Tolerance and Adverse drug reactions

Objectives:-

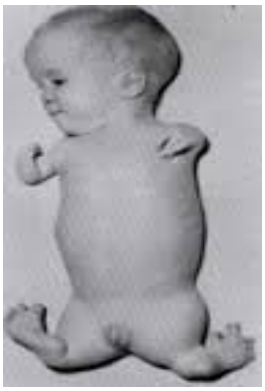
- Distinguish difference between tolerance and desensitization (tachyphylaxis) and reasons for their development.
- Recognize patterns of adverse drug reactions (ADR).

Titles
Very important
Extra information
Terms

ALMOST DONE

Phocomelia:

it's a disease caused by Thalidomide crisis (drug) was marketed in 1958 in West Germany as a hypnotic & for morning sickness during pregnancy).

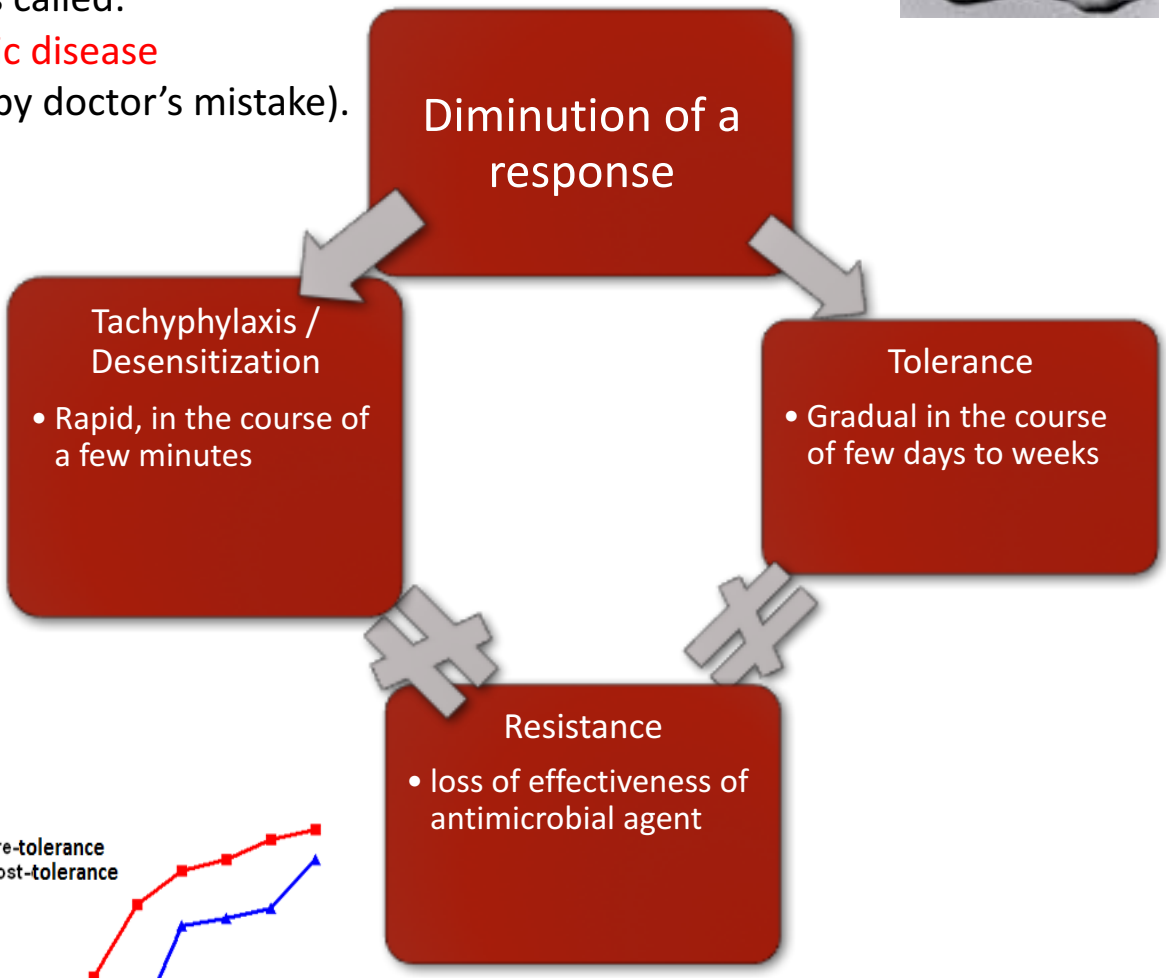


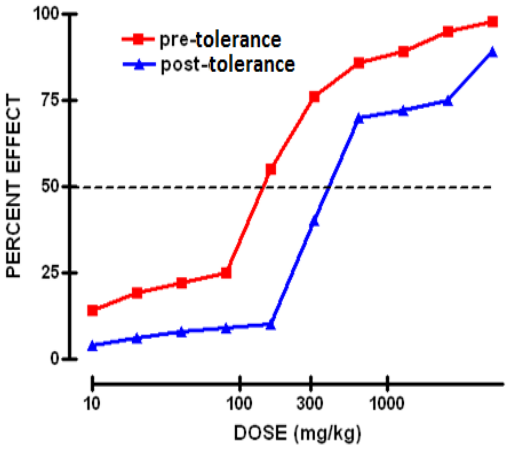
In 1961 a report of out break of phocomelia in the newborn babies (40000-100000 cases)

❖ This is called:

Iatrogenic disease

(caused by doctor's mistake).





In tolerance and desensitization , the dose is no longer enough to produce the desired effect.

Tolerance & Desensitization

Males: Phenomenon of variation in drug response, whereby there is a gradual diminution* of the response to the drug when given continuously or repeatedly.

Females: a need for markedly increased amounts of the substance to achieve intoxication or desired effect.

Or

markedly diminished effect with continued use of the same amount of the substance.

*:تناقص تدريجي

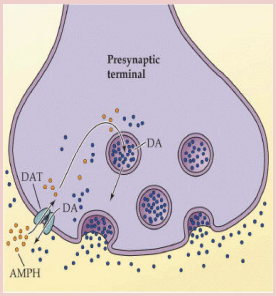
Reasons for Development of Tolerance:

1. Pre-receptor Events
2. Events at Receptors
3. Post Receptor Events

Pre-receptor Events	Post Receptor Events
↓ drug availability at the relevant receptors due to pharmacokinetic variables Drug becomes: 1-More metabolized or excreted 2-Less absorbed altered distribution to tissues. e.g. Barbiturates (enzyme inducers) increase metabolism of Contraceptive pills which means the availability will reduce. ↓	Nullification (Remove - Cencel) of drug response by a physiological adaptive homeostatic response. e.g. Antihypertensive effects of ACEIs become nullified by activation of renin angiotensin system (RAS) by NSAIDs ↓
They both Loss the therapeutic efficacy (Refractoriness)	

Events at Receptors

1-Exhaustion of mediators :
e.g Depletion of mediator stores by **amphetamine**



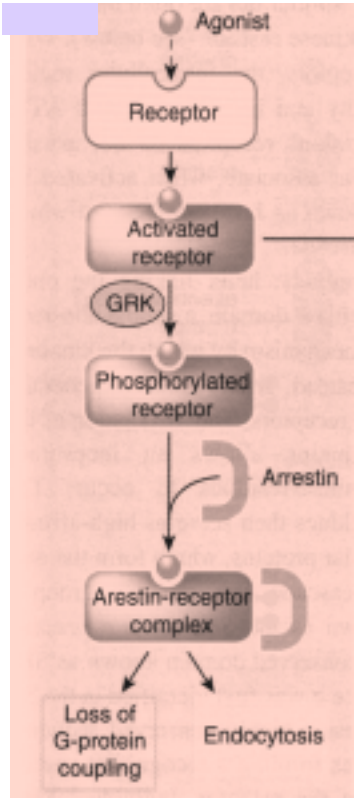
2-Binding alteration
Phosphorylation of R by **ß-adrenoceptors** which will Reduce the activation of AC (Adenyl Cyclase) to related ionic channel [functional defect]

3-Down regulation
↓ number of receptors.
Isoprenaline activation to b receptors which will Increase the receptors recycling by endocytosis **[structural defect]**

Down Regulation and Binding Alteration:

G protein-coupled receptor kinases (GRKs) : regulate the activity of GPCRs by phosphorylating their intracellular domains after their associated G proteins have been released and activated.

Arrestin is a protein that prevent the re-association of the G proteins with their receptors, thereby **preventing** reactivation of the signaling pathway.



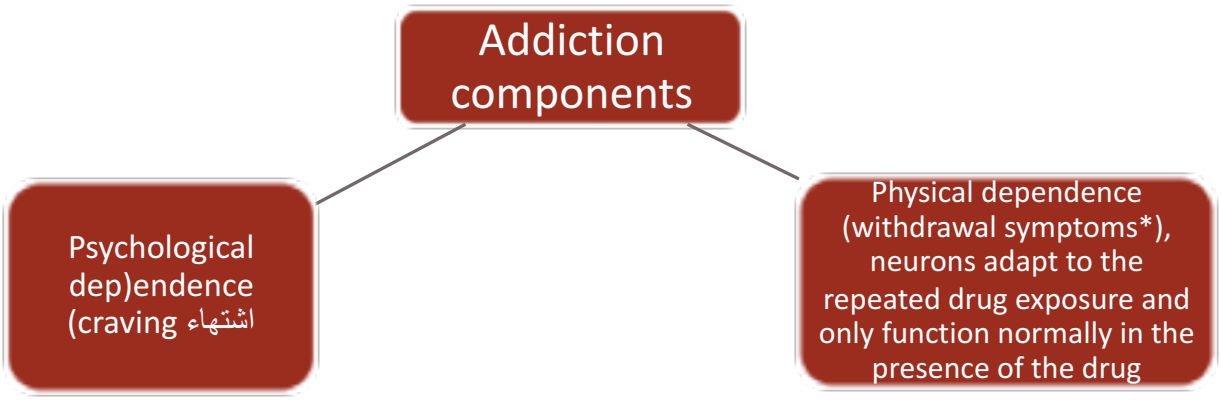
BINDING ALTERATION

DOWN REGULATION

Only in female's slides

Addiction

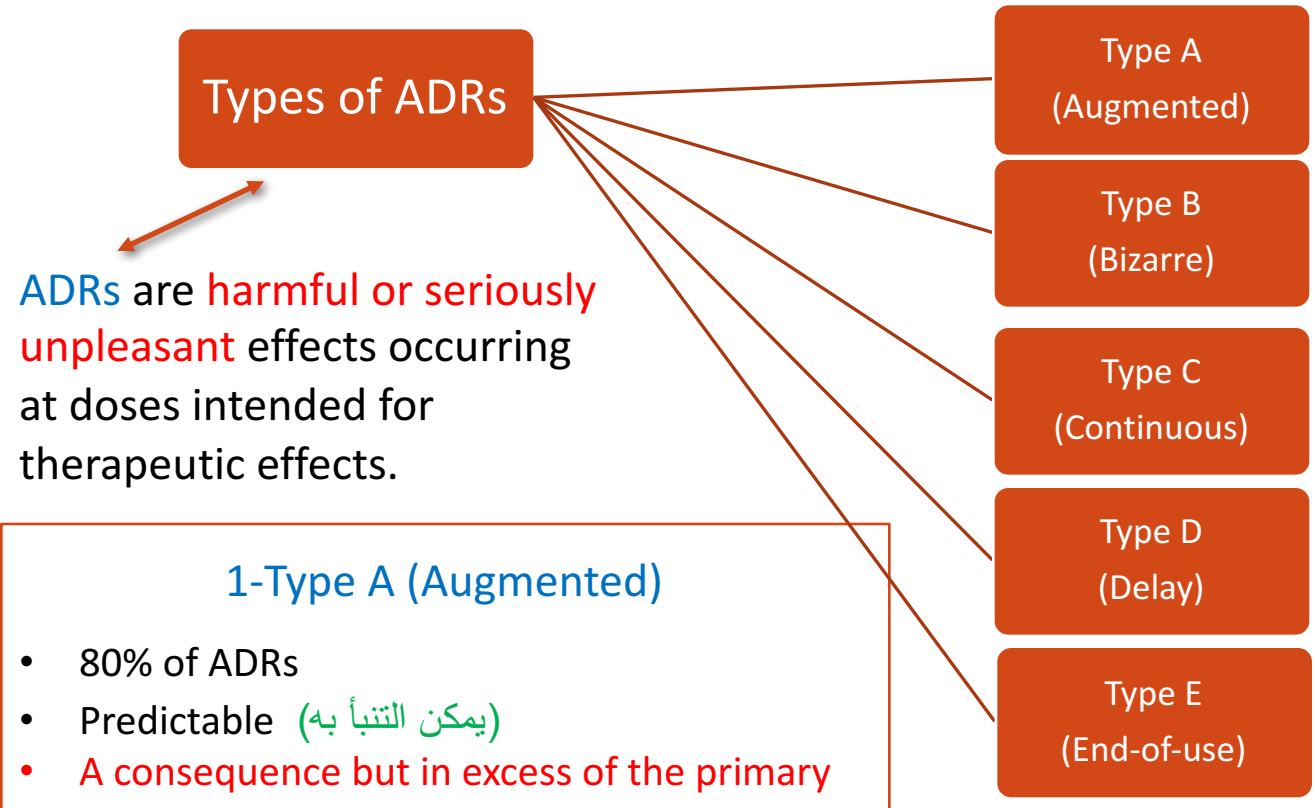
- The initial decision to use drugs is voluntary.
- Definition: a chronic, relapsing brain disease.
- Characterized by:
  - Compulsive مجبر behavior of a person (loss of control)
  - Continue taking drugs despite their many adverse health and negative consequences
  - Craving: dysphoric مكتئب.



*: similar to end of use ADR, e.g. tachycardia, flushing, and muscle cramps

Drugs of addiction :

- Stimulants
  - stimulate the central nervous system
  - amphetamines, cocaine, nicotine
- Depressants مثبطات
  - depress the CNS
  - alcohol, barbiturates, benzodiazepines (sedation)
- Analgesics مسكنات (depress the CNS, and produce Euphoria سعادة)
  - powerful painkillers
  - from opium poppy , morphine, heroin
- Hallucinogens مهلوسات
  - dramatically alter perception الإدراك
  - LSD, cannabis, Marijuana



ADRs are harmful or seriously unpleasant effects occurring at doses intended for therapeutic effects.

1-Type A (Augmented)

- 80% of ADRs
- Predictable (يمكن التنبأ به)
- A consequence but in excess of the primary pharmacological effect of the drug.

(يعني السايد ايفيكت للدواء عبارة عن زيادة تأثير الشي اللي نبغى الدواء يسويه)

- e.g. bleeding from warfarin
  e.g. Hypoglycemia from hypoglycemic drug

2. Type B (Bizarre)

- occur rarely and unpredictably
- Occurs different to known drug pharmacological effect [**idiosyncratic or heterogenous**] Usually due to patient's genetic defect or immunological response and qualitative nature.

(السايد ايفيكت هنا ما يعمل نفس عمل الدواء , يعمل شي مختلف وغريب)

e.g. * Penicillin➔ Anaphylactic shock
* Thrombocytopenia ➔ Quinine

- **it has Immunological Predisposition :-**

The drug or its bi-product [protein macromolecules or haptens] react as antigens and provoke immune response that results in damage to the tissue→ Hypersensitivity Reaction

1st exposure to a drug ➔ Sensitization

Repeated exposures ➔ HYPERSENSITIVITY REACTION

Comparison between type A & B

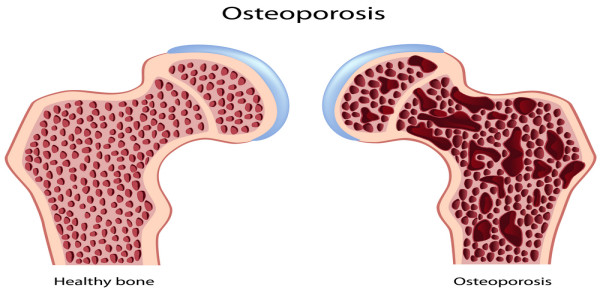
	Type A Augmentation	Type B Idiosyncratic
Pharmacological predictability	Yes	No
Nature	Quantitative [extension of pharmacology effect]	Qualitative [immune or genetic base]
Dose- dependent	Yes (dose response relationship present)	No (dose response relationship absent)
Onset of symptoms	Usually Rapid	Usually delayed
Incidence and morbidity	High	Low
Mortality	Low	High
Treatment	Dose adjustment or Substitute by > selective + Antagonize unwanted effect of 1st drug	Stop drug + Symptomatic treatment
Example	Bradycardia ➔β- ADR Blockers Hemorrhage ➔Warfarin	Apnea ➔succinylcholine Thrombocytopenia ➔Quinine

Examples of TYPE A & B

Drug	Type A	Type B
Chlorpromazine	Sedation	Cholestatic jaundice
Naproxen	GIT haemorrhage	Agranulocytosis
Phenytoin	Ataxia	Hepatitis, lymphadenopathy
Thiazides	Hypokalaemia	Thrombocytopenia
Quinine	Tinnitus	Thrombocytopenia
Warfarin	Bleeding	Breast necrosis

3. Type C (Continuous)

- Occurs during chronic drug administration
- e.g. * Osteoporosis secondary to chronic corticosteroid intake.
  *Dependence
  a. Psychological [Craving] as by cannabis
  b. Psychological [Craving]
  + Physical withdrawal manifestations (syndrome)
  = Addiction as by morphine



Type D (delayed)

- Occurs after long period of time even after drug stoppage.

Examples:

- ❑ Teratogenicity after retinoids.
- ❑ Carcinogenicity after tobacco smoking.

❖ **Teratogenic** drugs: A **teratogen** is an agent that can disturb the development of the embryo or fetus.

Type E (End of use)

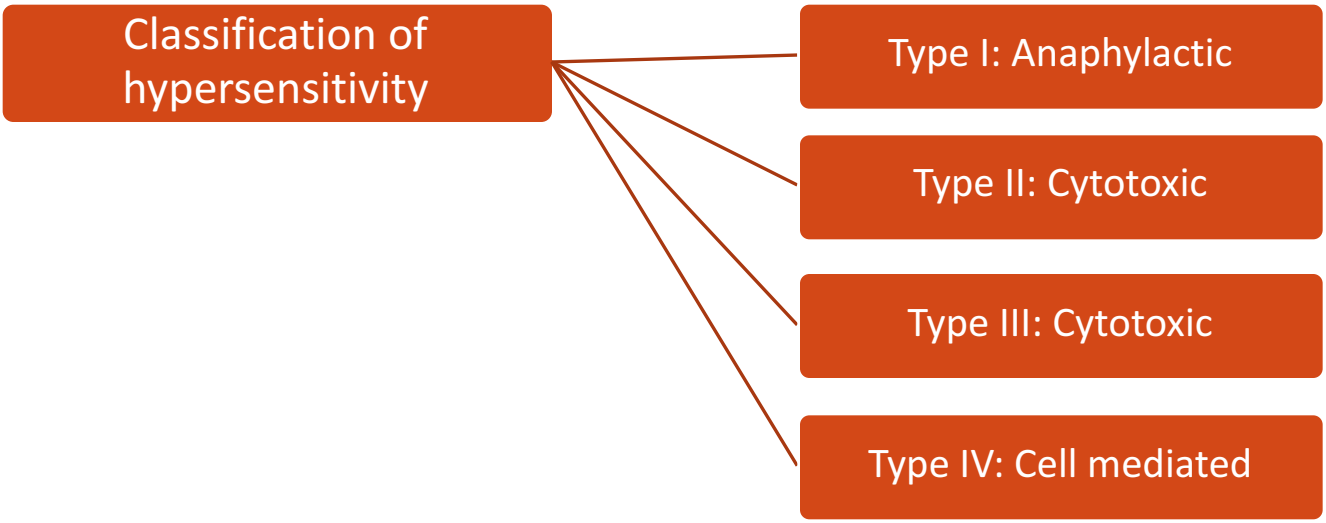
-Occurs after sudden stoppage of chronic drug use due to existing adaptive changes

e.g. Patients on stoppage of

- Clonidine develop rebound hypertension

- Morphine develop withdrawal syndrome

-Diazepam develop anxiety and insomnia



Type I : Anaphylactic

-is an allergic reaction provoked by re-exposure to a specific antigen

-response occurs in minutes, The reaction usually takes 15 - 30 minutes from the time of exposure to the antigen.

-The reaction is mediated by IgE antibodies and produced by the immediate release of histamine, serotonin, leukotrienes from tissue mast cells or blood basophils

-The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from anaphylactic shock.

examples:

1-Allergic asthma.
2-Allergic conjunctivitis.
3-Allergic rhinitis. *hay fever*
4-urticarial. *hives*
5-anaphylaxis.

❖ May be caused by Penicillin, streptomycin.

Type II : Cytotoxic

- Antibody-dependent.
- The antigens may be endogenous or exogenous chemicals (haptens) which can attach to cell membranes.
- The antibodies (IgM or IgG) produced by the immune response bind to antigens on the patient's own cell surfaces that is perceived by the immune system as foreign, leading to cellular destruction.
- The reaction takes hours to a day.

Examples: Drug-induced haemolytic anemia , thrombocytopenia.

❖ may be caused by Penicillin, Quinidine.

Type III : Immune complex

- Soluble immune complexes (aggregations of antigens and IgG and IgM antibodies) form in the blood, are not completely removed by macrophages and are deposited in various tissues (typically the skin, kidney and joints).
- The reaction takes hours to days to develop.

Example: Serum sickness *(fever, arthritis, enlarged lymph nodes, urticaria)*

❖ Can be caused by Sulphonamides, Penicillin, Streptomycin.

Type IV : Cell-mediated

- also known as delayed type hypersensitivity as the reaction takes two to three days to develop.
- Unlike the other types, it is not antibody- mediated but rather is a type of cell-mediated response.
- Cytotoxic T cells cause direct damage whereas helper T cells secrete cytokines that attracts inflammatory cell infiltrate

Example : Contact dermatitis by local anesthetics creams, anti -histamine creams, topical antibiotics.

Hypersensitivity Reactions

Characteristics	Type-1 (Anaphylactic)	Type-2 (cytotoxic)	Type-3 (immune complex)	Type-4 (Cell mediated /delayed type)
Antibody	IgE- mediated	Antibody- dependent IgG, IgM	IgG, igM	Not antibody-mediated
Antigen	Re-exposure by a specific antigen (exogenous)	On patient's own cell surface that is perceived as foreign, leading to cellular destruction	Soluble in the blood, so they're not completely removed by macrophages	Tissue and organs
Response time	FAST- Occurs in minutes (15-30 minutes)	Hours to a day	Hours to days	Two to three days
Histology (Type of the cell)	Basophil & Mast cells	-	-	T-cells (cytotoxic & helper)
Cell-mediators	Histamine, serotonin, leukotrienes	-	-	It is cell mediated response
FURTHER INFORMATION	1-The reaction can be local or systemic 2-In severe cases, It might lead to death	-	It get deposited in various tissue (typically the skin, kidney and joints)	cytotoxic T cells cause direct damage whereas T-helper secrete cytokines
EXAMPLE	Allergic asthma, high fever, rhinitis, and Anaphylaxis (Most Severe)	Drug-induced haemolytic anemia, thrombocytopeni a	Serum sickness (fever, arthritis, enlarged lymph nodes, urtcaria)	Contact dermatitis
CAUSED BY	Penicillin, streptomycin	Penicillin, Quinidine	Sulphonamides, penicillin, streptomycin	Local anesthetic creams, anti-histamine creams &topical antibiotics

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