ADVERSE DRUG REACTIONS

• Harmful or seriously unpleasant effects occurring at doses intended for therapeutic (prophylactic or diagnostic) effect & which call for reduction of dose or withdrawal of the drug or indicate caution in future use of the same drug.

• PREDICTABLE (TYPE A)

• UNPREDICTABLE (TYPE B)
Side effects

- Unwanted, unavoidable
- Occur at therapeutic doses
- Can be predicted from pharmacological profile.
- Decrease in dose generally ameliorates the symptoms
- Based on same action as therapeutic effect-
  - e.g. atropine in preanesthetic medication
- On different facet of action-
  - Antihistaminics produce sedation
S/Es

- Therapeutic in one context, S/E in another-
- Codeine for cough produces constipation, can be used as a therapeutic effect in traveller diarrhoea.
Secondary Effects

• Indirect consequences of a primary drug action.
• Opportunistic infections due to broad spectrum of antibiotic use, due to alteration of normal flora.
Toxicity

Direct action of the drug, at high dose, damaging the cells – e.g.

• Liver damage from Paracetamol overdose.

Intolerance

Low threshold to the normal pharmacodynamic action of the drug.
Appearance of characteristic toxic effects of a drug in an individual at therapeutic doses.
Idiosyncrasy

• Genetically determined abnormal reactivity to a chemical e.g.

• Barbiturates- excitement & mental confusion in some.
Classification of ADRs

• Type A – Augmented
• Type B - Bizarre
• Type C – Chronic
• Type D – Delayed
• Type E – Ending of use
Type A

- Occurs in everyone if enough of dose is given.
- Due to excess of normal, predictable, dose related pharmacodynamic effects
- Common
  - e.g. postural hypotension due to alpha blockers
  - Hypoglycemia due to insulin
Type B

- In some people
- Not as a part of normal pharmacology of drug
- Not dose related
- Unpredictable for the individual
- Idiosyncrasy, drug allergy
Type C

- Long term exposure
- Analgesic nephropathy

Type D

- Delayed effects following prolonged exposure
- e.g. carcinogenesis or
- short term exposure at critical time
- e.g. teratogenesis
Type E

- Abrupt discontinuation of chronic therapy
- e.g. adrenal steroid
Drug abuse

• Drugs are abused (used in the ways that are not medically approved) because they cause strong feelings of euphoria or altered perception.

• Repetitive exposure induces widespread adaptive changes in the brain. As a consequence drug use may become compulsive: Addiction.
Drug Addiction

- Compulsive drug use characterised by the overwhelming involvement with the use of a drug.
- Amphetamines, cocaine, cannabis, LSD.
Drug Habituation

• Less intensive involvement with the drug.
• Withdrawl leads to mild discomfort.
• Tea, coffee, tobacco, social drinking
Teratogenecity

• Capacity of a drug to cause foetal abnormalities when given in a pregnant mother.
• Drug can affect the foetus at three stages-
  • **Fertilization & Implantation** – Conception (17 days) - failure of pregnancy
  • **Organogenesis** – (18-55 days of gestation)
    Most vulnerable
    Deformitis
  • **Growth and development**- 56 days onwards
    Developmental and functional abnormalities.
    ACE inhibitors – hypoplasia of organs
    NSAIDs- premature closure of ductus arteriosus.
- AVOID IF POSSIBLE
- CATEGORIES – A, B, C, D, X
- A, B, C, D – LOOK FOR RISK- BENEFIT RATIO.
- X- POTENTIAL RISK OUTWEIGHS THE BENEFIT.
- CARCINOGENICITY
Drug Induced Reactions

• **IATROGENIC** (physician Induced)
  • Functional disturbances caused by the drug which persist even after the offending drug has been withdrawn & largely eliminated.
  • e.g. peptic ulcer by salicylates & corticosteroids.
  • Parkinsonism by phenothizines
  • Hepatitis by isoniazid
Drug Allergy

- Immunologically mediated reaction producing stereotype symptoms which are unrelated to pharmacodynamic profile of the drug and are largely independent of the dosage.
- In a small proportion
- Prior exposure, sensitization is needed.
- A latent period of 1-2 wks after the first exposure.
- AG, AB production.
TYPES OF ALLERGIC REACTIONS

A. HUMORAL
B. CELL MEDIATED

HUMORAL

TYPE- 1. ANAPHYLACTIC REACTION
TYPE – II. CYTOLYTIC REACTION
TYPE- III. ARTHRUS REACTION

CELL-MEDIATED

TYPE – IV. DELAYED HYPERSENSITIVITY
TYPE 1

- IgE antibodies are produced, get fixed to mast cells.
- On exposure to the drug,
- AG: AB reaction on mast cell surface
- Release of mediators-
  - Histamine
  - 5-HT
  - LT
  - PGs, PAF
Type II

- Cytolytic Reactions
- After the drug & component of a specific tissue cell act as AG,
- IgG & IgM produced
- On reexposure AG:AB reaction on surface of these cells
- Complement activated
- CYTOLYSIS
TYPE- III

- ARTHRUS RECTIONS
- CIRCULATING AB - IgG
- Ag:Ab complexes bind complement
- Precipitation on vascular endothelium
- Destructive inflammatory response
- Rashes, serum sickness (fever, arthralgia, lymphadenopathy)
- PAN
- Steven-Johnson Syndrome (erythema multiforme, arthritis, nephritis, myocarditis, mental symptoms)
DELAYED H/S

- > 12 HRS TO DEVELOP
- Through sensitized T-lymphocytes carrying receptors for antigen
- On contact with Antigen-
- Lymphokines
- Attract granulocytes
- Inflammatory response
- Contact dermatitis, rashes, fever, photosensitization
TREATMENT OF DRUG ALLERGY

• Stop the drug.
• For Type 1 - Antihistaminics
• For Anaphylactic shock or Angiodema of larynx:
  • Recline the patient
  • Give oxygen at high flow rate
  • Cardiopulmonary resuscitation
  • Inj. Adrenaline 0.5 mg (0.5 ml of 1 in 1000).
  • Antihistaminic, Chlorpheniramine 10-20mg i/m or slow i/v.
  • I/V glucocorticoid, Hydrocortisone 100-200 mg.
PHOTOSENSITIVITY

• Drug induced sensitization of skin to uv radiation

• PHOTOTOXIC:
  • Drug accumulates in the skin
  • Absorbs light
  • Undergoes a photochemical reaction
  • Photobiological reaction
  • Local tissue damage i.e. erythema, edema
    Followed by Hyperpigmentation and desquamation
• Drugs-
nalidixic acid, fluoroquinolones, sulfones sulfonamides, phenothiazines, thiazides, amiodarone.
PHOTOALLERGIC

• Drug induces CMI
• On exposure to sunlight – papular or eczematous contact dermatitis
• Drugs – sulphonamide, sulphonylureas, Griseofulvin, chloroquine
Drug Dependence

• A state arising from repeated, periodic or continuous administration of a drug, that results in harm to the individual and sometimes to the society.

• The subject feels a desire, need, or compulsion to continue using the drug and feels if abruptly deprived of it (abstinence or withdrawal syn).

• Psychological dependence

• Physical dependence
Psychological dependence

- Person believes that optimal state of wellbeing is achieved only through the actions of the drug.
- Liking – compulsive drug use.
- Desire – craving
- **Reinforcement** - Ability of the drug to produce effects that make the user wish to take it again.
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)
• Drugs - opioids, barbiturates, alcohol, benzodiazepines.
• Stimulant drugs – amphetamines, cocaine.
PHARMACOVIGILANCE

• Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.
ADR MONITORING SYSTEMS

• Collecting a new information from reliable scientific sources.
• Classifying & analyzing above information
• Circulating its contents as well as any action taken on specific drug to all health sectors.
ADR REPORTING

4 ELEMENTS-
• PATIENT
• A DRUG
• AN ADVERSE DRUG REACTION
• REPORTER OF THE REPORT
METHODS OF COLLECTING DATA ON ADVERSE DRUG REACTION

• EXPERIMENTAL STUDIES – FORMAL THERAPEUTIC TRIALS OF PHASES 1-3. DETECT AN INCIDENCE OF UP TO ABOUT 1:200.
• OBSERVATIONAL STUDIES - Where the drug is observed, epidemiologically under conditions of normal use in the community i.e. pharmacoepidemiology. Observational cohort & case – control study.
• Spontaneous/ voluntary reporting
• Prescription event monitoring
• Record linkage system
PHARMACOVIGILANCE CENTERS

• NATIONAL PHARMACOVIGILANCE CENTRE
  CENTRAL DRUG STANDARD CONTROL ORGANISATION (CDSCO)

  2 ZONAL CENTERS
  KEM HOSPITAL, MUMBAI
  AIIMS, N.DELHI

  5 REGIONAL CENTERS
  KOLKATA, MUMBAI, NAGPUR, DELHI, JIPMER

  24 PERIPHERAL
  ORISSA, KOLKATA, GUWAHATI, GOA,
  GUJRAT, AHEMDABAD....