Adverse Drug Reaction

Definition:

- The negative and undesirable effects of drug therapy are known as Adverse Drug Reaction (**ADRs**).
- According to WHO(1972) "ADR is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function".

Difference b/w Adverse Drug Reaction (ADR) & Adverse Drug Event (ADE)

The difference b/w ADR & ADE is that ADRs can occur even after appropriate prescription and correct dosing and ADE are generally associated with inappropriate use of the drug that occurs during the therapy.

History about ADRs

- **In 1922:** JAUNDICE associated with the use of SALVARSAN, an organic arsenical used in the treatment of Syphillis.
- **In 1937:** In USA, 107 people died from taking an ELIXIR OF SULFANILAMIDE that contained the SOLVENT DIETHYLENE GLYCOL

Establishment of the FOOD AND DRUG ADMINISTRATION (FDA), which was given the task of enquiring into the safety of new drugs before allowing them to be marketed.

- **In 1958:** Thalidomide markated in West Germany as a non barbiturate hypnotic & for morning sickness during pregnancy based on animal toxicity report. **1959-61 (4000-100000 case)** thalidomide disaster
- **In 1959-1961**, it was reported in that there was an outbreak of **PHOCOMELIA** (hypoplastic and aplastic limb deformities) in the new born babies.
  The **THALIDOMIDE INCIDENT** led to a public outcry, to the institution all round the world of **DRUG REGULATORY AUTHORITIES**, to the development of a much more sophisticated approach to the preclinical testing and clinical evaluation of drugs before marketing, and to a greatly increased awareness of adverse effect of drugs and methods of detecting them...

Types of ADR

1. Traditional Classification

As proposed by Rawlins and Thompson (1977):
Type A (Augmented)
Type B (Bizarre)

2. Newer Classification

As proposed by Rene J Royer (1997):
Type A (Augmented)
Type B (Bizarre)
Type C (Continuous)
Type D (Delayed effects)

3. <u>Wills and Brown classification</u>: To overcome the limitations of Rawlins and Thompson classification, adverse reactions are classified into nine categories based on their mechanism:
1.Type A (Augmented) Dose related
2.Type B (Bugs) Non- dose related
3.Type C (Chemical/Chronic) Dose related & time related
4.Type D (Delivery/Delayed) Time related
5.Type E (Exit/End of use) Withdrawal
6.Type F (Familial/Failure) Failure of therapy
7.Type G (Genotoxicity)
8.Type H (Hypersensitivity)
9.Type U (Unclassified)

1. Type A (Augmented) Dose related:
• Reactions which can be predicted from the known pharmacology of the drug
• Dose dependent,
• Can be alleviated by a dose reduction
E.g.
• Anticoagulants →→ Bleeding
• Beta blockers →→ Bradycardia

2. Type B (Bizarre) reactions Non- dose related
- Cannot be predicted from the pharmacology of the drug
- Not dose dependent, Host dependent factors important in predisposition

E.g.
Penicillin Anaphylaxis,
Anticonvulsant → Hypersensitivity

3. Type C (Chemical/Chronic) Dose related & time related
Type C reactions are irritant reaction that is related to drug concentration. eg: contact dermatitis.
Biological characteristics can be predicted from the chemical structure of the drug/metabolite
E.g.
Paracetamol- Hepatotoxicity

4. Type D (Delivery/Delayed) Time related
- Occur after many years of treatment.
- Can be due to accumulation.

E.g.
Chemotherapy →Secondary tumours
Phenytoin during pregnancy → Teratogenic effects
Antipsychotics → Tardive dyskinesia

5. Type E (Exit/End of use) Withdrawal
- Occur on withdrawal especially when drug is stopped abruptly

E.g.
Phenytoin withdrawal→ Seizures
Steroid withdrawal → Adrenocortical insufficiency.

6. Type F (Familial/Failure) Failure of therapy
- They only occur in genetically predisposed patient. It can be improved if medicine withdrawn. eg: hemolytic anemia with primaquin in G6PD deficient individuals.

7. Type G (Genotoxicity)

- Irreversible genetic damage is caused by this Type G adverse reaction. eg: teratogenic agent like Thalidomide causes genetic damage to the developing fetus.

8. Type H (Hypersensitivity)

- They are also known as drug allergy and is often immune mediated response.

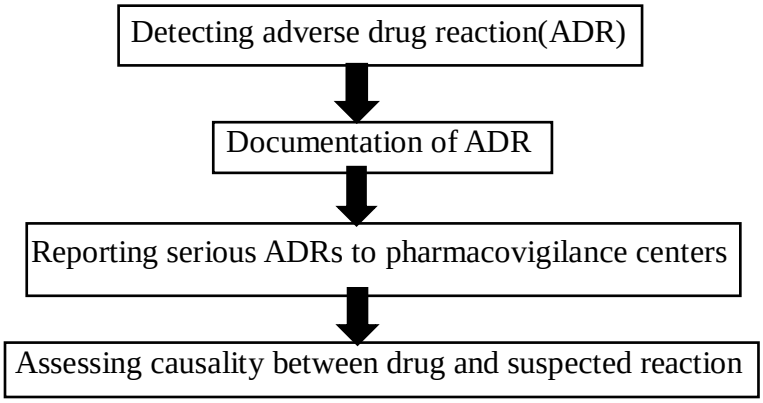
9. Type U (Unclassified)

- This includes those reactions in which the mechanism is unclear.

eg: Taste disturbances associated with Simvastatin.

<u>Detection and Reporting Mehod</u>

Monitoring of ADR



Methods of Detection of ADRs:

1) Pre marketing Studies
2) Post marketing surveillance
3) Casuality assessment
4) Electronic health records (EHRs)
5) Active Surveillance
6) Prescription Event Monitoring (PEM)
7) Intensive Monitoring

1. <u>Pre-Marketing Studies:</u>

- Animal Studies:
  - Acute/Chronic Toxicity study
  - Mutagenecity & Carcinogenecity
  - Teratogenecity
- Human Studies:
  - Phase 0
  - Phase I
  - Phase II
  - Phase III

2. <u>Post-Marketing Surveillance:</u>

A. Spontaneous Reports
B. Epidemiological methods:
   i) Case Control Studies
   ii) Cohort Studies

C. Meta Analysis of Clinical Study
D. Published Case Report

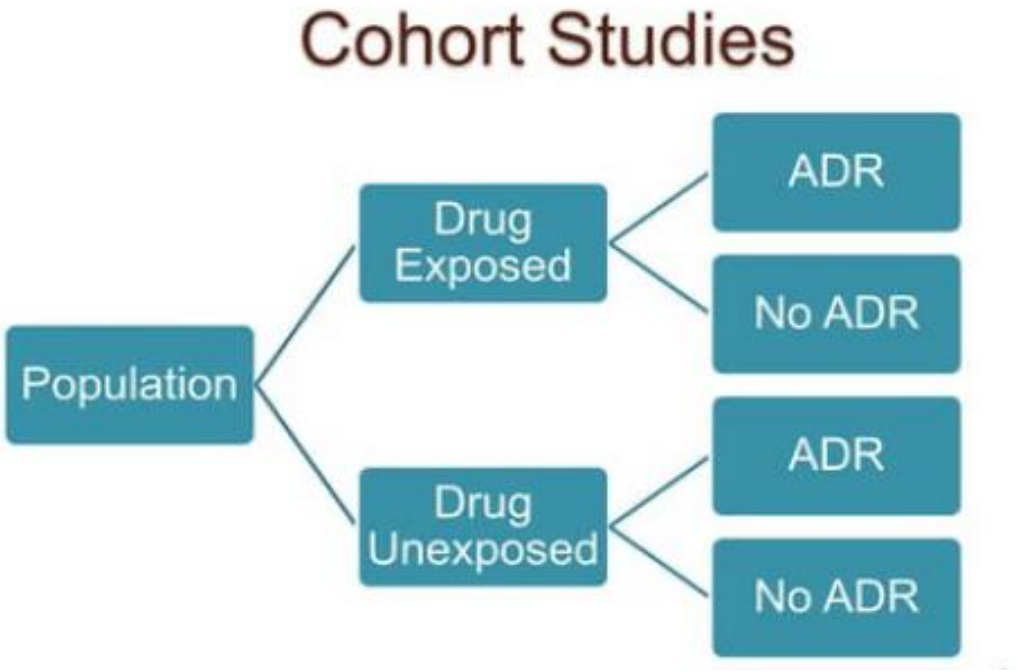
A. Spontaneous Reports

This method involves healthcare professionals, patients, or caregivers reporting ADRs to regulatory agencies or pharmaceutical companies voluntarily. This is the most common method for detecting ADRs. The strengths of this method include its simplicity, low cost, and ability to detect rare and unexpected ADRs. However, it is subject to underreporting due to lack of awareness, reluctance to report, and variability in reporting criteria.

B. Epidemiological methods:

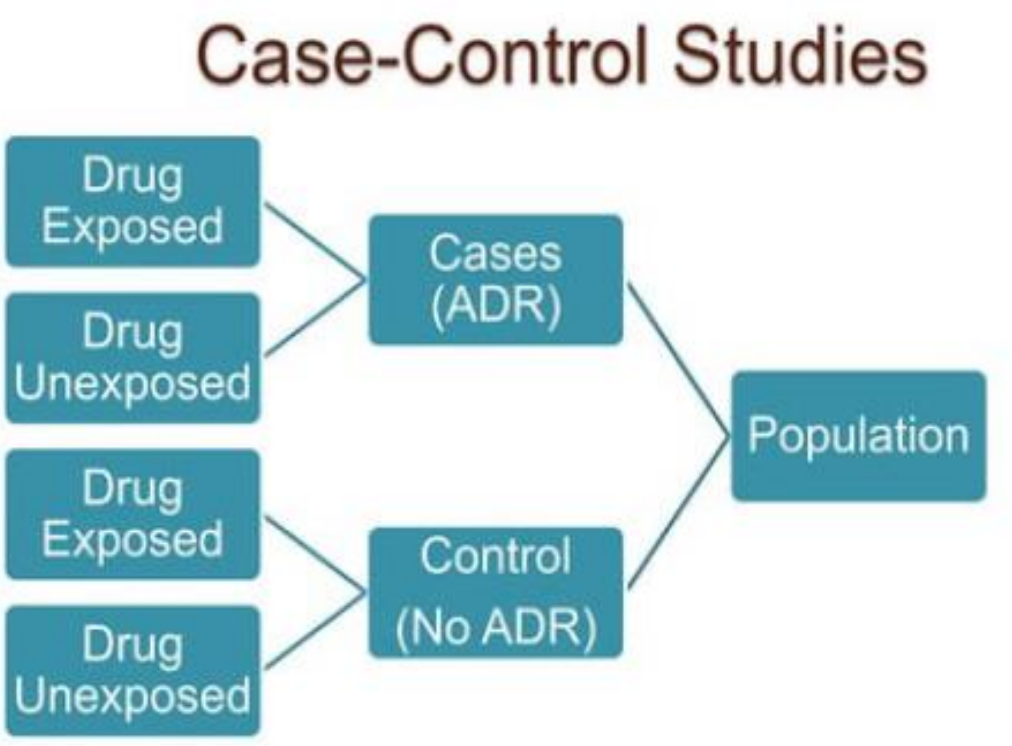
I. Cohort Studies:

- CEM involves monitoring patients who have been prescribed a specific medication over a prolonged period, usually several months or years.
- Healthcare professionals collect data on adverse events that occur during the monitoring period.
- This method can detect ADRs that occur after long-term medication use and can detect previously unknown ADRs. However, it is time-consuming and expensive.



II. Case control studies:

- Individuals affected by the adverse event being studied are identified.
- Each case is matched with several disease free control patients, randomly recruited from the study base.
- Drug histories of both the groups are traced backwards for the comparison.
- The suspicion is strengthened if high association is found. Advantage: Can be analyzed quickly as number of patients analyzed is small.



3. **Casuality Assesment**
   - **a.** Strenght of association
   - **b.** Consistency of observed evidence
   - **c.** Temporality of relationship Dose response relationship
   - **d.** Confounding report

4. **Electronic Health Records (EHRs):**
   EHRs are computerized patient records that contain information about medications, medical history, laboratory results, and other relevant information. EHRs can be used to detect ADRs by analyzing patterns of medication use and associated adverse events. EHRs also have the potential to provide real-time ADR detection and automated reporting. However, limitations include incomplete or inaccurate data, privacy concerns, and lack of standardization.

5. **Active Surveillance:**
   This method involves healthcare professionals systematically searching for ADRs in patients using specific tools, such as questionnaires or interviews. Active surveillance can be used to detect ADRs that are difficult to identify through spontaneous reporting. This method is particularly useful for detecting ADRs that have a delayed onset or are not recognized by patients or healthcare professionals.

6. **Prescription Event Monitoring (PEM):**
   PEM involves monitoring patients who have recently started taking a new medication. Healthcare professionals collect data on adverse events that occur within a specified time

frame after the patient starts taking the medication. This method is useful for detecting ADRs that occur shortly after medication initiation and can detect previously unknown ADRs. However, it is limited by its narrow focus on specific medications.

7. **Intensive Monitoring:**
   Intensive monitoring involves monitoring a select group of patients who are at high risk of developing ADRs. This method can be used to detect rare or severe ADRs that may not be detected through other methods. However, it is resource-intensive and may not be feasible for large populations.

Role of Healthcare Professionals in Detecting ADRs:

- Possibility of an ADR should always be considered during differential diagnosis.
- ADR may be detected during ward round with the medical team.
- Patient counselling, medication history interview and communicating with other healthcare professional may provide additional clues.
- Patients who are at higher risk should be monitored closely-

i. Patients with renal or hepatic impairment.
ii. Patients who had history of allergic reactions. Patients taking multiple drugs.
iii. Pregnant and breastfeeding women

ADR REPORTING METHOD

A) Who can Report?

All healthcare professionals (clinicians, dentists, pharmacists, nurses etc) and Non-healthcare professionals including consumers can report suspected adverse drug reaction.

B) Where to report ?

- ❑ Duly filled Suspected Adverse Drug Reaction Reporting Form can be send to the nearest Adverse Drug Reaction Monitoring Centre (AMC) or directly to the National Coordination Centre(NCC).
- ❑ Call on Helpline (Toll Free) 1800 180 3024 to report ADRs.
- ❑ Or can directly mail this filled form to pvpi@ipcindia.net orpvpi.ipcindia@gmail.com
- ❑ A list of nationwide AMCs is available at:
  http://www.ipc.gov.in
  http://www.ipc.gov.in/PvPI/pv_home.html

C) **What to report ?**

Report serious adverse drug reactions. A reaction is serious when the patient outcome is:
•Life-threatening
• Hospitalization (initial or prolonged)
•Disability (significant, persistent or permanent)
• Congenital anomaly
• Required intervention to prevent permanent impairment or damage
Report non-serious, known or unknown, frequent or rare adverse drug reactions due to Medicines, Vaccines and Herbal products

Mandatory field for suspected ADR reporting form

- ❑ Patient initials

- ❑ Age at onset of reaction
- ❑ Reaction terms
- ❑ Date of onset of reaction
- ❑ Suspected medications reporter information.

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

CDSCO

Central Drugs Standard Control Organization

A. Patient information

B. Suspected Adverse Reaction

C. Suspected medications(s)

D. Reporter (see confidentiality section on first page)

SEVERITY AND SERIOUSNESS ASSESSMENT OF ADR

SEVERITY:

- The term severity is often used to describe the intensity of medical event.
- Severity assessment categorizes the ADR as mild, moderate, or severe based on the steps taken for management of ADRs.

KARCH AND LASAGNA classified severity into minor, moderate, severe and lethal as defined below:

- ✓ **Minor**: No antidote, treatment or prolongation of hospitalization required.
- ✓ **Moderate:** A change in drug therapy (e.g.: modified dosage, addition of a drug), but not necessarily discontinuation of the drug is required; hospitalization may be prolonged, or specific treatment may be required.
- ✓ **Severe**: Potentially life threatening, causing permanent damage or requiring intensive medical care. Requires drug discontinuation.
- ✓ **Lethal**: Directly or indirectly contributes to the death of the patient.

MODIFIED HARTWIG'S AND SIEGEL ASSESSMENT SCALE

Hartwig et. al robustly categorized ADR severity into seven levels according to clinical consequence, including resultant harm and intensity of medical intervention required.

- Level 1 and 2 fall under mild category
- Level 3 and 4 fall under moderate category
- Level 5, 6 and 7 fall under category severe category.

Mild:

- **Level 1**: The ADR requires no change in treatment with the suspected drug.
- **Level 2:** The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. NO antidote or other treatment is required, and there is no increase in length of stay.

Moderate:

- **Level 3:** The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and / or an antidote or other treatment is required. There is no increase in length of stay.
- **Level 4 (a):** Any level 3 ADR that increases length of stay by at least one day.
- **Level 4 (b):** The ADR is the reason for admission.

SERIOUSNESS CLASSIFICATION

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolong hospitalization
- Results in persistent or significant disability
- Is a congenital anomaly/birth defect

PREVENTABILITY AND PREDICTABILITY OF ADRs

PREVENTABILITY OF ADRs:

- Whether an ADR is preventable or not Schumack and Thornton proposed in 1992 that its answer would depend on the answers of the following seven questions.
- If the answer is yes' to one or more of these questions, the final answer would be yes, the ADR is preventable.
- The questions are:
  1. Was the drug involved in the ADR not considered appropriate for the patient's clinical condition?
  2. Were the dose, route, and frequency of administration not appropriate for the patient's age, weight, and disease state?
  3. Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
  4. Was there a history of allergy or previous reactions to the drug?
  5. Was a drug interaction involved in the reaction?

6. Was a toxic serum drug level documented?
7. Was poor compliance involved in the reaction?

PREDICTABILITY OF ADRs

1. **Type A (Predictable):**
   - ✓ Extension of pharmacological effect
   - ✓ Often predictable and dose dependent
   - ✓ Example: Dry mouth induced by anti-cholinergics.
2. **Type B (Non-predictable):**
   - ✓ Idiosyncratic or immunologic reactions
   - ✓ Rare and unpredictable
   - ✓ Example: Penicillin induced anaphylactic shock