# PHARMACOVIGILANCE & ADVERSE DRUG REACTIONS

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# ADVERSE DRUG REACTION

- Harmful or unpleasant reaction

**which is:**

- ✓ **Due to a drug**
- ✓ **At doses normally used in man**
- ✓ **May requires treatment or decrease in dose or**
- ✓ **Caution in the future use of the same drug**

# SIDE EFFECTS

- UNWANTED UNAVOIDABLE PHARMACOLOGICAL EFFECTS OF THE DRUG.
- OCCUR AT THERAPEUTIC DOSES.
- PREDICTABLE

**EXAMPLES.**

H1 ANTI-HISTAMINICS: SEDATION

ASPIRIN: ANTITHROMBOTIC EFFECT

**An effect may be therapeutic in one context but side effect in another context**

- INCIDENCE OF ADR MORE
  - POLYPHARMACY
  - ELDERLY
  - CHILDREN
  - PATIENT WITH MULTIPLE DISEASES
  - PREGNANCY
  - MALNOURISHED
  - IMMUNOSUPPRESSION
  - DRUG ABUSERS AND ADDICTS
- DEVELOP
  - IMMEDIATELY

  OR
  - PROLONGED MEDICATION

  OR
  - AFTER STOPPING

# GRADING OF SEVERITY OF ADVERSE DRUG REACTIONS

- **MINOR** : NO THERAPY IS REQUIRED.

- **MODERATE:** REQUIRES CHANGE IN DRUG THERAPY, SPECIFIC TREATMENT OR PROLONGS HOSPITAL STAY.

- **SEVERE:** POTENTIALLY LIFE-THREATENING, CAUSES PERMANENT DAMAGE OR REQUIRES INTENSIVE MEDICAL TREATMENT.

- **LETHAL** : DIRECTLY OR INDIRECTLY CONTRIBUTES TO DEATH OF THE PATIENT.

# CLASSIFICATIONS OF ADR

- **A (AUGMENTED)**
- **B (BIZARRE)**
- **C (CONTINUOUS)**
- **D (DELAYED)**
- **E (ENDING USE)**
- **F (FAILURE OF RESPONSE)**

**Broadly**

Type- A (Predictable)- Based on pharmacological properties

Type- B (Non-predictable) – Based on Immunological response and genetic makeup of person

# TYPE A- AUGMENTED

- THESE ARE BASED ON THE PHARMACOLOGICAL ACTIONS OF THE DRUG SO CAN BE PREDICTED.
- THEY ARE COMMON AND ACCOUNT FOR 75% OF ADRS
- DOSE-RELATED AND PREVENTABLE MOSTLY REVERSIBLE.

EXAMPLES:-

- ANTICOAGULANTS (E.G., WARFARIN, HEPARIN) – BLEEDING
- ANTI-HYPERTENSIVES (E.G.. A1-ANTAGONISTS) – HYPOTENSION
- ANTI-DIABETICS (E.G. INSULIN) - HYPOGLYCEMIA

**Predictable**

# TYPE B- BIZZARE

- HAVE **NO DIRECT RELATIONSHIP** TO THE DOSE OF THE DRUG OR THE PHARMACOLOGICAL ACTIONS OF THE DRUG.
- DEVELOP ON THE BASIS OF:
  - IMMUNOLOGICAL REACTION TO THE DRUG (**ALLERGY**)
  - GENETIC PREDISPOSITION (**IDIOSYNCRACY**): ABNORMAL DRUG REACTIONS.
  - **EXAMPLES**????
- MORE SERIOUS CLINICAL OUTCOMES WITH HIGHER MORTALITY AND MORBIDITY.
- MOSTLY REQUIRE IMMEDIATE WITHDRAWAL OF THE DRUG.
- UNCOMMON

**Un-predictable**

# TYPE C – CHRONIC (CONTINOUS) USE

- THEY ARE MOSTLY ASSOCIATED WITH **CUMULATIVE-LONG TERM** EXPOSURE

**EXAMPLE:-**

ANALGESIC (NSAID)– INTERSTITIAL NEPHRITIS, PAPILLARY SCLEROSIS

**Predictable**

# TYPE D – DELAYED

- THEY MANIFEST THEMSELVES WITH SIGNIFICANT DELAY
  - **TERATOGENESIS -**THALIDOMIDE – PHOCOMELIA (FLIPPER-LIKE LIMBS)
  - **MUTAGENESIS**
  - **CANCEROGENESIS**

**Predictable**

# TERATOGENICITY (TERATOS- MONSTER)

•DRUG TO CAUSE FOETAL ABNORMALITIES WHEN ADMINISTERED TO THE PREGNANT MOTHER.

•**DRUGS CAN AFFECT THE FOETUS AT 3 STAGES-**

**(I) FERTILIZATION AND IMPLANTATION**-CONCEPTION TO 17 DAYS-FAILURE OF PREGNANCY WHICH OFTEN GOES UNNOTICED.

**(II) ORGANOGENESIS-18 TO 55 DAYS** OF GESTATION MOST VULNERABLE PERIOD, DEFORMITIES ARE PRODUCED.

**(III) GROWTH AND DEVELOPMENT**-56 DAYS ONWARDS DEVELOPMENTAL AND FUNCTIONAL ABNORMALITIES CAN OCCUR,

E.G. ACE INHIBITORS(GROWTH RETARDATION) , THALIDOMIDE, WARFARIN (EYE AND HAND DEFECTS, ANTIEPILEPTIC DRUGS (CLEFT LIP/PALATE).

# MUTAGENICITY AND CARCINOGENICITY

- CAUSE GENETIC DEFECTS AND CANCER RESPECTIVELY.
- **MUTAGENICITY**: REACTIVE INTERMEDIATES WHICH AFFECT GENES AND MAY CAUSE STRUCTURAL CHANGES IN THE CHROMOSOMES
- **CARCINOGENICITY**: CERTAIN CHEMICALS CAN PROMOTE MALIGNANT CHANGE IN GENETICALLY DAMAGED CELLS, RESULTING IN CARCINOGENESIS.
- **EXAMPLES**- ANTICANCER DRUGS, RADIOISOTOPES, ESTROGENS, TOBACCO

# TYPE E – END OF USE

- DRUG WITHDRAWAL SYNDROMES AND REBOUND PHENOMENONS
  - EXAMPLE – SUDDEN WITHDRAWAL OF LONG TERM THERAPY WITH **β-BLOCKERS** CAN INDUCE REBOUND TACHYCARDIA AND HYPERTENSION

**Predictable**

# TYPE F- FAILURE OF RESPONSE (TOLERANCE)

- FAILURE OF RESPONSIVENESS TO THE USUAL DOSE OF A DRUG
- **TYPES:** 1- AQUIRED 2- CONGENITAL
- **ACQUIRED TOLERANCE:**
- IT OCCURS ON REPEATED ADMINISTRATION OF THE DRUG.
- MORE DOSES ARE NEEDED TO OBTAIN THE ORIGINAL EFFECT.
- IT IS REVERSIBLE: IT DISAPPEARS WHEN THE DRUG IS STOPPED FOR SOME TIME.
- **EXAMPLES** OF DRUGS CAUSING TOLERANCE: MORPHINE, NITRATES, XANTHINES AND BARBITURATES.

- **MECHANISM OF ACQUIRED TOLERANCE:**

1. DECREASED INTESTINAL ABSORPTION OF DRUGS.
2. INCREASED RENAL EXCRETION OF DRUGS.
3. INCREASED METABOLISM OF DRUGS DUE TO ENZYME INDUCTION.
4. CELLULAR ADAPTATION TO THE PRESENCE OF THE DRUG.

- **SPECIAL TYPES** OF ACQUIRED TOLERANCE

1. **TACHYPHYLAXIS:**

- IT IS ACUTE RAPID DEVELOPMENT OF ACQUIRED TOLERANCE.
- THE ORIGINAL EFFECT CAN NOT BE OBTAINED BY INCREASING THE DOSE.

- **EXAMPLE:** TACHYPHYLAXIS TO ACTION OF EPHEDRINE ON BLOOD PRESSURE
- MECHANISM OF TACHYPHYLAXIS TO EPHEDRINE:
    - A - RATE OF DISSOCIATION OF EPHEDRINE IS MODERATE SO FEWER AND FEWER RECEPTORS ARE AVAILABLE.

b. DOWN REGULATION OF RECEPTORS

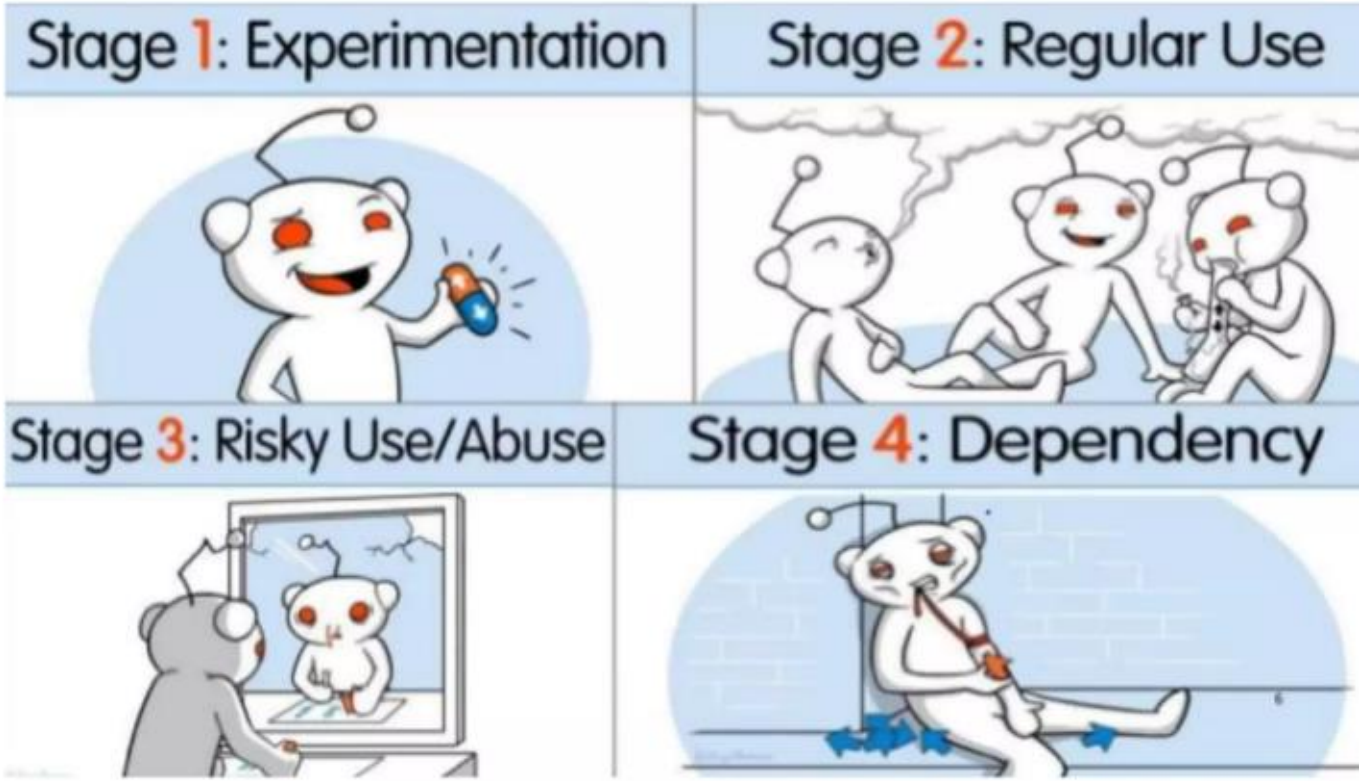
c. DEPLETION OF NORADRENALINE STORES

1. **CROSS-TOLERANCE:** TOLERANCE FOR DRUGS OF RELATED GROUPS E.G. MORPHINE AND PETHIDINE.
2. **TISSUE TOLERANCE:** TO SOME ACTIONS OF THE DRUG. E.G. MORPHINE TOLERANCE TO ANALEGESIC AND RESPIRATORY DEPRESSANT ACTIONS BUT NOT TO ITS MIOTIC AND CONSTIPATING ACTIONS .
3. **BACTERIAL RESISTANCE** TO ANTIBIOTICS.

# CONGENITAL TOLERANCE

1. RACIAL: EPHEDRINE IS NOT MYDRIATIC IN NEGROS .
2. SPECIES: RABBITS TOLERATE LARGE AMOUNTS OF ATROPINE AS RABBITS' BLOOD AND PLASMA CONTAIN ATROPINASE ENZYME WHICH RAPIDLY DETOXICATE ATROPINE.
3. INDIVIDUAL TOLERANCE

# STAGES OF ADDICTION



# TOP TEN DRUGS

- MARIJUANA
- HEROIN
- COCAINE
- ALCOHOL
- TOBACCO
- LSD (Lysergic acid diethylamide)
- SPEEDBALL
- MDMA
- KETAMINE
- CRYSTAL- METH

# DRUG DEPENDENCE

- USE OF DRUGS FOR PERSONAL SATISFACTION

**PHYSICAL DEPENDENCE** IT IS AN 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.**

- **DRUG ABUSE :**

REFERS TO 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 ADDICTION**
- COMPULSIVE DRUG SEEKING AND USE DESPITE ADVERSE CONSEQUENCES.

- **DRUG HABITUATION (PSYCHOLOGICAL DEPENDENCE)**
- LESS INTENSIVE INVOLVEMENT WITH THE DRUG, SO THAT ITS WITHDRAWAL PRODUCES ONLY MILD DISCOMFORT.
- CONSUMPTION OF TEA, COFFEE, TOBACCO, SOCIAL DRINKING ARE REGARDED HABITUATING, PHYSICAL DEPENDENCE IS ABSENT

# INTOLERANCE

- IT IS EXAGGERATED PHARMACOLOGICAL RESPONSE TO THE USUAL DOSE OF THE DRUG
- EXAMPLE: ADRENALINE IN THYROTOXICOSIS

**Un-Predictable**

# DRUG INDUCED DISEASES

- THESE ARE ALSO CALLED **IATROGENIC (PHYSICIAN INDUCED)** DISEASES, AND ARE DISEASE CAUSED BY DRUGS .
- **EXAMPLES:**
- HEPATITIS BY ISONIAZID AND RIFAMPICIN
- PEPTIC ULCER BY SALICYLATES AND CORTICOSTEROIDS
- **RETINAL DAMAGE BY CHLOROQUINE**

# MANAGEMENT OF ADRS

- STOP THE SUSPECT DRUG(S), OR
- REDUCE THE DOSE OF SUSPECT DRUGS(S)
- CONSIDER WHY THE DRUG THERAPY IS PRESCRIBED
- CONSIDER WHETHER ALTERNATIVE TREATMENT IS AVAILABLE
- AND TREAT THE SYMPTOMS (WHERE POSSIBLE)

# PREVENTION OF ADVERSE EFFECTS TO DRUGS

- **AVOID INAPPROPRIATE USE** OF DRUGS .
- **APPROPRIATE DRUG ADMINISTRATION (RATIONAL THERAPEUTICS)**
  - DOSE
  - DOSAGE FORM
  - DURATION
  - ROUTE
  - FREQUENCY
  - TECHNIQUE
- **ASK** FOR PREVIOUS HISTORY OF DRUG REACTIONS AND ALLERGIES
- **ALWAYS** SUSPECT ADR WHEN NEW SYMPTOM ARISES AFTER INITIATION OF TREATMENT.
- ASK FOR LABORATORY FINDINGS LIKE SERUM CREATININE ETC.

# PHARMACOVIGILANCE (DAUP)

THE **'SCIENCE AND ACTIVITIES RELATING TO THE DETECTION, ASSESSMENT, UNDERSTANDING AND PREVENTION OF ADVERSE EFFECTS OR ANY OTHER DRUG RELATED PROBLEMS'**

THE INFORMATION GENERATED IS USEFUL IN EDUCATING DOCTORS AND IN THE OFFICIAL REGULATION OF DRUG USE.

IT HAS AN IMPORTANT ROLE IN **RATIONAL USE** OF MEDICINES, AS IT PROVIDES THE BASIS FOR ASSESSING **SAFETY** OF MEDICINES.

# VARIOUS ACTIVITIES INVOLVED IN PHARMACOVIGILANCE ARE:

- **POST MARKETING SURVEILLANCE** AND OTHER METHODS OF ADR MONITORING SUCH AS VOLUNTARY REPORTING BY DOCTORS' PRESCRIPTION.

- **DISSEMINATION OF ADR DATA** THROUGH 'DRUG ALERTS', 'MEDICAL LETTERS,' ADVISORIES SENT TO DOCTORS BY PHARMACEUTICALS AND REGULATORY AGENCIES.

- **CHANGES IN THE LABELLING** OF MEDICINES INDICATING RESTRICTIONS IN USE OR WARNINGS, PRECAUTIONS, OR EVEN WITHDRAWAL OF THE DRUG.

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# THANK YOU