

# ADVERSE DRUG REACTIONS



# **Lesson plan**

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

# What is ADRs?

Cur'd yesterday of my disease  
I died last night of my physician.

## WHO Definition

Any response to a drug which is noxious & unintended & which occurs at doses in man for prophylaxis, diagnosis or treatment.



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# History about ADRs

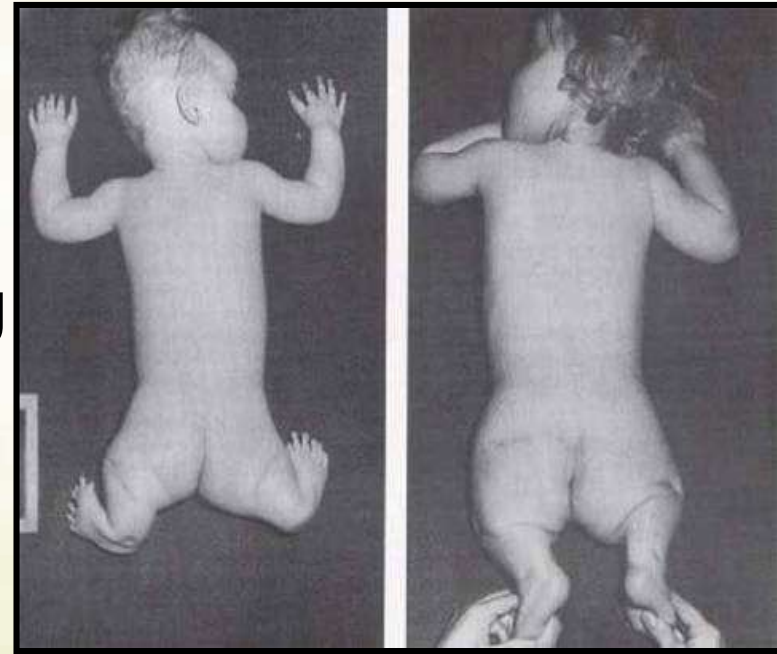
1922 : JAUNDICE associated with the use of SALVARSAN, an organic arsenical used in the treatment of Syphilis.

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.

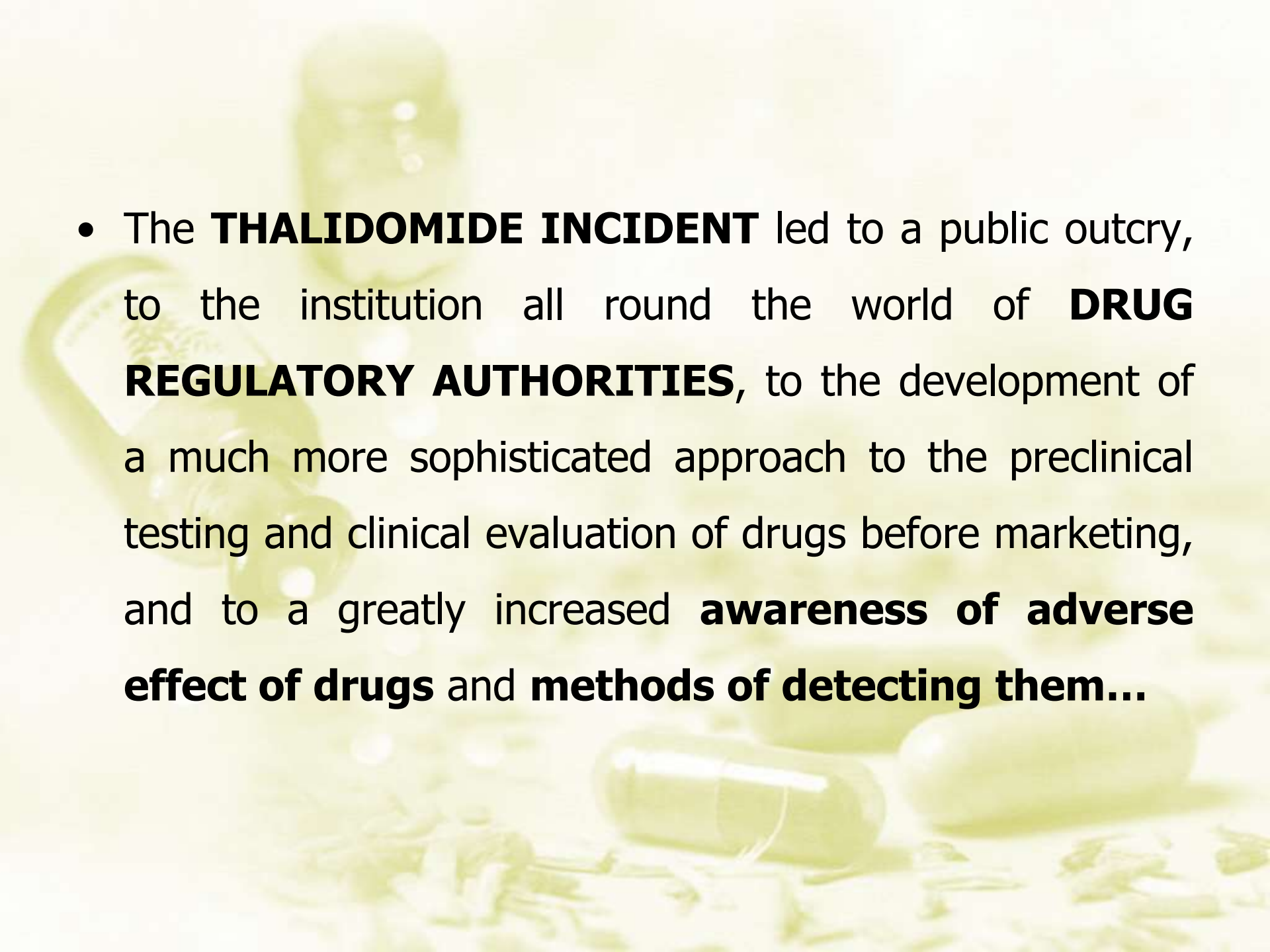


- 1958: Thalidomide marketed in West Germany as a non barbiturate hypnotic & for morning sickness during pregnancy based on animal toxicity report.



1959-61 thalidomide disaster  
(4000-100000 case)

- 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...**

# Classification of ADRs

- Depending on....
- **Onset of event:** Acute (<60 minutes), Sub-acute (1-24 hrs) and Latent (>2 days)
- **Type of reaction: (Wills and brown)**  
Type A (Augmented), B (Bizarre), C (Chronic),  
D (Delayed), E (End of treatment)
- **Severity:** Minor, Moderate, Severe, Lethal ADRs
- **Others:** Side effects, Secondary effects, Toxic effects, Intolerance, Idiosyncrasy, Drug allergy, Mutagenicity, Photosensitivity, Drug Dependence, Drug Withdrawal Reactions, Teratogenicity, Carcinogenicity, Drug induced disease (Iatrogenic).

# 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
- common
- Skilled management reduces their incidence.

## E.g.

- Anticoagulants → Bleeding
- Beta blockers → Bradycardia
- Nitrates → Headache
- Prazosin → Postural hypotension



# Type B (Bizarre) reactions

- Predictable where the mechanism is known, otherwise unpredictable for the individual, although the incidence may be known.
- Dose independent, rare
- Host dependent factors important in predisposition
- unwanted effects due to inherited abnormalities (idiosyncrasy) and immunological processes (drug allergy).
- These account for most drug fatalities.

**E.g.** Penicillin → Anaphylaxis,

Anticonvulsant → Hypersensitivity

## **Type C ( Chronic)**

- Reactions due to long time exposure.
- e.g. Analgesic neuropathy

Dyskinesia with levodopa

# Type D (Delayed) reactions

- Occur due to prolonged exposure.
- Can be due to accumulation.

**E.g.**

Carcinogenesis, or short term exposure at a critical time e.g.teratogenesis.

# Type E (End of use) reactions

- Occur on withdrawal especially when drug is stopped abruptly

## E.g.

- Phenytoin withdrawal → Seizures
- Steroid withdrawal → Adrenocortical insufficiency.
- opioid causing the withdrawal syndrome.



# Types of ADRs.....

Type	Type of effect	characteristics	example
A	Augmented	Dose dependent predicted from the known pharmacology of the drug	Hypoglycaemia-insulin
B	Bizarre	Unpredictable Dose independent Rare,fatal	Anaphylaxis to penicillin
C	Chronic	Prolong treatment	Analgesic neuropathy
D	Delayed	After years of treatment	Antipsycotic –turdive dyskinesia
E	End of use	Withdrawal effect	GC withdrawal→ adrenocortical

# 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 at least 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, occur at therapeutic doses
- Predicted from the pharmacological profile of a drug
- Known to occur in a given percentage of drug recipients
- **E.g.**  
Atropine → dryness of mouth  
Promethazine (anti-allergic) → sedation  
Codeine (anti-tussive) → constipation → Used in Traveller's diarrhoea

# 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.
- Sulfonamides used as antibacterials were found to produce hypoglycemia and acidosis as side effects → development of Hypoglycemic Sulfonylureas...



## ➤ **Untoward effect –**

- Slight more serious effect than side effect produced with therapeutic dose.
- Seriously unpleasant.
- Harmful.
- e.g. Superinfection produced by broad spectrum antibiotic, vomiting by morphine in postoperative patients, hypokalaemia by thiazide diuretics.

## » Toxic effects

### • Predictable

- → Dose dependent
- → Rebound response
- Excess pharmacological effect in high dose.
- These are known.  
Detected by  
pharmacologist

### Unpredictable

- Allergy
- Idiosyncrasy
- Not found in clinical trial.
- Pharmacologist may  
not be able to  
detect  
this during study  
of drug development

# **Predictable toxic effects**

➤ Dose dependent adverse effect may be –

- **Direct damaging effect to tissue** e.g.

Paracetamol overdose leads to hepatotoxicity,  
Aminoglycoside (Gentamicin) causes  
nephrotoxicity.

➤ **Rebound response** – ( due to R-upregulation)  
abrupt withdrawal after chronic use.  
e.g. propranolol stoppage leads to precipitation of  
MI, Glucocorticoid withdrawal leads to acute  
adrenal insufficiency. morphine – due to R  
supersensitivity.

# Pharmacologically Predictable ADRs

Type	Example	Toxicity	Mechanism
Pharmaceutical	Phenytoin	Phenytoin toxicity (ataxia, nystagmus, etc)	Increase in bioavailability as a result of a change in formulation
Pharmacokinetic (can involve absorption, distribution, metabolism and excretion)	Digoxin	Digoxin toxicity (nausea, arrhythmias, etc)	Decreased elimination if renal function is impaired
Pharmacodynamic	Indomethacin	Left ventricular failure	Water and sodium retention
Genetic	Nortriptyline	Confusion	Reduced hepatic elimination as a result of a deficiency of CYP2D6
Drug-drug interactions (can involve any of the above processes)	Lithium- nonsteroidal anti- inflammatory drugs	Lithium toxicity	Inhibition of excretion of lithium



- **Excess pharmacological effect:** Result of excessive pharmacological action of the drug due to over dosage or prolonged use.
- e.g. Excess insulin-hypoglycemia even death from hypoglycemic shock  
Antihypertensive - hypotension  
Anticoagulant-severe bleeding.

## Warfarin

- Number of users UK:  
**600,000**
- Dose (mg) range per day:  
**0.5-20**
- Fold variability in dose:  
**40**
- Major bleeding rate per 100-person years:  
**2.6**
- Ranking in ADR list:  
**3**



Approved for human use in 1954



# Unpredictable toxic effects

- **Dose independent**
- Less than therapeutic dose may lead to toxic effect

# Idiosyncrasy -

- unusual response to a drug due to genetic abnormality.
- Drug interacts with some unique feature of the individual, not found in majority subjects, and produces the uncharacteristic reaction.
- E.g.
  - **Isoniazid:** *N*-Acetylation affects the metabolism of isoniazid
  - **Slow *N*-Acetylation:** Isoniazid is more likely to cause peripheral neuritis.
  - **Fast *N*-Acetylation:** cause hepatotoxicity in this group.

- **Succinylcholine** can produce **apnea** in people with abnormal serum cholinesterase. Their cholinesterase is incapable of degrading the succinylcholine, thus it builds up and depolarization blockade results.
  - **Primaquine, Sulfonamides** induce acute hemolytic anemia in patients with **Glucose-6-Phosphate Dehydrogenase deficiency**.
- They have an inability to regenerate NADPH in RBC. G-6-p deficiency is most prevalent in blacks & Semitics. It is rare in Caucasians & Asians.



# Drug allergy

- Acquired, altered reaction of the body to drug.
- Immunologically mediated reaction.
- occur even with much smaller doses
- Also called Drug hypersensitivity
- Not genetic, not occurred in all
- Occurs on reexposure
- E.g. penicillin → 1<sup>st</sup> time → stimulate antibody  
→ Ag-Ab reaction → allergy
- Chief organ: Skin, respiratory tract, GIT, Blood & blood vessels

Type of reaction	Time before clinical sign	Characteristics	Example
Anaphylactic (Immediate IgE-mediated anaphylaxis)	< 30 min	IgE binds to mast cell or basophil, causes degranulation of mast cell & basophil & release of reactive substances. histamine	<b>Penicillin anaphylaxis</b>
Cytotoxic (Antibody-Dependent Cellular Cytotoxicity)	5 – 12 hr	Antigen causes formation of IgG or IgM antibodies to bind that . Drug forms an antigenic complex with the surface of the cell and combination with antibody activates complement system causing cell destruction.	<b>Hemolytic anemia:</b> Penicillin or Methyldopa <b>Thrombocytopenia</b> : Quinidine <b>SLE:</b> Hydralazine or Procainamide.
Immune complex mediated	8-10	antigen antibody form complexes that causes inflammation	<b>Steven-Johnson Syn Serum Sicknessdrome</b>
Cell mediated allergy(delayed type)	24 to 48 hrs	Antigen specific receptors develop on T-lymphocytes. Subsequent administration leads to local or tissue allergy.	Contact dermatitis Rejection of transplanted tissue

## **Certain tissues which are vulnerable**

### ➤ **Hemopoietic system & bone marrow –**

- Quinine, Rifampicin, Sulfonamide, Thiazide – drug allergy (type II reaction) – Thrombocytopenia.
- Carbamazepine, Sulfonamide, carbimazole, clozapine (fatal neutropenia) - drug allergy (type II reaction) – Granulocytopenia.
- Chloramphenicol (idiosyncrasy) -Aplastic anemia.
- Anti cancer, cytotoxic drugs -direct bone marrow depression
- primaquine, quinine, chloroquine, dapson, sulfonamide(due to idiosyncrasy) Methyldopa used in pregnancy – Hemolytic anemia.

## ➤ **Liver damage/ Hepatic injury –**

- Chloroform, Halothane, Enflurane – when given in repeated dose – hepatotoxicity – jaundice (so, before anesthesia H/O jaundice taken).
- Chlorpromazine, Flucloxacillin, OCP –(type II) cholestatic jaundice( causes edematous bile canaliculi-stasis of bile)
- INH, Rifampicin, Methyldopa – hepatocellular necrosis – jaundice (cause is unknown).
- Methotrexate, Alcohol – cirrhosis of liver.
- Paracetamol overdose (8 – 10 gm of paracetamol in 10 – 24 hours if taken) – toxic metabolite (Epoxide) – Hepatocellular necrosis.
- Minocycline (newer tetracycline) – Chronic Active Hepatitis.

➤ **Renal damage –**

- Phenylbutazone, Sulfonamide, Hydralazine – damage to glomerular membrane – Glomerulonephritis.
- Aminoglycoside (Gentamicin), Amphotericin (antifungal), High dose paracetamol, Cefalothin – Acute tubular necrosis.
- NSAID, Lithium, Penicillamine – long term use in rheumatoid arthritis – Acute interstitial nephritis.
- ACEI – Renal vascular damage.



# Intolerance

- 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

# Tolerance –

- ↓ pharmacological effect on repeated administration of the drug.
- **Pharmacokinetic Tolerance:** ↑ the enzymes responsible for metabolizing the drug.  
e.g. Phenobarbitone induces metabolism of its own by increasing its own metabolic enzyme.
- **Pharmacodynamic Tolerance:** Cellular tolerance, due to down-regulation of receptors.
- **Depletion of stores** e.g. Amphetamine

# **Tachyphylaxis:**

- When responsiveness diminishes rapidly after administration of a drug, the response is said to be subject to tachyphylaxis.
- Tyramine can cause depletion of all NE stores if you use it long enough, resulting in tachyphylaxis.

# 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, hyper pigmentation)
  - E.g.** Tetracyclines (esp. Demeclocycline), and Tar products, Nalidixic acid, Fluoroquinolones, Sulfones etc
- **Photoallergic:** 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, Sulfonyleureas, 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.

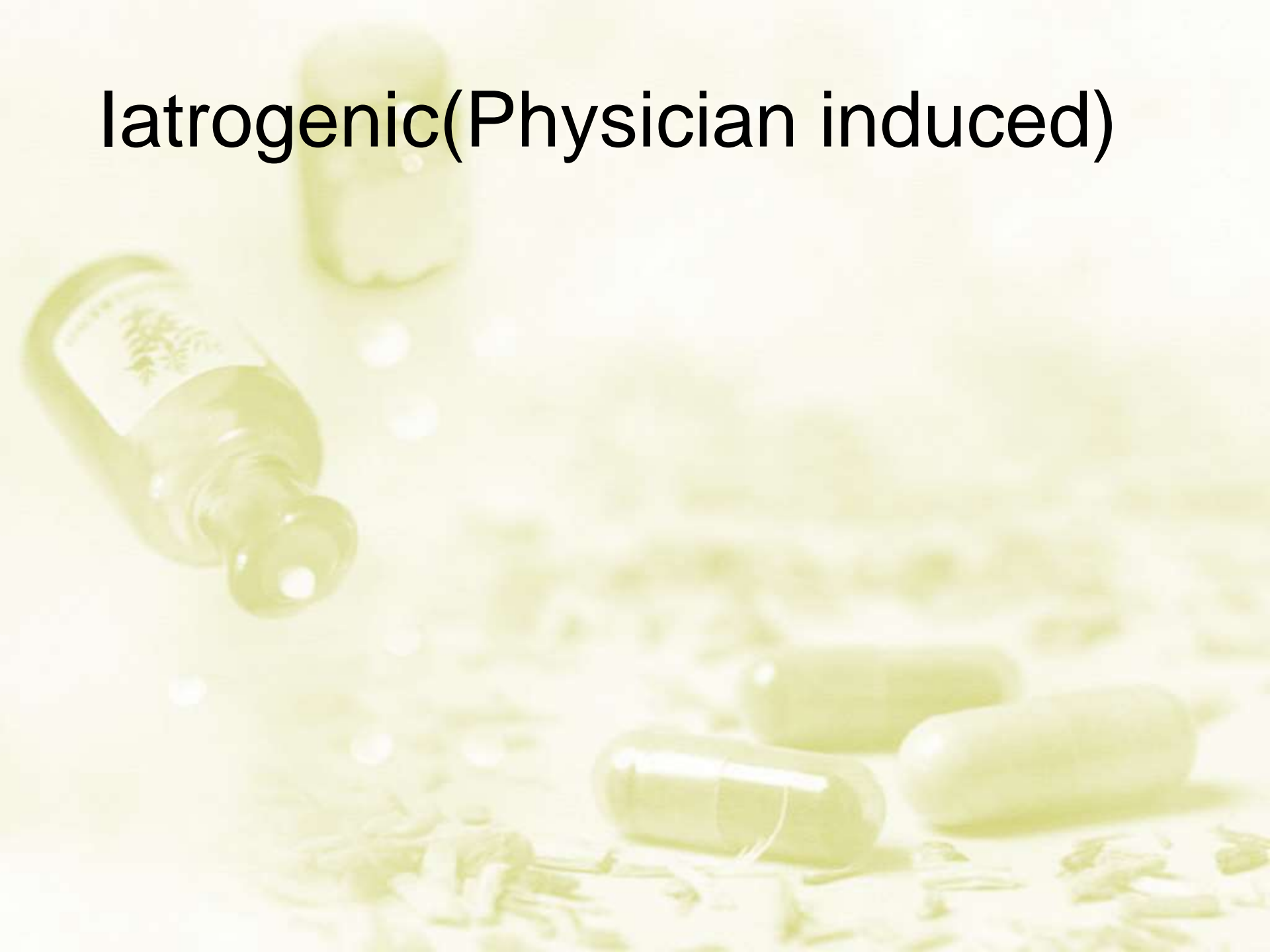
# Mutagenecity and Carcinogenicity

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

e.g.

- Estrogen- Endometrial carcinoma.
- OCP- Ca cervix, breast Ca
- Iron S/C or I/M – blackening of area – increase incidence of sarcoma (cause is unknown).
- Anticancer drug.

# Iatrogenic(Physician induced)



# 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



## FDA Pharmaceutical Pregnancy Categories

Category A	Adequate and well-controlled human studies demonstrate no risk.
Category B	Animal studies demonstrate no risk, but no human studies have been performed. OR Animal studies demonstrate a risk, but human studies have demonstrated no risk.
Category C	Animal studies demonstrate a risk, but no human studies have been performed. Potential benefits may outweigh the risks.
Category D	Human studies demonstrate a risk. Potential benefits may outweigh the risks.
Category X	Animal or human studies demonstrate a risk. The risks outweigh the potential benefits.



# Drugs known to be teratogenic

- Anticancer drugs – Methotrexate – multiple deformity.
- Steroid – cleft palate and other.
- Oral anticoagulants – bony abnormality (Hypoplastic nasal structures), optic atrophy, mental retardation.
- Oral hypoglycemic agents - multiple deformity.
- Androgenic hormone – virilization, hermaphrodite, lid retraction.
- Tetracycline – inhibit bony growth.

# Cont'd

- Trimethoprim – cleft palate.
- Phenytoin, carbamazepine, valproate -  
Malformation of fingers, cleft palate, neural tube defect (spina bifida)
- Diethylstilbestrol - Oral contraceptive is no longer used because it causes reproductive cancers in daughters born to mothers taking the drug.
- Androgen- virulization of female fetus
- Aminoglycosides, Chloroquine – Deafness.

# **Teratogens in first trimester**

- Phenytoin, carbamazepine, valproate - neural tube defects (spina bifida)
- lithium – cardiac malformations
- Warfarin - bone deformation, chondrodysplasia, CNS defects
- Heparin (demineralization of bone in mother – switch to LMW)
- Retinoids-def. CNS, heart, limbs, liver
- oncologic drugs (fluorouracil, methotrexate, cyclophosphamide, busulfan)

# Drugs cannot be given in last trimester

- Antithyroid drugs: Hypothyroidism in neonates
- Streptomycin - Ototoxicity
- Morphine: Respiratory depression
- Chloroquine: Retinopathy of fetus
- Aspirin: delay labour pain.

# Individual variation in response to drug

- Variation due to age, sex, body weight, surface area, nutrition, alcoholic, cigarette smoking, pregnancy, genetic factor, environment, and pathological condition.
- 4 general mechanism:
  - A) **Alteration in concentration of drug that reaches the receptors** –
    - rate of absorption of a drug
    - distributing it through body compartments
    - clearing the drug from the blood.



- **B) Variation in concentration of an endogenous receptor ligand –**
  - variability in responses to pharmacological antagonist.
  - propranolol will markedly slow the HR of a patient whose endogenous catecholamine are elevated (as in pheochromocytoma), but will not affect the resting HR of a well trained marathon runner.
- **C) Alteration in number or function of receptor –**  $\uparrow$  or  $\downarrow$  in number or alteration in efficiency of coupling of receptor to distal effector mechanism – change in responsiveness.

e.g. Thyroid hormone increase number of  $\beta$  receptor in heart and increase sensitivity of cardiac muscle to catecholamine – tachycardia of thyrotoxicosis.

- **D) Changes in components of response distal to the receptor** – Response depend on the functional integrity of biochemical process in the responding cell and physiological regulation by interacting organ system.

## Cont'd...

- Medicines are supposed to save lives

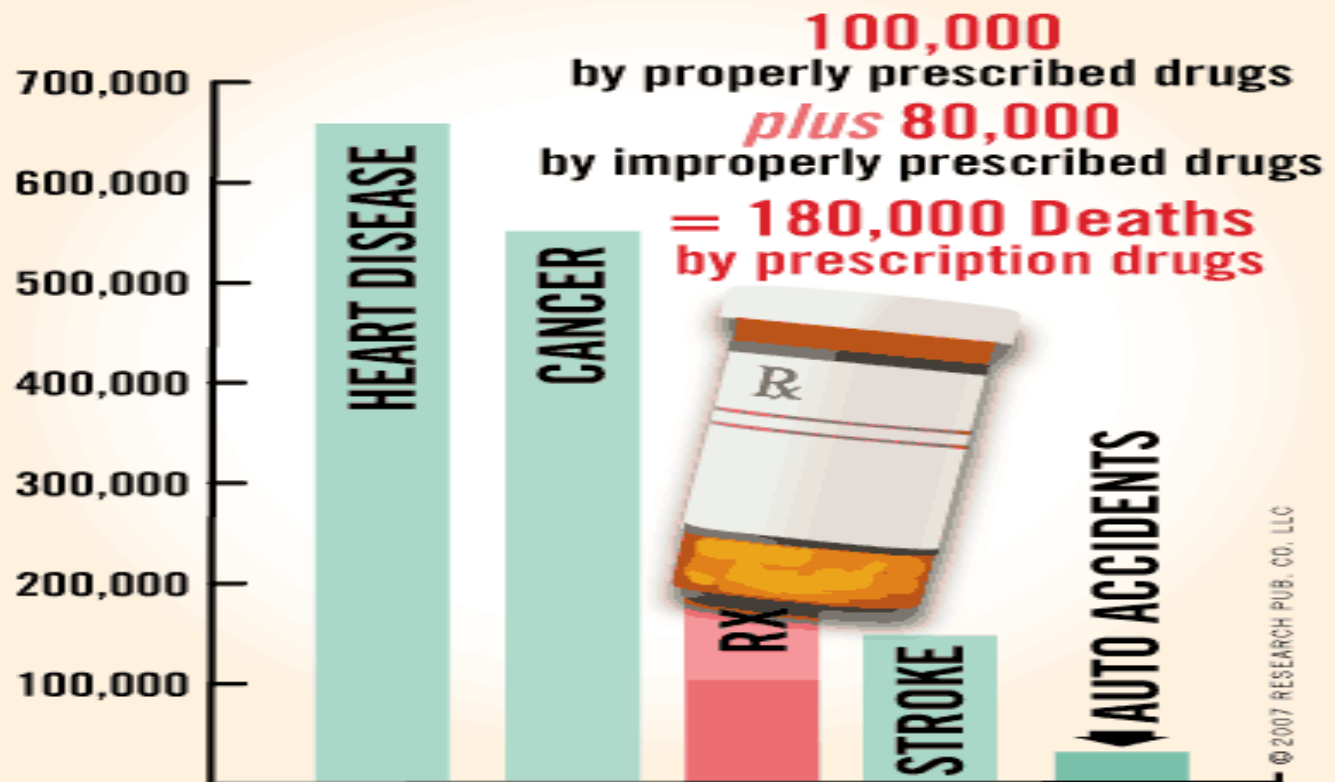
Dying from a disease is sometimes unavoidable;  
dying from a medicine is unacceptable. Lepakhin

V. Geneva 2005

# Cont'd...

- Among the Leading cause of death-

## Leading Causes of Death in U.S.



# Cont'd...

## ➤ ADRs are expensive !!

Cost of ADRs in the US:

Cost of drug related morbidity and mortality exceeded \$177.4 billion in 2000 (*Ernst FR & Grizzle AJ, 2001: J American Pharm. Assoc*)

ADR related cost to the country exceeds the cost of the medications themselves.




# Cont'd...

## ➤ Ethics:

To know of something that is harmful to another person who does not know, and not telling, is unethical.

➤ No medicine is risk free,  
Vigilant assessment of the  
risks and benefits of medicine  
promote safety.



***"No drug which is pharmacologically active is entirely without hazard. The hazard may be insignificant or may be acceptable in relation to the drug's therapeutic action. Furthermore, not all hazards can be known before a drug is marketed:..."***

*Report by the  
Committee on the Safety of Drugs,  
United Kingdom, 1970*

# **Aims of knowing ADRs**

- To improve patient care and safety
- To improve public health and safety
- To contribute to the assessment of benefit, harm, effectiveness and risk of medicine.

# Adverse drug reactions[ADRs] monitoring

## ➤ Monitoring centre:

- WHO collaborating centre for international drug monitoring, Uppsala Monitoring Centre, Sweden.

- Established in 1968.

## ➤ In Bangladesh:

- Directorate General of Drug Administration.

105-106, Motijheel Commercial Area, Dhaka-1000,  
Bangladesh.

# Cont'd...

## ➤ Monitoring of ADRs:

- Clinical trial monitoring
- Prescription event monitoring
- Yellow card system

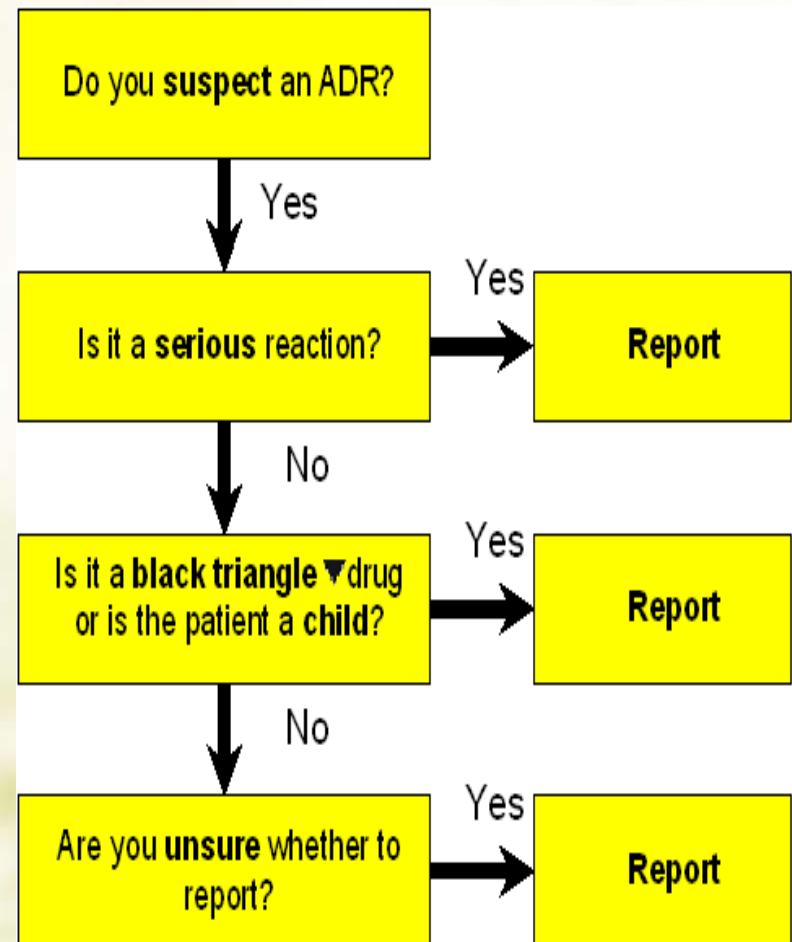
# ADRs reporting:

## ➤ Who to report:

- All health care professionals.

## ➤ What to report:

- Apparent ADRs previously unknown to the reporters
- Serious ADRs
- **All suspected ADRs** to new drugs
- Cases of suspected dependence





# Cont'd...

## ➤ How to report:

- ADRs form
- Assessment tool: Naranjo scale

## ➤ Where to report:

- National body (Directorate General of Drug Administration. 105-106, Motijheel Commercial Area Dhaka-1000, Bangladesh






**Safety comes first**

La seguridad es lo primero

La sécurité d'abord

A still life photograph of various medical supplies. In the foreground, a small glass vial with a white label and a black cap lies on its side. To its right, a larger plastic bottle with a white cap is partially visible. Several white, oval-shaped capsules are scattered on the surface. The background is a light, textured surface, possibly a tablecloth or paper. The overall lighting is soft and even.

Thank you.....