

ADRs and pharmacovigilance –lec 10

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.

1-H1 Anti-histamines: Sedation

2-Aspirin: antithrombotic effect

An effect may be therapeutic in one context but side effect in another context Incidence of ADR more in:

Adverse drug reactions : **Harmful** unwanted drug reactions .

Which is:

-Due to a drug

-At normal therapeutic doses

-May requires treatment, decrease in dose, stop the drug or caution in the future use of the same drug

-ADR increase in : Polypharmacy, Elderly, Children, Patient with multiple diseases, Pregnancy, Malnourished, Immunosuppression, Drug Abusers and addicts

-Adverse drug reactions develop Immediately, prolonged drug administration or after drug withdrawal.

CLASSIFICATIONS OF ADR

Type A: Augmented

Predictable, dose-related,
pharmacological action-based, reversible,
common (75% of ADRs).

Warfarin/Heparin:
Bleeding Insulin:
Hypoglycemia Anti-
hypertensives:
Hypotension

Type B: Bizarre

Unpredictable, not dose-related,
often immune-mediated or genetically
predisposed, serious outcomes.

Requires immediate
withdrawal
Commonly includes allergies
or **idiosyncratic** reactions

Type C: Chronic (Continuous)

Due to **long-term drug exposure**,
often **predictable**.

NSAIDs (Aspirin): Interstitial
nephritis, papillary sclerosis

Type D: Delayed

Effects manifest significantly **later**, often
involve teratogenic or mutagenic and
cancerogenous effects
Predictable

Thalidomide: Phocomelia
Mutagenicity & Carcinogenicity:
DNA/chromosome alteration
(e.g., anticancer drugs)

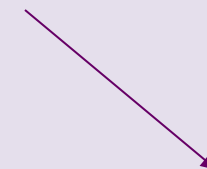
Type E: End of Use

Withdrawal syndromes or rebound
phenomena upon cessation.
Predictable

β -blocker withdrawal:
Rebound tachycardia and
hypertension (upregulation of
receptors)

Type F: Failure of Response

Failure of responsiveness to the
usual dose of a drug
Unpredictable



Type F- FAILURE OF RESPONSE (TOLERANCE)

Types:

- 1- ACQUIRED
- 2- CONGENITAL: atropine can not cause mydriasis in rabbits due to atropinse

•Acquired tolerance:

- Repeated administration
- More doses are needed to obtain the original effect.
- It is **reversible**: it disappears when the drug is stopped for some time.
- Ex: morphine, nitrates.

•Special types of acquired tolerance:

1. Tachyphylaxis: 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.
- 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 (irreversible)

- **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.

- **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.**

- **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
- Methamphetamine (shabu) cause paranoia and schizophrenia like symptoms

➤ **Teratogenicity:**

The ability of a drug to cause fetal defects.

Drugs can affect the fetus at 3 stages:

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.

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).

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➤ **Carcinogenicity and Mutagenicity:**

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

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

Examples: anticancer drugs, radioisotopes, oestrogens, tobacco

• **DRUG-INDUCED DISEASES** :These are also called **iatrogenic** (physician-induced) diseases, and are disease caused by drugs .

EX: Hepatitis induced by **isoniazid** and **Rifampicin** /Peptic ulcer induced by **salicylates** and **corticosteroids** /Ototoxicity of **streptomycin** irreversible

PREVENTION OF ADVERSE EFFECTS TO DRUGS:

- **A**void inappropriate use of drugs .
- **A**ppropriate drug administration (Rational Therapeutics) (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:

- Rational use of medicines
- 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.