



ADVERSE DRUG REACTIONS

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Objectives

- **Definition of terms associated with Adverse Drug Reactions (ADRs)**
- **Classification of ADRs**
- **Discussion on each type of ADR with examples**



Definitions



- **Adverse Event (AE):** Any untoward 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 Reaction (ADR):** Any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in future use of the same drug.
- Therefore, an adverse drug reaction is an adverse event with a causal link to a drug.

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graph TD; A[Drug administered] --> B[Pt. develops a new condition/symptom  
ADE]; B --> C[Drug suspected?]; C -- Yes --> D[Check literature]; D --> E["Documented ?  
(for the product  
Or  
similar class of products)"]; E -- Yes --> F[Highly suggestive of ADR];
```

Drug administered

Pt. develops a new condition/symptom
ADE

Drug suspected?

Yes

Check literature

**Documented ?
(for the product
Or
similar class of products)**

Yes

Highly suggestive of ADR

Not documented in literature

```
graph TD; A[Not documented in literature] --> B[Drug continued]; A --> C[Drug discontinued]; B --> D[Worsening of symptoms]; D --> E[Any other possible causes?]; E --> E1[• Concomitant therapy]; E --> E2[• Underlying conditions]; C --> F[Symptoms improve (+ve dechallenge)]; F --> G[Drug restarted]; G --> H[Symptoms recur (+ve rechallenge)];
```

Drug continued

Worsening of symptoms

Any other possible causes?

- Concomitant therapy
- Underlying conditions

Drug discontinued

Symptoms improve
(+ve dechallenge)

Drug restarted

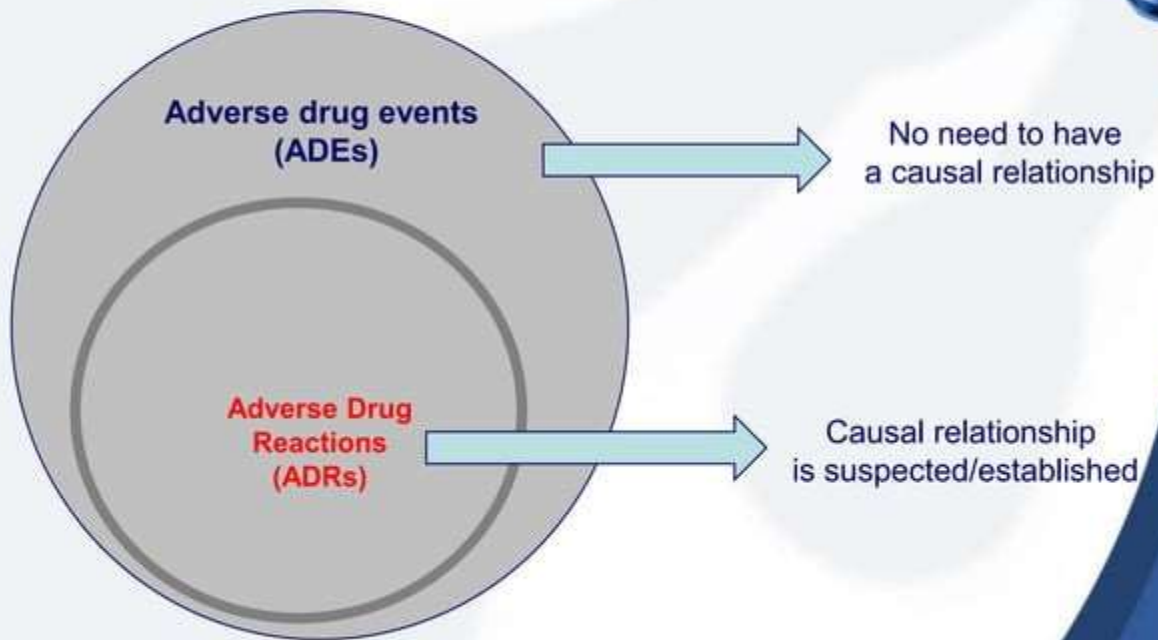
Symptoms recur
(+ve rechallenge)

Simply....



- **Adverse:** Untoward, unintended, possibly causing harm (noxious)
- **AE:** Adverse Event, Effect or Experience
- **ADE (Adverse Drug Event):** An AE which happens in a patient taking a drug
- **ADR (Adverse Drug Reaction):** An ADE in which a causal association is suspected between the drug and the event

ADEs Vs ADRs



Classification of ADRs



- Depending on....
- **Onset of event:** Acute (<60 minutes), Sub-acute (1-24 hrs) and Latent (>2 days)
- **Type of reaction:** Type A (Augmented), B (Bizarre), C (Chemical), D (Delayed), E (Exit), F (Familial), G (Genotoxicity), H (Hypersensitivity), U (Un classified)
- **Severity:** Minor, Moderate, Severe, Lethal ADRs
- **Others:** Side effects, Secondary effects, Toxic effects, Intolerance, Idiosyncrasy, Drug allergy, Photosensitivity, Drug Dependence, Drug Withdrawal Reactions, Teratogenicity, Mutagenicity, Carcinogenicity, Drug induced disease (Iatrogenic)

Classification of ADRs....

Wills and brown

- Type A (Augmented)
- Type B (Bizarre)
- Type C (Chemical)
- Type D (Delayed)
- Type E (Exit/End of treatment)
- Type F (Familial)
- Type G (Genotoxicity)
- Type H (Hypersensitivity)
- Type U (Un classified)



Type A (Augmented) reactions



- 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,
- Nitrates → Headache,
- Prazosin → Postural hypotension.

Type B (Bizarre) reactions

A blue stethoscope is positioned in the top right corner of the slide, partially overlapping the dark blue header.

- Cannot be predicted from the pharmacology of the drug
- Not dose dependent,
- Host dependent factors important in predisposition

E.g.

- Penicillin → Anaphylaxis,
- Anticonvulsant → Hypersensitivity

Type C (Chemical) reactions



- Biological characteristics can be predicted from the chemical structure of the drug/metabolite

E.g.

- Paracetamol → Hepatotoxicity

Type D (Delayed) reactions

A blue stethoscope is positioned in the top right corner of the slide, partially overlapping the dark blue header area.

- Occur after many years of treatment.
- Can be due to accumulation.

E.g.

- Chemotherapy → Secondary tumours
- Phenytoin during pregnancy → Teratogenic effects
- Antipsychotics → Tardive dyskinesia
- Analgesics → Nephropathy

Type E (End of treatment) reactions

A graphic of a stethoscope is positioned in the top right corner of the slide, partially overlapping the blue header area.

- Occur on withdrawal especially when drug is stopped abruptly

E.g.

- Phenytoin withdrawal → Seizures,
- Steroid withdrawal → Adrenocortical insufficiency.

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.

Side effects



- Unwanted but often unavoidable, pharmacodynamic effects that occur at therapeutic doses
- Predicted from the pharmacological profile of a drug
- Known to occur in a given percentage of drug recipients

- **E.g.**
- Side effect based on therapeutic effect:
 - Atropine (preanaesthetic) → dryness of mouth
 - Acetazolamide (diuretic-bicarbonate excretion) → Acidosis
- Side effect based on a different action:
 - Promethazine (anti-allergic) → sedation
 - Estrogen (Anti ovulatory) → Nausea
- Depending on the context:
 - Codeine (anti-tussive) → constipation → Used in Traveller's diarrhea

Side effects....



- **Drug discovery**
- Occasionally, “adverse” effects may be exploited to develop an entirely new indication for a drug.
- **E.g:**
- Unwanted hair growth during Minoxidil treatment of severely hypertensive patients → development of the drug for hair growth.
- Sildenafil was initially developed as an antianginal, but its effects to alleviate erectile dysfunction → a new drug indication in erectile tissue.
- Sulfonamides used as antibacterials were found to produce hypoglycemia and acidosis as side effects → development of Hypoglycemic Sulfonylureas and Carbonic anhydrase inhibitor Acetazolamide.

Secondary effects

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- Indirect consequences of a primary action of the drug
- **E.g.**
- Tetracyclines → Suppression of bacterial flora
→ Superinfections
- Corticosteroids → Weaken host defence → Activation of latent tuberculosis

Toxic effects



- Result of excessive pharmacological action of the drug due to over dosage or prolonged use.
- Over dosage may be
 1. Absolute (Accidental, homicidal, suicidal)
 2. Relative (Gentamycin in Renal failure)
- Result from
 1. Extension of therapeutic effect:
 - E.g. Barbiturates → Coma,
 - Digoxin → Complete A-V block,
 - Heparin → Bleeding
 2. Functional alteration:
 - E.g. Atropine → Delirium
 3. Drug induced tissue damage:
 - E.g. Paracetamol → Hepatic necrosis

Intolerance

A blue stethoscope is positioned in the top right corner of the slide, partially overlapping the dark blue background.

- Appearance of characteristic toxic effects of a drug in an individual at therapeutic doses
- Converse of tolerance,
- Indicates a low threshold of the individual

- **E.g.**
- Triflupromazine (single dose) → Muscular dystonias in some individuals
- Carbamazepine (few doses) → Ataxia in some individuals
- Chloroquine (single tablet) → Vomiting and abdominal pain in some individuals

Idiosyncrasy

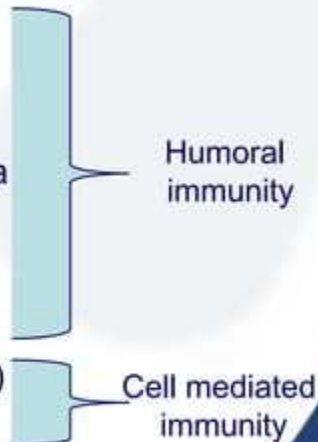


- Genetically determined abnormal reactivity to a chemical
- Certain Bizarre drug effects due to peculiarities of an individual for which no definite genotype has been described, are also included.
- Drug interacts with some unique feature of the individual, not found in majority subjects, and produces the uncharacteristic reaction.
- **E.g.**
- Barbiturates → Excitement and mental confusion in some individuals
- Quinine → Cramps, diarrhea, asthma, vascular collapse in some individuals
- Chloramphenicol → Aplastic anemia in rare individuals

Drug allergy

- Immunologically mediated reaction producing stereotype symptoms, unrelated to the pharmacodynamic profile of the drug
- Generally occur even with much smaller doses
- Also called Drug hypersensitivity
- Types:

- Type I: Immediate, anaphylactic (IgE)
 - **E.g:** Penicillins → Anaphylaxis
- Type II: Cytotoxic antibody (IgG, IgM)
 - **E.g:** Methyldopa → hemolytic anemia
- Type III: Serum sickness (IgG, IgM)
 - Antigen-antibody complex
 - **E.g:** Procainamide-induced lupus
- Type IV: Delayed hypersensitivity (T cell)
 - **E.g:** Contact dermatitis



Photosensitivity



- Cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. The reactions are of two types
- **Phototoxic:** Drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction resulting in local tissue damage (sunburn-like, i.e., erythema, edema, blistering, hyperpigmentation)
 - E.g. Tetracyclines (esp. Demeclocycline), and Tar products, Nalidixic acid, Fluoroquinolones, Sulfones etc
- **Photo allergic:** Drug or its metabolite induces a cell mediated immune response which on exposure to light (longer wave length) produces a papular or eczematous contact dermatitis like picture.
 - E.g. Sulfonamides, Sulfonylureas, Griseofulvin, Chloroquine, Chlorpromazine

Drug dependence



- Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, withdrawal from reality, social adjustment, etc.
- **Psychological dependence:** Individual believes that optimal state of well being is achieved only through the actions of the drug.
- **E.g.** Opioids, Cocaine.
- **Physical dependence:** Altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic withdrawal (abstinence) syndrome.
- **E.g.** Opioids, Barbiturates, Alcohol, Benzodiazepines

Drug dependence....



- **Drug abuse:** Use of a drug by self medication in a manner and amount, that deviates from the approved medical and social patterns in a given culture at a given time.
Drug abuse refers to any use of an illicit drug.
- **Drug addiction:** Compulsive drug use characterized by overwhelming involvement with the use of a drug.
- **Drug habituation:** Less intensive involvement with the drug, withdrawal produces only mild discomfort.
- Habituation and addiction imply different degrees of psychological dependence.

Drug withdrawal reactions



- Sudden interruption of therapy with certain drugs result in adverse consequences, mostly in the form of worsening of the clinical condition for which the drug was being used.
- **E.g:**
- Corticosteroid → Adrenal insufficiency
- β -blockers → worsening of angina, precipitation of MI
- Clonidine → severe HTN, restlessness, sympathetic over activity

Teratogenicity



- Capacity of a drug to cause foetal abnormalities when administered to the pregnant mother.
- Drugs can affect the foetus at 3 stages:
 1. Fertilization and implantation (Conception to 17 days): failure of pregnancy which often goes unnoticed.
 2. Organogenesis(18 days to 55 days): most vulnerable period, deformities are produced.
 3. Growth and development (> 56 days): developmental and functional abnormalities can occur.
- **E.g:**
- Thalidomide → Phocomelia, multiple defects
- Anticancer drugs → Cleft palate, hydrocephalus, multiple defects
- ACE inhibitors → Hypoplasia of organs (lungs, kidney)

Mutagenecity and Carcinogenicity



- Capacity of a drug to cause genetic defects and cancer respectively.
- Chemical carcinogenesis generally takes several (10-40) years to develop.

- **E.g.**
- Anticancer drugs,
- Radio-isotypes,
- Estrogens,
- Tobacco.

Drug induced disease



- Also called Iatrogenic(Physician induced) diseases.
- Functional disturbances caused by drugs which persist even after the offending drug has been withdrawn and largely eliminated

- **E.g.**
- Salicylates, Corticosteroids → Peptic ulcer
- Phenothiazines, other antipsychotics → Parkinsonism
- Isoniazid → Hepatitis
- Hydralazine → DLE

Summary



- **Adverse Drug Reactions (ADRs)** are adverse events with a causal link to a drug.
- **Types of Classification of ADRs:**
- **Onset of event:** Acute (<60 minutes), Sub-acute (1-24 hrs) and Latent (>2 days)
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