



ADVERSE DRUG REACTIONS & PHARMACOVIGILANCE

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Objectives

- What are adverse drug reactions?
- Difference between adverse effects and side effects
- Classification of adverse drug reactions
- Explanation and understanding of drug adverse drug reactions
- Drug abuse
- Pharmacovigilance

1- what's the ADR?

2- what're the causes does it occur in?

3- what is the way of reducing it?

Adverse drug reactions

- **Adverse drug reactions are:** Harmful unwanted drug reactions 🌐
- **Which is:**
 - ✓ Due to a drug
 - ✓ At normal therapeutic doses
 - ✓ May requires treatment^①, decrease in dose^②, stop the drug^③ or caution^④ in the future use of the same drug

- 1- what's the side effect?
- 2- where does they occur?
- 3- Give an example about it?

Side Effects

- Unwanted (at time of treatment) unavoidable Pharmacological effects of the drug.
- They can be harmful or beneficial depending on time of use
- Occur at therapeutic doses.
- Predictable ✓

Examples.

- H1 Anti-histamines: Sedation → hypersensitivity anti-allergy it'll applied in any doses = side effect.
- Aspirin: antithrombotic effect → anti-pyretic / anti-thrombotic.

if I give the aspirin for fever.

An effect may be therapeutic in one context but side effect in another context

1- what're the incidence cases of ADR?

2- How does they developed?

3- what're the classification of the ADR?

4- what's the difference between type A and B?

Adverse drug reactions

↑ Take many drugs
↑ AE

• Incidence of ADR more in:

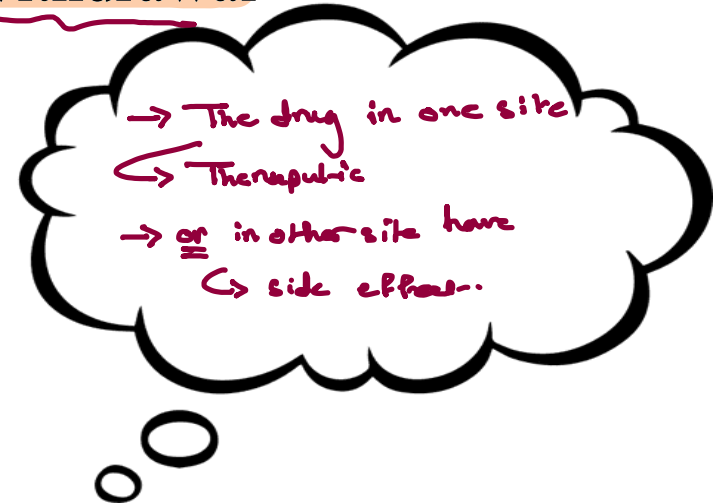
- Polypharmacy ^①, Elderly ^②, Children ^③, Patient with multiple diseases ^⑧, Pregnancy ^④, Malnourished ^⑤, Immunosuppression ^⑥, Drug Abusers ^⑦ and addicts
- ↳ Aids, autoimmune disease.
- قد من

• Adverse drug reactions develop:

• Immediately, ^{a-} prolonged drug administration or after drug withdrawal

↳ allergy

↳ After stop of drug.



CLASSIFICATIONS OF ADR

- A (Augmented) مُجمَع / مَعْبَد
- B (Bizarre) عَنَوَانِي
- C (Continuous, chronic) لَدَوِيَّة / مَزْمِنَة
- D (Delayed) بَعْدَ فِتْرَةٍ
- E (Ending Use) بَعْدَ انْتِهَائِيَّة
- F (Failure of response) عَكْسَ السُّجَايَةِ

Type- A (Predictable)- Based on pharmacological properties

Type- B (Non-predictable) – Based on Immunological response and genetic makeup of person

- 1- what is the feature of it?
- 2- what is the important of it?
- 3- what're the example of drug + ADR?

Type A- Augmented

does dependent. (+)
predictable. (+)

but with increasing the dose.

- These are based on the pharmacological actions of the drug so can be predicted.
- They are common and account for 75% of ADRs ✓
- Dose-related and preventable mostly reversible.

• Examples:-

- Anticoagulants (e.g., warfarin, heparin) – bleeding ... in case of increasing the dose
- Anti-hypertensives (e.g. α 1-antagonists: prazosin) – hypotension ... " "
- Anti-diabetics (e.g. insulin) - hypoglycemia

Normal job = neutralize the glucose level
in case of hyperglycemia → exaggerated

Predictable ✓

- 1- what's the feature of it?
- 2- what's the cases does it developed on?
- 3- what's the result of it?

عشوائى

Type B- Bizarre *non-predictable.*

• Have no direct relationship to the dose of the drug or the pharmacological actions of the drug.

• Develop on the basis of:

• Immunological reaction to the drug (Allergy) ... penicilline ... famous drug causes

• Genetic predisposition (Idiosyncrasy): abnormal drug reactions to the usual dose of the drug.

تفاعل عيب
The cases of them
genetic defect.

• **Examples????**

• More serious clinical outcomes with higher mortality and morbidity. *allergy...*

anaphylactic shock

• Mostly require immediate withdrawal of the drug.

سرعة

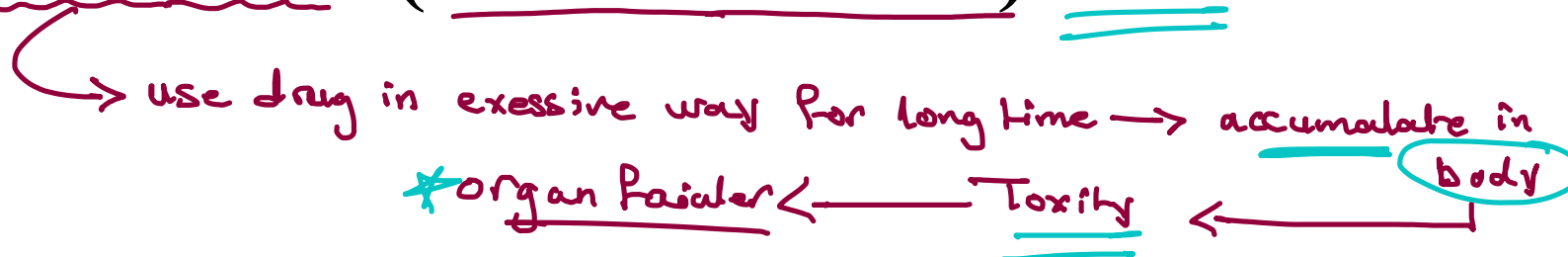
• Uncommon

⊕ Un-predictable ✓

1- Describe the chronic type ?

TYPE C - CHRONIC (CONTINUOUS) USE

2- what's the feature of it- ?



3- Give an example? and its ADR ?

• They are mostly associated with **cumulative-long term exposure**

• **Example:-**

• Analgesic (NSAID: aspirin) - ^①interstitial nephritis, ^②papillary sclerosis

المسكنات
 { nonsteroidal anti-inflammatory } → Kidney Failure
 ①
 ②

Predictable ✓

1- what're the significant delay of this type?
2- what is the basis of flipper limb?

Type D – Delayed متأخر

- They manifest themselves with significant delay
- Teratogenesis - Thalidomide – Phocomelia (flipper-like limbs) نشوءات الأضلاع
- Mutagenesis
- Cancerogenesis



Predictable ✓

- 1- what is the teratogenicity?
- 2- what're the stages of drug defect?

TERATOGENICITY (Teratos- Monster)

- 3- Give an example about drug causes ?

• The ability of a drug to cause defects in a developing fetus when it is administered during pregnancy. ✓

• Drugs can affect the foetus at 3 stages: 0-17 day

1- Fertilization and implantation: conception to 17 days: failure of pregnancy which often goes unnoticed. ✓

2- Organogenesis: 18 to 55 days of gestation most vulnerable period, deformities are produced. most vulnerable (dangerous) period.

3- Growth and development: 56 days onwards: developmental and functional abnormalities can occur

Examples: ACE inhibitors (growth retardation), Thalidomide, Warfarin (eye and hand defects), antiepileptic drugs (cleft lip/palate).

السيفنة الأرونية ١

②
↳ phocomelia

③

1- How does the mutagenicity developed?

2- How does the carcinogenicity developed?

3- what're the examples that causes mutagenicity and carcino... ?

Mutagenicity And Carcinogenicity

• Drugs that can Cause genetic defects and cancer respectively.

During metabolism of drug :- it release.

• **Mutagenicity:** Reactive intermediate metabolites of the drug can affect genes and may cause structural changes in the chromosomes

• **Carcinogenicity:** Certain chemicals and drugs can promote malignant change in genetically damaged cells, resulting in carcinogenesis.

• **Examples:** anticancer drugs, radioisotopes, oestrogens, tobacco

↪ Cancer breast

*↪ smoking
↪ cancer.*

1-> what're the cases does it occur in?

2-> Give an example about Type E?

Type E – End Of Use

الأعراض التي تسببها

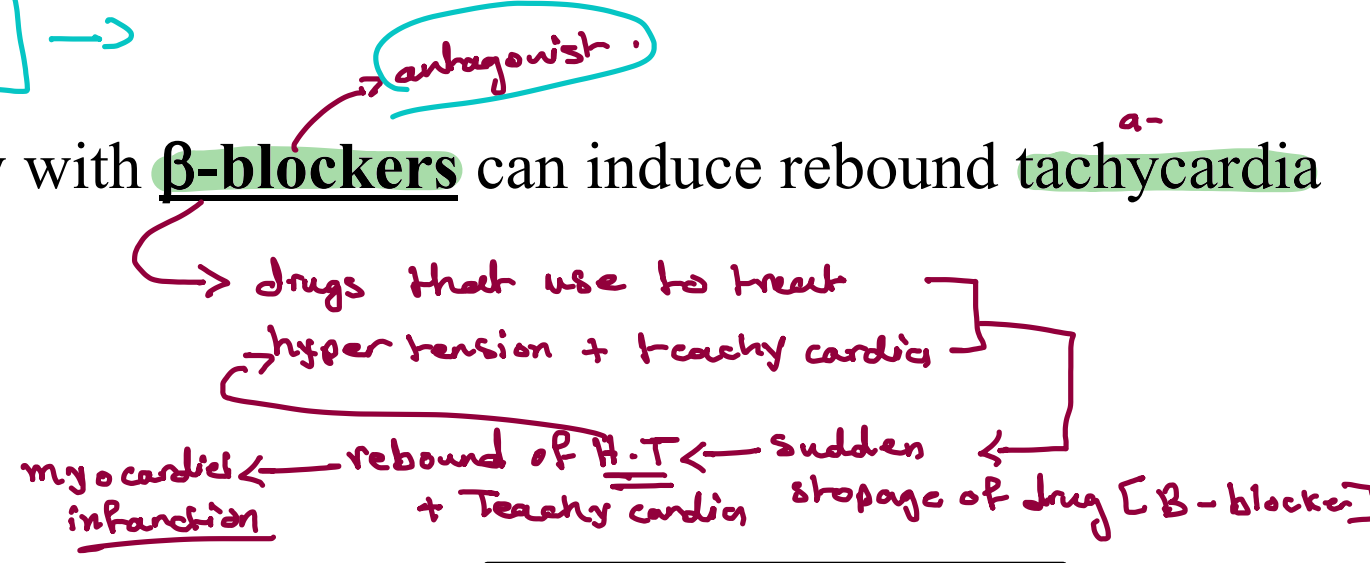
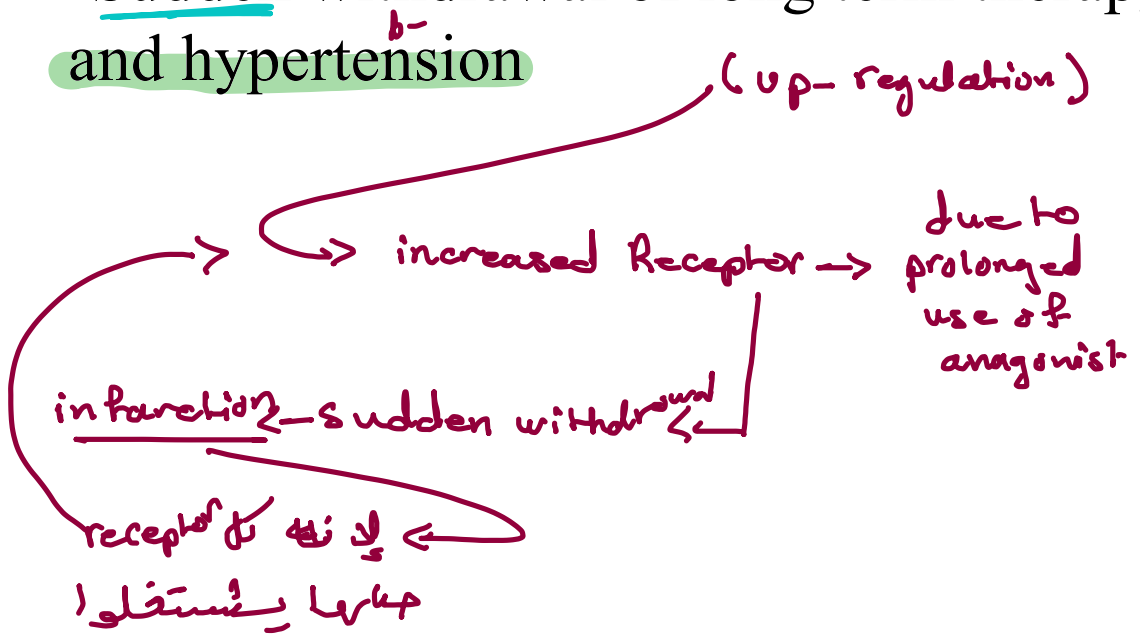
الأعراض التي ترتد اوية .

• Drug withdrawal syndromes and rebound phenomenon



• **Example:**

• Sudden withdrawal of long term therapy with β -blockers can induce rebound tachycardia and hypertension



Predictable

1- what is the Type F?

2- what're the types of F?

3- Give an example about congenital?

← Type F- FAILURE OF RESPONSE (TOLERANCE) →

unpredictable.

repeated doses → ↓ therapeutic effect
increasing doses ... Avoid Tolerance.

• Failure of responsiveness to the usual dose of a drug

• Types: 1- AQUIRED 2- CONGENITAL: atropine can not cause mydriasis in rabbits due to atropine

• Acquired tolerance:

• It occurs on repeated administration of the drug.

• More doses are needed to obtain the original effect.

• It is reversible: it disappears when the drug is stopped for some time.

• Examples of drugs causing tolerance: morphine, nitrate.

• Special types of acquired tolerance

1. Tachyphylaxis: Tachyphylaxis (Greek word, tachys, "rapid", and phylaxis "protection") → occur after one dose.

▪ Acute, sudden decrease in response to a drug after its administration (a rapid and short-term onset of drug tolerance).

▪ It can occur after an initial dose or after a series of small doses.

• The original effect can not be obtained by increasing the dose. ... irreversible.

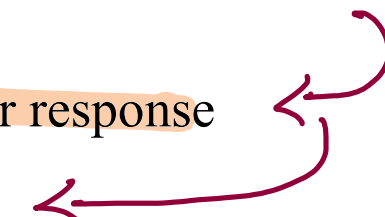
• Example: tachyphylaxis to action of salbutamol (beta 2 agonist bronchodilator) used for treatment of bronchial asthma

• single-use bronchodilator response followed by a significant decline in bronchodilator response

• Mechanism: polymorphism of beta 2 receptors leading to receptor downregulation

break down the atropine. ✓

الفرق بين
Tolerance
والحادى



Tolerance

- There is not a biochemical, histological marker, or laboratory test that will predict tolerance or degree of tolerance in an individual.

Un-predictable

Drug abuse

- **Tolerance is the basis of drug abuse and addiction**: When a person uses a drug repeatedly, the body may develop tolerance to the drug.
- **Tolerance** may lead to **drug dependence**—the body develops a chemical need for the drug and can't function normally without it.
- **Drug abuse occurs when people intentionally use any kind of drugs for non-medical purposes.**
- A mood-altering drug, also called a **psychoactive drug**, is a chemical that affects brain activity (morphine, cocaine, methamphetamine).
- Most abused drugs are psychoactive.

• Drug abuse (psychoactive drugs) → tolerance → dependence → addiction

↪ No medical indication
بدون دوائی
و بیفایدہ
سوز استخوان

↪ change the structure and chemistry of brain.

↪ lead to increasing the dose

⊕ of your body to drug.

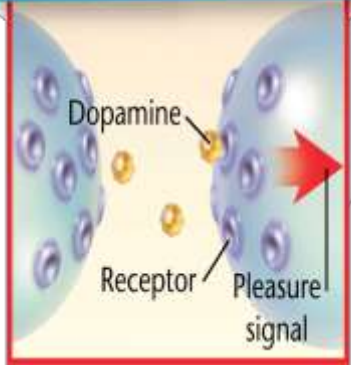
مدمت

جائزة The Reward (system) Pathway

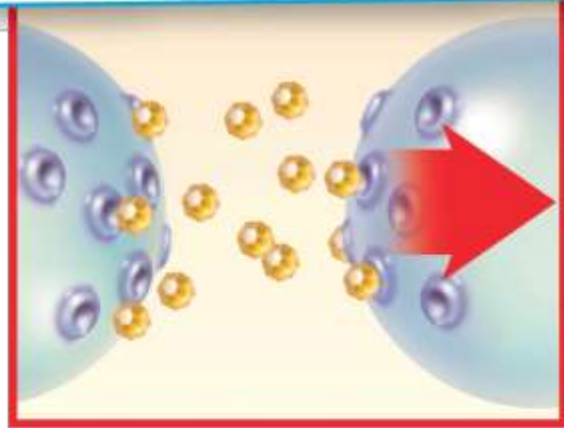
- Many **psychoactive drugs** trigger activity along a pathway of cells in the brain called the “**reward pathway.**”
- Brain cells along the activated reward pathway release a chemical called **dopamine.**
- The extra dopamine released during drug use can cause the user to ignore the harmful effects of the drug and want to continue using it.
- **Flooding** the reward pathway with dopamine may lead to **intense cravings** for the drug.

How Drugs Affect the Brain?

1 Under Normal Conditions
The chemical dopamine travels between brain cells, producing pleasurable sensations.

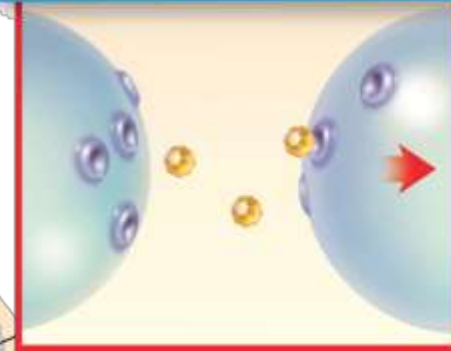


2 On Drugs
Cells release extra dopamine, causing a stronger signal.

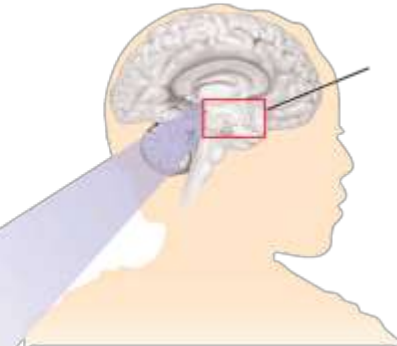


Area of the brain's "reward pathway"

3 After Repeated Drug Use
Brain cells lose receptors for dopamine, becoming less able to process the chemical. The pleasure signal weakens.



Tolerance



○ Dopamine index:	
○ Cheeseburger	<u>1.5</u>
○ Sex	<u>2.0</u>
○ Nicotine	<u>2.0</u>
○ Cocaine	4.1
○ Methamphetamine	11.0

استخدام قهري Addiction

- Abuse of psychoactive drugs may result in **addiction**.
- Addiction is the **compulsive use** of a drug, despite any cost to health, family, or social standing.
- **Addiction is a disease** that changes the structure and chemistry of the brain.
- **Withdrawal symptoms:** If a person who is dependent on a psychoactive drug stops taking the drug, that person will experience withdrawal symptoms including:
 - Nausea, vomiting, headache, indigestion, paranoia or panic
 - Tremors, seizures or death



DRUG-INDUCED DISEASES

- These are also called **iatrogenic (physician-induced)** diseases, and are disease caused by drugs .
- **Examples:**
- Hepatitis induced by isoniazid and Rifampicin
- Peptic ulcer induced by salicylates and corticosteroids
- Ototoxicity of streptomycin
- **Reversible or not?**

PREVENTION OF ADVERSE EFFECTS TO DRUGS

- **A**void inappropriate use of drugs .
- **A**ppropriate drug administration (**R**ational **T**herapeutics)
 - Dose
 - Dosage form
 - Duration
 - Route
 - Frequency
 - Technique
- **A**sk for previous history of drug reactions and allergies
- **A**lways suspect ADR when new symptom arises after initiation of treatment.
- **A**sk for laboratory findings like serum creatinine etc.

PHARMACOVIGILANCE (DAUP)

- The science and activities related to the **d**etection, **a**ssessment, **u**nderstanding and **p**revention of adverse reactions
- The information generated is useful in educating doctors and in the official regulation of drug use.
- **Significance:**
 - 1- **Rational use** of medicines
 - 2- **Assessment of safety** of medicines.

Various activities involved in pharmacovigilance

- **Post marketing surveillance** and other methods of ADR monitoring such as voluntary reporting by doctors.
- **Dissemination of ADR data** through 'drug alerts', 'medical letters,' sent to doctors by pharmaceuticals and regulatory agencies.
- **Changes in the labelling** of medicines indicating restrictions in use or warnings, precautions, or even withdrawal of the drug.