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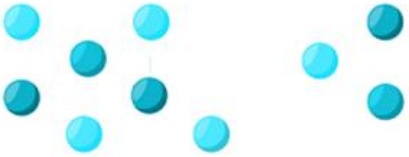

Pharmacology

Doctor 2017 | Medicine | JU

◉Sheet ○Slides

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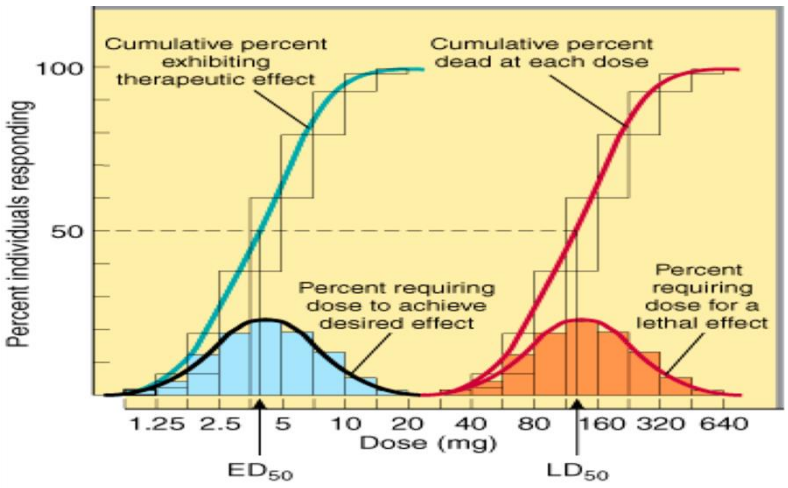
Quantal Dose-Effect Curve

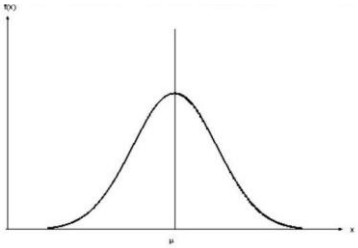
- The Quantal Dose-Effect Curves (or can be called Quantal Dose-Response Curves) are curves which show the percentage of a population that showed the desired effect of the drug.

- It is used to determine the dose of the drug required to produce a specific magnitude of effect.

- These curves study the all-or-none effect. If we take painkiller as the example here, then this curve would study if the painkiller did actually decrease the pain or not regardless of how much it actually decreased.



- It obeys normal frequency distribution (seen in the bell-shaped graphs). Such graphs which obey the normal distribution help in showing what the majority's results/preferences are (in our case, what the majority's ideal drug dose is).



Bell Shaped Curves

- When transformed into cumulative, they will result is a sigmoid curve (straight line for most of the line).

- In a case of Quantal Dose-Effect Curves, we have to specify the quantal effect. For example, if we are using a drug that decreases the heart rate, then we should set a standard drop (ex: 20bpm drop) to say that the effect happened. Any result less that the quantal effect we set is considered a no.

- These curves help us calculate the Therapeutic Index (TI) .

The Therapeutic Index (TI)

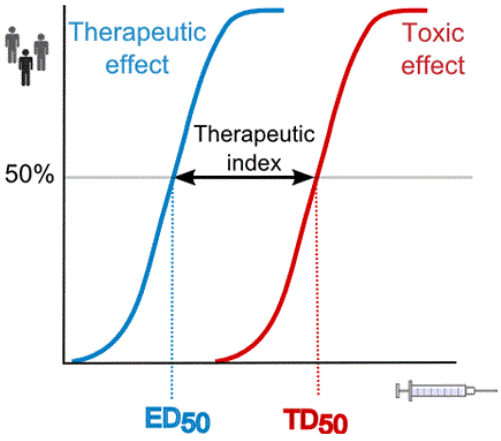
- It is the ratio of the minimum dose that produces toxicity effects for 50% of the population (TD_{50}) (or can be called LD_{50}) over the minimum dose that produces an effective response in 50% of the population (ED_{50}).

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

****NOTE: ED_{50} here is different than ED_{50} used in the Graded Response curve.****

- In humans, side effects may be used as the toxic or lethal point you are trying to reach (you can say that 50% of the patients had headaches for example at one specific dose. this dose, for your study, will be considered the TD_{50}).

- TI should preferably be high. For a safe medication, we need to have a large TD_{50} value which is much higher than that of the ED_{50}. this makes us insure that even if we increase the dose of the medication, we will still not reach the TD_{50} value, thus, in a safe drug, the difference between them TD_{50} and ED_{50} values is large.



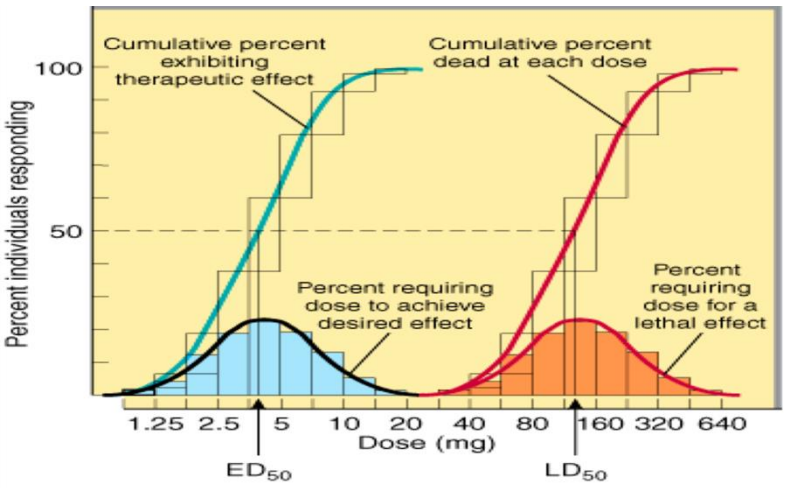
- Here's an example:
  for the sake of this example, say we have three drugs: A,B and C. these drugs have TI values of 5, 20 and 100 respectively.
  for drug A, if we increase the dose that was effective for 50% of the population (ED_{50}), we would then reach the dose that caused unwanted side effects (or toxic effects) for 50% of the population. Same goes for the other two drugs.

  we can then conclude that drug C is the safest of all, since we need to increase the ED50 dose 100 times to reach the TD50. This means that it has the largest therapeutic window, which will be explained after this.

Therapeutic Window

- The Therapeutic window is a range of doses that produces therapeutic response without causing any significant adverse effect in patients.

- Another definition is the range between the minimal toxic dose and the minimal therapeutic dose (between doses of a 1.25 and almost 20 in the graph).



- Here's a quick way to analyze the Quantal Response-Curve Graph to understand the Therapeutic window:

  -The bell-shaped graphs signify the normal distribution of patients and their quantal response to different doses of the medication, while the sigmoidal one is the accumulative one as explained in sheet 5.

  -The bell on the left is the percentage of patients exhibiting a wanted effect out of the drug, while the one on the right is the percentage of patients exhibiting an unwanted or lethal effect vs the drug dose.

  -You can tell that at a dose of almost 30, the patients are no longer exhibiting a wanted effect, and they start exhibiting unwanted/lethal effects.

  -any increase in the dose before reaching 30mg will probably cause no unwanted effects.

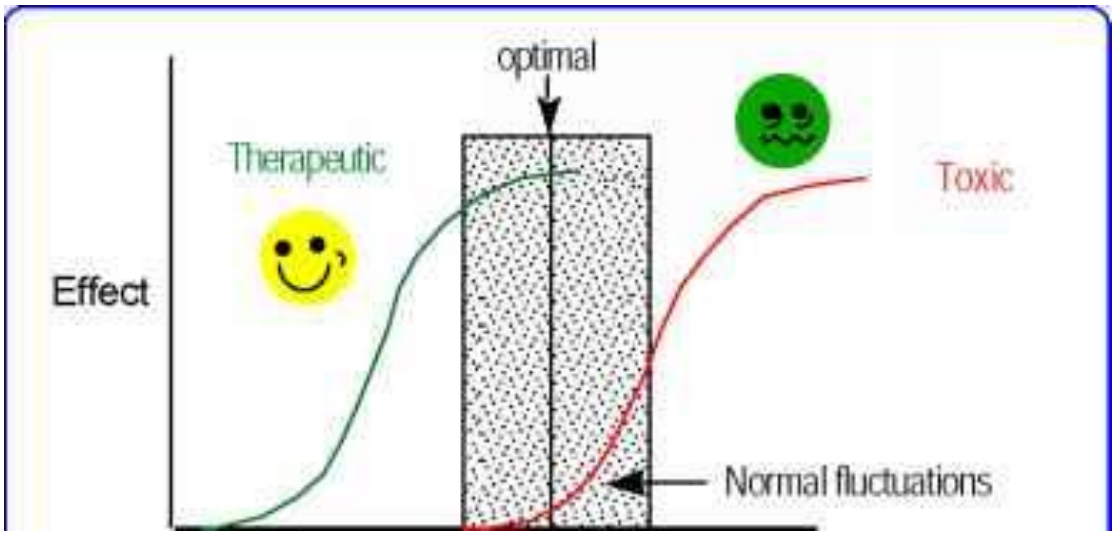
- The therapeutic window, along with the Graded-Dose response relationships (Potency and maximal efficacy) can actually determine the perfect dose of drug for the patients.

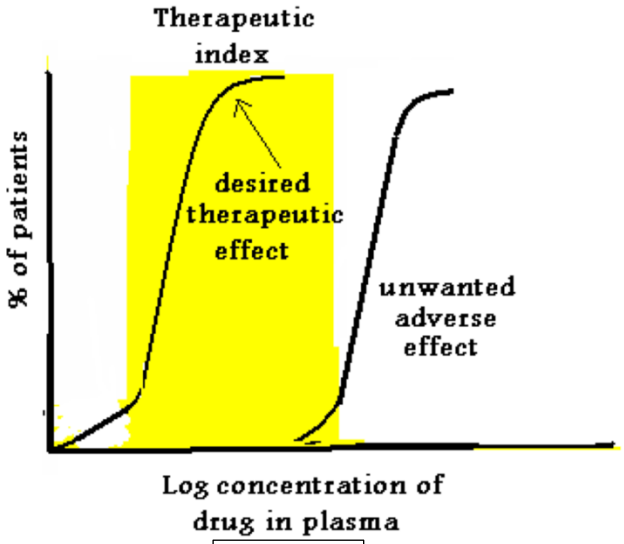
Therapeutic Index and Margin of Safety

- Margin safety is how much the drug is safe related to the increase of its dose.
- Another definition is that it's the margin between the therapeutic and toxic dose of a drug. (dose that is above an ineffective level, but below a toxic level)
- The larger the therapeutic window is, the larger the margin of safety is, the higher the therapeutic index, meaning the safer the drug is.

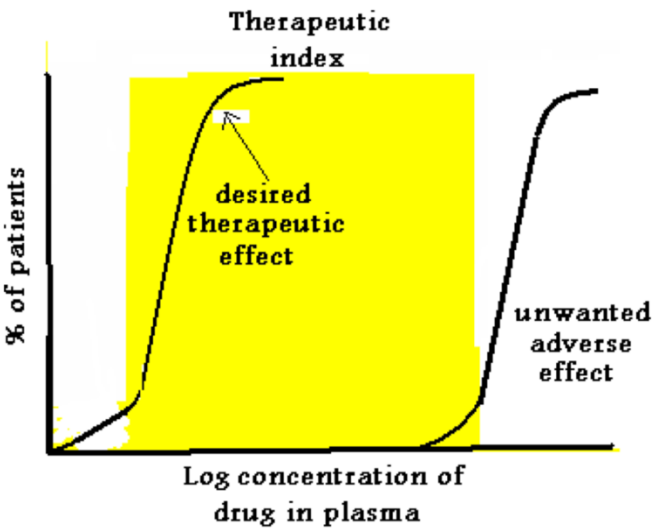
$$\text{Margin of safety} = \frac{\text{minimum dose of a drug to give an unwanted (toxic) effect}}{\text{Highest concentration to give the therapeutic effect}}$$

- This is a clear application on the therapeutic window discussed previously.





Drug A

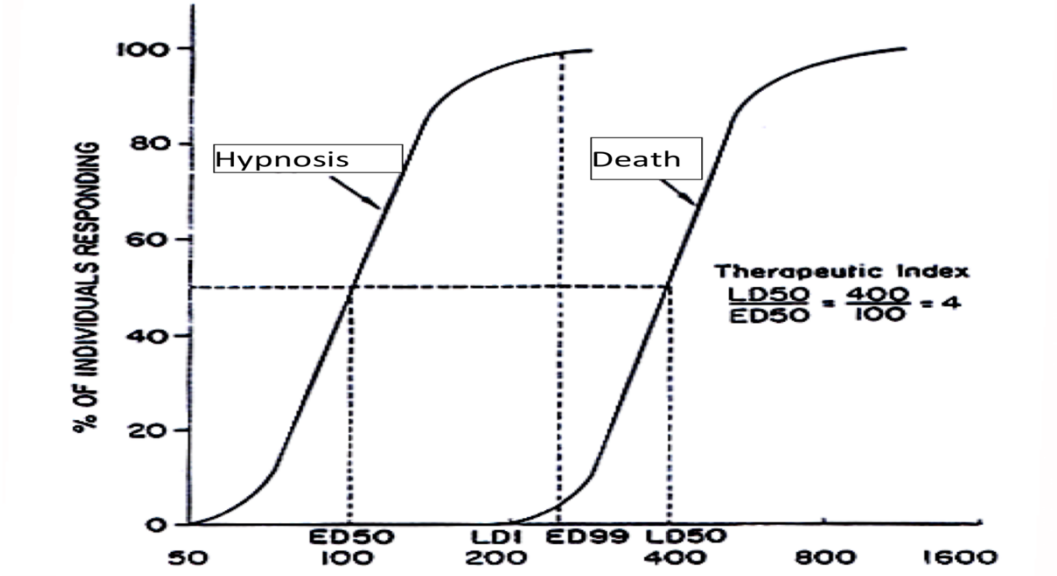


Drug B

- The graphs above show us the sigmoidal curves for the therapeutic/desired effects and the unwanted effects of two drugs. From the graph, we can tell that drug B has a larger therapeutic window than of drug A (remember the definition of the therapeutic window).

- This means that drug B has a larger margin of safety. From the graph, if you increase the dose in drug A a little bit more than the desired therapeutic effect, you will start to reach the toxicity effect range. Instead, if you do the same in drug B, you need more increase in drug to reach the toxicity effect range.

- Here's a question from the slides to revise:
  Calculate the Therapeutic Index from the graph?



Receptor Regulation

- In certain conditions in the body, due to taking some drugs, the body would have to increase or decrease the number of receptors on the cell surface to adapt with what certain medications do. This is called Up-regulation (an increase in the number of receptors) or Down-regulation (a decrease in the number of receptors).

1) Up-regulation (Sensitization): Up-regulation happens in two cases:

Sensitization means that receptor becomes more sensitive to its agonist due to some conditions.

Up-regulation means cells produce more Receptors than its normal.

A) Prolonged or continuous use of receptor blockers:

When using receptor blockers, such as β-adrenergic receptor antagonists, we are stopping a large number of receptors from working for a long period of the patient's life. The body then would realize that the signal is going low and tries to reach homeostasis by increasing the number of receptors (Up-regulation) and sends them back to the surface of the cell.

The problem in such cases, is that when these receptors increase in quantity, and the patient suddenly stops the drug, the number of working receptors would be higher than the number which already existed before using the drug. This results in cases such as Cardiac Arrhythmias or an increase in the heart rate in the case of adrenaline because there are so many receptors that the drug can bind to, meaning the effect would be higher. In the case of other receptors and their endogenous compounds, the effects would be different (probably a much higher effect)

B) Inhibition of synthesis or release of hormone/neurotransmitter - Denervation:

Say we are using a drug which works on the Central nervous System (CNS) and inhibits Epinephrine. The number of Epinephrine receptors would increase to reach homeostasis and get things back to normal. When the patient stops the drug, the same effects of the previous case would happen.

2) **Down-regulation (Desensitization):**

Down Regulation is when receptors become less sensitive to their agonist , so the cell Reduces the production of Receptors. This happens in two cases:

A) Prolonged use of agonist:
the receptor then becomes always active. Thus, to reach homeostasis, the cell would down-regulate its receptors.

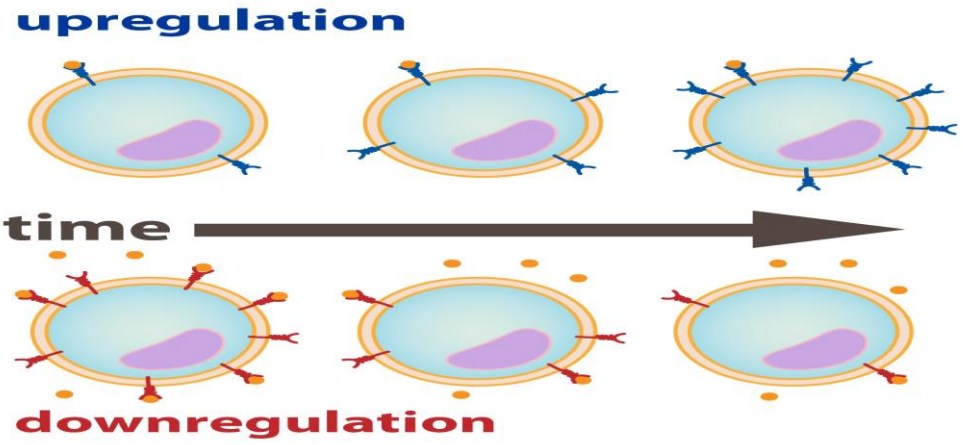
This is the reason why our bodies sometimes stop responding to certain drugs, after a period of time, just like painkillers, where sometimes our bodies no longer feel the effect of painkilling if these painkillers were taken continuously. This is why it is preferable that all drugs which follow the up-regulation or down-regulation mechanisms get stopped gradually.

B) Inhibition of degradation or uptake of agonist.

- **Can some drugs actually work on changing receptor numbers in a cell?**

The difference between the question and the previous cases is that in the case of the question, wanted therapeutic effect of the drug is to change receptor numbers in a cell. This can absolutely happen Nuclear transcription Factors, go to the DNA and increase the transcription of certain genes.

if these genes where genes responsible of synthesizing certain receptors, then these receptors would increase in number.



Possibilities of Drug Combinations:

Drugs usually work on their own. but, what effect is produced if we take two or more drugs together?

1) **No effect:** meaning that the drugs do not affect each other if taken together.

2) **Antagonistic effect:** Two drugs are antagonistic when their interaction causes a decrease in the effects of one or both of the drugs. This could be competitive or non-competitive.

3) **Additive Effect:** 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.

   Where: **EAB =EA +EB 1+1=2**

4) **Synergistic Effect:** Interaction between two or more drugs or agents resulting in a pharmacologic response greater than the sum of individual responses to each drug or agent. This is because these two drugs work on the same pathway (both work the same mechanism on two enzymes in the same pathway).

   for the example below, antibiotic A works 40% on its own, while B works 50% on its own. together, they work 100%. This is called the synergistic effect.

EAB >EA +EB 1+1>2

Sulfamethoxazole (Antibiotic) + trimethoprim (Antibiotic)

5) Potentiation Effect: Potentiation drug effect occurs if a drug lacking an effect on its own, increases the effect of a second active drug.

EAB >EA +EB 0+1>2

Full Agonists VS Partial Agonists:

Agonists are either full or partial, here are the differences between them:

1) Full Agonists:

- They give you the maximum effect of the drug.
- According to the Two-Model Theory, they shift the conformation of the receptors to their fully active conformation.

2) Partial Agonists:

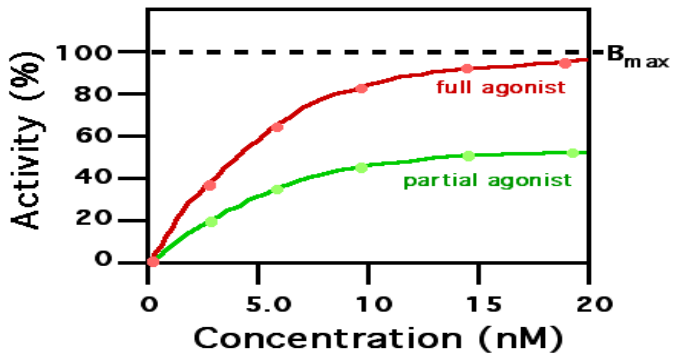
- They give you a partial effect of the drug.
- According to the Two-Model Theory, they shift the conformation of the receptors to their partially active conformation.

- Note: if we give a full agonist with a partial agonist, the partial agonist would work as an antagonist for the full agonist.

  Since both of them bind to the same receptors, they should occupy the receptor for some time. The receptors which are bound to the partial agonist will not work fully. This makes them partially not working, meaning that the partial agonist worked as an antagonist here.

This case is widely found in smokers trying to quit smoking. *Chantix* is a drug given to smokers whom are trying to quit smoking. This drug is a partial agonist to the nicotinic receptors, while the full agonist is nicotine. This way, smokers will partially get nicotine and will gradually stop smoking.

Note: Sometimes, the partial agonist has a higher affinity than the full agonist to a certain receptor.



This graph is not in the slides. It's just here to make you understand the concept more, so you don't have to know its details.

Causes of Variability in Drug Response

why do we respond differently to drugs although we are all humans?

There are multiple causes, including:

A) General Causes:

1. Body weight and size.
2. Age and Sex.
3. Genetics – pharmacogenetics.
4. Condition of health.
5. Placebo effect (the effect of psychology on the well-being). Here's a little bit of explanation:

What are Placebo Drugs?

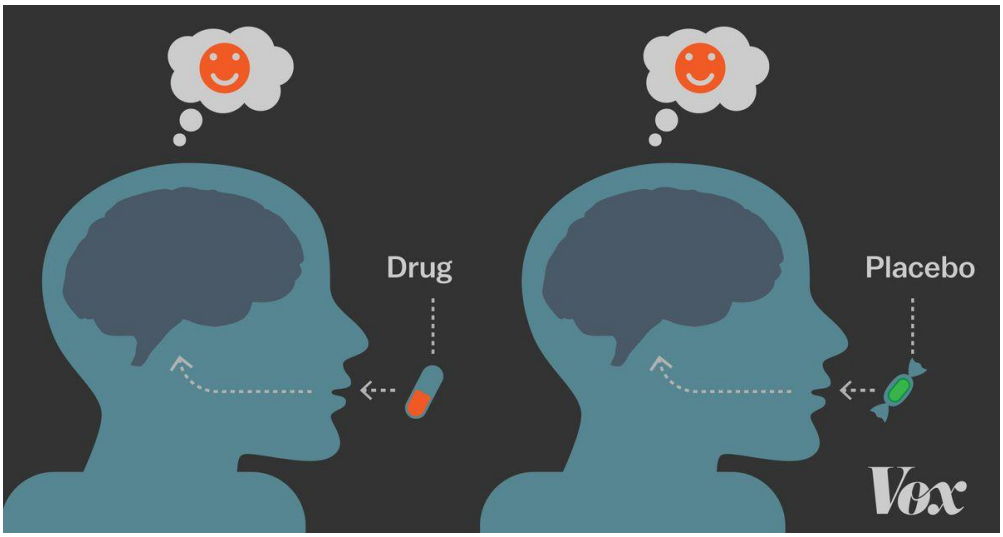
They are fake medicine which do not have an active material that affects the human body.

Why do people take them?

Some placebos can make some people feel better. Research says that if people think a tablet or pill will help them, they normally feel better, even if the tablet has no physical benefit.

How do placebos work?

Medical research says that if a patient takes a placebo, their brain thinks it is getting medicine. Their brain then reacts, producing chemicals that make the patient feel better.



B) Those related to the conditions of administration:

1) Dose, formulation and route of administration.

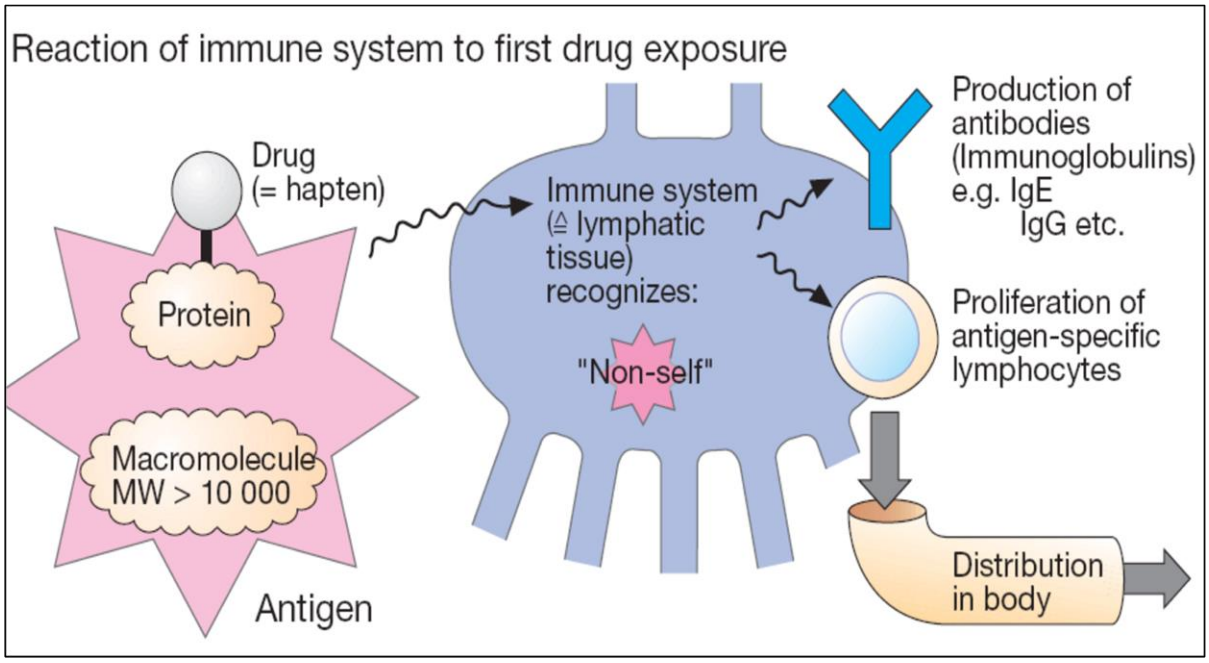
2) Resulting from repeated administration of drug:
drug resistance;
drug tolerance-tachyphylaxis;
drug allergy.

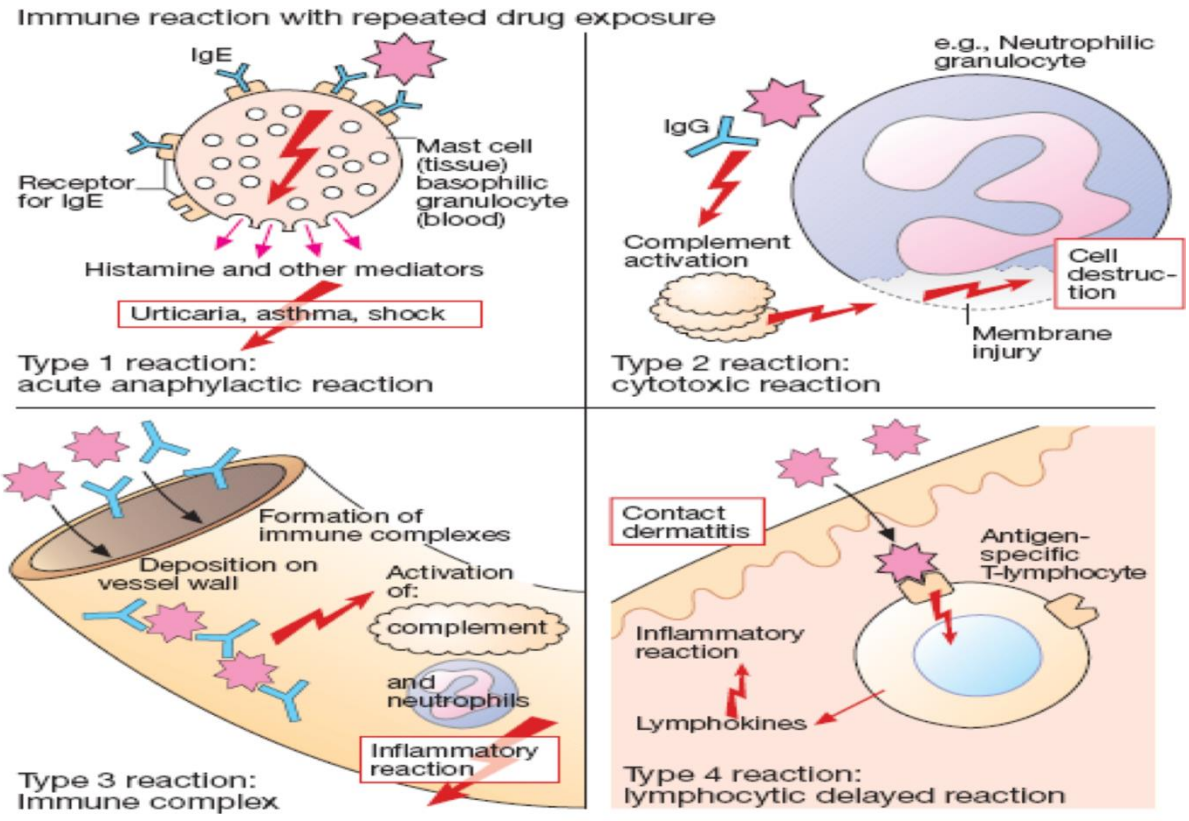
3) Drug interactions:
chemical or physical;
GI absorption;
protein binding/distribution;
metabolism (stimulation/inhibition);
excretion (pH/transport processes);
receptor (potentiation/antagonism);
changes in pH or electrolytes.

Drug Allergy

- It is defined as an adverse reaction to a drug by a specific immune response either directly to the drug or one or more of its metabolites alone, or to a drug bound to a body protein such as albumin, (Hapten).

- Such binding alters the structure of the drug/protein complex, rendering it antigenic.





- We have multiple types of drug allergies, discussed in the following table: (Anaphylactic is the most dangerous).

Classification of Allergic Reactions

Type	Mechanism	Time	Example
I	Anaphylactic	sec/min	Angioedema
II	Cytotoxic	--	Transfusion rx
III	Immune	6-8hrs	Serum sickness complex
IV	Cell mediated	48 hrs	Contact dermatitis

THE END!

Thank you so much for bearing!

**Note: in Dr Alia's slides, after the allergies are done, she leaves a couple of slides including all the important terms we learnt in pharmacodynamics. I didn't want to add them so that I don't make this sheet longer that it already is. Please please go back and memorize them, they are so important!

**if you prefer studying from the book, this lecture covered pages 36-39 of Katzung's Basic and clinical Pharmacology 14th Edition.