PHARMACOLOGY

Modified no. 8

Writer: Leen Abd

Corrector: Sara Omar

Doctor: Suheil Zmeili

Major receptor families:

1. - Ligand-gated ion channels
2. - G protein-coupled receptors
3. - Enzyme (tyrosine kinase)-linked receptors
4. - Intracellular receptors (ligand-activated transcription factors)

NOTE: ■
This is very important!
Understand this very well
then memorize

1. Ligand-gated ion channels

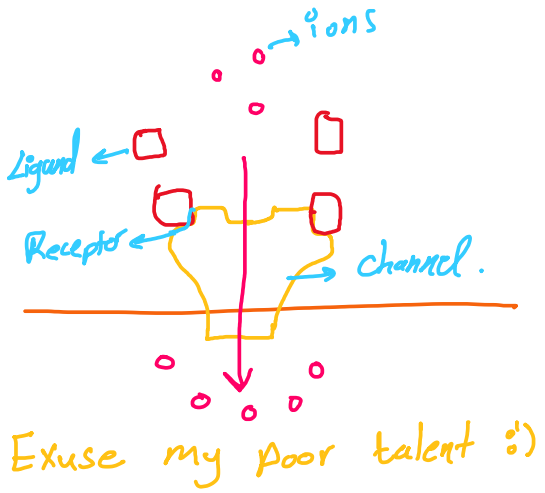
- Responsible for regulation of the flow of ions through channels across cell membranes
- Regulated by binding of a ligand to the channels

e.g. the nicotinic receptors, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle

NOTE: ■

It's simply works by binding a receptor of certain drug with ion channel (potassium, sodium, etc..) , and when a drug binds with it's receptor this leads to open the ion channel , thus moving the ions out the cell or in, depending on the ion. Such as nicotinic receptors (acetylcholine) , it's binding leads to sodium influx thus the action potential take place in the cell.

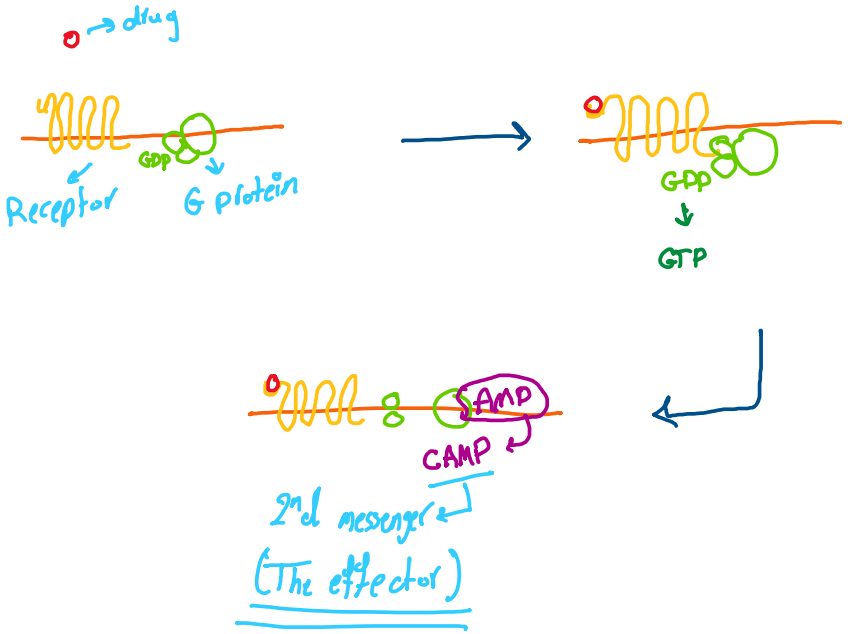
-very quick response



2. G protein-coupled receptors

Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as G proteins (transmembrane proteins)
e.g. Some hormones peptide receptors and neurotransmitter receptors (e.g., adrenergic and muscarinic receptors) depend on the G proteins that mediate their action on cells.

NOTE: ■
well, this receptors exist on the inner surface of plasma membrane (transmembrane)and coupled with G protein. When a drug binds to the receptor, this will cause conformational changes in the inactive G protein, activating it, and finally the G protein will activate the second messenger who will do the required effect.

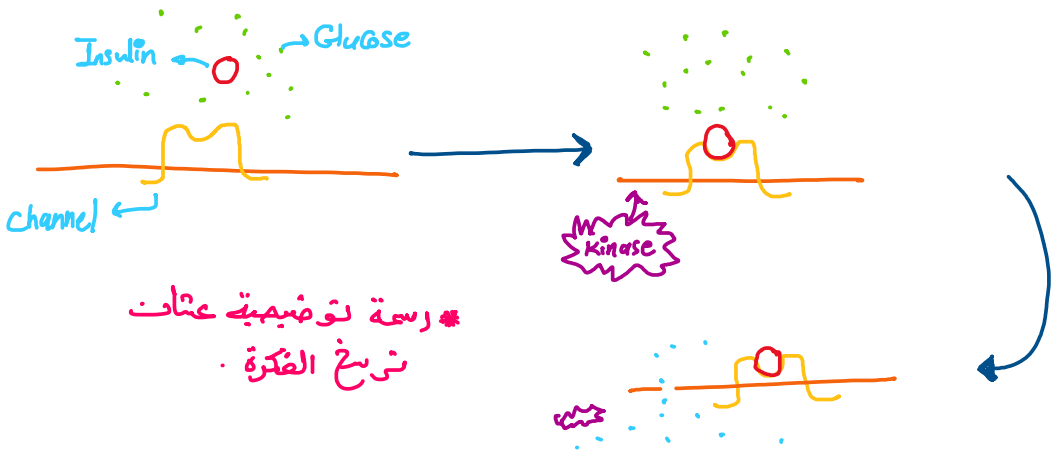


3. Enzyme-linked receptors

- Binding of the ligand to the extra cellular domain activates or inhibits the related cytosolic enzyme
- The most common are the receptors that have a tyrosine kinase activity as part of their structure, in which the binding results in phosphorylation of tyrosine residues of specific protein
- The addition of phosphate group can modify the three-dimensional structure of the target protein, and so resulting in molecular switch (cellular effect)

NOTE: ■

For instance to enzyme-linked receptors, Insulin which binds to it's receptor, thus activating tyrosine kinase inside the cell, which leads to make a slot in the membrane, allowing the glucose to inter from the bloodstream to inside the cell. These receptors mainly exist in muscles and adipose tissues.



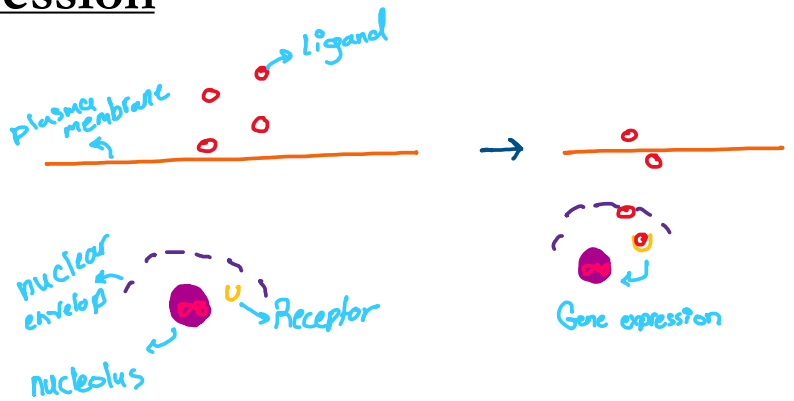
4. Intracellular receptors

- In this family the ligand must diffuse into the cell to interact with the receptors
- The ligand must have sufficient lipid solubilities to be able to move across the target cell membranes
- The best example being the steroids hormones (eg. Sex hormones). In which the activated ligand-receptor complex migrate to the nucleus, where it binds to a specific DNA sequences, resulting in regulation of the gene expression

NOTE: ■

These type of receptors found inside the cell, mainly in cytoplasm or nucleus. The ligand enters the cell through plasma membrane and sometimes it even penetrates the nuclear envelope and bind to specific nuclear receptors, thus changes gene expression of certain protein. Such as estrogen, testosterone, progesterone, etc..

-it is also called nuclear receptor



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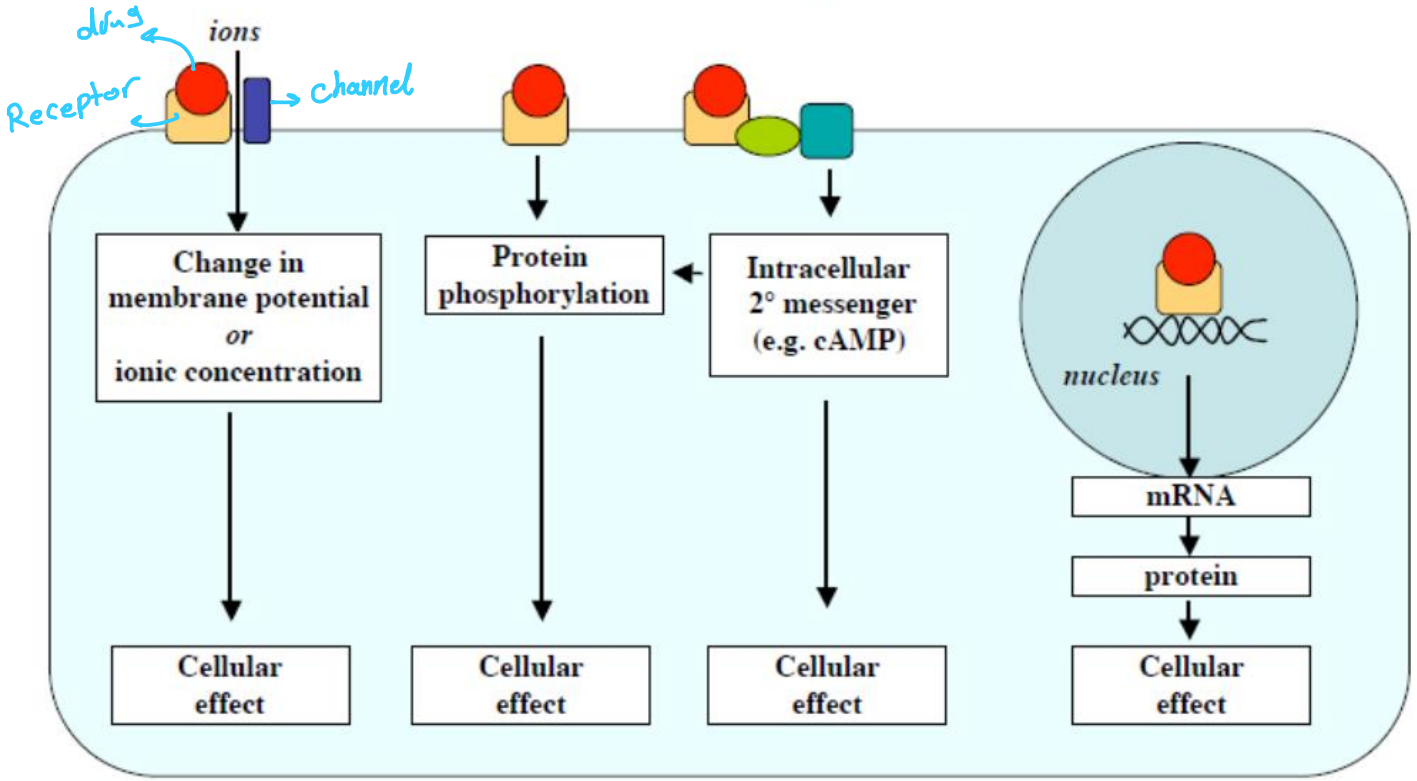
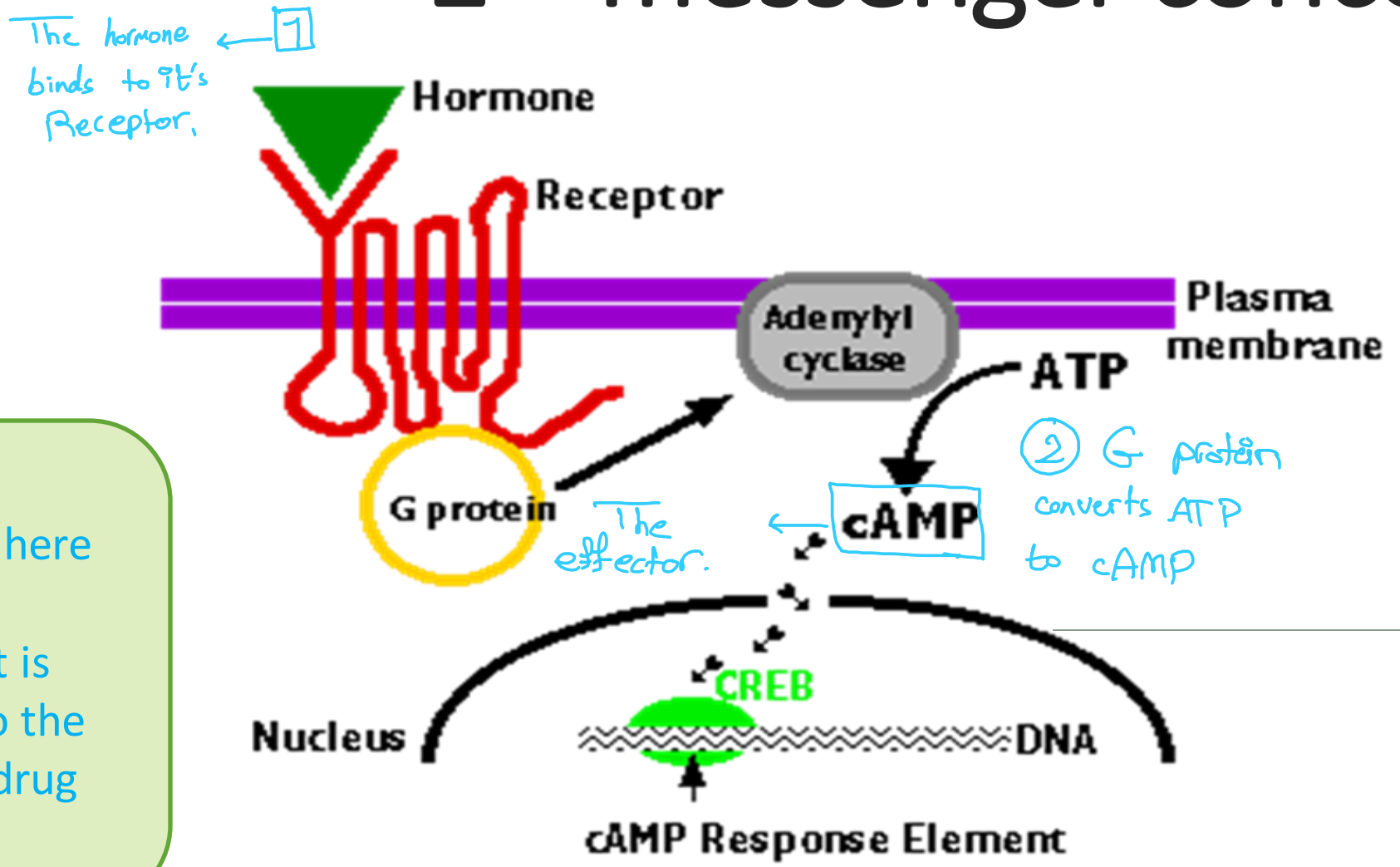
Ligand-gated ion channels	Tyrosine kinase-linked receptors	G-protein coupled receptors	Ligand-activated transcription factors



nicotinic acetylcholine receptor (milliseconds)	insulin receptor (seconds-minutes)	β-adrenergic receptor (seconds-minutes)	estrogen receptor (hours)

- Note: Examples are important
- Note: very quick
- Note: take long time

2nd messenger concept



NOTE: ■

So the effector here is the second messenger that is released due to the binding of the drug to it's receptor.

2^{nd} messengers involved in mediating effects of different drugs include:

cAMP;
cGMP;
DAG;
Ca^{++} ;
ITP (IP_3)...

NOTE: ■
Some examples of 2^{nd} messengers, none of them is major. However, it depends on the site of action.. For instance, cAMP is the major 2^{nd} messenger in specific tissue, not in all.

The complement in this slide:

- **How to know the the second messenger for specific ligand such as TSH ?**

First step we take a thyroid gland (target organ of TSH) and section it ,then we add different 2^{nd} messengers to each section , the section that gives the same response of TSH is the specific 2^{nd} messenger for TSH Wich IP3.

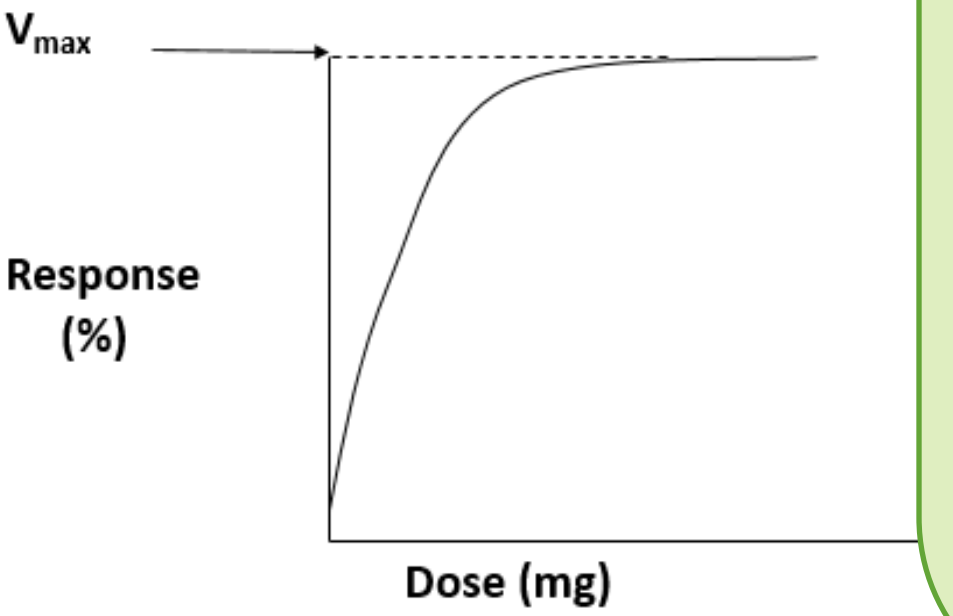
- **Why we don't give the second messenger directly to the patient instead of the ligand?**

Because it is not specific, it will go to different tissues and do different responses.

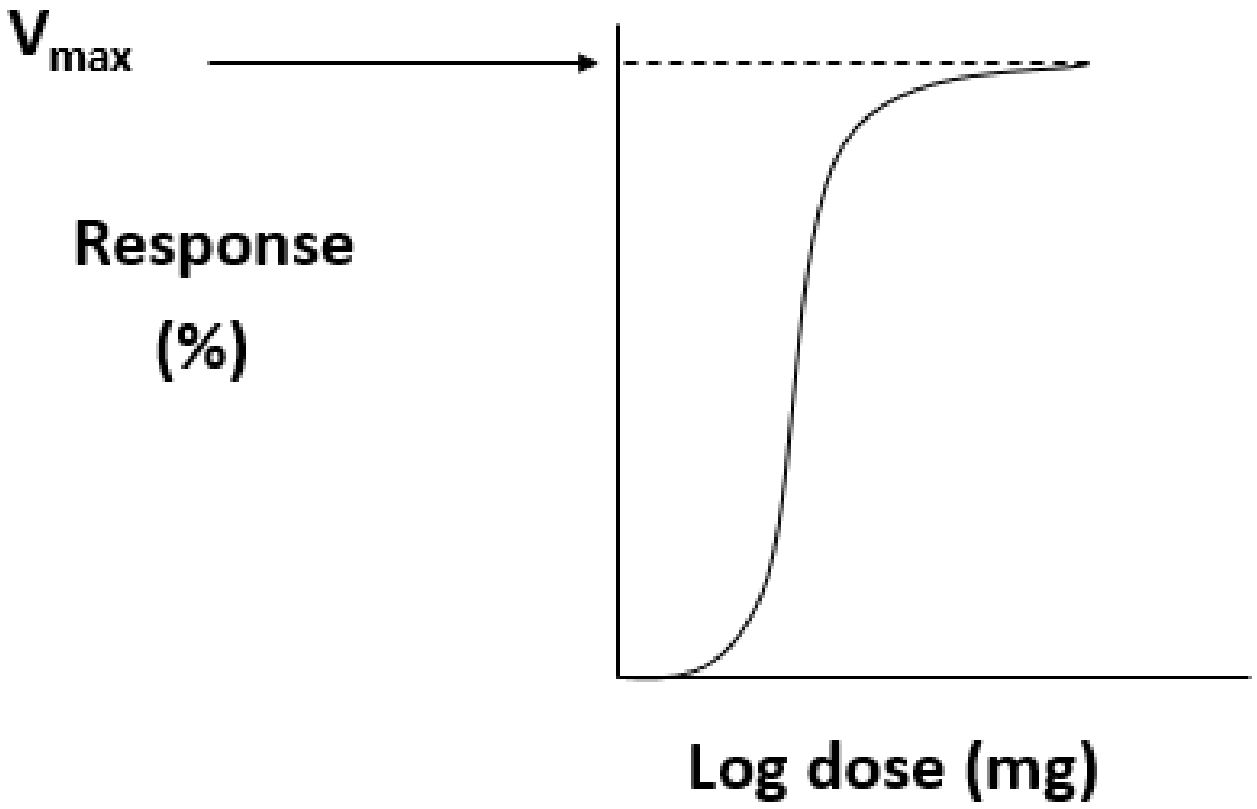
Quantitative studies of drug action

Dose response curves:

- Graded dose-response curves

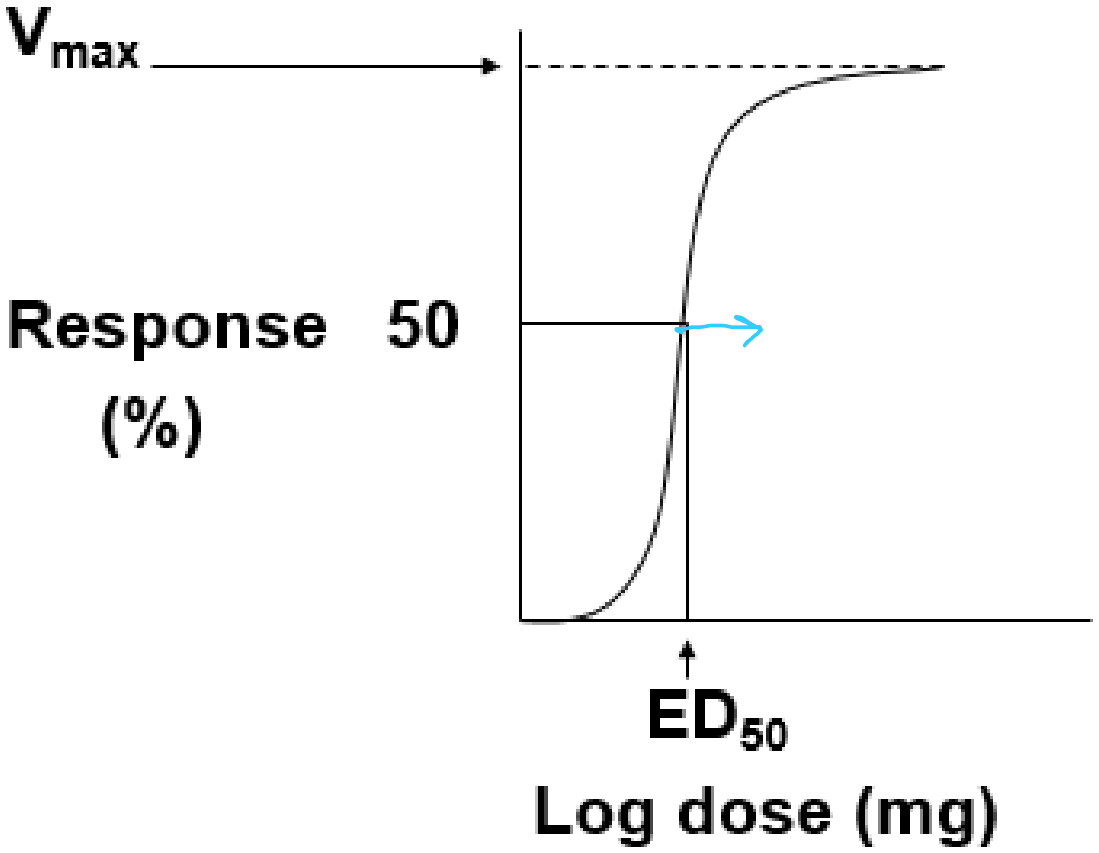


- **NOTE:**Here we measure the effect of a dose of certain drug, to a response to certain tissue. We see at this figure, when we increase the dose, the response increases.
- However, at specific point the response will stop increasing even if we increases the dose, this point is called V_{max} (maximal response).
- Also we must take into consideration that the v max should be in the therapeutic level.. If not ,it will be toxic.
- What is the importance for those studies? I can know the suitable dose , for example, if the V_{max} for a drug occurs within 10 grams, there's no need to give the patient 15 grams; because there will not be a response and may cause side effects



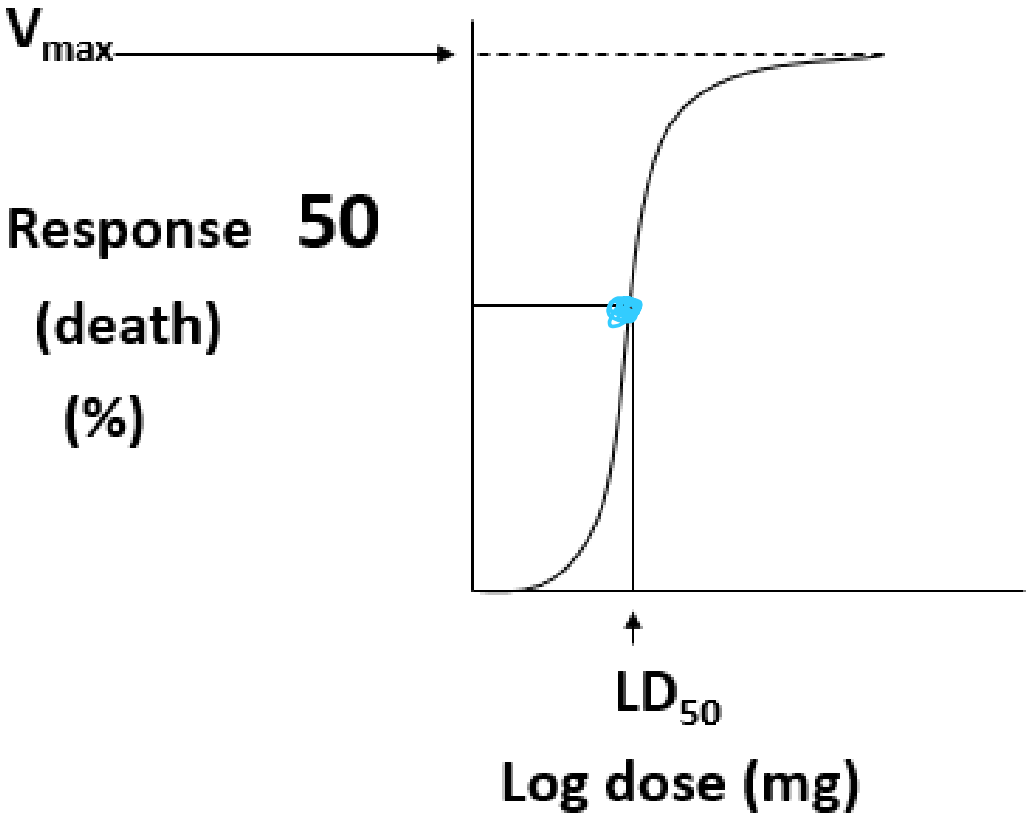
NOTE: ■

The log is used in pharmacology, because it gives sigmoidal shape, which is easier in studying and comparison between the drugs. But don't worry in the exam you will not see logs 🤓.



NOTE:

In the sigmoidal shape that we studied in the previous slide, we can see a point in the middle whereas 50% of the response is done by the dose. We define this as ED50 (effective dose)

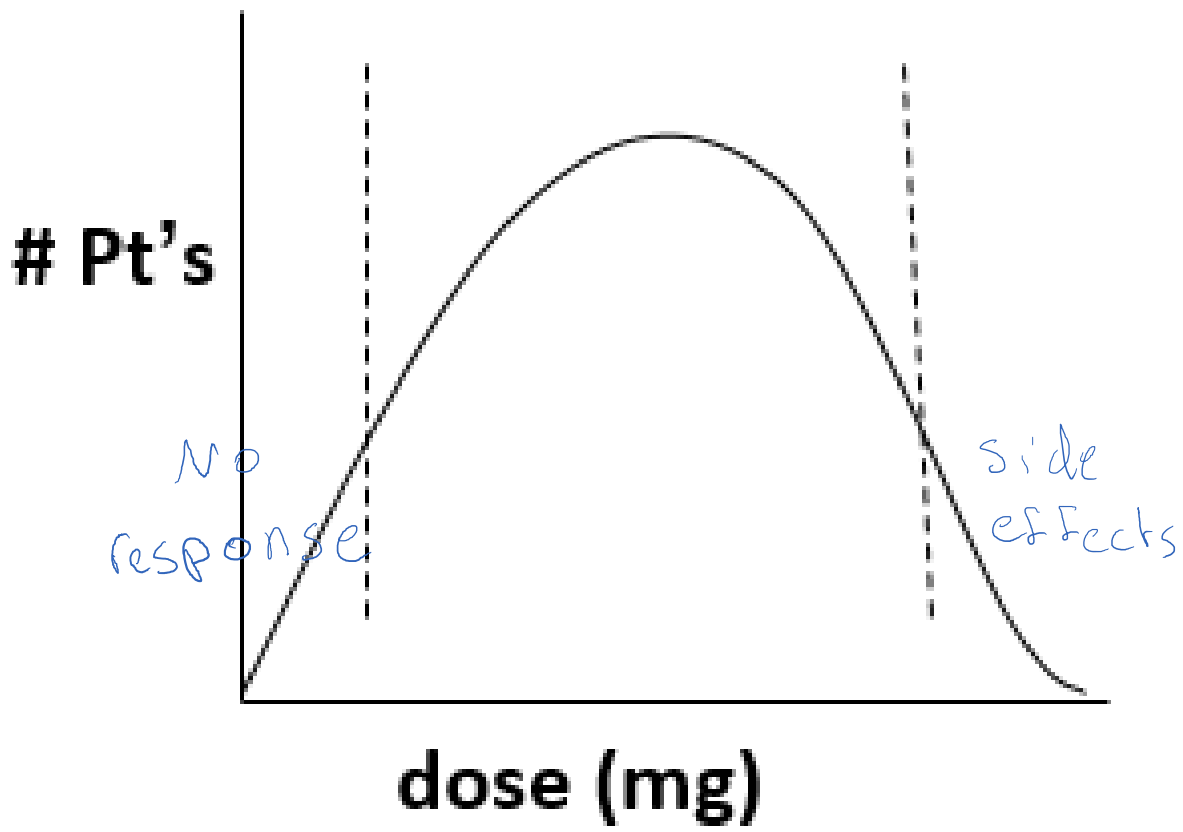


NOTE: ■

As previous slide, this is sigmoidal shape, and the point represents the dose which causes 50% of deaths in animals. We call it LD50(lethal dose).

In humans the same curve will be used but it measures the side effects.

- Quantal dose response curves

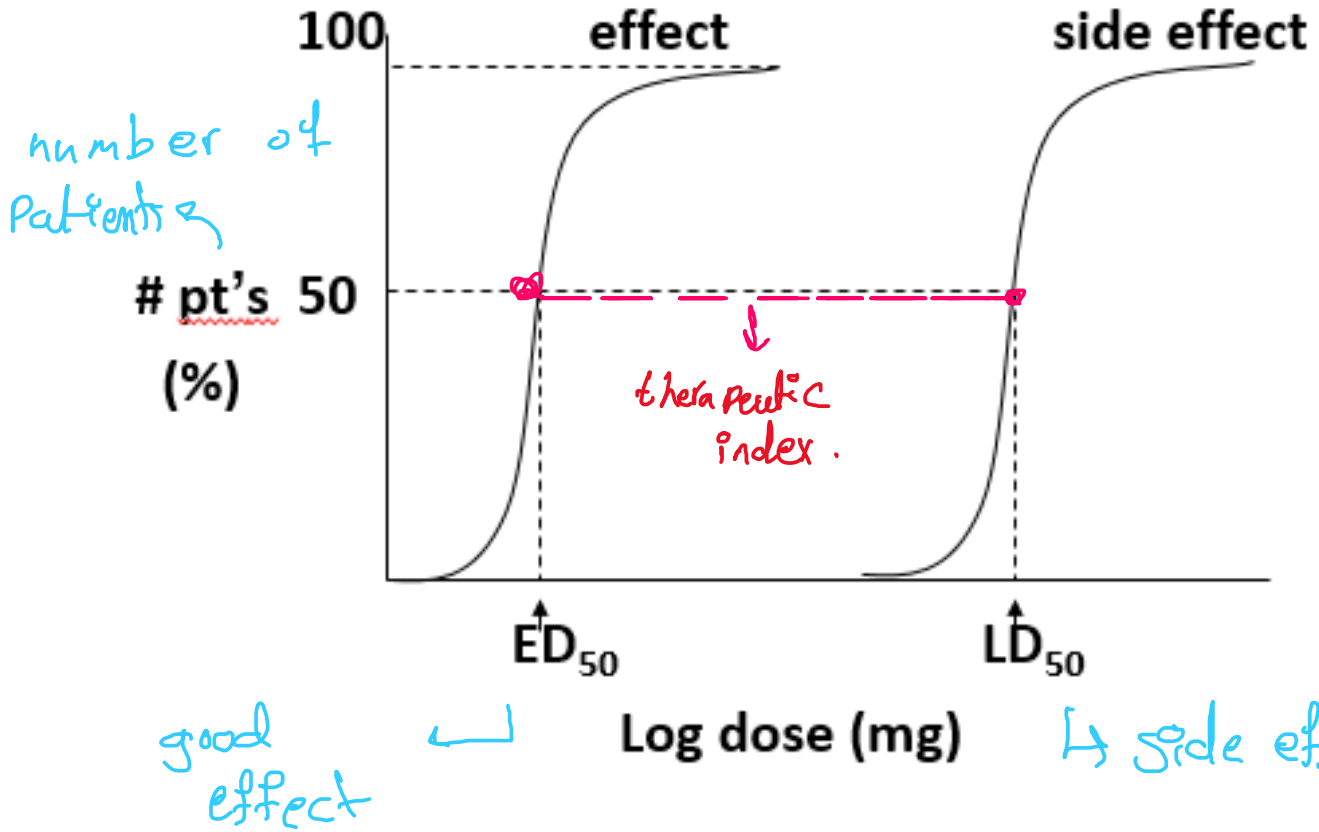


NOTE: ■

This is a normal distribution for dose response in humans.

Be aware that in previous dose response curve we studied the response in tissues or animals not human.

Most people will have the required dose, also few people will have side effects or don't respond to the drug.



NOTE: ■

The distance between ED50 and LD50 , the farther away it is, the safer the drug is.

Exam question ?!

The red line indicates to which of these below?

Ans: therapeutic index or therapeutic window.

- V_{max}:

Maximum response. Also known as efficacy or intrinsic activity. It is important in pharmacology

- ED_{50}:

The dose which produces 50% of response.

- LD_{50}:

The dose which produces death in 50% of animals .

*** Death is considered the most severe side effect to any drug**

- Therapeutic index (TI):

A measure of the safety of drugs

$$TI = LD_{50}/ED_{50}$$

<u>The larger the TI the more safe is the drug</u>

- Potency:

A term used whenever we compare the activity of two drugs producing the <u>same effect</u>

Defined as the dose of one drug necessary to produce a specific response as compared to a second drug producing the same effect

- Affinity:

The ability of a drug to form a stable complex with the receptor ← الألفة

NOTE: ■

Its very important to know that potency just to compare between two drugs that give the same effect. يعني مقارنة برتقالة ببرتقالة أخرى . as Dr said

The Simply, potency means the power of the drug, so if we have drug X which produces an effect with 10 grams, drug Y produces same effect with 2 grams, then Y is more potent than X. <u>Consequently, lower dose, more potent drug. (For same effect and same drug class).</u> Potency is not important as efficacy, because simply we can give the patient any dose since it's in therapeutic level.

• Evaluation of drug safety:

1. Therapeutic index (TI) (LD50/ED50)
2. Margin of safety (LD0.1/ED99.9) (should be more than 1)

A ratio of more than 1 means that the given dose is effective in > 99% of people and producing death or side effects in < 1% of people

NOTE:

The larger IT , the safer is the drug .

The larger the margin of safety the safer is the drug

NOTE:

Margin of safety is not required for the exam

NOTE: READ ONLY

Margin of safety= $\frac{\text{LD1 - ED99}}{\text{(ED99)}}$ x 100%

For example, if a 100mg of drug causes toxicity in 1% of the population and 10mg is effective in 99 %, then the standard margin of safety equals to:

$$\frac{(100 - 10)}{10} \times 100 = 900$$

This means that the dose which is effective in 99 % must be increased 900 % to be toxic to 1% of the population

TI & margin of safety are only one measure to assess safety of drugs for use in medicine

e.g digoxin has a TI of 2 and yet is very important in treating pt's with heart failure (one has to balance dangerous effects of disease vs side effects of drug)

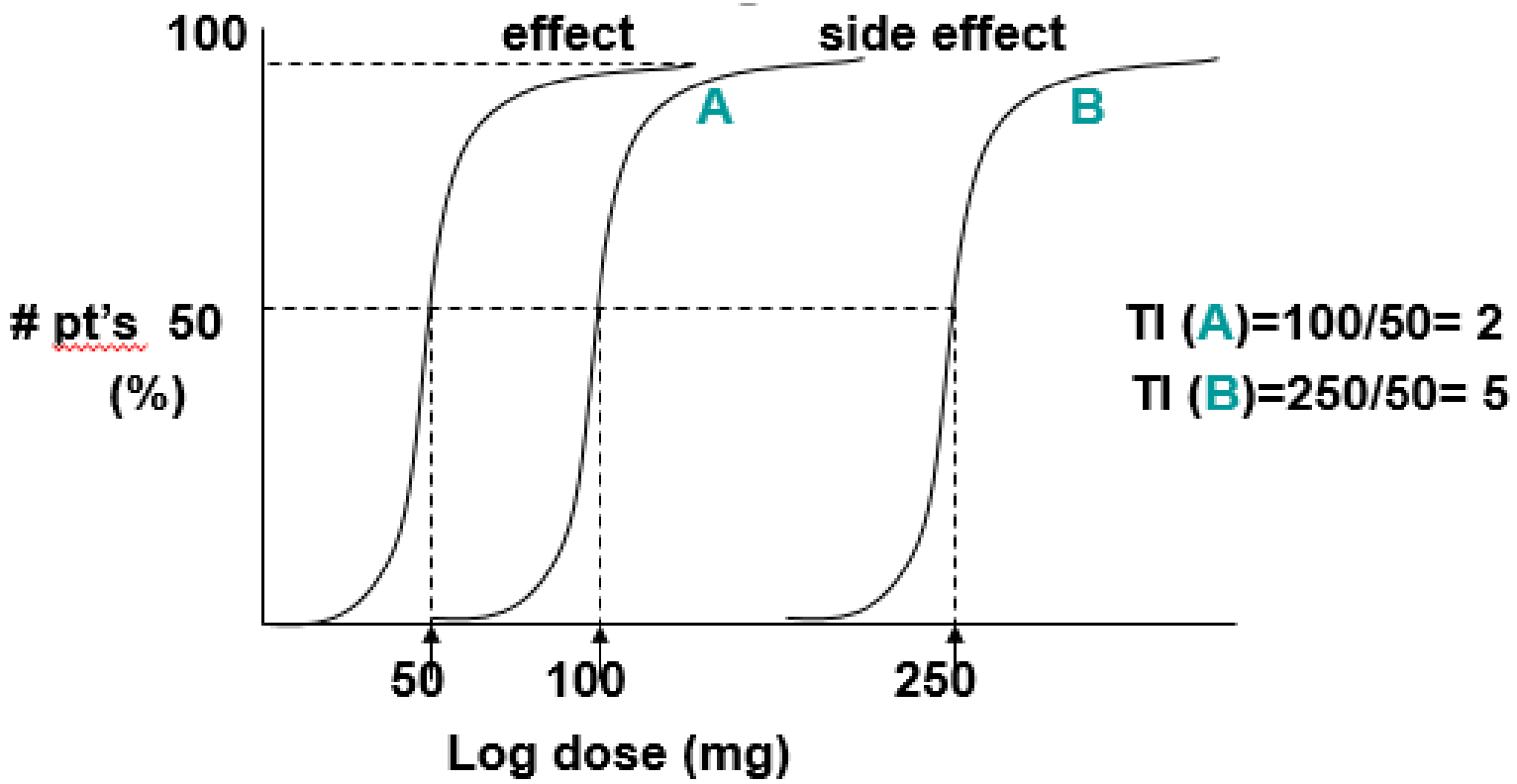
The same applies to anticancerous drugs

3. Protective index (PI)

NOTE: more sensitive than TI ; measures side effects rather than deaths

$$PI = \frac{\text{ED50 producing side effects}}{\text{ED50 producing desired effect}}$$

- Considered the best measure to assess safety of drugs since most drugs produce side effects in doses lower than those which produce death
- The larger the PI the better the drug
- PI of 1 means that the dose which produces the desired effect in 50% of pt's still produces side effects in 50% of them

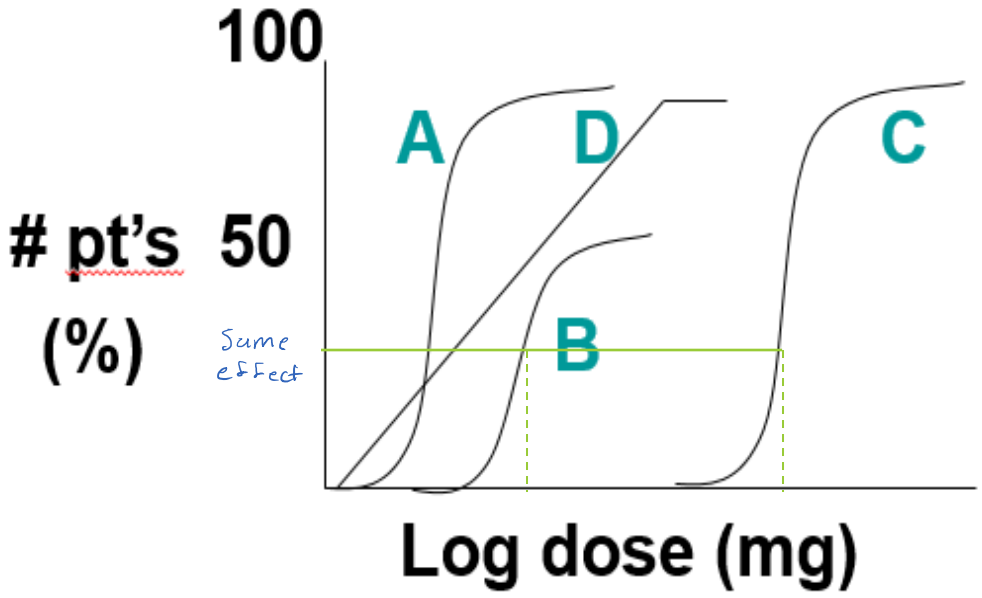


TI (A)=100/50= 2

TI (B)=250/50= 5

NOTE: ■

B is safer than A since TI(B) is higher than TI(A)



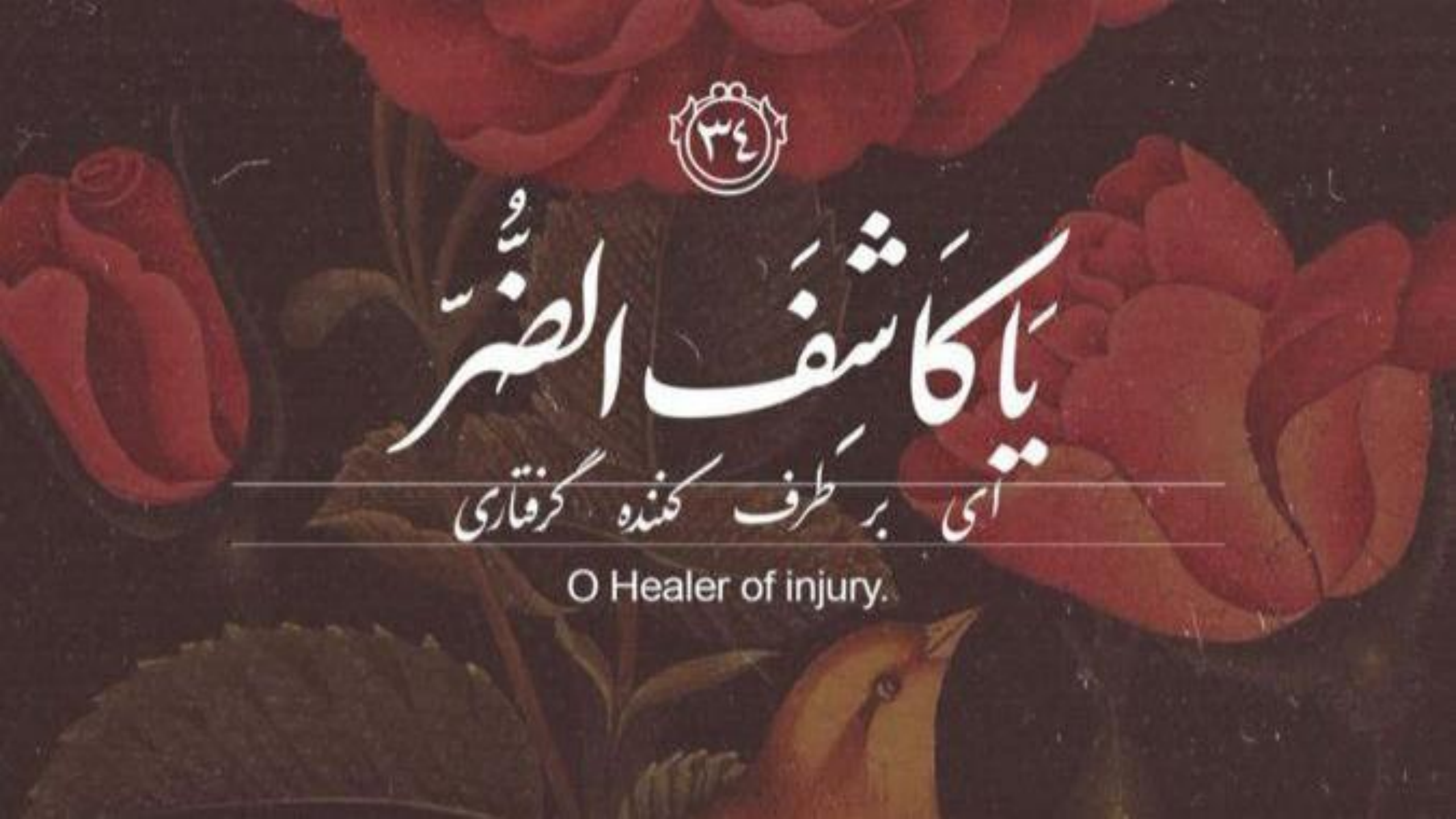
To summarize:
A&C same efficacy,
B is less efficacy than A&C,
B is more potent than C,
B is less potency than A,
D potency not comparable with the other drugs class however D has the same efficacy as C&A and they are all higher than B.

NOTE:
Let's test our knowledge
Determine whether the following statements are correct or false
- A produces Vmax ? Correct ✓
- B produces less efficacy than A? Correct ✓
- A produces higher efficacy than B? Correct ✓
- C produces same efficacy as A? Correct ✓
- A produces less efficacy compared to C? False ✗
- A is more potent than B? Correct ✓
- B is less potent than C? False ✗ why ?

Look at B, it has a lower dose for the same effect, making it more potent.

- D is more potent than A? We can't compare D to A in terms of potency since they belong to different classes.

V2:
Slide 6 : eg. Sex hormones
Slide 23: is required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يَا كَاشِفَ الضُّرِّ
ای برطرف کننده گرفتاری
O Healer of injury.