ADVERSE DRUG REACTIONS



Definition Of Adverse Drug Reactions

- **According to WHO (1972)**

"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".

Classification of ADRs

Depending upon……..

- **Type of reaction:**
  - Type A
  - Type B
  - Type C
  - Type D
  - Type E
  - Type F
- **Onset of event:** Acute (<60 minutes)
  Sub-acute (1-24 hrs)
  Latent (>2 days)
- **Severity**: Minor, Moderate, Severe, Lethal ADRs.

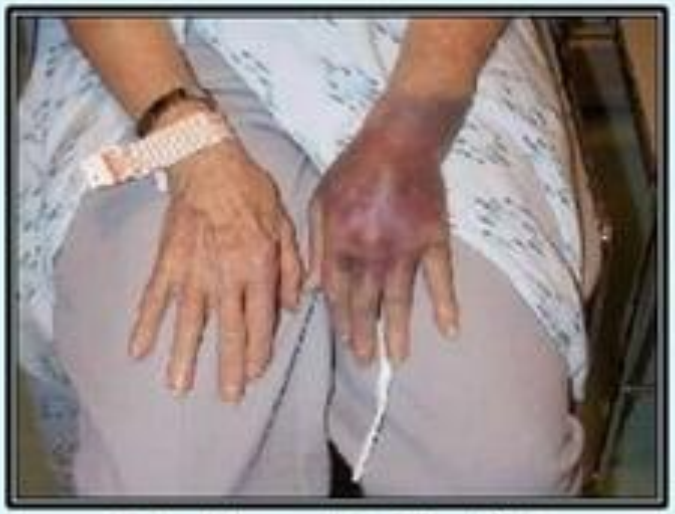
Types of Adverse Drug Reactions

- **A**ugmented (Dose Related)
- **B**izzare (Non-Dose Related)
- **C**hronic (Dose Related and Time Related)
- **D**elayed (Time Related)
- **E**nd of Use (Withdrawal)
- **F**ailure (Unexpected Failure of Therapy)

Augmented (Dose Related)

Features

- Common Related to the pharmacologic action of the drug – exaggerated pharmacologic response
- Predictable
- Low mortality



Bleeding with Warfarin

Example

- Dry mouth with Tricyclic Antidepressants
- Respiratory Depression with Opioids
- Bleeding with Warfarin

Management

- Reduce Dose or Withhold Drug
- Consider effects of concomitant therapy

Bizzare (Non-Dose Related)

Features

- Uncommon
- Not related to the pharmacologic action of the drug
- Unpredictable
- High mortality

Penicillin Allergy

Example

- Immunologic reactions: anaphylaxis to penicillin
- Idiosyncratic reactions: malignant hyperthermia with general anesthetics

Management

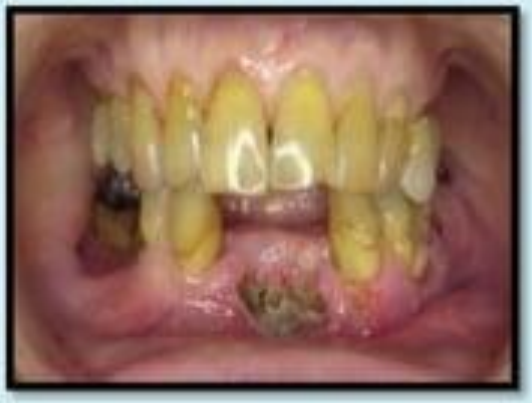
- Withhold and avoid in future

Chronic
(Dose Related and Time Related)

Features
- Uncommon
- Related to the cumulative dose

Example
- Hypothalamic-pituitary-adrenal axis suppression by corticosteroids.
- Osteonecrosis of the jaw with bisphosphonates

Management
- Reduce dose or use an alternate day therapy
- withdrawal may have to be prolonged



Osteonecrosis of Jaw with Bisphosphonates

Delayed (Time Related)

Features

- Uncommon
- Usually dose related
- Occurs or becomes apparent sometime after use of the drug

Example

- Carcinogenesis
- Teratogenesis
- Tardive dyskinesia
- Leucopenia with lomustine

Management

- Often intractable

Tardive dyskinesia

End of use (Withdrawal)

Features

- Uncommon
- Occurs soon after withdrawal of the drug

Example

- Withdrawal syndrome with opiates or benzodiazepines (e.g., insomnia, anxiety)

Management

- Reintroduce drug and withdraw slowly

Insomnia

Failure (Unexpected Failure of Therapy)

Features

- Common
- Dose related
- Often caused by drug interactions

Example

- Inadequate dosage of an oral contraceptive when used with an enzyme inducer.
- Resistance to antimicrobial agents

Management

- Increase dosage
- Consider effects of concomitant therapy

Onset of Event

- Acute
- Within 60 minutes
  - Anaphylactic shock
  - Severe bronchoconstriction
  - Nausea or vomiting
- Sub-acute
- 1 to 24 hours
  - Maculopapular rash
  - Serum sickness
  - Antibiotic-associated diarrhea
- Latent
- After 2 days
  - Organ toxicity,
  - Dyskinesia

Classification of ADRs…. Depending on Severity

- **Minor ADRs:** No therapy, antidote or prolongation of hospitalization is required.
- **Moderate ADRs:** Requires change in drug therapy, specific treatment or prolongs hospital stay by atleast 1 day.
- **Severe ADRs:** Potentially life threatening, causes permanent damage or requires intensive medical treatment.
- **Lethal:** Directly or indirectly contributes to death of the patient.

Monitoring ADRs

Detecting adverse drug reaction(ADR).

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Documentation of ADR

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Reporting serious ADRs to pharmacovigilance centers

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Assessing causality between drug and suspected reaction

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

- Patients with renal or hepatic impairment.
- Patients who had histrory of allergic reactions.
- Patients taking multiple drugs.
- Pregnant and breastfeeding women.

Reporting an ADR

What may happen when you don't report?

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 or pvpi.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.

D) Mandatory field for suspected ADR reporting form.

- Patient initials,
- Age at onset of reaction,
- Reaction term(s),
- Date of onset of reaction,
- Suspected medication(s)
- reporter information.

Version 1.1

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION

(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

FOR AMC/NCC USE ONLY

AMC Report No.

Worldwide Unique No.

Report Type: Initial / Follow up

A. PATIENT INFORMATION

1. Patient Initials: _____
2. Age at time of Event or Date of Birth: _____
3. M / F / Other
4. Weight _____ kg

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)
6. Date of recovery (dd/mm/yyyy)
7. Describe reaction or problem

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)

14. Seriousness of the reaction: No / If Yes (please tick anyone)
- Death ( )
- Life threatening
- Hospitalization/Prolonged
- Disability
- Congenital anomaly
- Required intervention to Prevent permanent impairment/damage
- Other (specify)

15. Outcomes
- Recovered
- Recovering
- Not recovered
- Fatal
- Recovered with sequelae
- Unknown

C. SUSPECTED MEDICATION(S)

S.No	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates: Date started	Therapy dates: Date stopped	Indication	Causality Assessment
i											
ii											
iii											
iv											

S.No as per C	9. Action Taken (please tick) Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	10. Reaction reappeared after reintroduction (please tick) Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates: Date started	Therapy dates: Date stopped	Indication
i							
ii							
iii							

Additional Information:

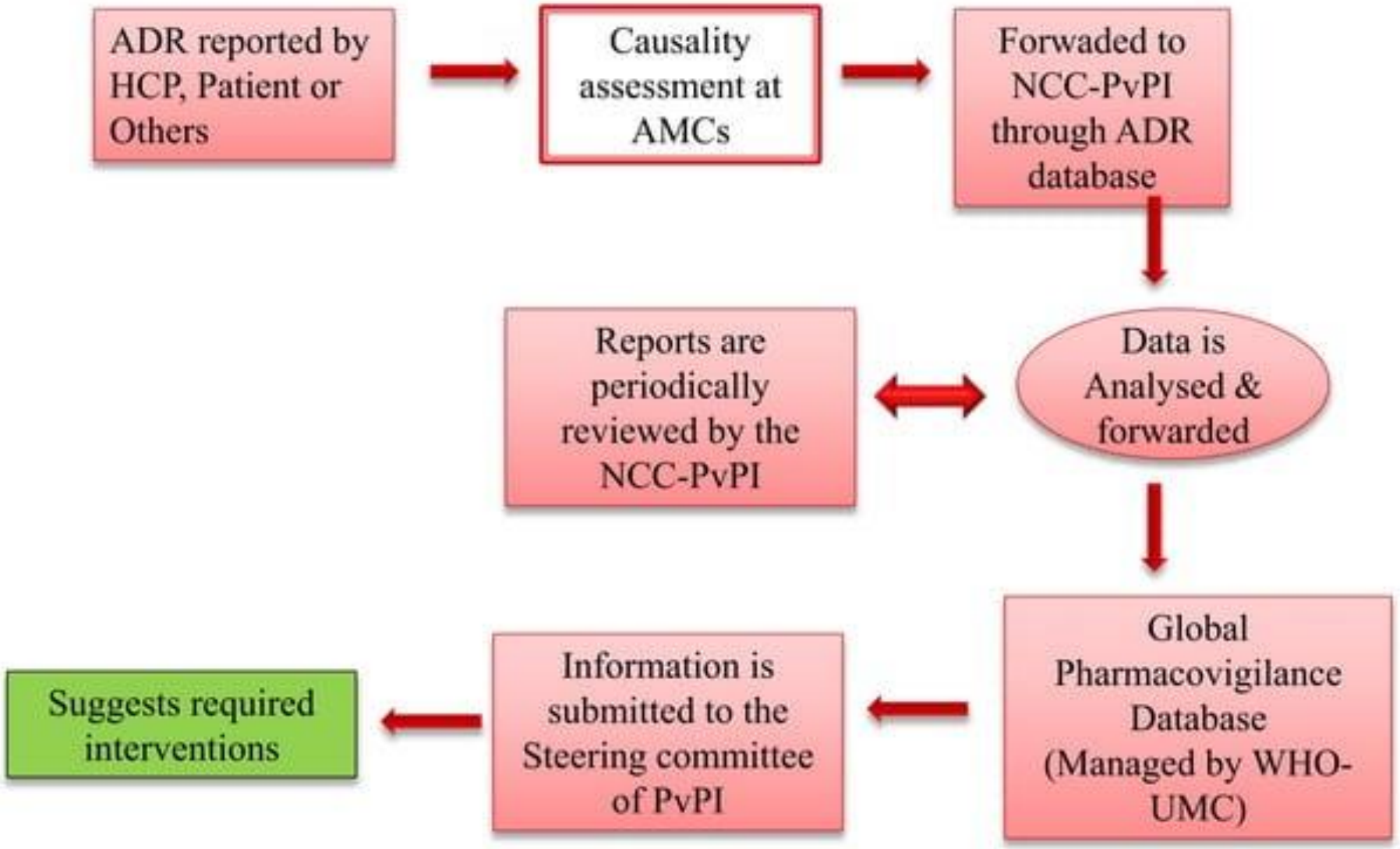
D. REPORTER DETAILS

16. Name and Professional Address: _____
Pin: _____ E-mail: _____
Tel. No. (with STD Code): _____
Occupation: _____ Signature: _____

17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

D) What happens to the submitted information?



Assessing Causality

Causality assessment is the method by which the extent of the relationship between a drug and a suspected reaction is estimated .

Methods Of Causality Assessment

Group-1
Opinion of Experts, Clinical Judgment or Global introspection methods

Group-2
Algorithms (with or without scoring) or standardised assesment methods

Group-1 Opinion of Experts, Clinical Judgment or Global Introspection methods

Causation is established based on the clinical judgment of the expert or panel of the experts. Such Judgements are mostly based on the **WHO-UMC causality assesment scale** given below.

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required

Causality term	Assessment criteria*
Possible	•Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	•Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Group-2 Algorithms (Naranjo's Algorithms)

S.No	Questions	Yes	No	Don't Know
1	Are there previous conclusive reports on this reaction?	−1	0	0
2	Did the adverse event appear after the suspected drug was given?	+2	−1	0
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0
4	Did the adverse reaction appear when the drug was readministered?	+2	−1	0
5	Are there alternative causes that could have caused the reaction?	−1	2	0
6	Did the reaction reappear when a placebo was given?	−1	+1	0
7	Was the drug detected in any body fluid in toxic concentrations?	+1	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0

Scoring

Definite ≥ 9
Probable 5-8
Possible 1-4
Unlikely ≤ 0

But Still There Is No Universally Accepted Method For The Causality Assessment Of Adrs

Preventing ADR

Terminologies of ADR

- Adverse Drug Reaction: A Response to a medicine which is noxious and which occurs at doses normally used in man.
- Adverse Drug Event: Any untoward medical occurance that may present during the treatment with a medicine but which does not necessarily have a causal relationship with this treatment.
- Side Effects: an unpleasant effect of a drug that happens in addition to the main effect.
- Benefit and risk analysis: Examination of favorable (benefit) & Unfavorable result of undertaking a special cause of action.
- Adverse Case Report: A case report in ADR is a notification relating to a patient with an adverse effect or laboratory test abnormality suspected to be induced by medicinal product

Some Recently Reported ADRs

Country	Drug	Therapeutic Action	Reported ADR
Oman	Voriconazole	Anti Fungal	Hepatotoxicity and neurologic adverse effects (e.g. hallucinations, confusion)
Zimbabwe	Efavirenz, Saquinavir	Anti Viral	Gynaecomastia

References:

1. Adverse Drug Reactions By Stephanie N. Schatz, Pharm.D., BCPS; and Robert J. Weber, Pharm.D., BCPS Reviewed by Kyle E. Hultgren, Pharm.D.; Erin M. Timpe Behnen, Pharm.D., BCPS; and Michael C. Barros, Pharm.D., BCPS, BCACP.
2. https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf.
3. Naranjo et.al. Clin Pharmacol Ther. 1981 Aug;30(2):239-45
4. http://www.cpnet.nl/media/1223/naranjo-causality-scale.pdf
5. http://www.who.int/medicines/regulation/medicines-safety/rpvs-meeting/Bloemfontein_may2016.pdf
6. A Textbook of clinical Pharmacy by Parthasarathi, Nyfort –Hansen, Nahata, Second Edition.

If you suspect an ADR do not assume someone else will report it……