# PHARMACOLOGY
# lecture #8

**Second year**
**Passion batch**

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*All slides covered in lecture are included
*Sheet means this slide is from the record

# Pharmacodynamics 2

## General Pharmacology

## M212

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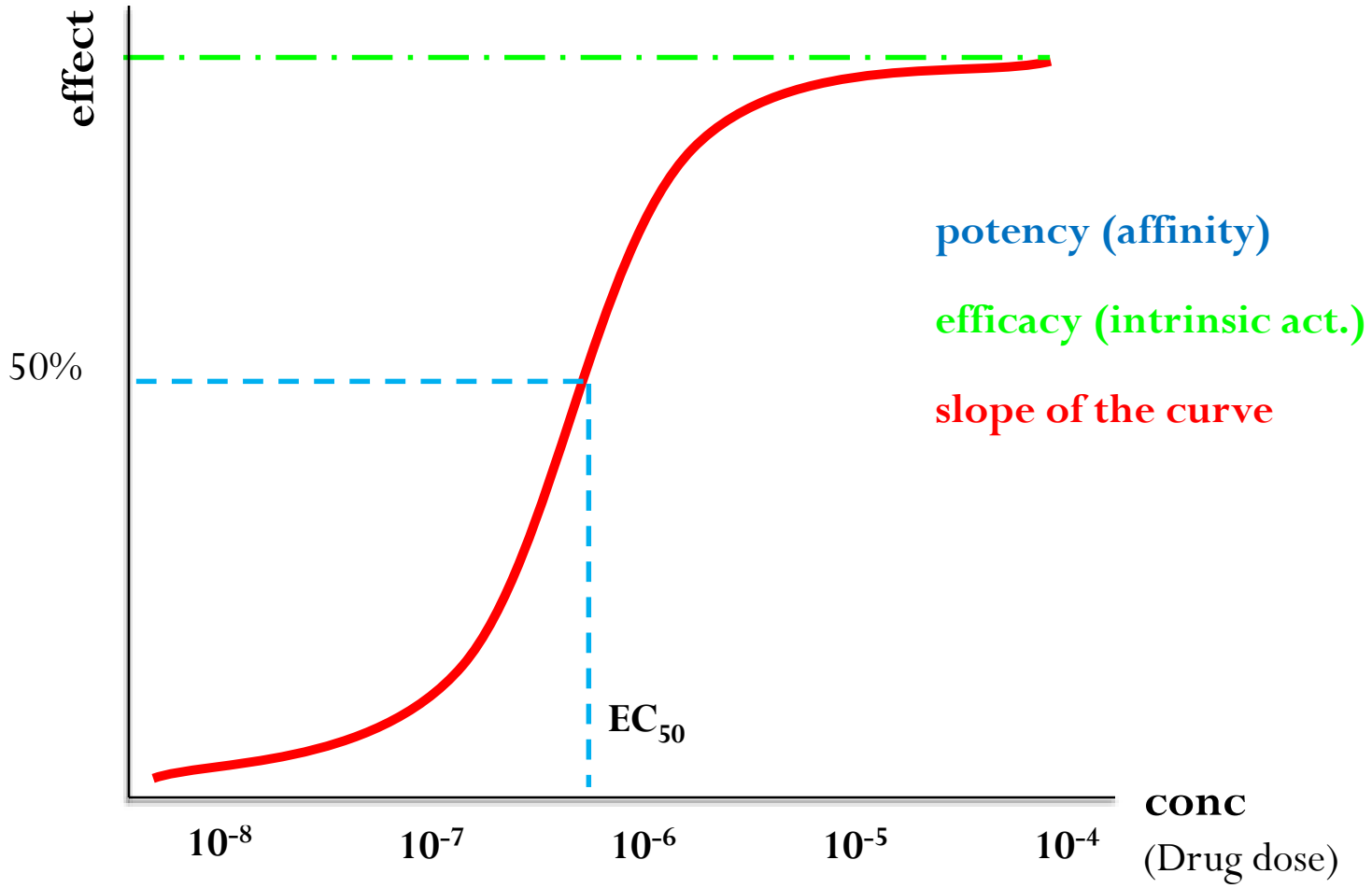
# Drug Effectiveness

- Dose-response (DR) curve: represent the relation between drug dose and magnitude of drug effect

- Two important properties of drugs can be determined by graded DRC:
- 1- Potency : a measure of the amount of drug necessary to produce an effect of a given magnitude.

- 2- Efficacy (intrinsic activity) of the drug, the ability to elicit a response when it interacts with a receptor.

# Dose-response curve
# (DRC)



SHEET 1

# From previous slide :

- Drug response curve : is the effect with concentration.
- This curve will show how much the efficacy and potency of a drug is reached
- Efficacy is the maximum effect.
- If you gave an 100g drug to decrease the temp of the body , but it didn't do the treatment and didn't kill the bacteria , so this drug is NOT efficacy.
- We care more about the efficacy because tablets in clinical use has constant amounts .

# SHEET 2

- Potency means “affinity”
- If you gave 2 drugs , A is 20 mg and B is 100 mg ,and both of them has the same effect ,which is more potent ?

  Answer: A

- We have 100% population , and we have a drug 20 mg can treat a 50 % of the population , and if you have another drug with 100mg can also treat 50% of population , which is more potent ?

  Answer :the drug with 20mg because its more affinity , higher binding to the receptor (like to go to receptors)

- IN CLINICAL USE :Famotidin 20 mg (drug for acidity)

  And ranitidine 150 mg . Famotidin is more potent but both have the same effect .

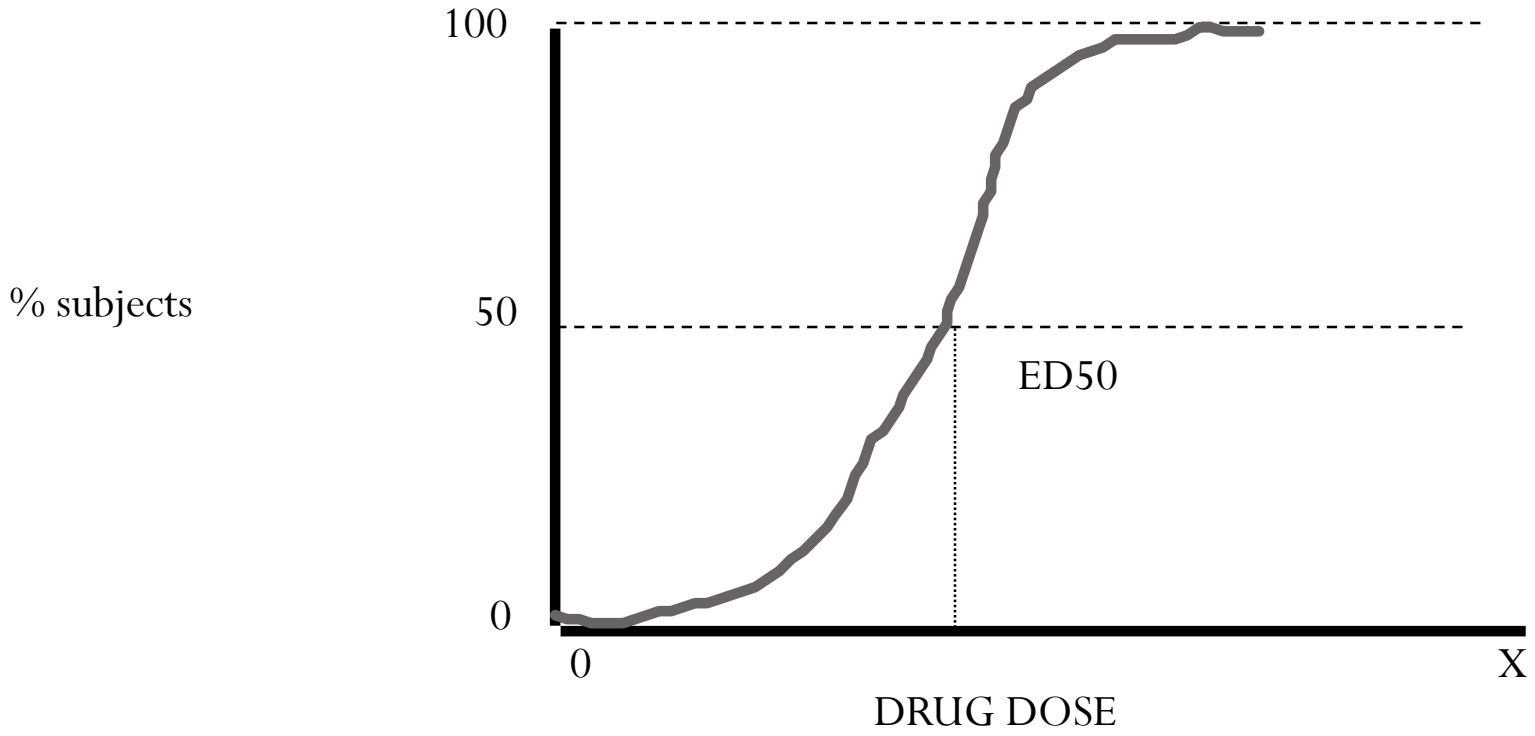
# 1. Potency (Affinity)

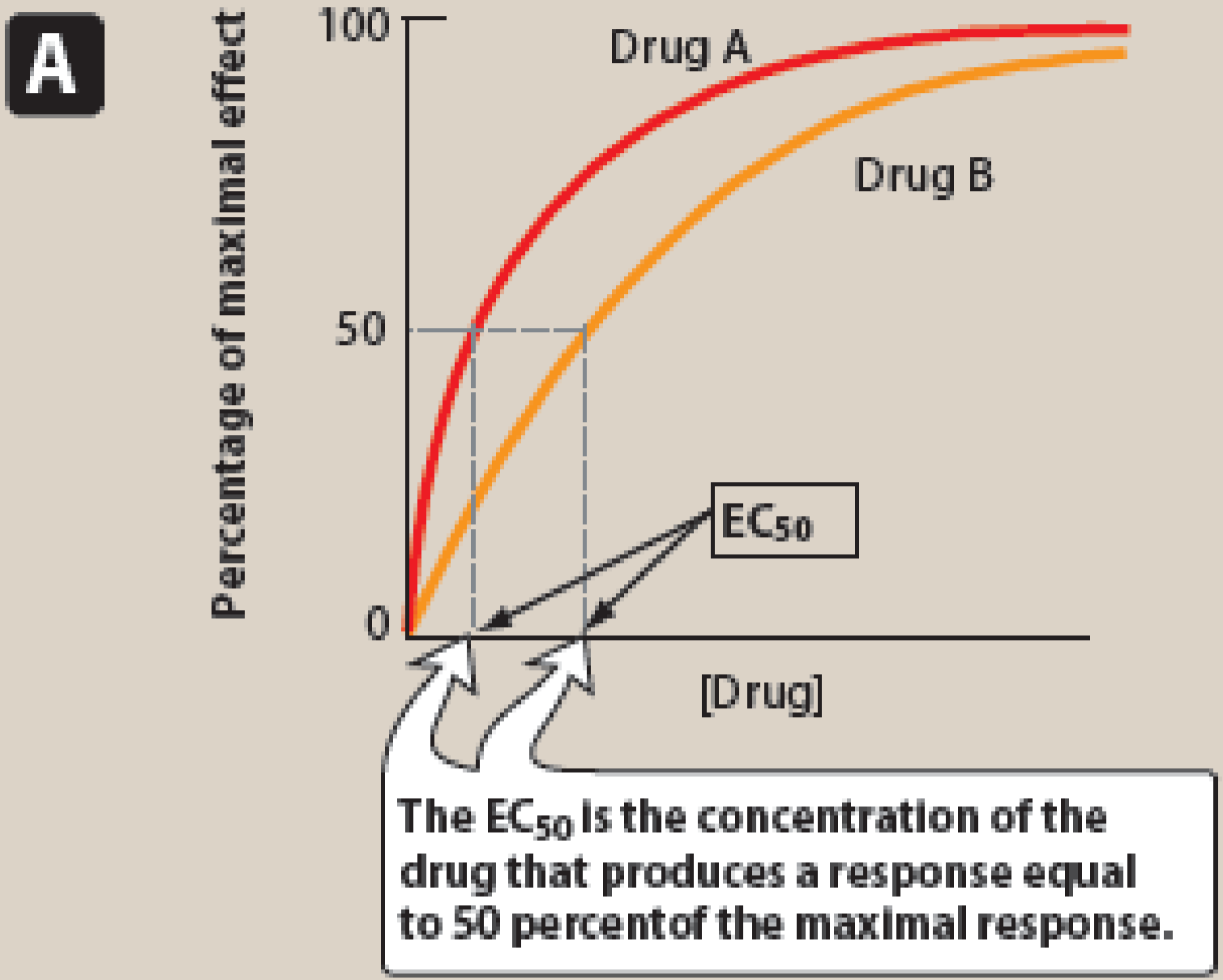
- **A measure of the amount of drug necessary to produce an effect (response) of a given magnitude**
- **The lower the dose, the more potent the drug**

- **To determine potency we used: $EC_{50}$ or $ED_{50}$ = the concentration or dose needed to produce a 50% maximal response**
- **$EC_{50}$, or $ED_{50}$ = parameters of affinity of a drug**

**$\Rightarrow$ the lower $EC_{50}$ or $ED_{50}$ , the higher affinity**

# $ED_{50}$ = effective dose in 50% of population






50% is just for comparison

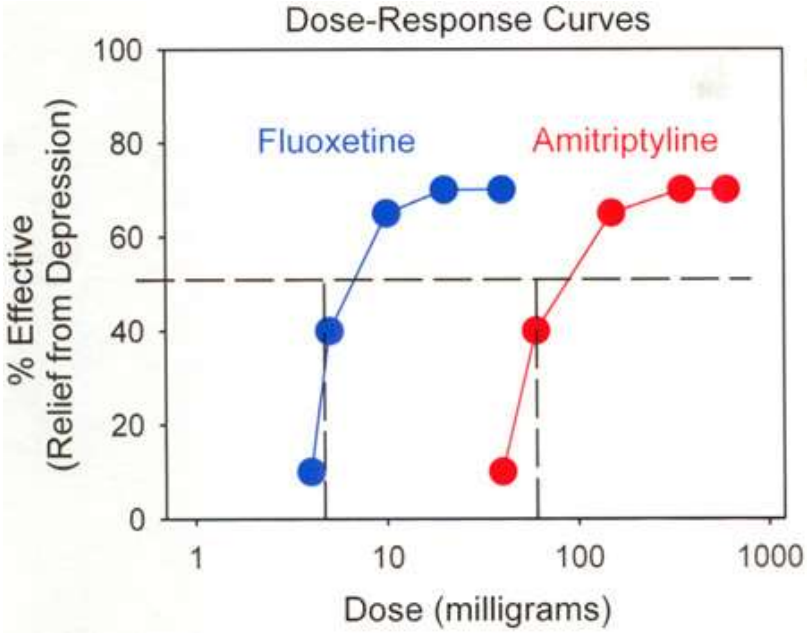
# SHEET 3

From the diagram in previous slide :

- Drug A according to B : is less dose (less conc.) , more potent , same efficacy as B
- So we can use A instead of B because both have the same effect , and A with less dose means less side effects .

# Potency

- D-R curve shifts left with greater potency
- The potency of an agonist is inversely related to its $EC_{50}$ value



SHEET 4

# From previous diagram:

- Both are drugs fluoxetine & amitriptyline used for depression and do the same effect but with different doses .
- fluoxetine dose is always low , less than 10 mg but amitriptyline is around 100 mg. which means fluoxetine is more potent but both has the same efficacy.
- This is just an indicator for the affinity of fluoxetine to receptors and neurotransmitter .
- Both increase GABA in the brain (GABA is inhibitory ) so increasing it will calm the patient.

  And both affect selective serotonin reuptake inhibitor
- The drug with more efficacy is more therapeutically beneficial than one which is more potent .
- We focus on THERAPUTIC EFFECT not potency
- The dose of drug cant be changed because tablets already designed with constant dose.

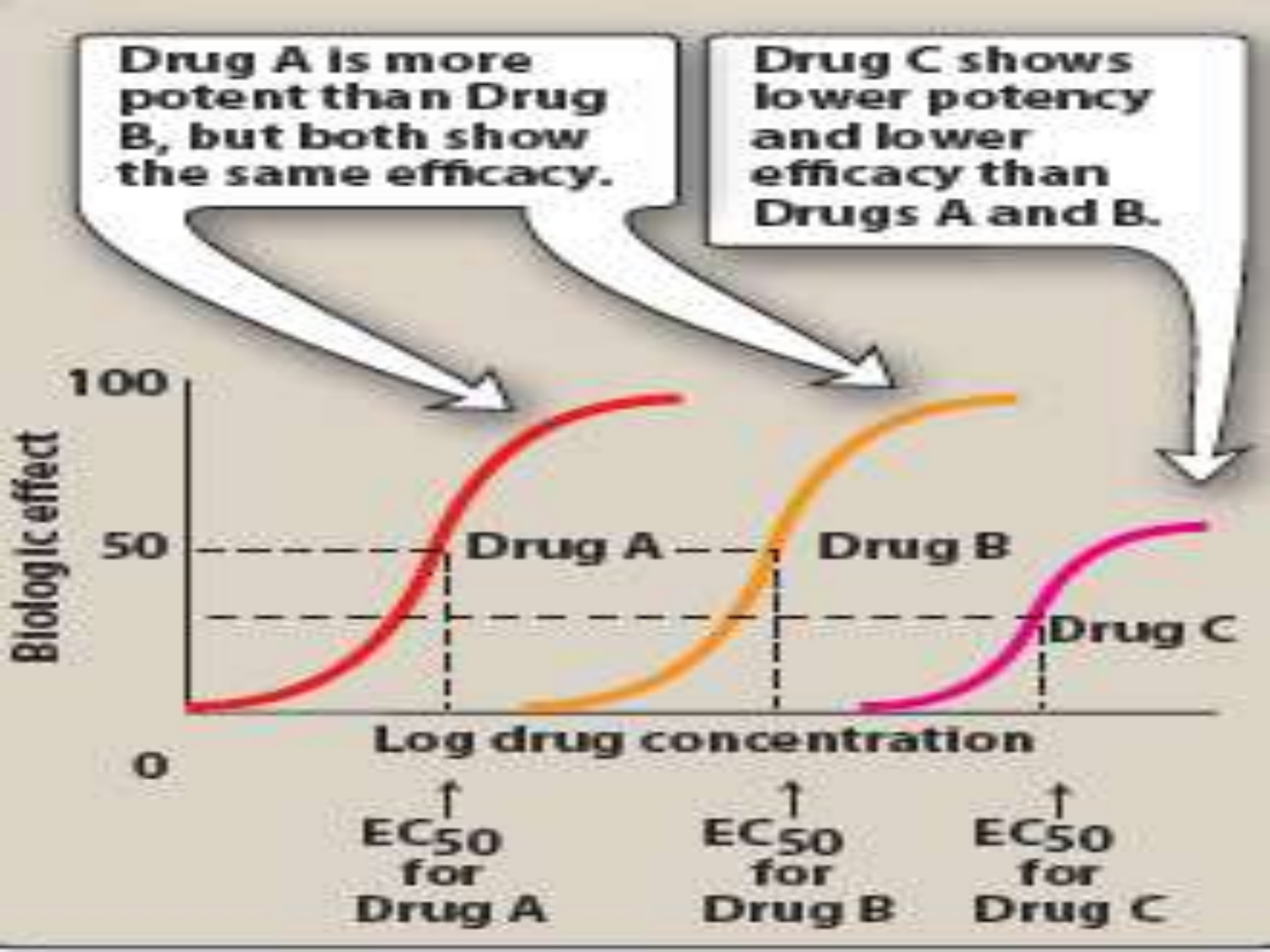
## 2. EFFICACY (intrinsic activity)

• **Efficacy: is the ability of a drug to produce a response when it interacts with a receptor**

•**The maximal response produced by a drug ($E_{max}$), depends on:**

1. **the number of drug-receptor complexes**
2. **the efficiency with which the activated receptor produces a cellular action {second messenger}.**

**•A drug with greater efficacy is more therapeutically beneficial than one that is more potent.**

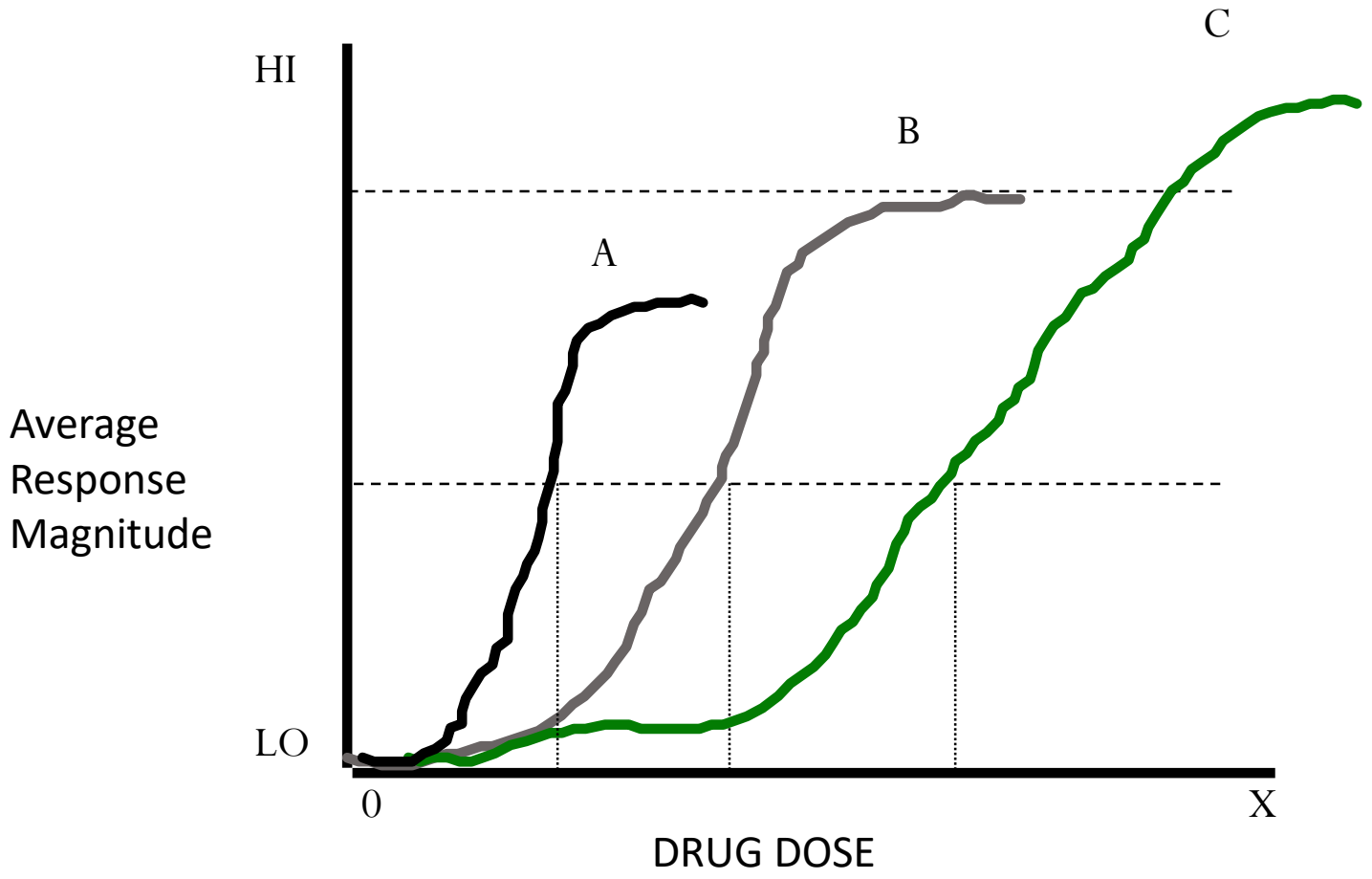

Drug A is more potent than Drug B, but both show the same efficacy.
Drug C shows lower potency and lower efficacy than Drugs A and B.
100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug C

SHEET 5

# From previous diagram

- Drug A has the same efficacy as B (reached 100 (maximum effect) )
- Drug C less efficacy (maximum dose but still not reached to maximum effect)
- For example if the drug is antibiotic it will not kill bacteria , or if the drug for diabetes it will not decrease sugar level to maximum effect . In other word ,The target is NOT achieved.
- So now C is excluded , even it is potent . Now A or B which is more potent ? A more potent because it needed least concentration with the same effect as B
- Less concentration achieve the same effect (50%) mean more potent
- The max effect reached by the drug mean more efficacy ( and here 90% differ than 100% )
- Note that : **Efficacy more important than potency**

# Comparisons



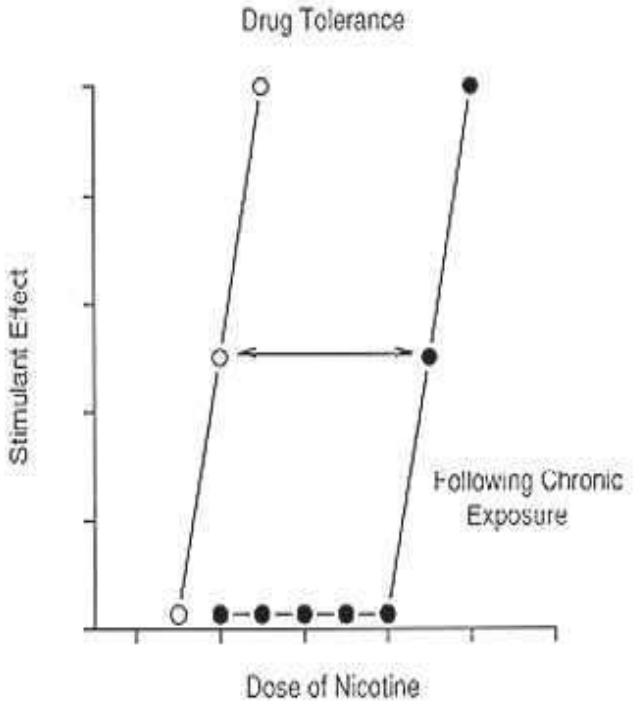
SHEET 6

# From previous diagram:

- A more potent , least efficacy .
- C has higher efficacy , least potent .
- As a doctor we pick B as the appropriate drug because its more potent than C and at the same time reached to required efficacy 100.
- Note that , more conc. means more side effects.

# Tolerance
## (desensitization)

- Tolerance is : Decreased response to same dose with repeated (**constant)** exposure
- *or* more drug needed to achieve same effect
- Right-ward shift of D-R curve
- Sometimes occurs in an acute dose (e.g. alcohol)
- Caused by compensatory mechanisms that oppose the effects of the drug




When the dose increase the line will shift to right →

# SHEET 7

- **Tolerance** means addiction ,or to get used to sth ,or dependence .
- It was noticed that sometimes when patients take the second , third or fourth dose of the drug , the efficacy will decrease , so they will need more drug(more conc. ) to achieve more response, so they will need to increase the dose and causes addiction .

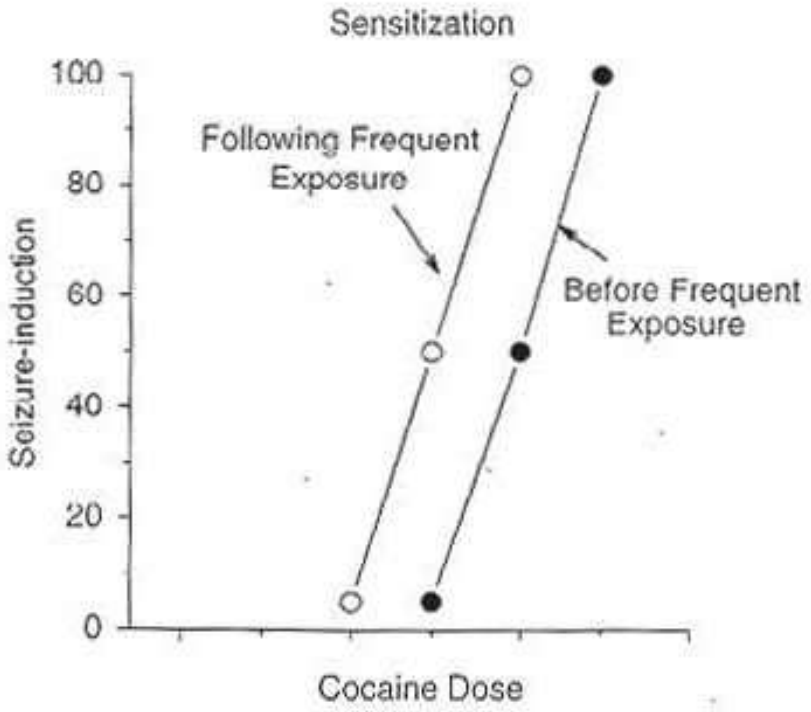
- For example : alcohol or a drug for depression (normal drugs like valium, Diazepam)
  - first dose of valium will calm the patient and send him to sleep
  - Second valium will be less effective
  - After a week the patient won't sleep, the drug wont affect him
  - He will need more drug, more doses.
  -(potency decreased) and the receptors worked first time won't do the same action next times .
- This lead to addiction and decreasing efficacy which we call tolerance .

- In these cases most patient increases the dose continuously until it reach the effective dose (the target ) which will be the toxic dose and may lead to death like people with addiction to morphine and heroine

# SHEET 8

- In Tolerance , after almost 5 doses the drug will not reach the effect
- These drugs have receptors , most these receptors in brain , if the dose kept increasing it will cause respiratory center depression in the brain .
- So he will die because of inability to breath (shut down the breathing center in brain)
- that's why most adductors die while they are taking the dose.

# Sensitization




- Increased response to same dose with repeated exposure
- *or* less drug needed to achieve same effect
- Left-ward shift in D-R curve
- Sometimes occurs in an acute dose (e.g. amphetamine)
- Can develop across drugs (cross-sensitization)

It is possible to develop tolerance to some side effects AND sensitization to other side effects of the same drug

# SHEET 9

- **Sensitization** is the opposite of tolerance
- Number of receptors will decrease .
- Receptor blocking or antagonist occur , the body will do feed back inhibition
- In other word , when you change sth in your body , your body will do sth inversely .
- Try to activate 100 receptors , your body will do down regulation of receptors (decrease no. of receptors)
- Try to block 100 receptors , your body will make new receptors , up regulation of receptors .

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- In Some specific drugs , the first dose will be effective , second dose more effective (Sensitization occur )
- The cause : when we stimulate a receptor it will still stimulated in next doses and get more sensitized so we need less doses of drugs. like amphetamine (kebtagone used for hyperkinetic deficit attention disorder ) first dose will be high but second will be lower .
- Amphetamine causes vasoconstriction & hypertension , so higher doses may cause a stroke
- The response is NOT CONSTANT even if the drug binds with the same receptor

# Mechanisms of Tolerance and Sensitization

- **Pharmacokinetic**
  - changes in drug availability at site of action (decreased bioavailability)
    - Decreased absorption
    - Increased binding to depot sites
- **Pharmacodynamic**
  - changes in drug-receptor interaction
    - G-protein uncoupling
    - Down regulation of receptors

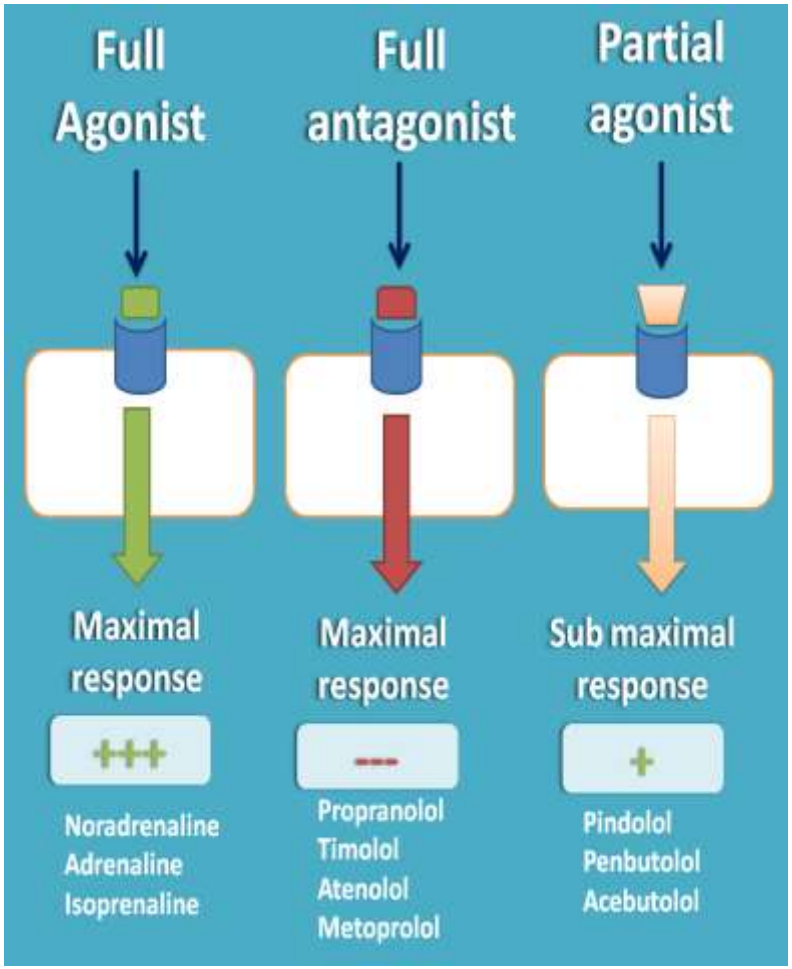
Kinetic & dynamic changes
Drug with time will affect the liver , drug metabolism will be delayed
Drug stay more than expected half life t1/2
decreasing no. of receptors
means the drug is overdose than required body needs

# Drugs-receptor interaction classification

## 1. Receptor Agonist

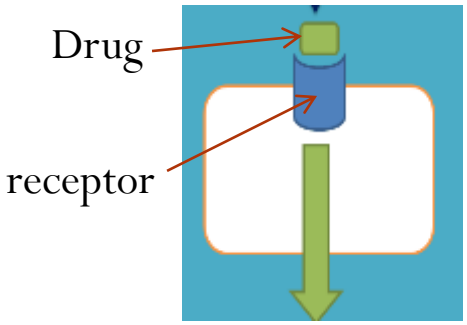
- Full agonist
- Partial agonist
- Inverse agonist

## 2. Receptor Antagonist



# SHEET 10

- When a drug push the receptor and turn it on and the receptor give the maximum effect this known as FULL AGONISTS (drug can bind to receptor and achieve 100% or 1 of efficacy).
- when a drug try to attach with the receptor but don't give the max effect ( drug with weak push on the receptor) Known as PARTIAL AGONIST ( efficacy around 50-70 % )




Imagine it like push button

# SHEET 11

- Example of full agonist :

  β-Receptor agonist : adrenaline , noradrenalin . when binds together they will increase heart rate to maximum also increase BP to maximum.
- If we gave the patient a drug called **pindolol** which is β –partial agonist (it will increase heart rate and BP but NOT to maximum , it makes a regulation to BP but a partial one)
- Partial agonist = partial antagonist . how ?
- Because partial agonist turned on half the effect(from 0% to 50% ) and partial antagonist decreased the effect (from 100% to 50%)
- Full antagonist block the receptor and turn it off ( no action for drug ) here the efficacy is 0% .
- The difference between INVERS AGONIST and ANTAGONIST :
- **Inverse agonist** it bind to receptor and do the opposite action (efficacy =-100%) it decrease the efficacy by 100% NOT just block but ALSO could inverse the action.
- **Antagonist** only block the receptor without affecting the action.

# Agonists and Antagonists

- **AGONIST** - Has affinity for receptor and efficacy.

- **ANTAGONIST** - Has affinity but no efficacy.
  - Competitive Antagonist
  - Noncompetitive Antagonist

- **Partial Agonist or Partial Antagonist** –
- Has affinity but *lower* efficacy than full agonist.

# Agonists

**Agonist:** A drug binds to a receptor and produces a biologic response that mimics the response to the endogenous ligand $\Rightarrow$ agonist.

**Types of agonists**:

1. **Full agonists -** induce a maximal response when all receptors are occupied
   E.g., phenylephrine is an agonist at $\alpha_1$-adrenoceptors because it produces effects that resemble the action of norepinephrine.

•A full agonist has a strong affinity for its receptor and good efficacy**.**
•**Efficacy = 100%**

SHEET 12

- Endogenously we have adrenaline which binds to **α-receptor** (normal in body)

- If we give the patient Phenylephrine (drug for stuffy nose) which is full agonist on **α-receptor** instead of adrenaline , that also binds to α-receptor and achieve 100% of norepinephrine (100% effect)

# Agonists

**2. Partial agonists:**

- **It cannot produce as high (max.) response as full agonist even in the case that all the receptors are occupied!**

**100> Efficacy > zero**

**•The partial agonist may be more, less, or equally potent. Potency is an independent factor**

**•In the presence of a full agonist, a partial agonist acts like a competitive inhibitor.**

**•The potential of partial agonists to act both agonistically and antagonistically may be used therapeutically .**

# SHEET 13

- **Partial agonist** is more therapeutically used than **full agonist** because full agonist activate receptors to the maximum which result in a lot of side effects like raising the pressure or heart rate to the maximum which is bad WHILE partial agonist make a moderate action.

For example :

- **estrogen** in females which is present in uterus , Mammary cells and bones . Which means it has many receptors in the body .
- Now if estrogen agonist is given, it won't reach and affect all receptors in our body in the same way . It will make a **partial agonist** in one of the receptors , and **partial antagonist** on another .
- After menopause , estrogen will decrease in our bones and osteoporosis occur , so we should give her estrogen BUT it must go to bones not to breast where it could cause cancer instead of treatment . So that why selectivity of partial agonist has a great medical benefit , if it where full agonist on the 3 receptors it will then cause a breast cancer.
- Another example :pindolol partial agonist to β-Receptor

# Agonists

3. **Inverse agonist**

- **it stabilizes receptor in its inactive form (R*)**

- **inverse agonists reverse the constitutive activity of receptors and exert the opposite pharmacological effect of receptor agonists.**

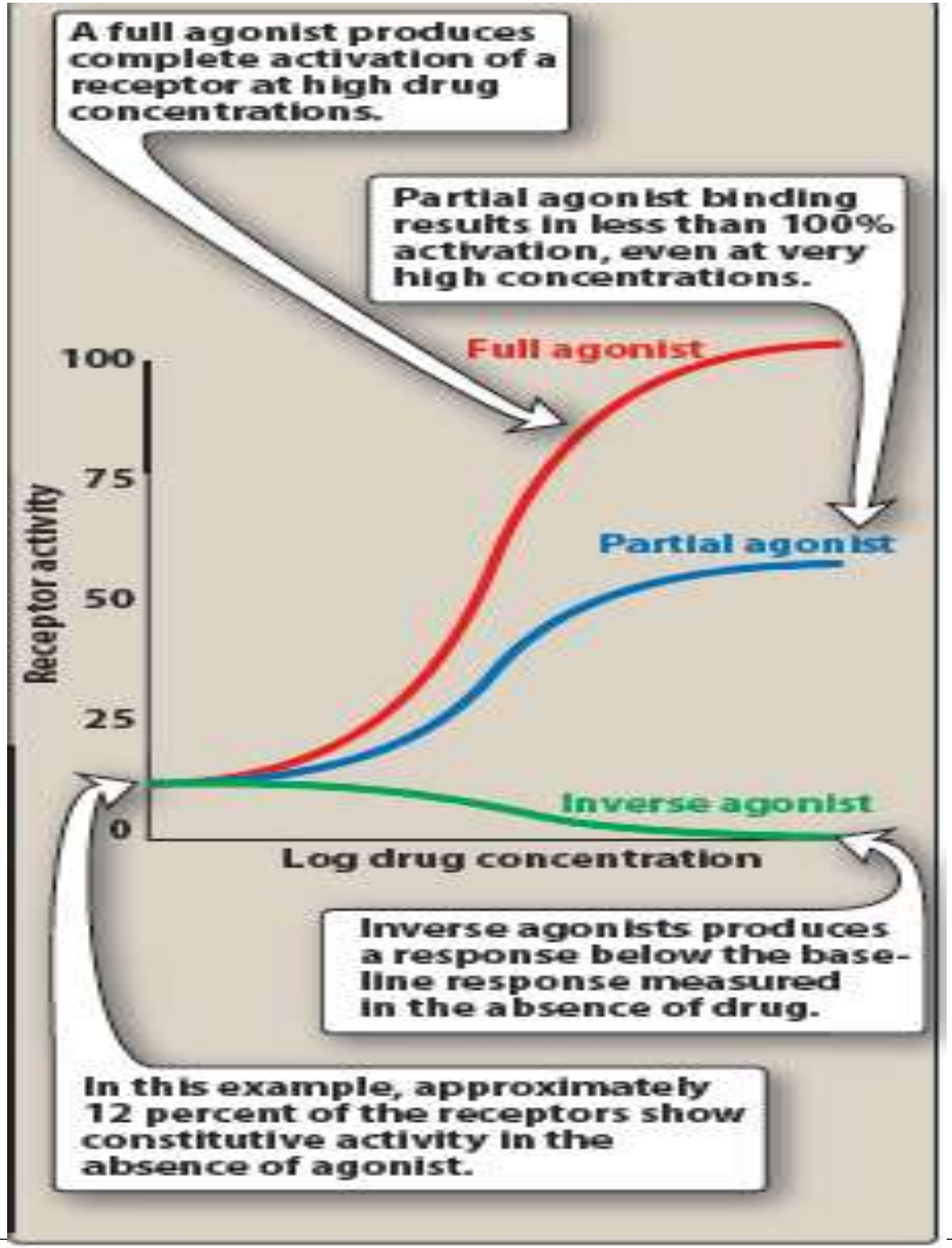
- **Inverse agonist effects are opposite to those of agonist; e.g – famotidine (H2-receptor blocker), metoprolol (β- receptor blocker))**

# SHEET 14

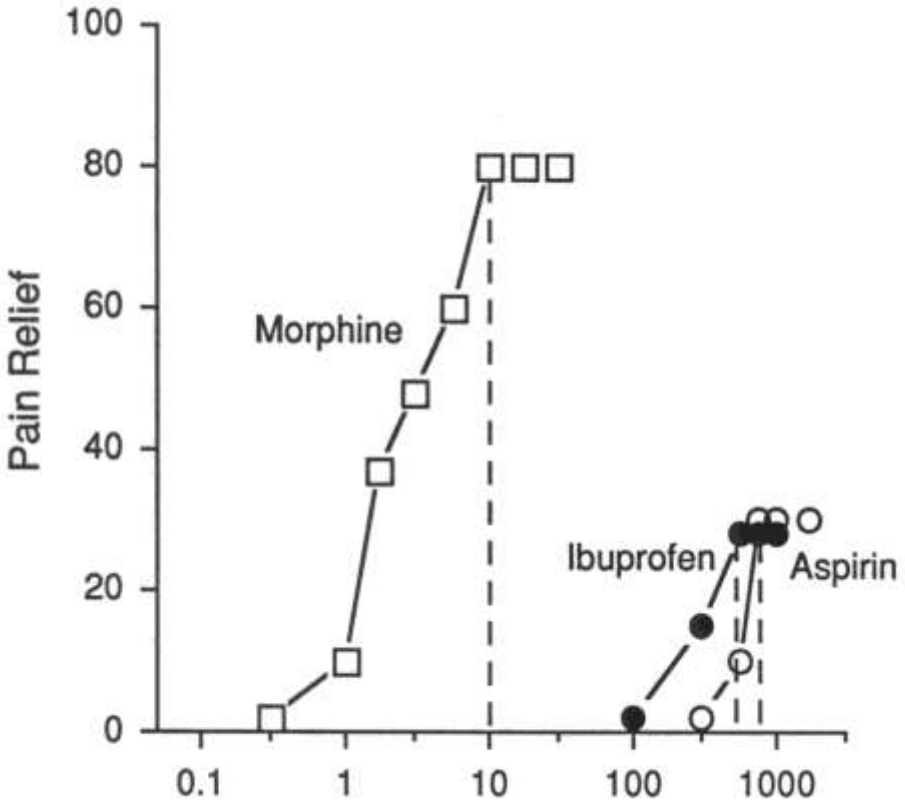
- **metoprolol** is a β- receptor blocker.
- So when β- receptor increase the heart rate , metoprolol will decrease it (not just stop the action but also inverse it).

- **famotidine** is **H2-receptor blocker** (H2-receptor is found in stomach and allow the HCL channel or proton channel to open and release HCL from it ) so when we give famotidine which is anti acid it will block the H2- receptor to prevent HCL excretion .

- Antagonist and inverse agonist are nearly the same but they're considered not the same when the antagonist block the receptor without action


A full agonist produces complete activation of a receptor at high drug concentrations.
Partial agonist binding results in less than 100% activation, even at very high concentrations.
Full agonist
Partial agonist
Inverse agonist
100
75
50
25
0
Receptor activity
Log drug concentration
Inverse agonists produces a response below the base-line response measured in the absence of drug.
In this example, approximately 12 percent of the receptors show constitutive activity in the absence of agonist.

# Efficacy




- Maximum possible effect relative to other agents
- Indicated by peak of D-R curve
- Full agonist = 100% efficacy
- Partial agonist = 50% efficacy
- Antagonist = 0% efficacy
- Inverse agonist = -100% efficacy

SHEET 15

# From previous diagram :

- 1st drug : morphine a drug used in analgesics to treat pain in final stages of cancer nearly stage 3 to 5 (in patient not out patient)
- In the diagram **morphine** efficacy as a pain killer reached 80%
- **Ibuprofen** is an analgesic drug for teeth pain and menstrual period pain .
- **Aspirin** is an analgesic but the dose that is required to do the effect is high and has a lot of side effects (so its given mostly as anti platelets in small doses)
- Comparison from diagram between morphine & ibuprofen :
- Morphine is higher efficacy
- Morphine More potent
- Morphine is Full agonist
- Ibuprofen is partial agonist (its appropriate for moderate pain)
- we use morphine with Severe pain ( stage 3-4 need full agonist ).

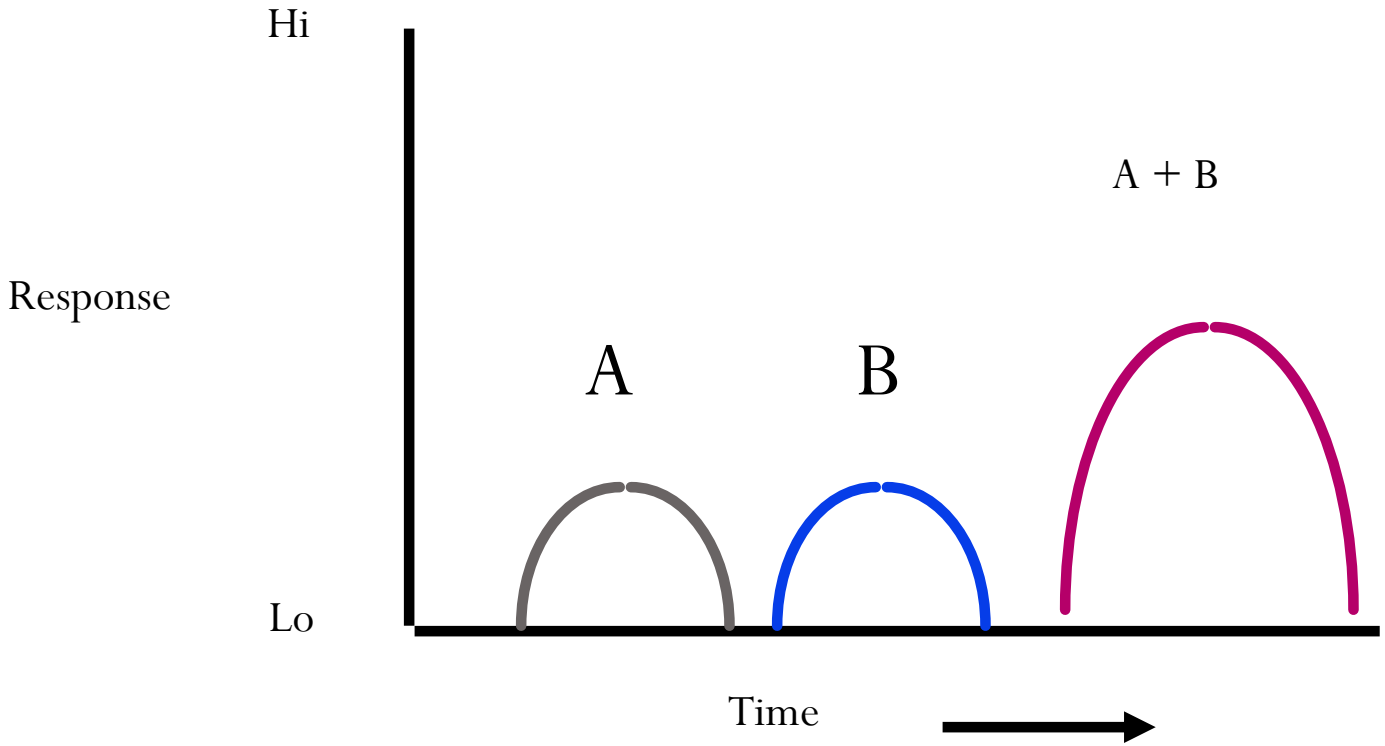
# Stages of pain :

- Stage (0-1) mild pain including mild headache
- Stage 2 like tooth pain , back pain
- Stage 3 inters sciatic nerve pain , cancer pain and delivery pain (give birth).

# 1. Drug synergism

## A. Additive Effects

1 +1 = 2




The effect of two chemicals is equal to the sum of the effect of the two chemicals taken separately, eg., aspirin and warfarin

Combine two antihypertensive drugs (diuretics and captopril)

Ibuprofen and paracetamole = extra analgesics

SHEET 17

## Additive Effects :

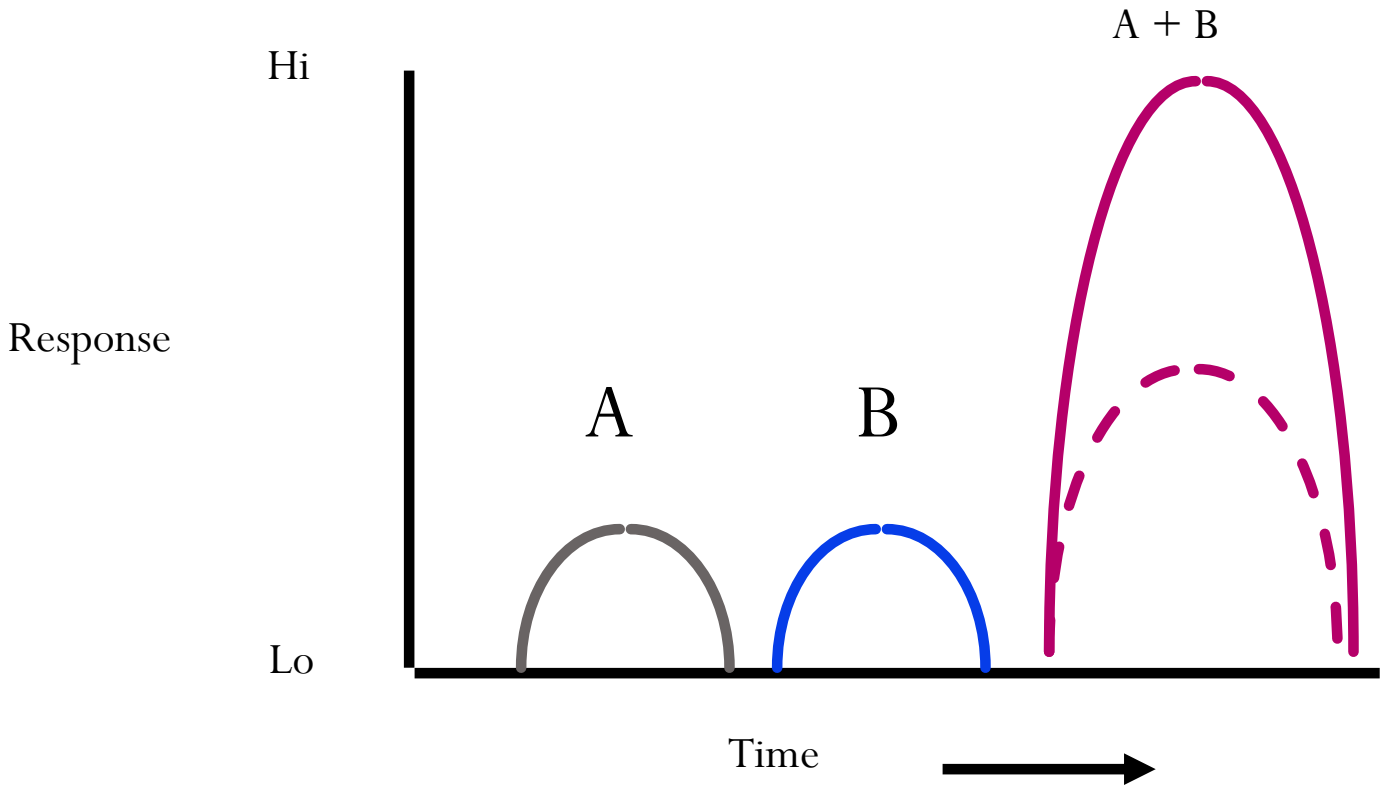
- To combine 2 drugs with **different mechanism** to achieve the final goal.
- it is a divided synergism
- Synergism means increase the effect (double the effect)
- Having a Headache → took paracetamol → felt like not fully effective →took with it profen → each one has different pathways & different mechanisms → the total effect will be the summation (1+1=2)

- **Therapeutic use** : high pressure→ give him diuretic →decrease blood volume→ pressure still not monitored → give him **captopril** (ACE inhibitor which make vasodilatation)→it will decrease pressure more(effective).
- Some times we may need 3 or 4 drugs but should be careful to overlapped mechanisms (if drugs have same mechanism it wont do the effect because only one of them will bind and activate).
- Another example: for diabetes to give glucophage with glibenclamide to do the effect .

# B. Potentiating Effects

1 +1 > 2

1+0=2




Antibiotics

The effect of two chemicals taken together is greater than the sum of their separate effect at the same doses, e.g., alcohol and other drugs, levodopa and carbidopa (1+0= 2) , sulfamethexazole and trimethoprim = 1+1>2

SHEET 18

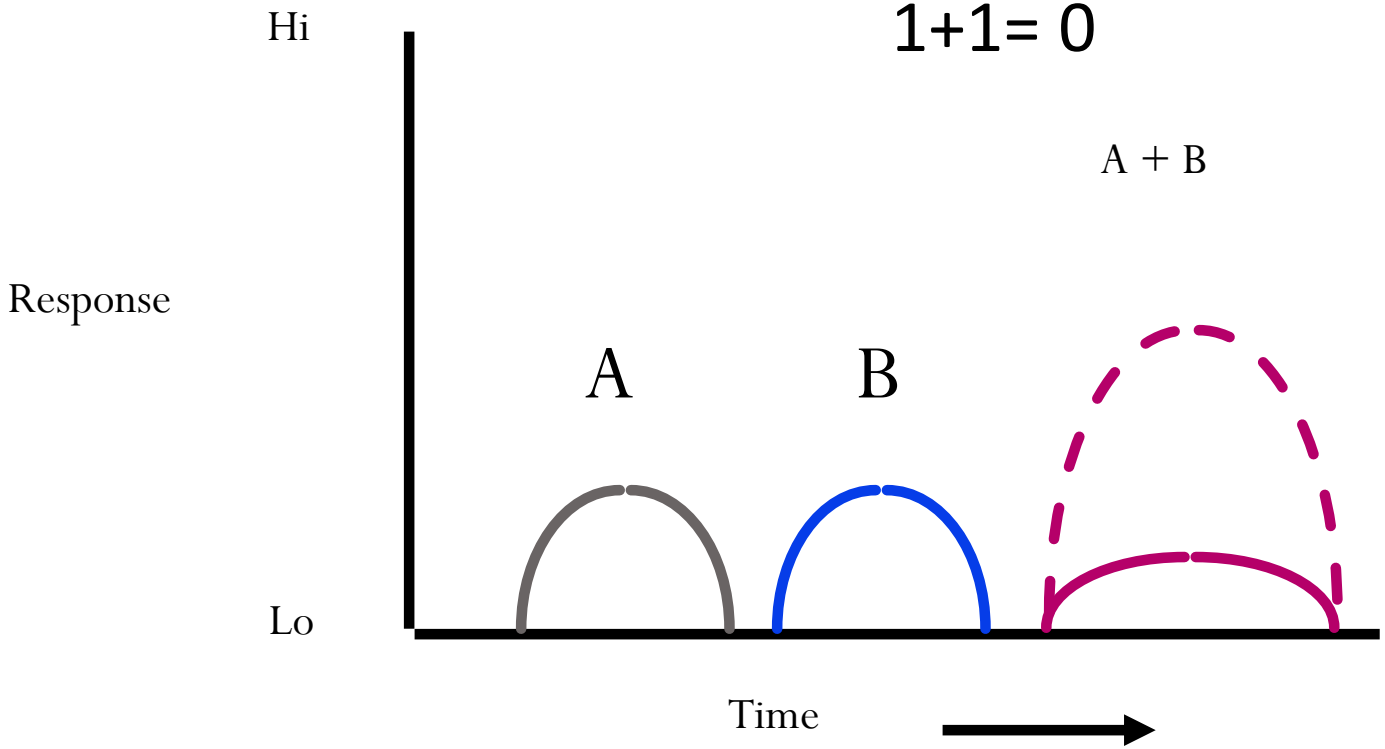
## Potentiating Effects :

- Synergism but potentiating one .
- 1+1=2 means if we gave 2 drugs and gave more effect.
- 1+0=2 (0 means with no effect) to give 2 drugs and only one of them will be activated (do the effect )and the other will increase its action without making a real effect
- Ex. in **Parkinson disease** there is dopamine deficiency , if we gave him dopamine it will break down in stomach and won't reach the brain ,big & have COH can't enter BBB , we give him **levodopa** the precursor of dopamine to do decarboxylation in brain .
- Levodopa will have decarboxylation in GIT & in the brain
- If we want to increase the amount in the brain we must decrease the levodopa in the stomach and increase entering it to brain .
- so I stop the levodopa action in stomach by **carbidopa** (enzyme inhibitor) which prevent breaking the levodopa in stomach and induce it to go to brain
- Ex: sometimes the inhibitor prevent drug from breaking down in the kidney to increase the drug effect like cancer cases

# 2. Antagonism

1 +1 < 2

1+1= 0




The effect of two chemicals taken together is less than the sum of their separate effect at the same doses:
Adrenaline and acetylcoline

# SHEET 19

- Example : A patient with a heart attack takes **Salbutamol**, a β-2 agonist (in lung) to dilate the Bronchial , at the same times takes β-blocker (for pressure)
- A drug for pressure to a patient with heart attack will lead to death (because one is β-agonist and the other a β-blocker) →leads to **antagonist** means there might be less effect or no effect according to the drug that binds with the receptor ( if blocker binds that mean it will decrease the effect and the attack will increase) .

- Another example : Adrenaline and acetylcholine

Other interactions between the drugs can be

>* Addition : 1+1 = 2
e.g: combined therapy of ephedrine and aminophylline in asthma

>* Synergism : 1+1 =>2
e.g: Sulphonamides with trimethoprim used as antibacterial drugs ..

>* Potentiation : 0+1=>1
e.g: Carbidopa and levodopa in treatment of Parkinsonism ,, !

# Drug Antagonism

## pharmacodynamic Antagonism by receptor block

**Antagonists in this sense are drugs that bind to receptors but do not activate them and thereby it decrease the effect of an agonist**

***A) competitive (reversible) antagonism*:**

- **Competitive antagonists bind reversibly with receptors at the same site as the agonist but induce no action – they block the receptor for agonist**
- **The response can be returned to normal by increasing the dose of agonist.**
- **The ability of higher doses of agonist to overcome the effects of the antagonist ⇒ a parallel shift of the dose-response curve to the right**

# SHEET 20

- Drug Antagonism means **drug-drug interaction**.
- It's not necessary mean that the 2 drugs must bind to the receptor to make antagonism
- It could be on:

**1) pharmacodynamic** → one agonist with another antagonist

- Drugs work on receptors leads to **competition** ( to give 2 drugs both like to bind to the same receptor , want to make an action , but one of them could be agonist and the other blocker on same receptor
- It also could happen from inside the body with one drug, like adrenaline inside the body binds to β-receptor , and when a similar drug to it, given to the body, the body can consider them competitors on same receptor
- If agonist given alone (like heart attack drug) then after a while by mistake he is given another drug antagonism (blocker) , **in normal doses** only one of them will be activated , but **in an overdose** of agonist with time the blocker will release and the agonist will do the action
- Which means it affect the potency , so we need more doses to achieve same efficacy (increasing the conc. of one of the 2 drugs will release another **according to the increased drug .**
- If the drugs are not competitors antagonism , then even if we increased any of the drugs, the drugs cant be released ( always try to avoid this) and this affect THE EFFICACY (less action) potency not affected

**2)Physical antagonism** → same chemical or physiological pharmacokinetic

# Drug Antagonism

***A) competitive (reversible) antagonism*:**

- **The maximum response is not depressed**

**e.g., *Propranolol competes with the endogenous ligand, norepinephrine,* at β-receptor**

THE END

# BEST OF LUCK