PC

Pharmacology Concepts
By Rajesh Choudhary

Adverse Drug Reaction

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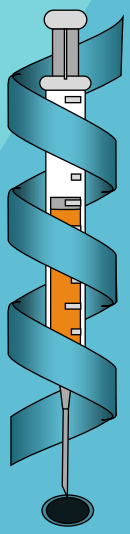
PC

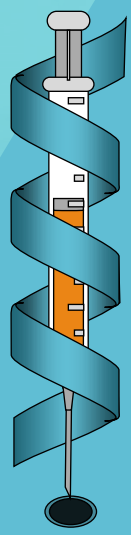
BASIC TERMS

- **Side effect-** Any **unintended/unwanted effect** of a pharmaceutical product occurring at normal dosage which is related to the pharmacological properties of the drug.
- **Adverse drug reaction-** A response to a drug which is noxious and unwanted and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function like allergic reactions
- **Adverse event-** Any unpleasant medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.
- **Adverse drug events** extend beyond adverse drug reactions and include in addition harmful effects due to overdoses, underdoses and medication errors.



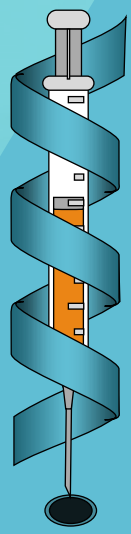
BASIC TERMS

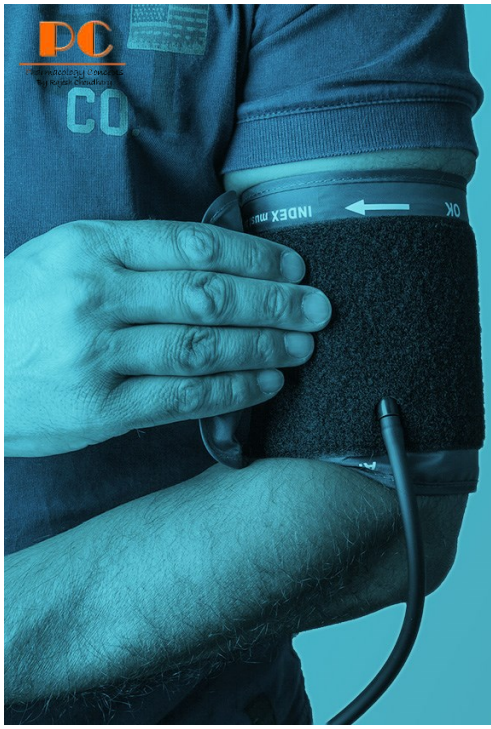
- **Unexpected adverse reaction-** An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug.
- **Serious unexpected adverse drug reaction (SUADR)-** A serious adverse drug reaction that is not identified in nature, severity or frequency by the risk information provided in the clinical investigator's brochure (CIB) or on the drug label.
- **Signal-** Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.
- **Prescribing error-** Incorrect medicine ordering by a prescriber



BASIC TERMS

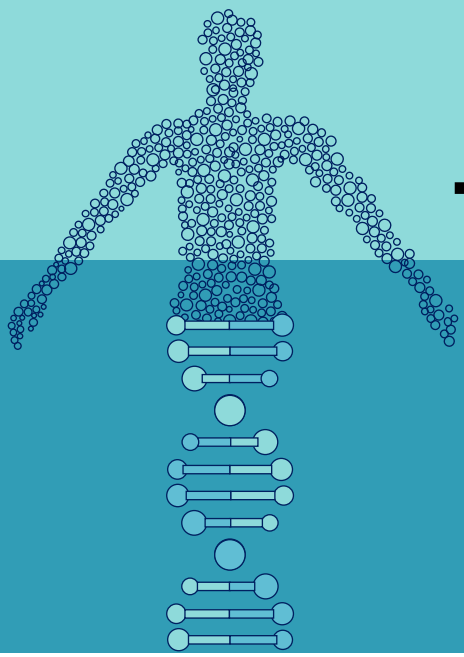
- **Medication error-** Administration of a medicine or dose that differs from the written order
- **Negligence-**Medical decision making or care below the accepted standards of practice



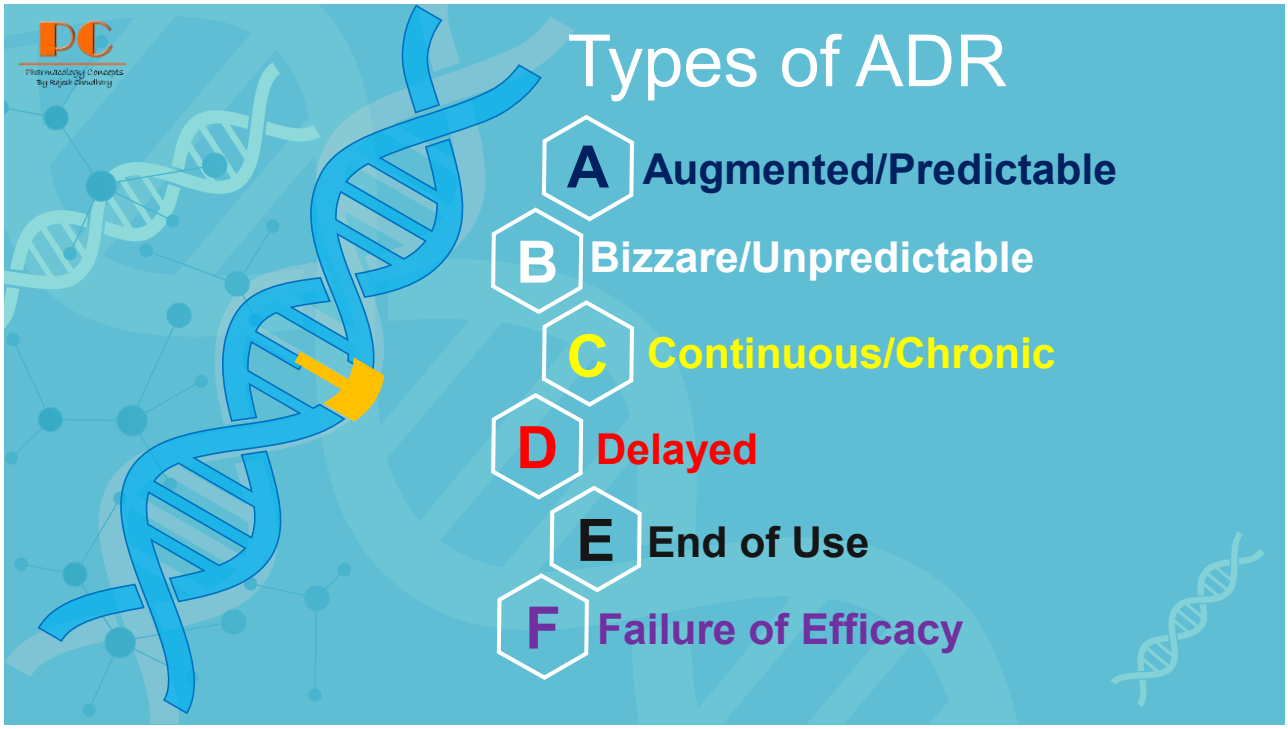


Pharmacovigilance

Pharmacovigilance has been defined by the WHO (2002) as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" and includes herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines.



TYPES OF ADR



Type A
Augmented/Predictable

- Dose related augmented pharmacologic effects which are predictable and includes-intolerance and side effects
- These reactions occur due to pharmacokinetic or pharmacodynamic factor producing an excess of a known pharmacological effect of the drug.
- Overdose / Toxicity: exaggerated but characteristic pharmacological effect from supratherapeutic dose
- Teratogen: drug may produce developmental defects in fetus

Type A
Augmented/Predictable

- Characteristics of Type A ADR
  - account for 80% + of all ADRs
  - extension of pharmacological effect
  - dose-related and generally not severe
  - usually do not require discontinuation
  - dose reduction or titration may help minimize effect

Examples:

- Insulin induced hypoglycemia,
- Sedation by H1-antihistaminics,
- Hypotension by Prazosin (alfa 1 blocker)
- Bronchospasm by B-Blocker (Propranolol)
- Ototoxicity by Streptomycin overdose

Type B
Bizzare/Unpredictable

- Dose independent and unpredictable effects also known as bizarre effects.
- Idiosyncratic Reactions: uncharacteristic response to drug, unrelated to pharmacology e.g, sulpha based drugs (Sulfomamide) can cause an idiosyncratic Stevens Johnson Syndrome (SJS)
- Allergic / immune-mediated Reaction: does not occur on first exposure (up to 7d), immediate with subsequent exposure, may occur with low dose, resolves within 3-4 days of discontinuation. E.g., Anaphylactic reaction to penicillin
- Characteristics:
  - usually more severe
  - usually require discontinuation
  - not dose-related

Type C: Continuous/Chronic

- Dose and time dependent reactions produced due to long term therapy also known as chronic effects or continuous e.g., NSAID induced renal failure and peptic ulcer and Osteoporosis by steroids

Type D: Delayed

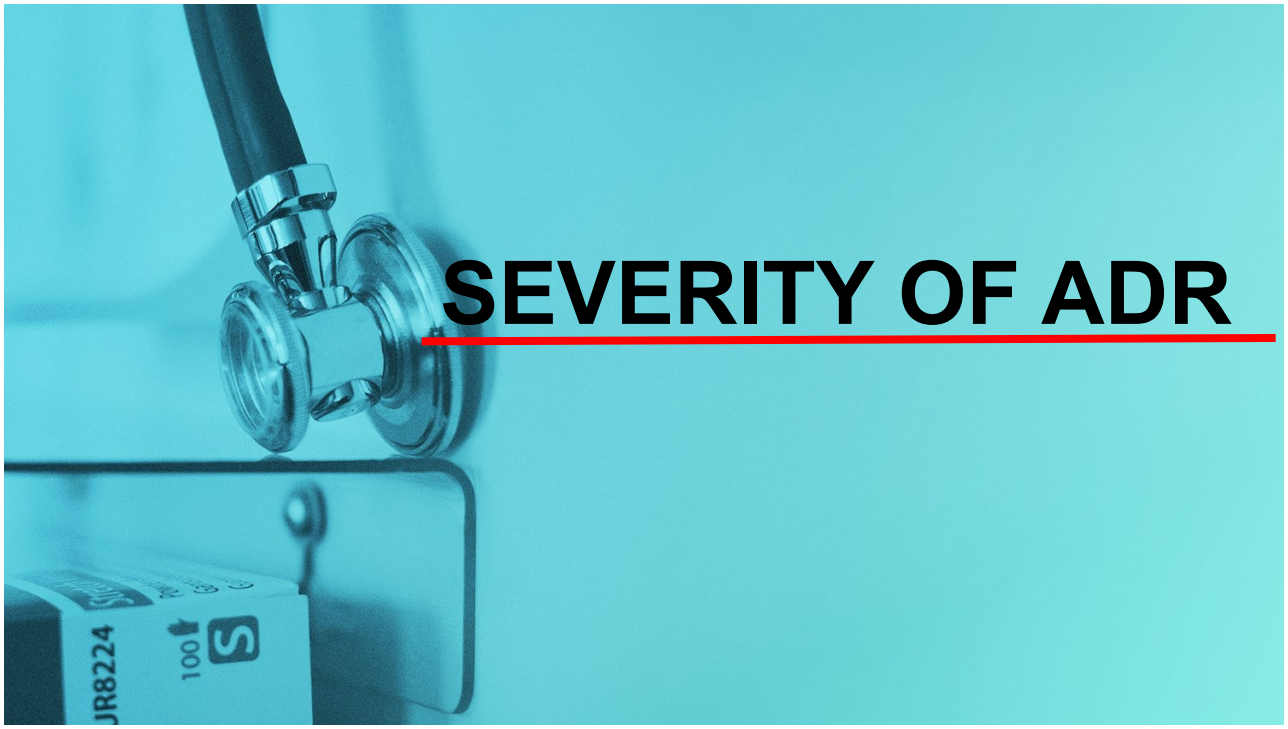
- Effects of drug which occur after a delayed period of exposure to drugs. These are also known as delayed effects e.g., carcinogenic and teratogenic effects, teratogenic effects by linsopril.

Type E: End of Use

- Effects which are observed when drug are withdrawn. Also known as end-of-treatment effects e.g., withdrawal symptoms of addictive drugs (morphine, Benzodiazepines), rebound hypertension produced on abrupt withdrawal of clonidine.

Type F: Failure of Efficacy

- Drug reactions which result in failure of therapy e.g., failure of antibiotics by resistance



SEVERITY OF ADR

SEVERITY OF ADR

- **Minor/Mild:** do not require therapy, antidote or prolongation of hospitalization.
- **Moderate:** Requires change in drug therapy, specific treatment or prolongs hospital stay by at least one day.
- **Severe:** Potentially life-threatening, causes permanent damage or requires intensive medical treatment.
- **Lethal:** Directly or indirectly contributes to death of the patient.

GRADING OF ADR

GRADING SCORE:

- 0-No adverse event or within normal limits
- 1-Mild adverse event
- 2-Moderate adverse event
- 3-Severe and undesirable adverse event
- 4-Life-threatening or disabling adverse event
- 5-Death related to adverse event.

CATEGORY OF ADR

1. ADRs are categorized based on frequency as-

- **Very common**- >10%
- **Common**- >1% and <10%
- **Uncommon**- > 0.1% and < 1 %
- **Rare**- > 0.01% and < 0.1%
- **Very rare**- < 0.01%

CATEGORY OF ADR

2. ADR are categorized based on avoidability as-

- **Definitely avoidable** – adverse drug reaction was due to a drug treatment / procedure inconsistent with present day knowledge of good medical practice.
- **Possibly avoidable** –adverse drug reaction could have been avoided by an effort exceeding the obligatory demands of present day knowledge of good medical practice.
- **Unavoidable**-adverse drug reaction could not have been avoided by any reasonable means.

MECHANISM OF TYPE-B ADR

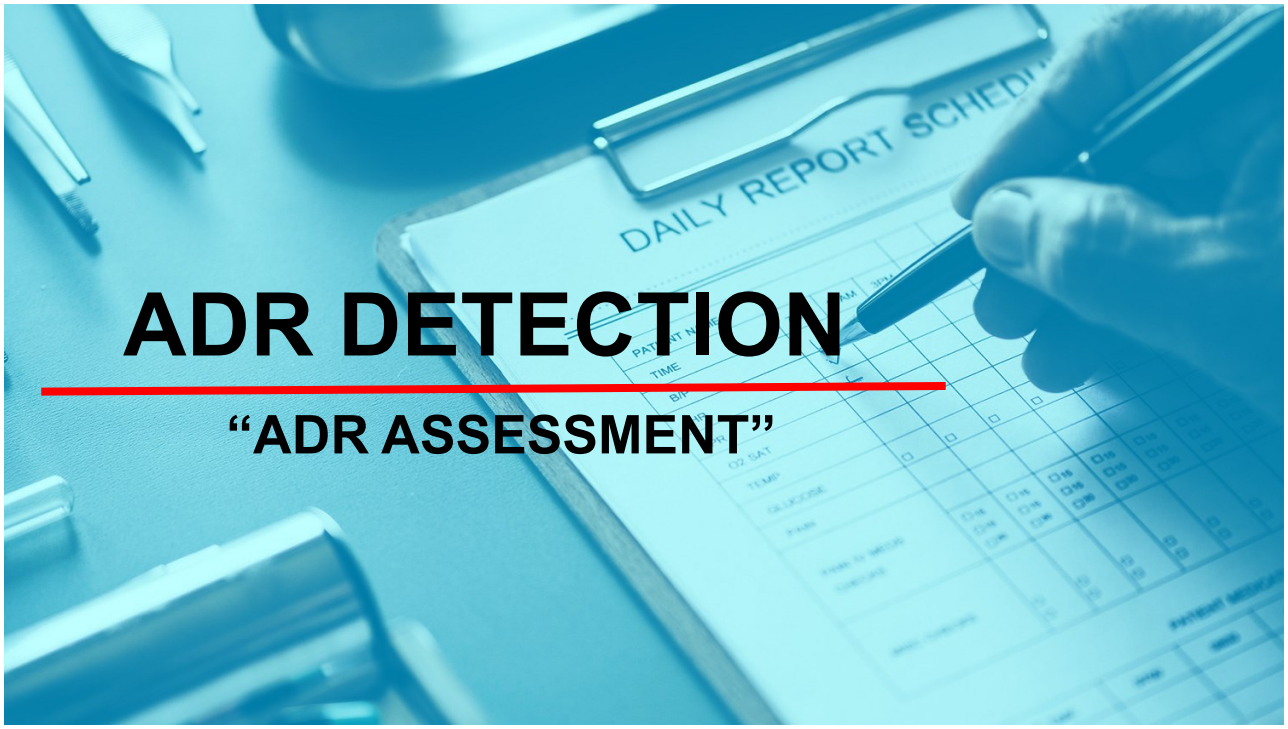
"HYPERSENSITIVE REACTION"

Humoral-Mediated

- **Type-I** or **Immediate hypersensitivity** reactions occur between drug(antigen) and IgE antibodies. Anaphylactic reactions to penicillin are type-I.
- **Type-II** or **Cytolytic reactions** occur when the drug bound to cell acts as antigen and react with IgG or IgM antibodies resulting in cell lysis e.g., thrombocytopenia, aplastic anemia, hemolysis, and Chloramphenicol induced agranulocytosis.
- **Type-III** or **Arthus reactions** occur when circulating antibodies bind to antigen, activate complement and precipitate on vascular endothelium giving rise to inflammatory response e.g., serum sickness, Stevens-Johnson syndrome, polyarthritis etc.

Cell-Mediated

- **Type-IV or delayed hypersensitivity reactions-** Drugs sensitized T-cells produce lymphokines which attract granulocyte and an inflammaotry response is generated e.g., contact dermatitis, rashes, fever, photosensitization etc.



ADR DETECTION

"ADR ASSESSMENT"

ADR ASSESSMENT

1. **Pre-marketing studies-** include pre-clinical animal testing using animal models such as models for carcinogenicity, teratogenicity and mutagenicity (Toxicity studies) and clinical trials (phase I-III)

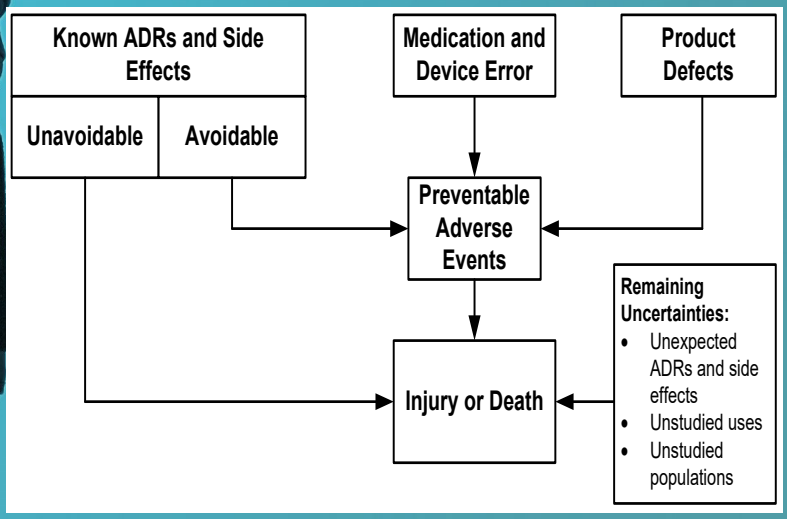
2. **Post marketing surveillance (Phase IV Clinical Trials)-** unknown drug effects can be detected by '**spontaneous reporting'** of adverse events and by epidemiological studies like '**cohort**' and '**case-control studies**'.

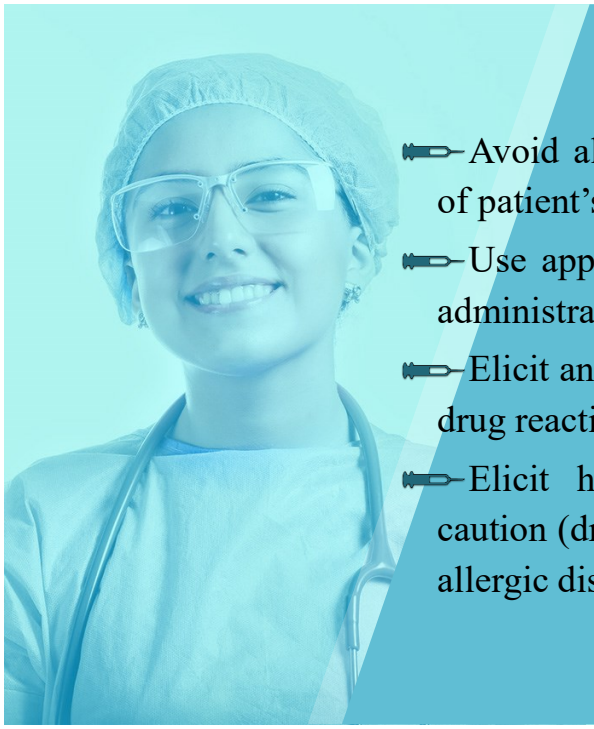
ADR ASSESSMENT

Spontaneous reporting involves voluntary reporting of adverse events in individual case safety reports (ICSR) by the health care workers. Its main limitation is under reporting**.**

- **'Vigibase'-** WHO- UMC maintained database of ADR reports provided by regulatory authorities and pharmaceutical companies.
- **Cohort study** involves comparative study between two groups of patients, one exposed to particular drug therapy and another unexposed, and monitoring over a period of time for the development of outcomes which are compared using the relative risk.
- **Case-control study** involves studying a group of patients who have been affected by a particular adverse reaction and linking it with drug use prior to reaction.

Schematic of preventable and unavoidable adverse events





PREVENTION OF ADR

- Avoid all inappropriate use of drugs in the context of patient's clinical condition.
- Use appropriate dose, route and frequency of drug administration based on patient's specific variables.
- Elicit and take into consideration previous history of drug reactions.
- Elicit history of allergic diseases and exercise caution (drug allergy is more common in patients with allergic diseases).

PREVENTION OF ADR

- Rule out possibility of drug interactions when more than one drug is prescribed.
- Adopt correct drug administration technique (e.g. intravenous injection of vancomycin must be slow).
- Carry out appropriate laboratory monitoring (e.g. prothrombin time with warfarin, serum drug levels with lithium

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