



Medical Committee  
The University of Jordan



# PHARMACOLOGY

**Lecture No.:** 12

**SHEET**



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**SLIDES**



## بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

### **ADVERSE EFFECTS**

\*At the beginning a student asked the Dr. about the names of the drugs that are mentioned in the lecture and he said **don't** memorize them now, you will be taking them with Dr. Ya'qoub , I will not ask you about names in the exam :D

Remember that drugs have an adverse effects , and adverse effects will increase with some sort of risk factors .People with such factors are more susceptible to having adverse effects. We are going to talk about **risk factors** a lot through this lecture and about **geriatrics** (طب الشيخوخة) and **pediatrics** (طب الأطفال) . Let's go through these topics one by one.

#### - **Risk Factors for Adverse Drug Reactions:**

##### 1) **Simultaneous use of several different drugs.**

Simultaneous use of several drugs together will risk the patient to develop more adverse effects because of drug – drug interaction. Also, the drugs affect the homeostasis of the body , means that drug **A** will influence changes on some body properties making it more susceptible for adverse effects of drug **B** .

##### 2) **Very young or very old in age.**

We have a group of special population and it includes: newborns or neonates “ the first 28 days after birth“/children/ geriatrics / pregnant women and lactating mothers = nursing mothers .

So we really need to take care of children , any child under 10 years old ,12 or sometimes under 18 years old ; because the body is still growing mentally and physically. But we worry more about infants( under one year ). Why are children and especially infants more susceptible to adverse drug effects?

- **Because they haven't been really/fully developed** , the functions of several organs such as liver or kidney are still undergoing massive development, even the absorption ( kinetics) of the drugs is different . And this is due to their different body composition. Children have greater amount of water in their bodies than fat compared to adults.

Conversely, old people have a lot of fat and less water component and their cells will undergo (**degeneration**) and **ultimately death**, so the more you advance in age , the more you are susceptible toward the side effects. (Cellular Senescence).

- **Pregnancy :-**

It is considered as a disease state although the pregnant lady is not really ill , but she has some sort of physiological changes which makes her more susceptible towards drugs.

The most crucial point in pregnancy is to :

**Never ever** try to risk the pregnant lady for drugs , **DON'T** ever try to give her a drug unless you have deep knowledge about the drug. Because all the consequent congenital malformations will be disastrous or fatal. Side effects may result because of the pregnancy and also during breast feeding. Most of the drugs are lipophilic and they will dissolve in the milk and eventually, they will be transferred to the newborn during breast-feeding and cause alterations. Pregnancy is the most important risk factor.

There is a famous case always being mentioned about a lady that was taking **Codeine** (not morphine) ( Codeine : an analgesic drug derived from morphine ) – that is used in Canada and America more widely unlike Jordan. She took it post-delivery and during breast feeding and it was transferred to the infant and the infant died as a result ! The Codeine was over-dosed and the infant had a respiratory depression and went dead.

- **Hereditary factors :-**

Some people are allergic to penicillin, others have allergic keratitis and some have asthma , all of these are due to genetic factors .

-A very important part that we need to understand which increase the risk of the adverse effects is the :

- **Disease status which may effect drug absorption, metabolism and/or elimination :-**

The most important organs that deal with drugs are **liver** and **kidneys** , always consider the health of these two organs. If the patient has a liver compromising function , you have to take it in consideration , also kidney failure or / compromising kidney function must be considered during treatment. **Because these two organs determine Bioavailability/ drug concentration in the blood and the patients will be largely affected when damaged.**

For example, patients who have heart failure, their circulation will be disturbed, they hardly can pump the blood out of the heart (the drug will be hardly distributed) so they have different sort of distribution, so this is another idea concerning the heart. So you must take in consideration when prescribing the drug the patient disease state.

## **Risk : benefit ratio:**

It is the most crucial point when you prescribe a drug .

**You mustn't prescribe the drug if your patient has more risk than benefit** , and these risks or benefits are determined by or dependent on the dynamics and the kinetics of this drug .

## **HINTS:**

### **1) Balance between over- prescription and under- prescription.**

What does this mean ?

Overprescribe means to prescribe unnecessary or excessive medication and this nowadays occurs most frequently with antibiotics being prescribed for flu patients. The flu is a viral infection mainly ( 90% of it ). Antibiotics obviously don't have any antiviral activity, so they are overprescribed being unnecessary with no effective treatment.

Under prescribe means prescription of an inadequate amount of a drug. When your patient needs the drug and you don't prescribe it, due to wrong prescription and underestimating the patient clinical case. You can kill the patient by under-prescription because it simply means you are not giving the necessary drug for your patient well being.

How can we balance between under and over prescription and give the just right prescription? By assessing the right risk: benefit ratio of the drug.

### **2) Avoid a pill for every ill.**

### **3) Always consider non pharmacological therapy.**

- Don't always jump to prescription! (Some doctors write the prescription before even seeing the patient!). Pharmacies also practice over-prescription by giving antibiotics for anyone that has sore throat! So we must avoid pills as much as possible and consider non pharmacological therapy.

Example:

Diabetes Mellitus and Hypertension can be controlled without the need to guide a drug therapy.

Some diabetic patients that are found in Jordan are in a good compliance with their strict diet preventing them from the need of any drug. This method is practiced a lot in Western countries but we lack it here in our countries due to the low level of education.

Hypertensive patients that practice exercise, reduce their Na<sup>+</sup> intake and reduce their body weight are in no need for drugs and their BP will decrease.

\*(most of the lecture today is about education more than science , a lot of doctors don't know about education in pharmacology , you need to understand this point very well ,



you are the decision maker.)

## **Communicating with the patient:**

We need to speak to our patients , إن شاء الله , after 2 years you will go to the hospital , you will not see anything of this , you will not see communication between the Dr. and the patients , you will not see the Dr. even ☺

Unfortunately, the time spent with our patients doesn't exceed five minutes but in developed countries it won't be less than 20 minutes in which the doctor will talk to his patient and communicate with him.

### **How to communicate:**

#### **• SPEAKING CLEARLY AND SLOWLY IS VERY IMPORTANT.**

-Talk with him in a language that he or she understands ( try to avoid the usage of English medical terms)

#### **• BE AWARE OF THE DIFFERENT LANGUAGES AND CULTURES.**

-Different words and different accents are found between various nationalities. Make sure that patients understand what you say, use normal language.

#### **• PATIENTS WILL SOMETIMES HAVE A DIFFERENT MEANING THAN THE PERSON TEACHING THE INFORMATION.**

Patients will understand things according to their background so you must ensure that he or she gets the exact point that you are trying to explain.

## Planning of medication:-

Each prescribed drug should be planned.

### 1. Decide the reason or goal for giving the medication.

Why am I giving this medication? What is the goal or the desired outcome?

For example : Metformin ( sold as glucophage) is an oral antidiabetic drug and also treats overweight and obesity. It has been commonly prescribed by doctors for ladies and some men without real necessity in order to achieve a desired weight and become slim. And this is not the actual goal of Glucophage which is to treat type 2 diabetes. You must identify your goal and never prescribe drugs for the sake of patients' wishes.

### 2. Learn specific information about the medication:

- a. The desired action of the drug.
- b. Side effects that may develop.
- c. The usual dosage, route, and frequency.
- d. Situations in which the drug should not be given (contraindications).

---→ Example : **pregnant** ladies shouldn't take Brufen.

**Peptic ulcer patients** shouldn't take Diclofenac ( a drug to reduce inflammation and sometimes as an analgesic) because it makes it worse.

#### e. Drug interactions (What is the influence of another drug given at the same time?)

You need to know all this information, **don't prescribe the drug if you don't know**, don't try to form speculations and predictions.

You **must** know, open iPad, laptop, anything, don't be shy or ashamed if you don't know the adverse effects of the drug. Just look for it !

### 3. Develop a teaching plan for the patient:

- a. What the patient needs to know about the medication's actions and side effects.
- b. What the patient needs to know about the administration of the medication.

For example a pharmacist, gave an old women patient rectal suppositories, she came the next day telling him that their taste is awful! You must tell the patients how to take their drug in order to get an effect. 50 % of people, who use inhalers such as Ventolin, use it inappropriately. There must be synchronization between the push and the breath and this is not easily achieved, so it must be taught to the patient.

- c. What the patient needs to report to the nurse or physician about the medication.

This is very important. You must monitor your drug prescription and aware the patients of the possible adverse effects and tell them to report their condition immediately if any of the adverse effects occur.

Some patients will develop an adverse effect and stop the drug by themselves and go for another drug. The adverse effect might be epigastric distress and this isn't an enough cause to stop the usage of the drug .We can manage this epigastric distress by giving him another drug to reduce it.

**So please plan your drug prescription , drugs aren't to be played with.**

## **DRUG RESPONSE VARIATION**

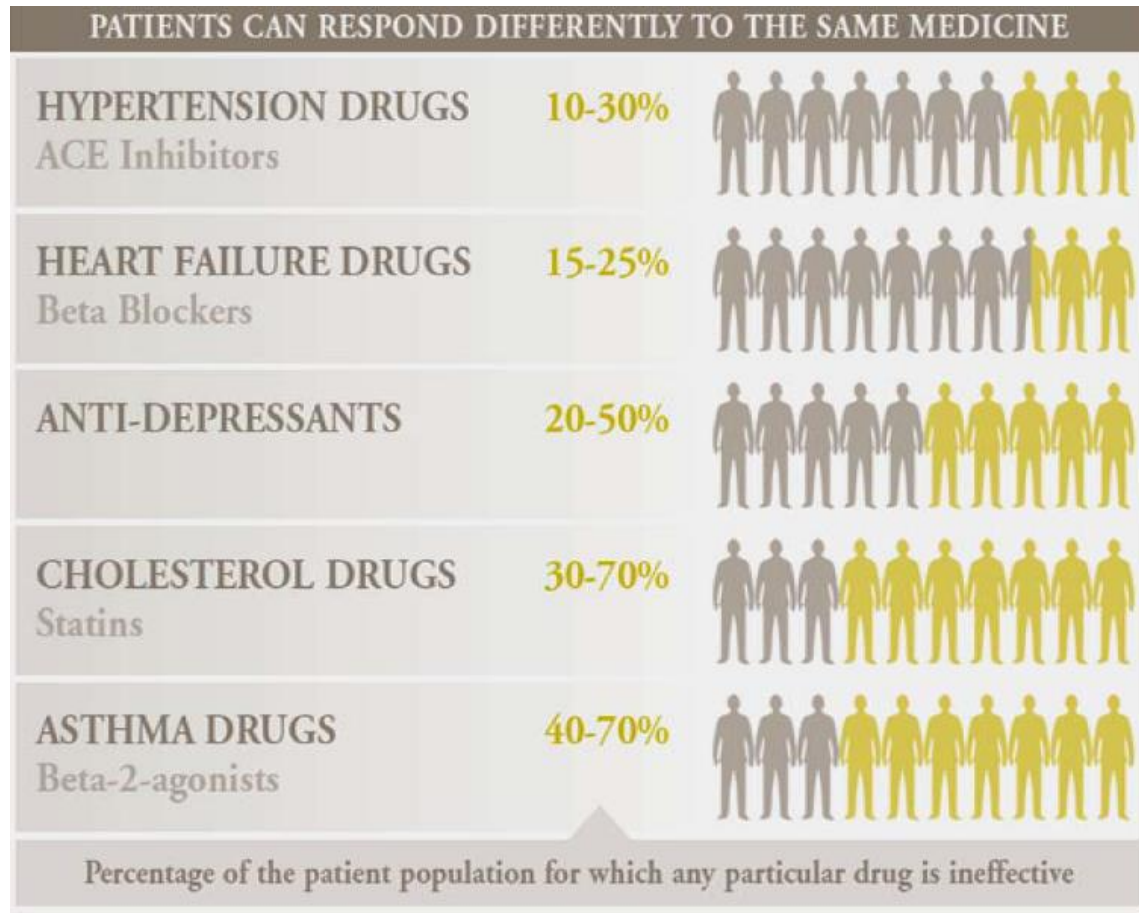
### **- We have "ONE- DRUG – FITS –ALL" policy:**

What does this mean ?

If we have a population with the same disease, for instance if I have 100 patients suffering from asthma, they are being treated in a similar manner without taking in count their individual varieties.

Physicians are moving towards "Personalized Medicine" which means using the genetic makeup of an individual patient to guide therapy. Why do we need Personalized Medicine?

Because asthma for example is expressed differently between individuals, it can be more or less inflammatory or as an allergic response. So we can't use the same drug for all patients, it might not be effective if we don't understand the situation and the case of the patient completely. This variation in drug response can be the reason for some drugs being ineffective even when we are giving the therapeutic dose.



- Hypertension drugs are very common ( approx. 50 % of Jordanians take anti-hypertensive drugs. )
- After reading the earlier figure we result in:

Due to the variation of drug response, drugs aren't effective with all patients and this is because of several factors such as:

1) **Age** which is a very important factor. Response to drugs varies with aging, For example elders respond differently to analgesics compared to adults, why?



One of the reasons is due to activity ( cellular and physical) they are less active and thus need less amount of analgesics.

**2) Sex (gender)** – We prescribe the same dose regardless of the patient gender but recently a drug emerged called Zolpidem which is a hypnotic drug used to treat insomnia and help patients to sleep restfully. It is used here in Jordan and according to the American FDA , the recommended dose for women is half the recommended dose for men. Because side effects are more prevalent in ladies than men so we reduce the dose and at the same time we are still having therapeutic effect. In other means ladies are more susceptible to develop an overdose . To date, the only medication for which the FDA has made a clear distinction between dosing for men and women is Zolpidem. ( Zolpidem was approved in 1992 and this dosage alteration was approved just last year).

- P- glycoproteins are expressed differently between ladies and men ( men have more p-glycoproteins than women , means that men are more protected towards harmful substances )

**3) Weight :** Fat people have larger amounts of fat , so lipid soluble drugs will dissolve more in fat due to the large amounts and as a result the blood concentration will decrease and the desired effect will not be achieved. We can't give a 60 kg or 100 kg patient the same dose ( whether a lipid soluble or water soluble drug) and this leads us again towards “ Personalized Medicine” discussed in the next lecture.

**4) Kidney and liver function:** Dysfunctions in liver or in kidney will lead to variation in drug response as well as increased susceptibility towards adverse effects ( discussed previously)

**5) Genetic variables :** we'll talk about it later.

**Correction Note:** In fact genetic variations influence susceptibility to many complex diseases as well as responsiveness to various therapeutic agents.( Pharamcogenomics).

## **Geriatrics:**

- Adults > 65 years old.
- Fastest growing population in US.

- 20% of hospitalizations for those >65 are due to medications. They're having either drug – drug interaction or side effects of single drug. And this is because we use the same dose with geriatrics as a normal adult.

### **-Pharmacokinetics:**

- Geriatrics have different pharmacokinetics , decreased total body water and increased total body fat and this effects the **VOLUME OF DISTRIBUTION**.
- If your drug is water soluble, the concentration in the blood will be high. If we increase the digoxin level in the elderly , that will cause a side effect , and may cause toxic effect. **Serum levels may go up with water soluble drugs due to decreased volume of distribution .**
- Fat soluble drugs will go to fat , so half life of these drug will increase. The fat will act as reservoir of the drug.
- There should be a geriatrics specialist in hospitals that knows how to deal with them.

### **-Metabolism :**

- Oxidative metabolism through cytochrome P450 system does decrease with aging, resulting in a decreased clearance of drugs.

### **-Excretion and elimination:**

- **GFR** : glomerular filtration rate .
- GFR generally declines with aging, but is extremely variable:
- 30% have little change
- 30% have moderate decrease
- 30% have severe decrease

Means not all patients will have compromised kidney function due to GFR decline.

### **Correction Note:**

- Creatinine – based approximations of the GFR:

In clinical practice, however, **creatinine clearance** or estimates of creatinine clearance based on the serum creatinine level are used to measure GFR and further indicates the kidney efficiency. Creatinine is produced naturally by the body (creatinine is a breakdown product of creatine phosphate, which is found in muscle). Serum Creatinine is unreliable marker because although it's freely filtered by the glomerulus it is actively secreted in very small amounts such that it overestimates actual GFR by 10-20%.

-The accuracy is improved by measuring the creatinine clearance ( not the serum creatinine) which is done through collecting urine over a time interval and doing further mathematical calculations.

Age	Scr	CrCl
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

This table doesn't necessarily apply to all patients, we can have 80 year patient with full functioning kidney. / Scr not very important.

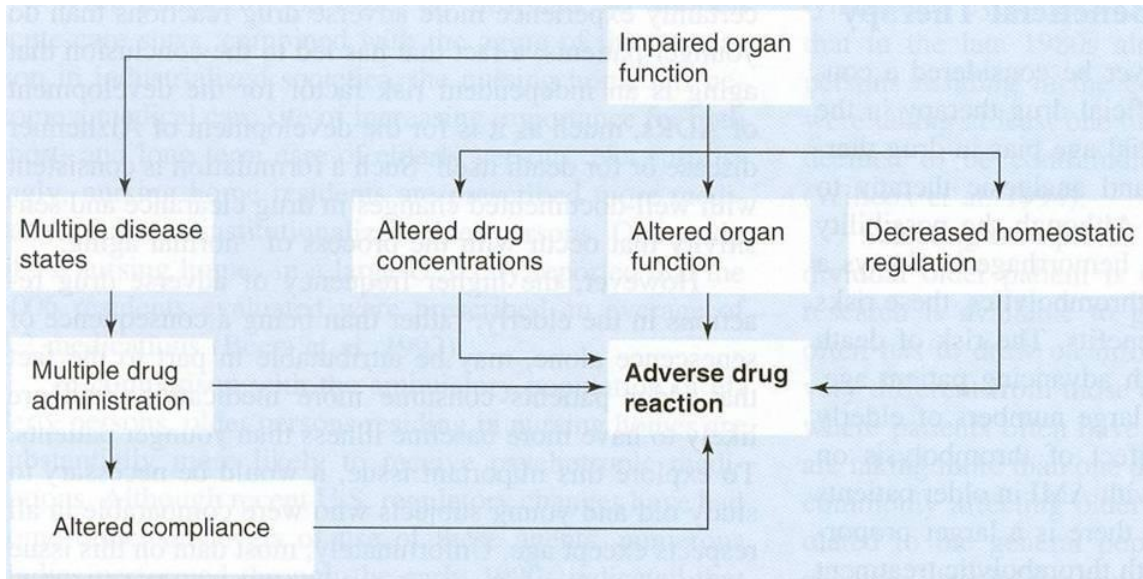
### -Pharmacodynamics

#### Age related changes:

- Increased sensitivity to sedation and psychomotor impairment with benzodiazepines ---  
→ happens in elderly .
- Increased level and duration of pain relief with narcotic agents --→like morphine.
- Increased drowsiness and lateral sway with alcohol --→ elderly who drink , their cerebellum المخيخ will be affected more .
- Decreased HR response to beta-blockers.
- Increased sensitivity to anti-cholinergic agents.

- Increased cardiac sensitivity to digoxin.

**Note :** You aren't required to memorize these alterations but just to show you the dynamics and kinetics in geriatrics are different and even between the geriatrics themselves that's why we need again " personalized medicine".



## Factors contributing to adverse drug reactions in elderly patients:

The end result in this figure is the adverse drug reaction. Elderly are more susceptible to develop adverse drug reactions. And this starts by having impaired organ function for example: the heart is weaker, kidney excretion is less, liver metabolism is decreased, thyroid will be less active (hypothyroidism) and this causes the person to feel too cold (thyroid hormones affect body temperature). And these dysfunctions will lead to multiple diseases state and eventually multiple drug administration. As a result drug-drug interaction will take place and the body homeostasis will be affected ending in adverse drug reactions.

On another aspect impaired organ function also cause altered drug concentration, altered organ function and decreased homeostatic regulation culminating in adverse effect reactions.

- Keep in mind that geriatrics are special population and they are "polypharmacy" taking many drugs at the same time.

## - Pediatrics:

- 1- They have higher proportion of water .
  - 2- They have lower plasma proteins level means drug that binds to albumin will be less because they have less plasma proteins concentration which results in increased drug availability.
  - 3- Immature liver / kidney:
    - liver metabolises more slowly.
    - kidney excrete more slowly
- That's why we have to deal with these patients in individualized way .  
And remember **“children are not small adults”**.

# Best wishes 😊

Corrected and modified by: Hiba Mihyar 😊