ADRs

Drugs have:

- Beneficial effects
- Harmful effects

Facts

- Drugs save life & improve health
- Drugs also threaten life

ADRs

"Cur'd yesterday of my disease

I died last night of my physician"

- Mathew Prior: 17th Century

From, the remedy worse than the disease

So, the important question is **ALWAYS**:

"Do the potential benefits of the medication outweigh the potential risks for the individual?"

ADRs

Definition

- ‘An adverse drug reaction is any **undesirable effect** of a drug beyond its anticipated therapeutic effects occurring **during clinical use.’**

- The term (ADR) usually excludes-
- nontherapeutic overdosage (e.g. toxicities due to accidental exposure or attempted suicide) and
- lack of efficacy of drug

ADRs

WHO definition:

- "Any response to a drug that is ***noxious*** *and* ***unintended*** and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function."

- It excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors

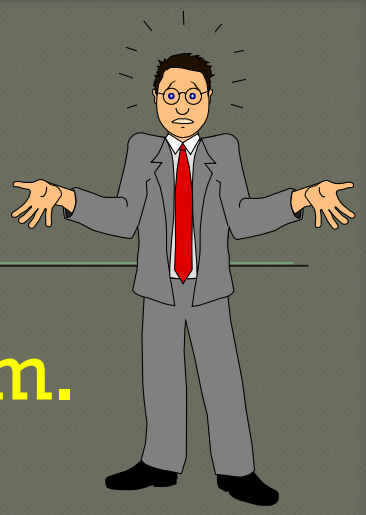
Adverse drug events (ADE):

- Injury resulting from the medical use of a drug.
- Includes Medication Error & ADR

- **Medication error:** An injury resulting from an error in preparing, procuring, prescribing, dispensing, administering, or monitoring.

- **Adverse drug reaction (ADR):** An injury resulting from the medical use of a drug where no error is involved.

Why are ADRs a problem?



ADRs are a common clinical problem.

- Causes adverse consequences to patients…
- From mere inconvenience to death and
- Have very high incidence in clinical practice

How common are ADRs?

For marketed drugs in USA

- Occur in 5% of all hospital admissions
- 10-20% of hospital inpatients
- About 25% in general practice
- Significant cause of death (0.5-0.9%)

- In the UK Non Steroidal Anti-Inflammatory Drug (NSAID) use alone accounts for[1]
  - 65,000 emergency admissions/year
  - 12,000 ulcer bleeding episodes/year
  - 2,000 deaths/year

[1] *Blower et al. Emergency admissions for upper gastrointestinal disease and their relation to NSAID use. Aliment Pharmacol Ther 1997; 11: 283-291*

ADRs

Consequences of ADRs:

- Adversely affects patients' quality of life
- Complicate drug therapy
- Decrease compliance and delay cure
- Increase cost of patient care
- Cause patients to lose confidence in their doctors
- May mimic disease, resulting in unnecessary investigations and delay in treatment

ADRs

ADRs are usually classified depending on

- Onset
- Severity
- Type

ADR: Onset of event:

- **Acute**
  - Within 60 minutes
- Sub-acute
  - 1 to 24 hours
- Latent
  - > 2 days

ADR: Severity of event:

Mild

- Do not require an antidote, therapy, or prolongation of hospitalization
- Commonly known as *side-effects*

Moderate

- Require a change in, but not necessarily cessation of the drug and may prolong hospitalization or require special treatment

ADR: Severity of event:

Severe

- Are potentially life threatening, requiring discontinuation of the drug and specific treatment of the adverse reaction

Lethal

- Directly or indirectly contributes to the patient's death

FDA: Serious ADR

- Result in death
- Life-threatening
- Require hospitalization
- Prolong hospitalization
- Cause disability
- Cause congenital anomalies
- Require intervention to prevent permanent injury

ADRs: Types of event

2 main types:

- Type A (**A**ugmented)
- Type B (**B**izarre)

3 other sub-types:

Type C, D & E

ADRs

Type A (known pharmacological adverse drug reactions)

- Type A reactions represent an **A**ugmentation of the pharmacological actions of a drug
- Predictable & dose-dependent

Type A

- Readily reversible on reducing the dose or withdrawing the drug.
- Commonest type of ADRs (accounting for over 80% of all ADRs)
- Not usually life threatening.

ADRs

Type A adverse reactions:

Are of 2 types:

A) Extension of primary effect
B) Secondary effect

A) Extension of primary effect:

- Effects due to extension of the **primary pharmacological actions** of the drug
- Augmentation of the drug's therapeutic actions

Example: Bradycardia with Propranolol
(due to effect on desirable beta1 blocking effect)

B) Secondary effect

- Effects due to the **secondary pharmacology** of the drug
- The action different from the drug's therapeutic actions
- The action still rationalisable from the known pharmacology of the drug

- Example: Bronchospasm with propranolol (due to effect on undesirable beta2 blocking effect)

ADRs

Thus, for propranolol:

- Bradycardia is primary pharmacological adverse effects
- Bronchospasm is a secondary pharmacological adverse effect.

- *More emphasis is now placed on the secondary pharmacology of new drugs during preclinical evaluation to anticipate problems that might arise once the drug is given to humans.*

ADRs

Type B adverse reactions: (unknown pharmacological adverse drug reactions)

- These are **Bizarre**
- Not predictable i.e., cannot be predicted from the known pharmacology of the drug.
- Not dose dependent
- Can't be readily reversed
- Less common but often serious
- Life threatening

ADRs

Type B ADRs may be:

1) Idiosyncrasy
2) Drug Allergy or Hypersensitivity

ADRs

Idiosyncrasy: (Pharmacogenetics)

- Inherent qualitative abnormal response to a drug
- Due to genetic abnormality, mainly due to deficiency of enzymes in the body
- Also may be due to abnormal receptor activity
- Incidence:
- Happens to very small population
- Rare but serious

ADRs

Idiosyncrasy due to enzyme abnormality

Hemolysis with primaquine

if glucose 6-phosphate dehydrogenase (G6PD) enzyme deficiency in any person

⇓

If primaquine given

⇓

Hemolysis leading to hemolytic anemia

ADRs

Idiosyncrasy due to receptor abnormality

- Malignant hyperthermia with general anesthetics (Halothane)

- Sudden huge rise in IC calcium concentration
- Increase in muscle contraction
- Increase in metabolic activities
- Rise of body temperature

ADRs

Drug allergy

Also known as hypersensitive reaction

- Due to antigen-antibody interactions
- 1st dose acts as an antigen
- Antibody is produced against the antigen in the body
- Subsequent dose causes antigen-antibody reaction

e.g. Penicillin induced anaphylaxis

(Type 1 hypersensitivity reaction)