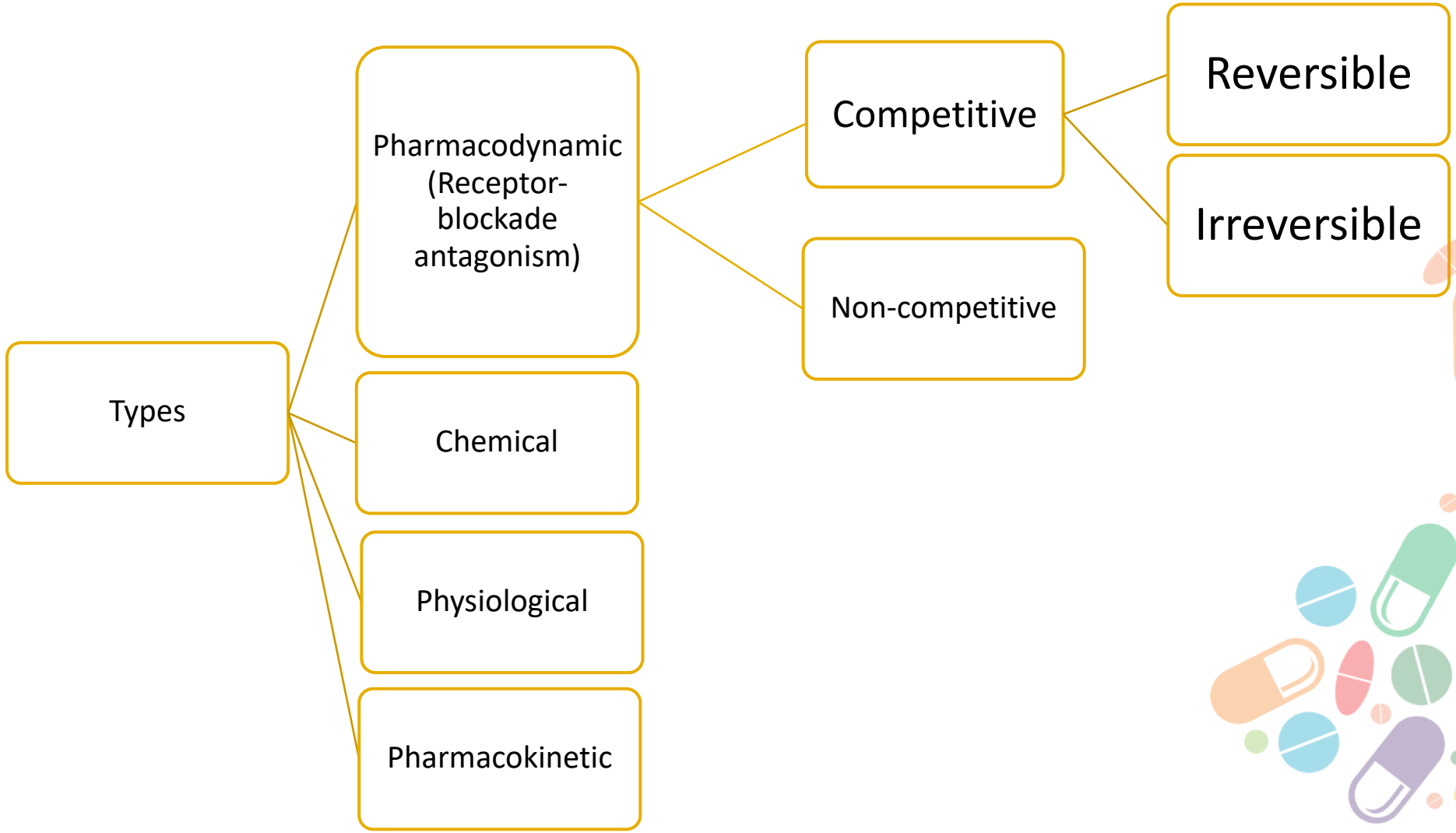


Therapeutic Window

Therapeutic Index

Antagonism

- It is the decrease or the complete abolishment (abolishment = إبطال) of the effect of one drug in the presence of another (Drug-Drug interaction).



PHYSIOLOGICAL ANTAGONISM:

- Two drugs act on **different receptors** to produce **opposite physiological effects**.
  e.g.(Histamine) & (Adrenaline)
  - Adrenaline > vasoconstriction and bronchodilatation > increase blood pressure
  - Histamine > vasodilatation and bronchoconstriction > decrease blood pressure
  - Adrenaline is used in anaphylactic shock.

CHEMICAL ANTAGONISM:

- Simple chemical reaction between 2 drugs resulting into loss of activity
- No receptor

  Ex. Dimercaprol (which reduces heavy metal toxicity E.g. Lead)

PHARMACOKINETIC:

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

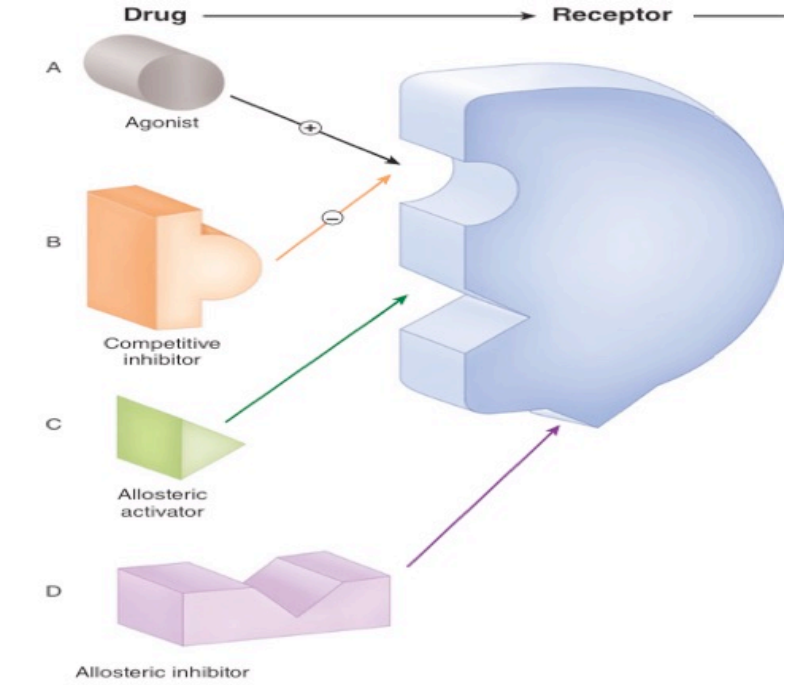
  Ex. Phenobarbitone (which accelerates hepatic metabolism of warfarin)

PHARMACODYNAMIC ANTAGONISM:

Competitive: Two drugs compete for the same receptor (only one is bound)

Reversible:

- 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 value

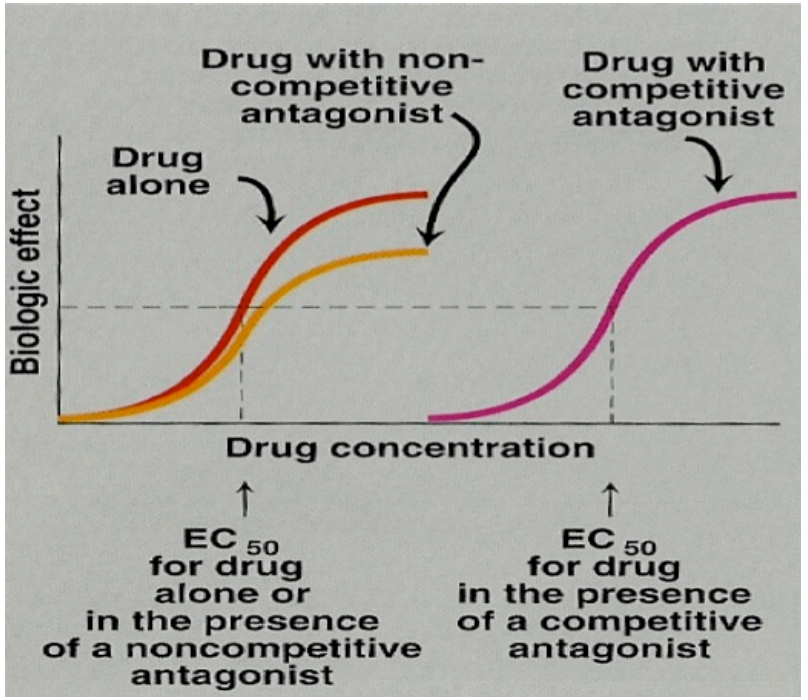


e.g. Acetylcholine and atropine

Irreversible:

- Antagonist forms **stable**, **permanent** chemical bond with receptor.
- The original response **can't be overcome** even by increasing the dose of the agonist.
- A decrease in slope and a reduced maximal response are obtained, without any parallel shift.

e.g. phenoxybenzamine and noradrenaline.

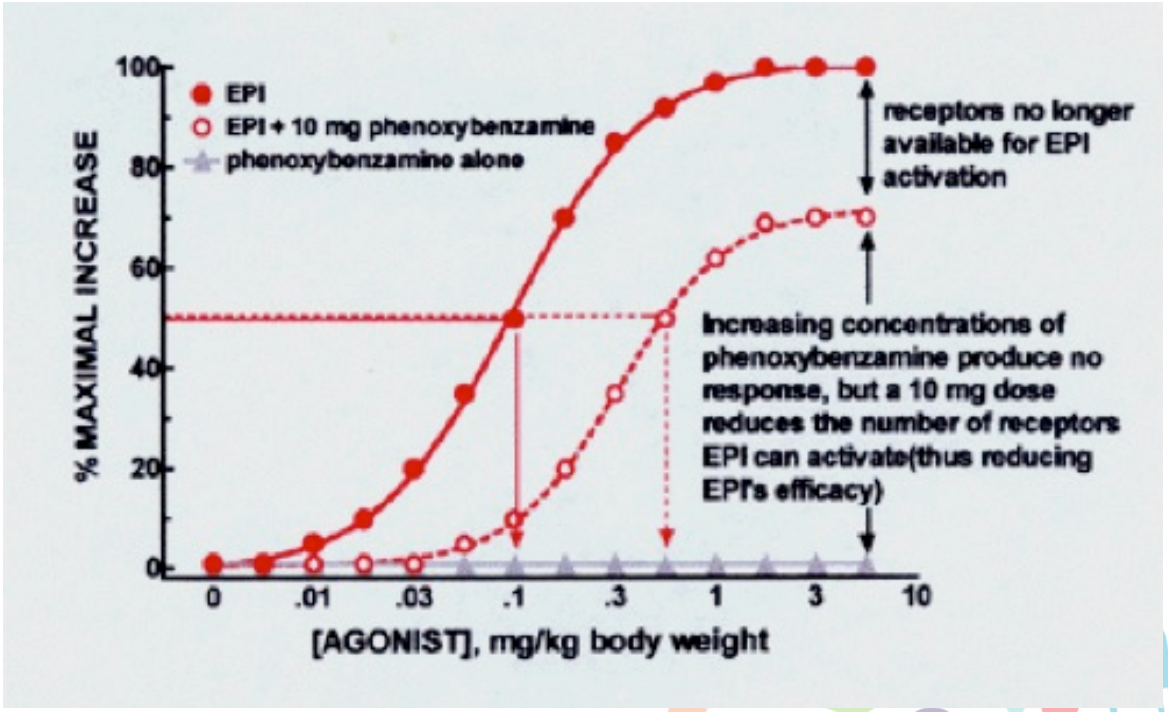


PHARMACODYNAMIC ANTAGONISM:

Non competitive

- Antagonist block at some point the chain of events that stimulates the response of agonist.
- Agonist and Antagonist can bound **simultaneously.**
- Antagonism **can't be overcome** by increasing concentration of agonist

e.g. verapamil and noradrenaline



Found in male's slides only

EC100:

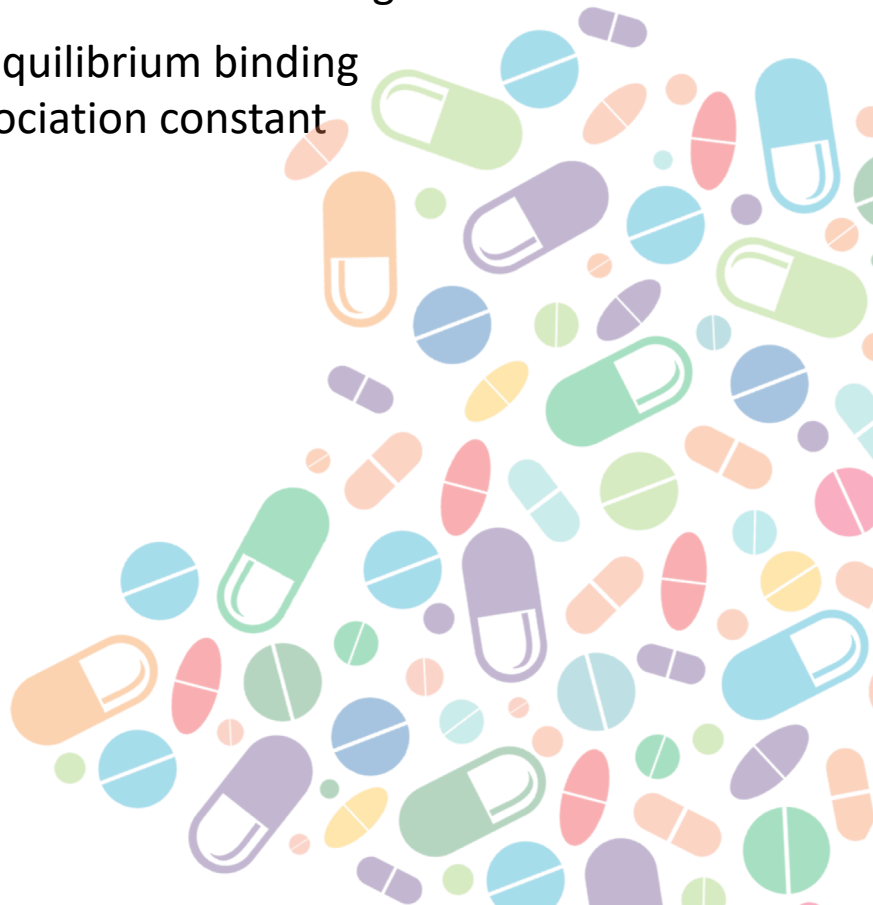
As the concentration (X) goes up, the dose-response equation (Y) gets closer and closer to the Top plateau. But it never reaches it.

When a drug binds to a receptor the fraction occupancy equals D/(D+K)

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.

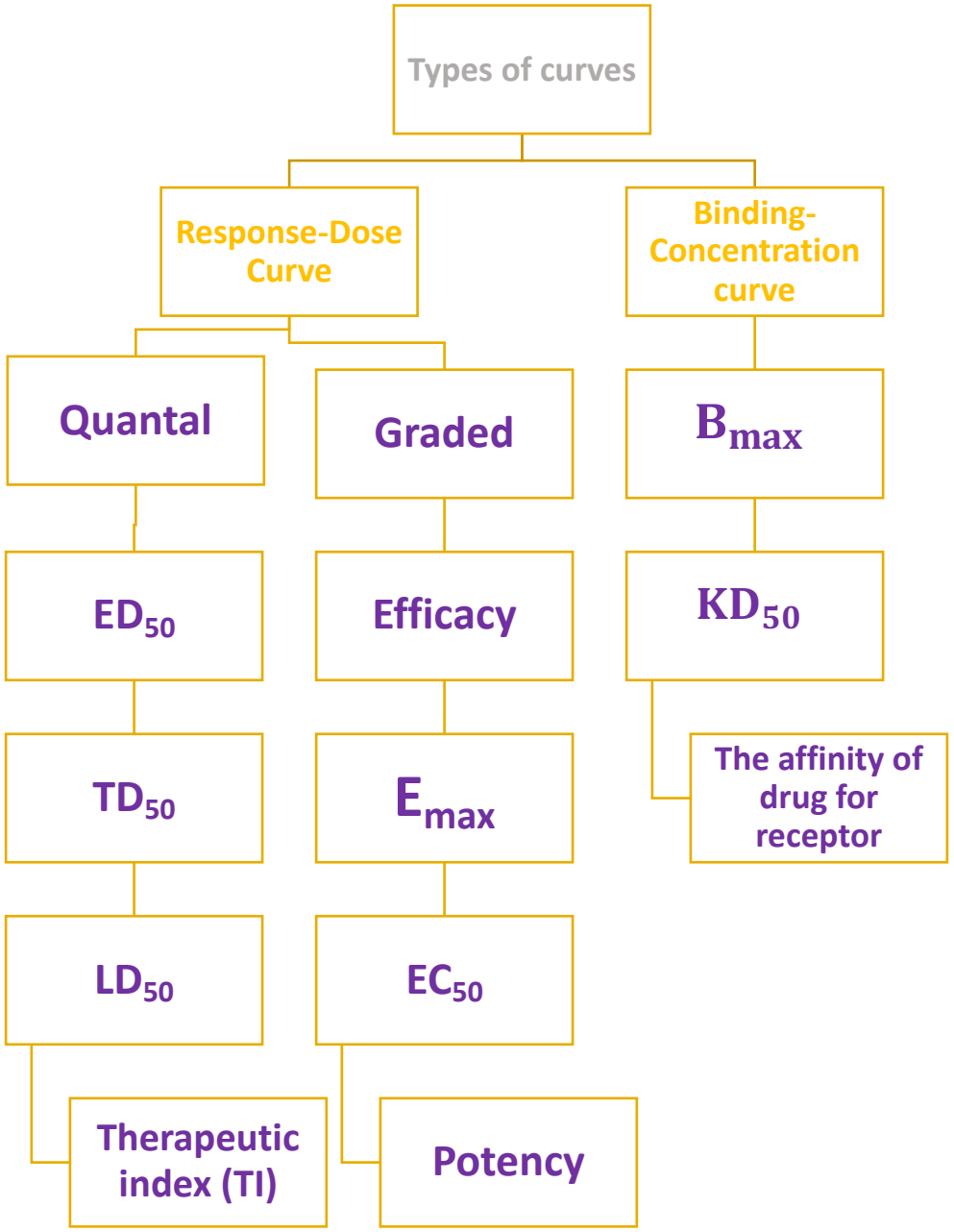
D=concentration of drug

K= equilibrium binding dissociation constant



In other words even if you increase D to a million there will always be a K in the denominator (المقام) and as such will never truly reach EC 100

SUMMARY


Types of curves
Response-Dose Curve
Binding-Concentration curve
Quantal
Graded
B_{max}
ED_{50}
Efficacy
KD_{50}
TD_{50}
E_{max}
The affinity of drug for receptor
LD_{50}
EC_{50}
Therapeutic index (TI)
Potency

Quiz (MCQ) :

Q1.The tendency of a drug to bind to the receptors is called?

A)Affinity B)Efficacy C)Potency

Q2.Which one of these the Concentration-Binding curves are used to determine?

A) ED_{50} B) E_{max} C) B_{max}

Q3.Relate drug concentration to % percentage of patients responding is referred to?

A)Graded Dose-Response Curve B) Quantal dose-response curve C) Concentration-Binding curves

Q4.A drug with wide margin of safety ?

A)warfarin B)diazepam C)digoxin

Q5.Which type of Antagonism has No receptors involved ?

A)Pharmacodynamic antagonism B)Physiological antagonism C)Chemical Antagonism

Q6.Two drugs compete for the same receptor and Decrease in maximum effect are referred to?

A)Competitive (irreversible) B)Competitive (reversible) C) Non-competitive

ANSWER : 1)A - 2)C - 3)B - 4)B - 5)C - 6)A

Quiz (SAQ) :

Q1.the relation between concentration & drug binding is referred to ?

Q2.What is the total density of receptors in the tissues ?

Q3.What are the types of Dose-Response Curve ?

Q4.In which one of Dose-Response Curve types the response is gradual and continuous ?

Q5. What the Quantal Dose-response Curve used to determine?

Q6. What is the dose of a drug required to produce death in 50 % of individuals?

Q7.What Is the measure of safety profile?

Q8.Give an example to a drug with a narrow margin of safety?

Q9.Give example to Two drugs act on different receptors to produce opposite physiological effects?

10.Give an example to a Pharmacodynamic antagonism Non-competitive drug ?

Answer(SAQ) :

1.Concentration-Binding curves

2.B_{max} (the binding capacity)

3. -Graded dose-response curve -Quantal dose-response curve

4.Graded dose-response curve

5. -ED_{50} _ TD_{50} -LD_{50} _Therapeutic index (**TI**)

6.Median Lethal Dose (LD_{50})

7.Therapeutic Index (TI)

8. digoxin, warfarin

9. histamine and adrenaline

10.verapamil and noradrenaline

Good luck

Thanks to the pharma team 435

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