# 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
- Pharmacovigilance

# Adverse drug reactions (ADR)

- **<u>Adverse drug reactions are</u>**: <u>Harmful</u> <u>unwanted</u> (<u>unintended</u>) drug reactions

- **<u>Which is:</u>**

✓ Due to a drug

✓ At usual therapeutic doses

✓ **<u>May requires :</u>**

✓ **Treatment**

✓ **Decrease in dose**

✓ **Stop the drug**

✓ or **Caution in the future use of the same drug**

# Side Effects

- **Unwanted** (at time of treatment) **unavoidable Pharmacological effects** of the drug.
- **Side effects are type of Adverse Drug Reaction (ADR)**
- They can be **harmful** or **beneficial depending on time of use**
- **Occur at therapeutic doses.**
- **Predictable**

**Examples.**

➢ **H1 Anti-histamines**: Sedation

➢ **Aspirin**: antithrombotic effect (bleeding)

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

# Incidence of drug reactions

- **Incidence of ADR more in**:
- Polypharmacy
- Elderly & Children
- Pregnancy
- Patient with multiple diseases
- Malnourished & Immunocompromised
- Drug Abusers and addicts
- **Adverse drug reactions develop:**
- Immediately, prolonged drug administration or after drug withdrawal

# Classifications Of ADR

- **A** (**A**ugmented)
- **B** (**B**izarre)
- **C** (**C**ontinuous, **c**hronic)
- **D** (**D**elayed)
- **E** (**En**ding Use)
- **F** (**F**ailure of response)

# Type A- Augmented

- These are **exaggeration of a drug's normal pharmacological actions** when given at the **usual therapeutic dose**.
- **Dose-dependent.**
- They are **common** and account for 75% of ADR
- **Preventable** mostly **reversible.**
- **Examples**:-
- **Anticoagulants** (e.g., warfarin, heparin) – **bleeding**
- **Anti-hypertensives** (e.g.α1-antagonists: prazocin) – **hypotension**
- **Anti-diabetics** (e.g. insulin) – **hypoglycemia**
- **Opioids**: (morphine)- **respiratory depression**

**Predictable**

# Type B- Bizarre

- Have **no direct relationship** to **the pharmacological actions** of the drug or **the dose of the drug** .
- **Develop on the basis of:**
- **Immunological reaction to the drug** (**Allergy**): Example: anaphylaxis
- **Genetic predisposition** (**Idiosyncrasy**): abnormal drug reactions to the usual dose of the drug.
- **NOT easily reversible**.
- **Examples**????
- **Serious clinical outcomes** with **higher mortality and morbidity**.
- Mostly require **immediate withdrawal of the drug**. **Patient must usually avoid the drug for life**
- **Uncommon: 10-15%**

**Un-predictable**

# TYPE C – CHRONIC (CONTINOUS) USE

- **Result from**: **cumulative-long term drug** exposure
- **Persist for a relatively long time, even after the drug is stopped**
- **Dose and Time-Related**
- **NOT easily reversible**

- **Example:-**
- **Analgesic** (NSAID: aspirin)– interstitial nephritis, papillary sclerosis
- **Corticosteroids**: osteoporosis

**Predictable**

# Type D – Delayed

- **<u>They are manifested with significant delay</u>**: become apparent some time after the use of a medicine
- **Teratogenesis** -Thalidomide – Phocomelia (flipper-like limbs)
- **Mutagenesis**
- **Cancerogenesis**

**Predictable**

# Teratogenicity (Teratos- Monster)

•The ability of a substance or agent (drug) to <u>cause birth defects or other harm</u> to a <u>developing embryo or fetus</u> if it is <u>administered during pregnancy.</u>

•<u>Drugs can affect the foetus at 3 stages:</u>

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

 2- **Organogenesis**: **18 to 55 days** of gestation **<u>most vulnerable period</u>**, **deformities** are produced.

 3- **Growth and development**: **56 days onwards**: **<u>developmental and functional abnormalities</u>** can occur

<u>Examples</u>:

❑ACE inhibitors (growth retardation)

❑Thalidomide (phocomelia): flipper-like limbs

❑Warfarin (eye and hand defects)

❑Antiepileptic drugs (cleft lip/palate).

# Mutagenicity And Carcinogenicity

- **Mutagenicity**:
- **Drugs** (**or their metabolites**) that can cause mutations in DNA by interacting with and altering the genetic material
- **Examples:**
- **Cyclophosphamide**: An alkylating agent used to treat various cancers
- **Molnupiravir**: An antiviral that is designed to introduce errors into the genetic code of RNA viruses.
- **Carcinogenicity**: Certain chemicals and drugs can **promote malignant change in genetically damaged cells**, resulting in carcinogenesis.

- **Examples**: anticancer drugs, radioisotopes, oestrogens, tobacco, alcohol

# Type E – End Of Use

- **Drug withdrawal syndromes** and **rebound phenomenon**
- **Rebound phenomenon:**
- **When the symptoms of a condition reappear or worsens after a drug used to treat it is suddenly stopped or reduced**
- **Examples:**
- Sudden withdrawal of long term therapy with **β-blockers** can induce **rebound tachycardia and hypertension**
- **Insomnia and anxiety following the withdrawal of benzodiazepines**
- **Management:** gradual tapering and medical supervision
- **Explanation??**                                    **Predictable**

Drug Withdrawal

# Withdrawal syndromes

- **Body response** to the **reduction or cessation of a substance** after **prolonged use**, **indicating physical dependence**.

- **Due to**: the **body's physiological adaptation** to continuous substance exposure

- **Symptoms** varying based on the **type of substance** and **duration of use.**

- **Examples:**

- Alcohol withdrawal delirium, Caffeine and opioids

**Predictable**

# Type F- FAILURE OF RESPONSE (TOLERANCE)

- Drug tolerance is a **physiological phenomenon** that occurs when an individual's **response to a drug** **diminishes over time** **after** **repeated use**.
- **Higher doses are required to achieve the same effects.**
- **Types:**
- 1- Acquired
- 2- Congenital: atropine can not cause mydriasis in rabbits due to atropinase
- **Acquired tolerance:**
- It occurs on **repeated administration** of the drug.

**Un-predictable**

- **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, nitrates.

# Special types of acquired tolerance

- **Tachyphylaxis**: **(acute drug desensitization)**
- **Tachyphylaxis** (Greek word, tachys, "rapid", and phylaxis "protection")
- **Definition:**
- **Acute**, **sudden decrease in response to a drug** after its administration (a rapid and short-term onset of drug tolerance).
- **Time of onset**: 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**.
- **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**
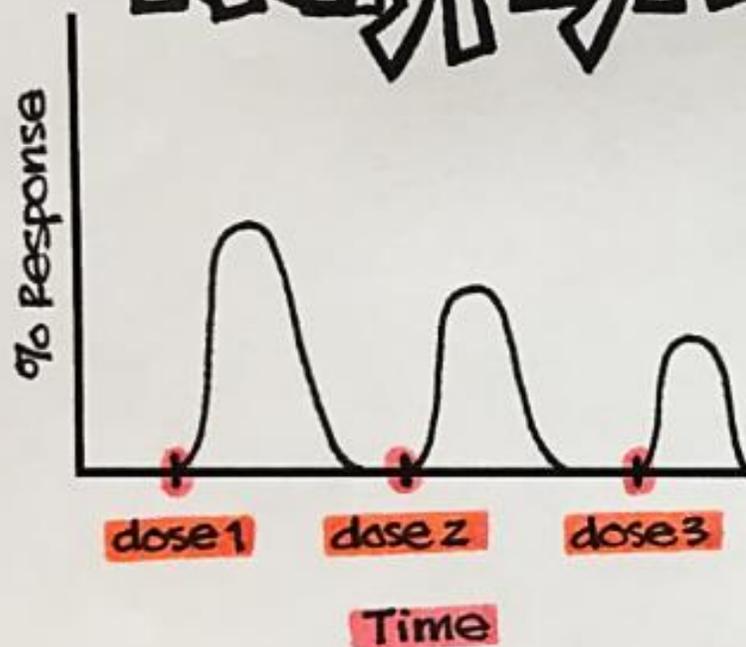
# Drug-induced Diseases (Iatrogenic Diseases)

- 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

• **Avoid inappropriate use** of drugs .

• **Appropriate drug administration (Rational Therapeutics)**

• Five rights – the **right drug** at the **right dose** by the **right route** at the **right time** for the **right patient** (according to WHO 1988)

• **Ask** for previous history of drug reactions and allergies

• **Always** 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 detection, assessment, understanding and prevention 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.

- **Spread 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.

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THANK YOU