DOCTOR 2020 | JU

PHARMACOLOGY

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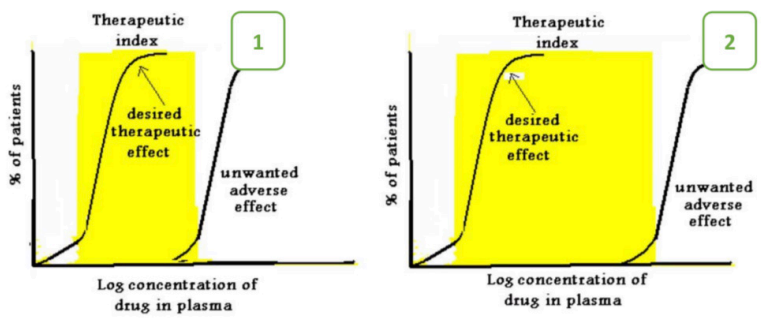
Therapeutic index and margin of safety

- Therapeutic index of a drug is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population individuals.
- Ideally the TD_{50} Should be a much higher dose than the ED_{50} so that the therapeutic index would be large.

$$TI = \frac{TD_{50}}{ED_{50}}$$

Where TD_{50} is the minimum dose that is toxic for 50% of the population, and ED_{50} is the minimum dose that is effective for 50% of the population.



According to the distance between the desired therapeutic effect and the unwanted adverse effect:

1- Narrow therapeutic index ----> **where small differences in dose may lead to serious therapeutic failures or adverse drug reactions.**

2- Wide therapeutic index----> **you have a wide range in which the drug can safely be used**

- Cyclosporine – 100-400ng/ml
- Carbamazapine- 4-10µg/ml
- Digoxin- 0.8-2ng/ml
- Phenotoin – 10-20µg/ml
- Qunindine- 2-6µg/ml

→ **The margin of safety for some drugs.**

Therapeutic index and margin of safety

Therapeutic index of a drug is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population individuals:

$$TI = \frac{TD_{50}}{ED_{50}}$$

Where TD_{50} is the minimum dose that is lethal or toxic for 50% of the population, and ED_{50} is the minimum dose that is effective for 50% of the population.

Ideally the TD_{50} Should be a much higher dose than the

Enhancement of drug effects

- Enhancement = increasing the effect of a drug

A. Additive drug effect: occurs if two drugs with the same effect, when given together produce an effect that is equal in magnitude to the sum of the effect.

E AB = EA + EB 1 + 1 = 2

- If drug A decreases the blood pressure by 10, and drug B decrease the blood pressure by 10, if we give them together to a patient, the Bp will decrease by 20.

B. Synergic drug effect: occurs if two drugs with the same effect, when given together, produce an effect that is greater in magnitude than the sum of effects when the drugs are given individually.

EAB > EA + EB 1 + 1 > 2

- We never combine two drugs with the same side effects due to the synergic effect.
- To kill the cancerous cells, doctors choose drugs with different side effects.

C. Potentiation drug effect: occurs if a drug lacking an effect of its own increase the effect of a second active drug.

EAB > EA + EB 0 + 1 > 2

- For example: Parkinson patients (who have a dopamine deficiency) ---> doctors give them levodopa carbidopa. **Why?** Levodopa works by being converted to dopamine in the brain. Carbidopa (alone it has zero effect)

works by preventing levodopa from being broken down before it reaches the brain, so increases the quantity of levodopa in the bloodstream that is available to enter the brain.

#Read the note in the last slide

Tow-state model of drug-receptor interaction

-remember ligand-receptor interaction; when an ligind or agonist binds to receptor it activates it, initiating a cascade leading to response, this indication that recaptor got activated only when an ligand or agonist binds to it, once receptor is free there is no response.

-But ne theory came (two state model of drug-receptor interaction) because was found that , accordingly to thermodynamics consideration even in the absence of agonist the receptor can be in active form (Ra).

*thermodynamics considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist-induced activity.

*The receptor is postulated to exist in the inactive nonfunctional form (Ri) and in the activated form (Ra).

Theory indicates that some free receptors give a some response as agonist does.

The receptors come in two forms :

1-Active form receptor (Ra) 2-inactive form receptor(Ri)

-The receptor keeps shifting between these two forms in equilibrium.

-free receptor has some effect of activity agonist (drug) will bind to receptor, shifting equilibrium to active conformation, this shows the affect on receptor for a long time.

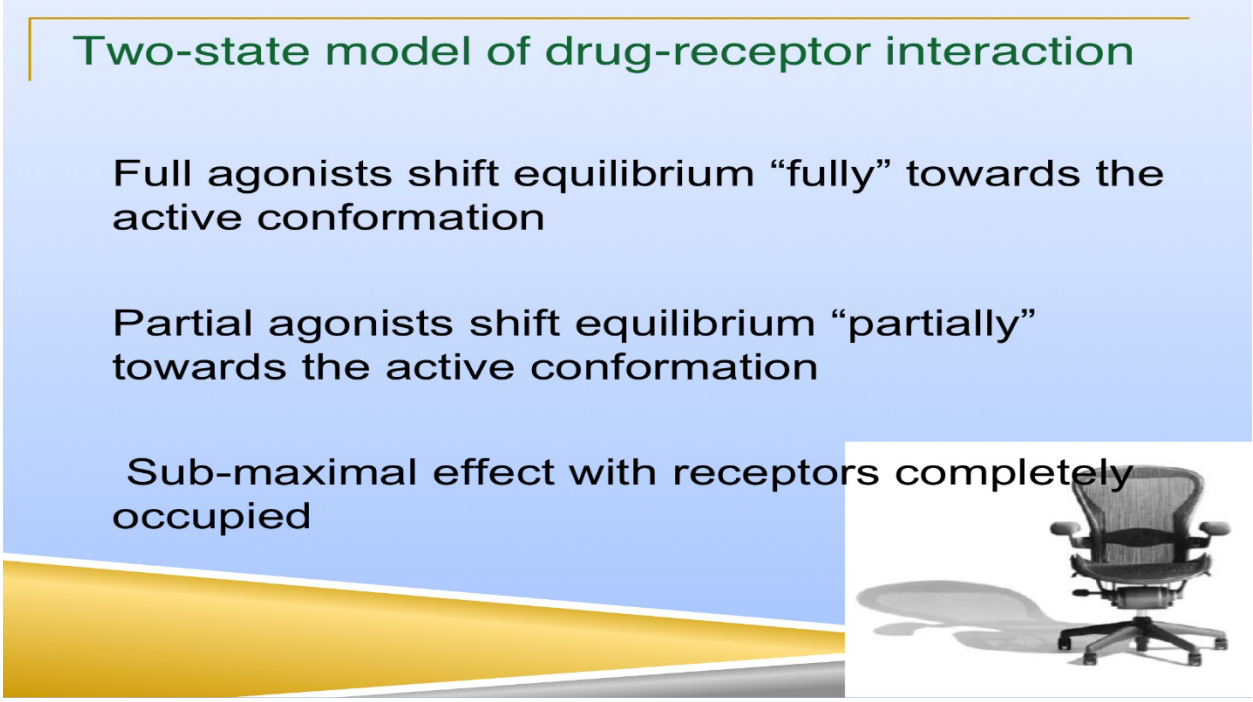
*Agonist have a much higher affinity for the Ra configuration and stabilize it, so that a large percentage of the total pool resides in the Ra-D fraction and a large effect is produced .

_in the absence of agonist, there is less effect on receptor considering as it was in an inactive form, But the theory came out to indicate that there is a high activity even in the absence of agonist, this is called CONSTITUTIVE ACTIVITY.

***Constitutive activity**

***** the effect of receptors, occurring in the absence of agonist, termed constitutive activity.

Remember the second part of the definition



-FULL AGONIST: is a drug that gives a maximum effect on receptor reaches to Emax, while PARTIAL AGONIST gives submaximal effect less than Emax.

Ex; I am teacher work on computer (prepare lecture), if I stand while working, will I be able to do any work on computer? NO ,because I am in my inactive state, when I bent I could do some function BUT I would return to my inactive state. What drug (chair) does that allows to be more comfortable in Active conformation **stabilizes receptor in an active conformation** , now I am more comfortable in my position to do work because of consuming less energy, this is the meaning of the THERMODYNAIMCS CONSIDERATION.

-(look at the picture) lets try to differentiate between full agonist and partial agonist in terms of concept; this chair is easy to work on it , so if I had this comfortable, rotatable and leather chair I would stay longer on it to produce more work . same in full agonist is a comfortable chair, drug that stabilizes receptor in an active conformation with less energy needed to stay on it BUT with partial agonist it is less comfortable so it would stay in a time less than full agonist .

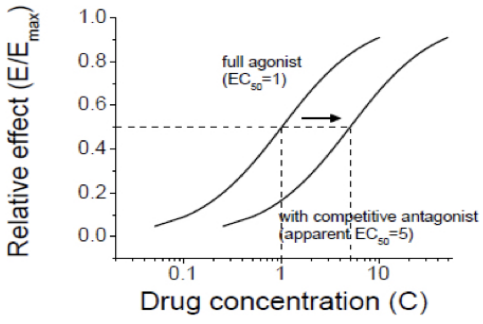
What is important in constitutive activity is the new kind of an agonist came to be, remember when we were talking about antagonist of receptor we said that it inhibit the action of receptor by binding to receptor and prevent the original part agonist from binding to receptor, we called that NEUTRAL ANTAGONIST , because it does not activate the cascade of event,

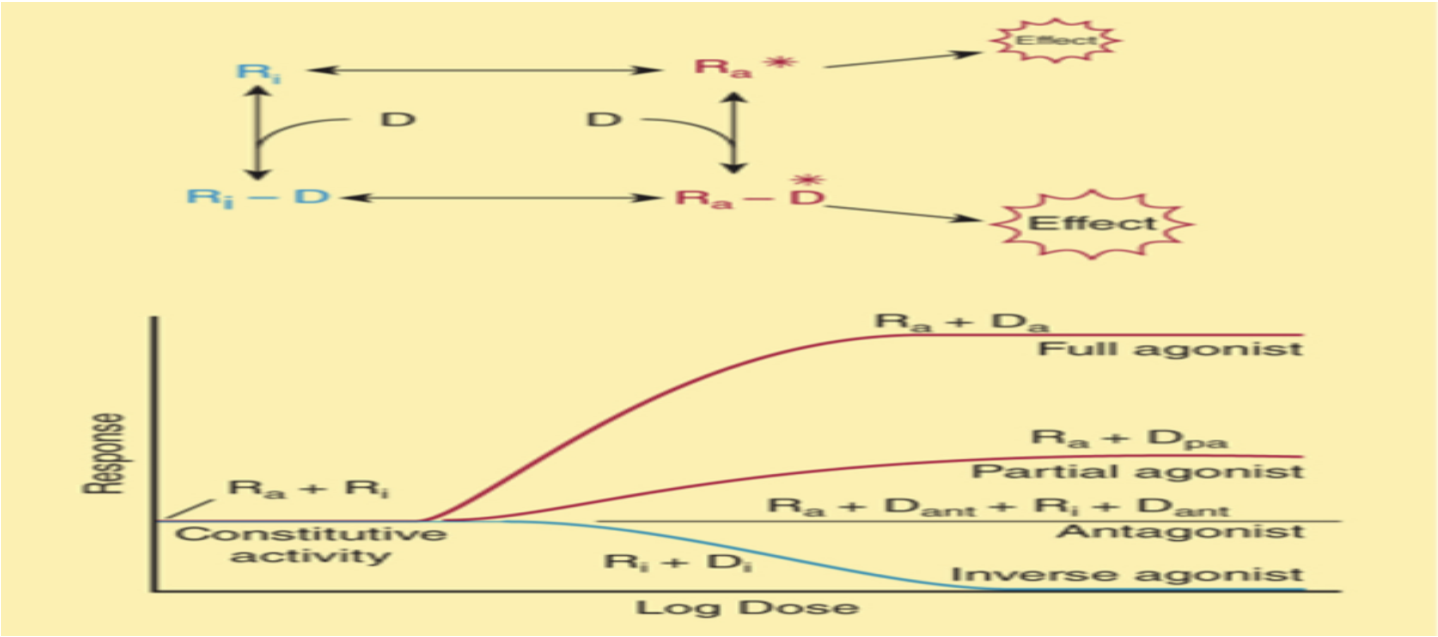
With regard to lecture concept , what neutral antagonist (competitive) mean?

-neutral antagonist does not shift the equilibrium toward active or inactive conformation

Competitive antagonists

- Bind agonist site
- Do not shift equilibrium towards active or inactive conformation
- "Neutral" antagonists





-DOSE RESPONSE CURVE, it is comparing a different kinds of drugs for receptors

1-full agonist giving Emax

2-partial agonist activates parts toward active conformation

3-neutral antagonist does nothing to equilibrium, the amount of activity same as constitutive activity so NO (-) or(+) effect, it is called NEUTRAL AGONIST

4-it is a negative activity, we have an INVERSE AGONIST, what is it?

Is a drug that shift equilibrium more toward an inactive comformation , why it is called agonist> because it is give a negative effect (it does a negative function) of agonist , what is called that does opposite effect of agonist ?

A/ ANTAGONIST as inverse agonist does.

NOTE: we call it ANTAGONIST because it does a FUNCTION (changing) something in system , that is why we differentiate it from antagonist neutral.

-neutral antagonist has no effect .

-inverse agonist has a lower (negative) effective than receptor effect of it is own.

Q/ which of the following true about inverse agonist.

A/Antagonist

*inverse agonist

While antagonists are traditionally thoughts to have no function effect in the absence of an agonist , some antagonist exhibit “inverse agonist “ activity because they also reduce receptor activity below basal levels observed in the absence of any agonist at all

Ex: Naloxone (is antidote of toxicity with certain opioid , means patients would have a side effect of from taking overdose morphine which causes respiratory depression or when people abuse these drugs and continue use it for a long period of time they become addicted to them, to treat this overdose problem of morphine they are given a Naloxone which works inverse ly of morphine (which is an agonist of the opioid cell surface receptor and activate them)so if morphine is an agonist and I give a drug that is also agonist to counter act the overdose of morphine, that makes sense because it is an inverse agonist.

The opioid receptor of morphine has subtype called the Mu opioid receptor,& naloxone is inverse agonist of this Mu receptor time 24…

-inverse agonist give antagonistic effect

-Ex/ adrenergic receptors in the heart used to contraction, if antagonist or inverse antagonist used both can do contraction and give an opposite effect.

-inverse antagonist came to be for a high constitutive activity.

_**(**look at the graph)

Constitutive activity is 10 or 20 so inverse agonist used to decrease the receptor activity to reach a constitutive effect or vasal effect because they are not in ZERO activity, we can not lower the activity of receptor if it was zero.

Also we can gave partial and full inverse agonist .

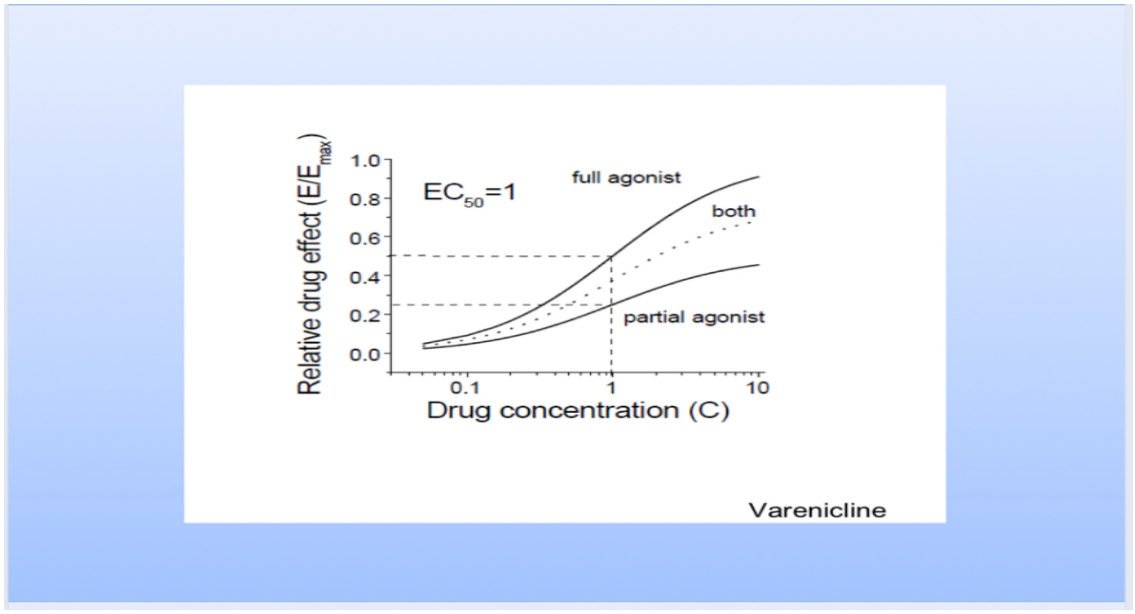
-both (inverse agonist & antagonist) have antagonistic effect with regards to mechanism, the neutral antagonist will bind to receptors but drug-receptor molecule in active conformation percentage divided by drug receptor molecule in an inactive conformation is equal to receptor when it was free so

DRA/DRI=RALRI

In case of inverse agonist we are shifting equilibrium toward inactive conformation, the differ is that it would have more DRI/DRA than original ratio which RI/RA.

The reference is we have something changed in equilibrium, so here(curve) the concentration of the receptor before the presence of the neutral antagonist in each of these position is the same after the adding of antagonist, but

With inverse agonist the percentage is shifting more toward RI conformation.



-look at the curve there are two agonists &same receptor &one of these is full agonist and other is partial agonist, so if I am combining tow drugs both of them have a positive effect, what do think the net effect would be?

-you would think that there would be an enhancement effect BUT it is not, the effect would be in between because both of them would compete each other for binding the receptors so in this curve the partial agonist would act as antagonist for full agonist, as a result more concentration of full agonist would be needed to have an effect of full agonist. So Ec50 is increased of the full agonist, this means I cause a right shift dose on the curve which is similar to the action of antagonist, so **partial agonist works as antagonist for the original drug.**

-Q/why do you think we should disrupt us of taking partial agonist to work as antagonist?

-A/ there are some clinical indication, a drug called Varenivline (chantix is its commercial name) which is used for treat smoking addiction, (it is a drug for smoking cessation).

-Q/ how does it work?

_A/it is a partial agonist of nicotine receptor , nicotine bind to nicotine receptor and give a full effect of it on the receptors, chantix is used to give up smoking gradually and not giving a full response, this occurs by **binding partially to the receptors(occupy some receptors) and it gives a reduced effect not full effect so chantix is acted as antagonist of the drug from its partially agonist.**

Note: partial agonist do not have to have higher affinity than full agonist, even with lower affinity there would be a competitive and occupation of receptors

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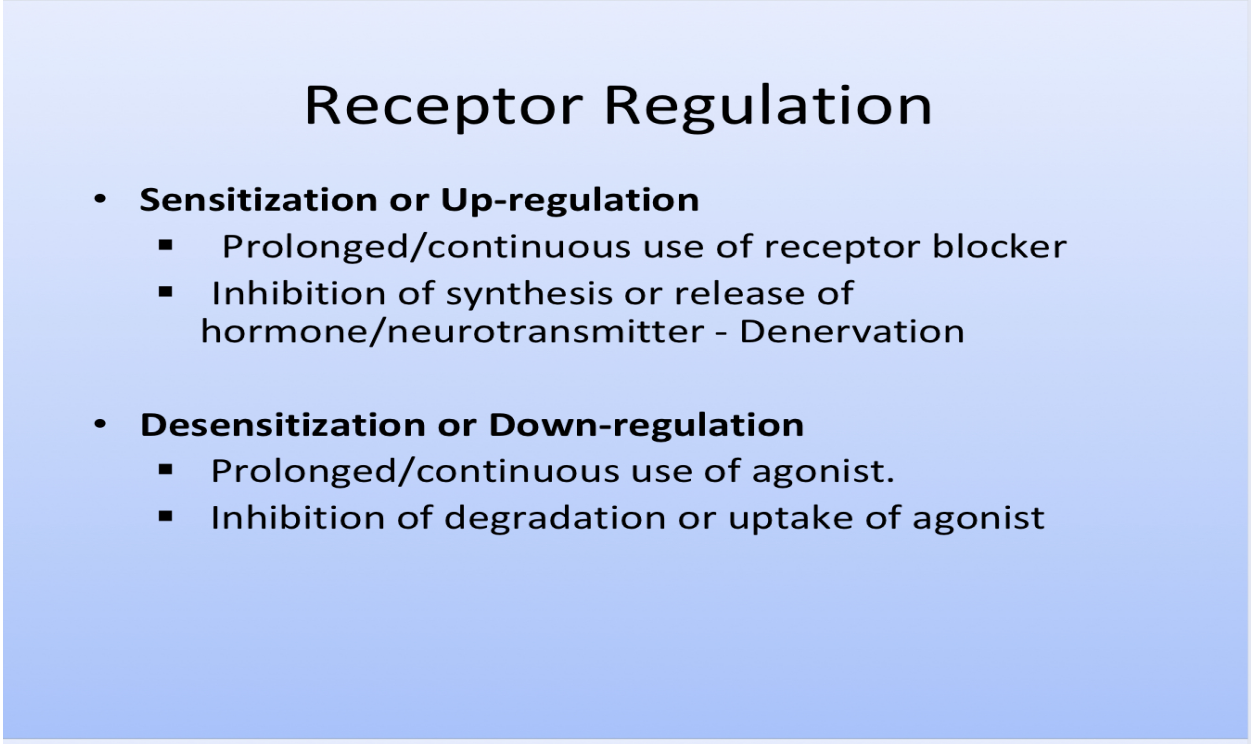


-Receptor Regulation means that in certain instances the body will change the receptors either up regulation or down regulation .

-Q/what instances this happen?

1st scenario when there is a prolonged or continuous use of receptor blocker.

-remember the example of beta blocker we mentioned, beta blockers are drugs that antagonist of beta adrenergic receptors and are used for treat condition of the heart like heart failure.

Q/what would happen if I use these kinds of drugs for long period of time?

A/the body wants to keep in homeostasis it does not like the change so if we change something in the body it would go ahead and try to reverse that change in some way, if I am taking a beta blocker or any kind of antagonist ,the cell of the heart is having a less of activation of signalling cascade that I am used to ,so there is something wrong and in order to compensate it by increases the number of receptors on the surface of tissue and there would be an up regulation of the number of receptors.

What is the problem with that is , when patient with the heart failure and is used to take beta blocker and suddenly stops taking these beta blockers, why?

Because there are same amount of adrenaline(agonist), **BUT higher number of receptors than before** so the receptors would have a higher stimulating & response, this high response may causes a cardic arrhythmia or heart attack.

Solution: patient should stops taking up these blockers gradually over a weeks to let the body regulate these changes and decrease the number of receptors.

-the opposite happens as well with agonist drugs;

If we have a prolonged use of morphine agonist of opioid receptors, when the cell is activated more and more with the higher signalling it would decrease the receptors number (down regulation), it does not need this high signaling.

What would happen to the patient? He is taking a morphine but he has a lower number of receptors so there would be a lower response, taking morphine with same doses but not getting the same response as yesterday it meanse (the response is decreased with the same continued administration) , what does this strategy means?

A/ TOLERANCE (as we took it in the first lecture).

Q/ what is the solution of morphine?

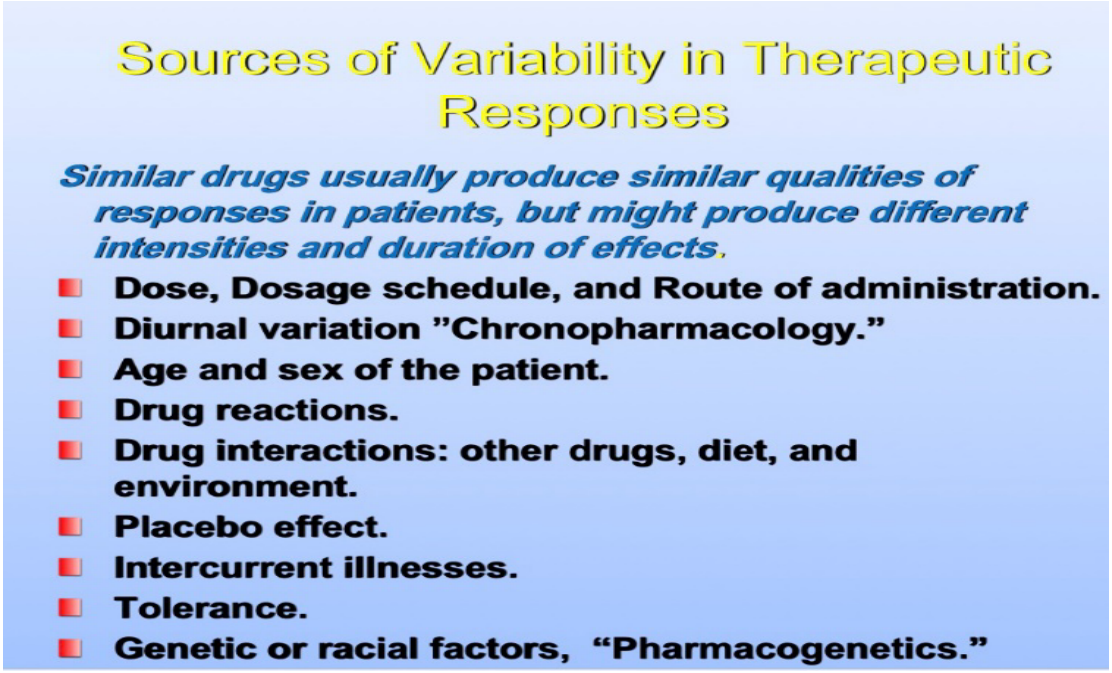
1-increasing the dose of morphine but with the limit because it has a high toxicity.

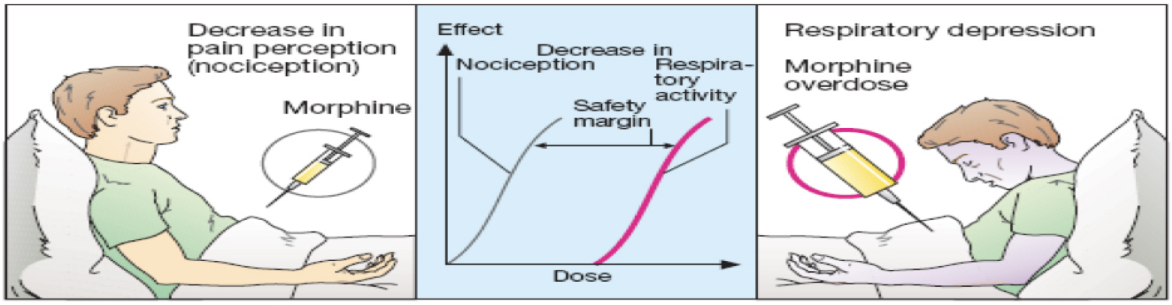
2-exchanging with another drug

3-giving morphine free intervals, means taking morphine every 12 hours hen stops 12 hours so the body will not have a continuous stimulation & will not have a response of decreasing the number of receptors.

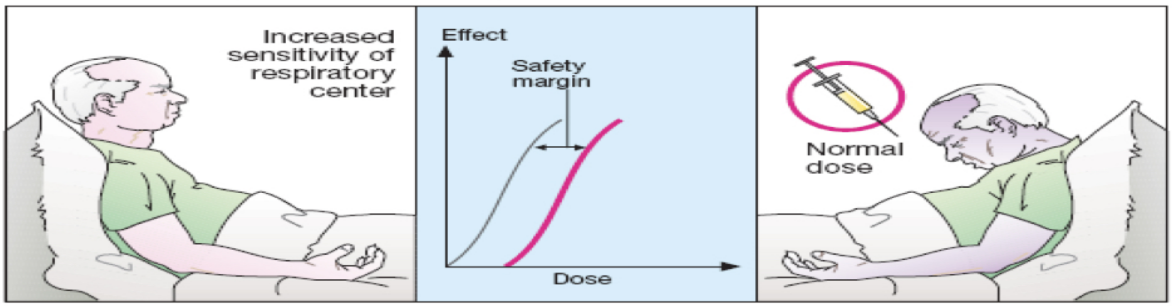
Why do some people respond for certain drug while other do not show the same response? Why some respond for a particular dose while other do not show the same response ?

A/ one of the factor is pharmacogenetics, the differences in the gene in an individual. Other factors are :





A. Adverse drug effect: overdosing



B. Adverse drug effect: increased sensitivity

If we have to patients on different sages (young &elderly pstient).

Young patient is given a morphine with a normal dose (calculated dose) he would be relieved, when elderly patient receives the same dose he reached the toxic effect of morphine which is respiratory depression. A normal dose for a young patient can be toxic for elderly patient, this is because we have changed in the dose response curve where the margin of safety or therapeutic window of the drug with aging is reduced , this is due to the sensitivity to the receptor.

Means; **elderly patient needs less dose of drug than young patient because the sensitivity of the receptors increases as getting older.**

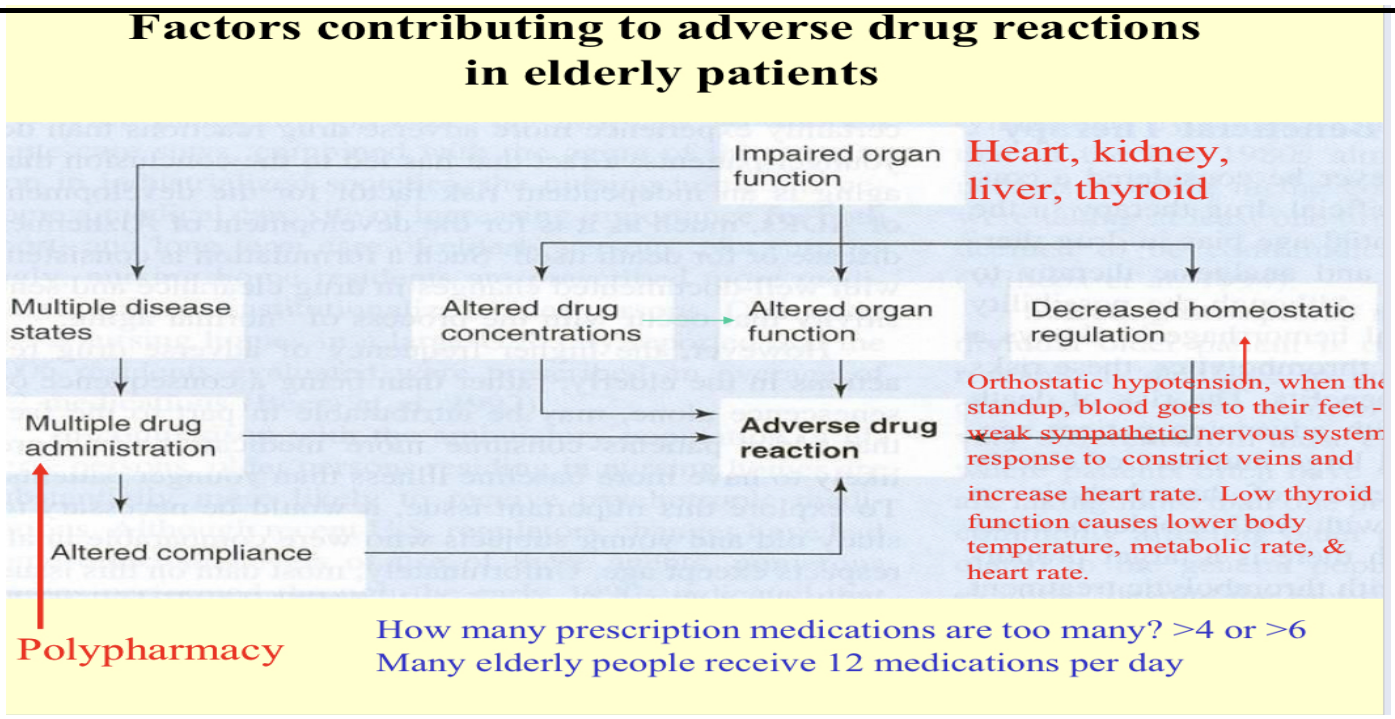
Other problem that come with aging is altered Compliance means;

Elderly opatients ususally take more than two or three drugs, the patients up 65 years old take up to 12 medication, that is why hospitalization occurs for these elderly patients.

*Adults oldervthan 65 years old

*growing population

*20% of the hospitalization for those older than 65 are due to medications they are taking .



Other than taking too many medication, we have a multiple drug administration also they have multiple disease take causes impaired organ function such as heart, kidney, liver.

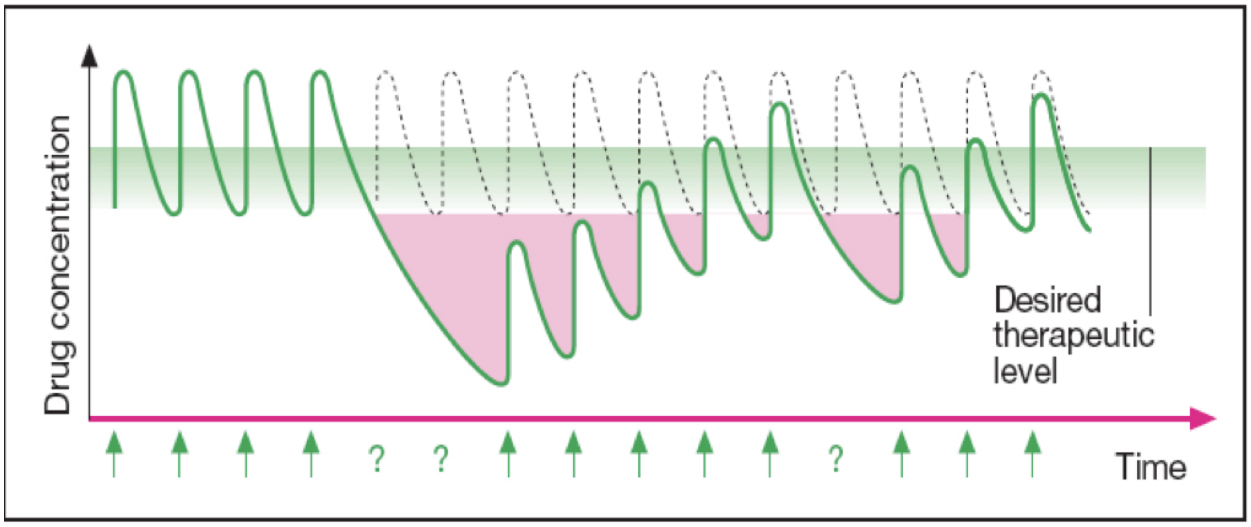
Altered organ function, for example the liver is the site where drug metabolism occurs, any problem in liver would affects the metabolism od drug also getting rid of from the body so the concentration of drug would increase which can give him toxicity.

All these can cause an adverse drug reaction as shown in the graph,

-what is altered compliance?

A/when a patient takes 12 drugs, probably he would miss one of these drugs so the concentration of the drug would drop on the body to a low concentration called concentration which is below the minimum effect , this is concentration required to give the effect ,although there might be a concentration of the drug in the body but has no effect because it is under the minimum effect of concentration and this the problem if you do not comply with the dosage (you do not follow the instruction of how many times taking and when you should take it).

Compliance



Time course of drug concentration with irregular intake

-we have to be careful of elderly patients with regards to drug intake and drug-drug interaction. Also to the changes regarding pharmacodynamics(PD)

Pharmacodynamics (PD)

- Definition: the time course and intensity of pharmacologic effect of a drug
- Age-related changes:
  - ↑sensitivity to sedation and psychomotor impairment with benzodiazepines
  - ↑level and duration of pain relief with narcotic agents
  - ↑drowsiness and lateral sway with alcohol
  - ↓HR response to beta-blockers
  - ↑sensitivity to anti-cholinergic agents
  - ↑cardiac sensitivity to digoxin

ملاحظة؛

الشيت شامل كلام الدكتورة والسلايدات لسكشن(٢-٦)

(-) كلام الدكتورة

(*)السلايدات