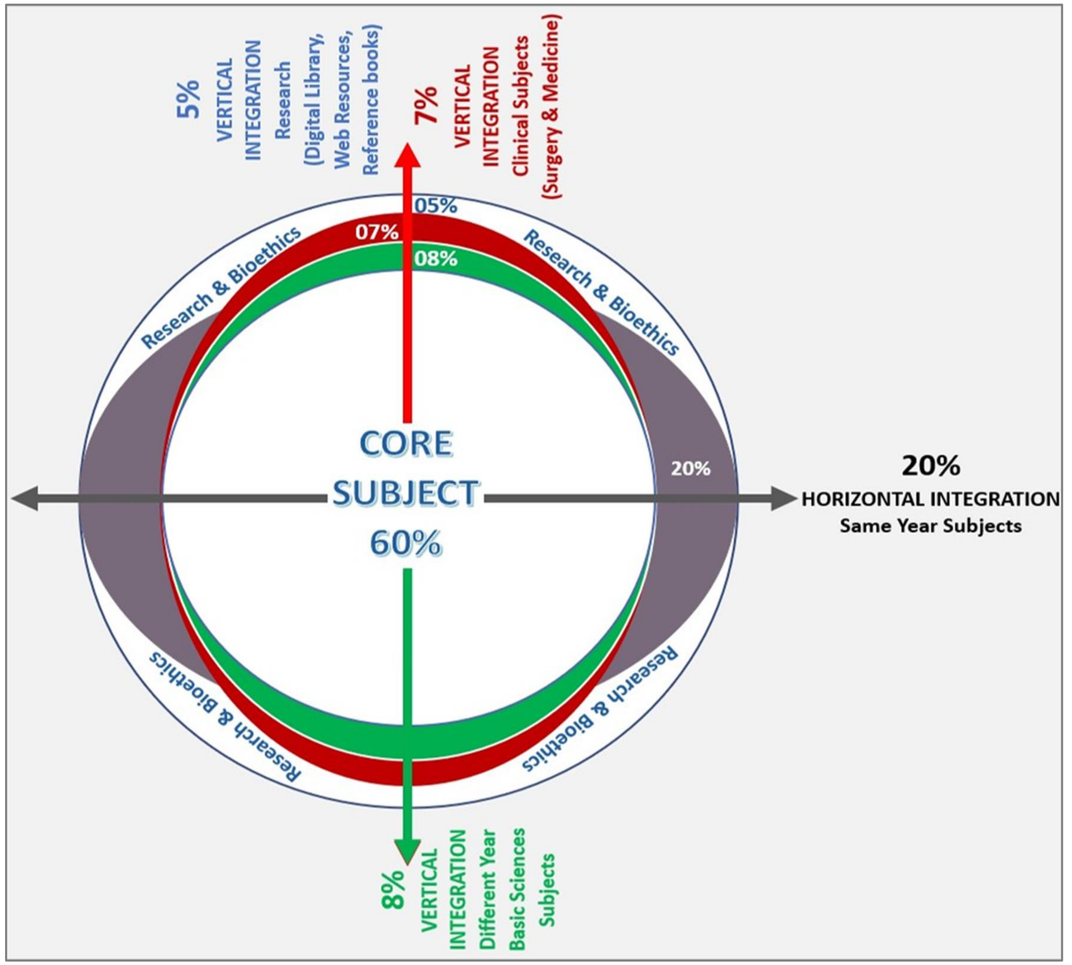
# ADVERSE DRUG REACTIONS

# SEQUENCE OF LECURE

- Core Subject
- Spiral Integration
- Horizontal Integration
- Vertical integration
- Digital Library References

( Research, Bioethics, Artificial Intelligence)

- EOLA(End of lecture assessment)

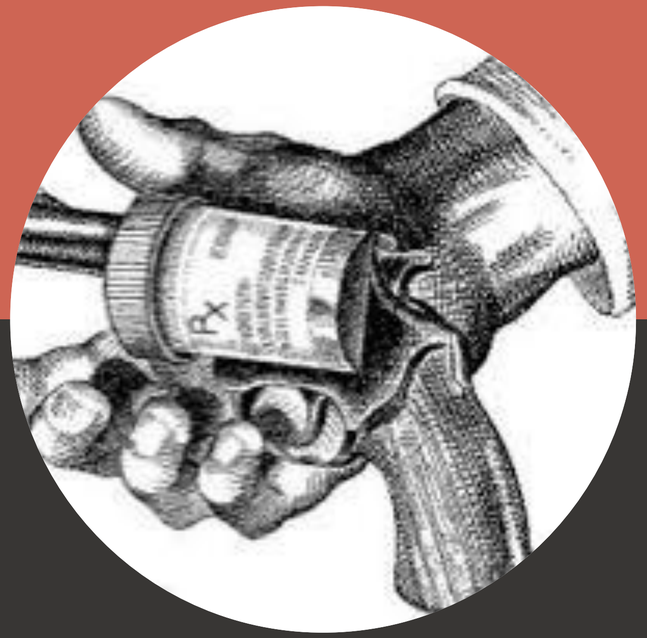


# LEARNING OBJECTIVES

At the end of the interactive lecture, students of 3rd Year MBBS will be able to :

- Define adverse drug reaction(ADR)
- Classify ADRs based on type and severity
- Describe the characteristic of each type of ADR
- Identify predisposing risk factors and approaches to ADR prevention
- Illustrate ways of ADR detection during pre & post marketing evaluation of drugs
- Correlate the importance of reporting a suspected ADR with drug safety

# CORE

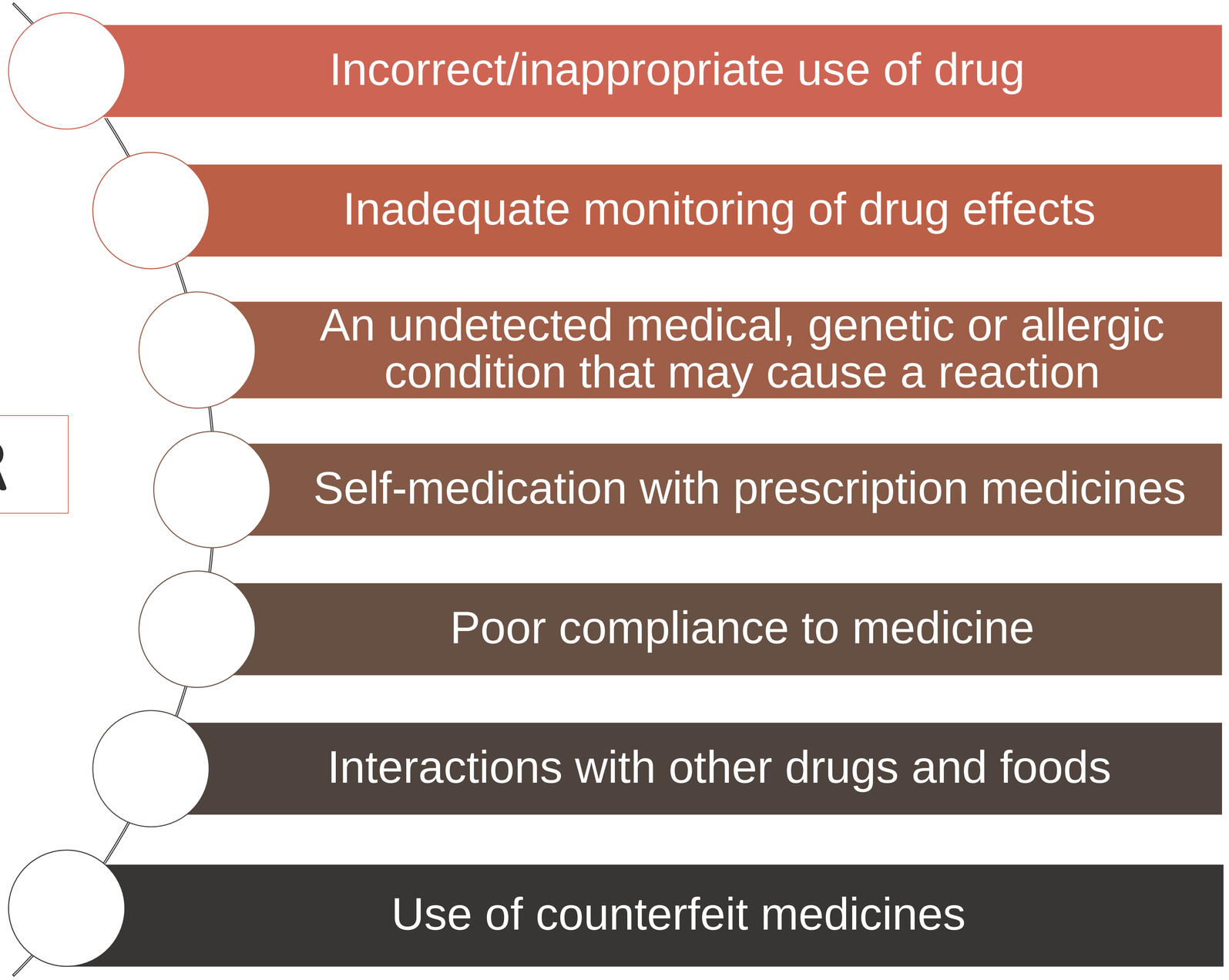



# ADVERSE DRUG REACTION

“A response to a drug that is noxious and un-intended and which occurs at doses used in humans for prophylaxis, diagnosis or therapy or for the modification of physiologic function ”

(WHO)

# CAUSES OF ADR



# CLASSIFICATION

- A — Augmented
- B — Bizarre
- C — Continuous
- D — Delayed
- E — Ending of use
- F — Failure

# Type-A Augmented

- Extension of the desired pharmacological effect as a result of change in exposure or sensitivity of drug
- Dose related
- Predictable

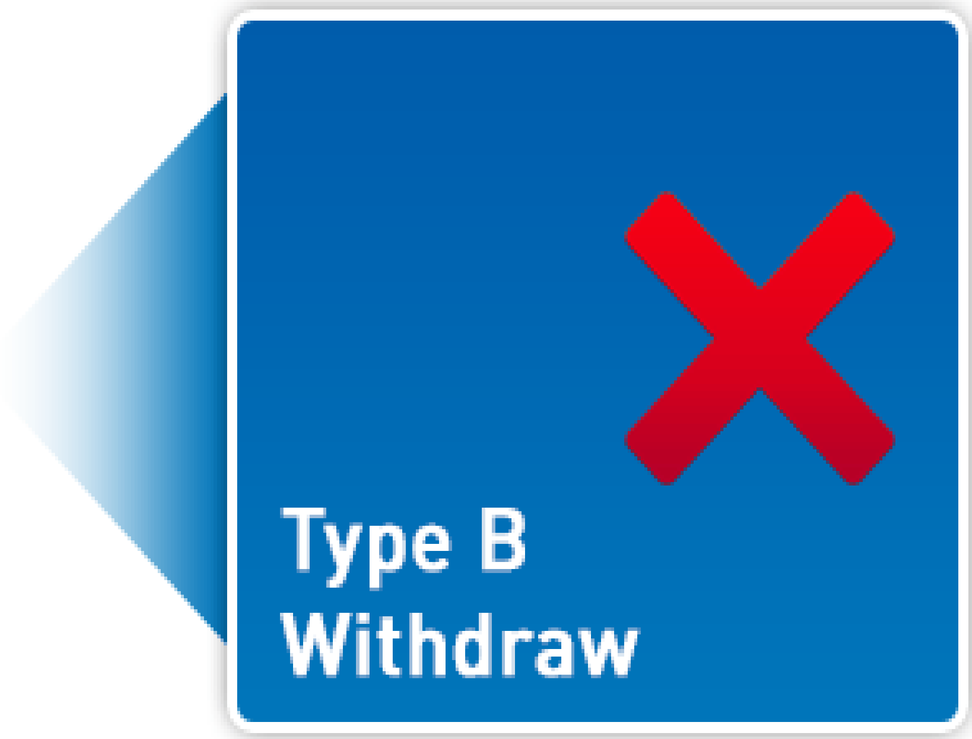
- Postural hypotension(antihypertensives)
- Hypogylcemia (oral hypoglycemics)

- **Side effect**


*Poisons in small doses are the best medicines and useful medicines in too large doses are poisons*
(William Withering)

# Type-B BIZARRE

- Unrelated to the pharmacological effect of the drug
- Not dose related BUT host dependent
- Unpredictable
  Predictable (test dose/other tests)
- Can be fatal
  - Immunological reactions
  - Idiosyncratic reactions
  - Hyper susceptibility




Qualitatively exaggerated response of drug
Abnormally prolonged sleep time after a normal dose of hypnotic

# HYPERSENSITIVITY/DRUG ALLERGY

Immune-mediated quantitatively abnormal response to a drug in a previously sensitized patient

| *Immune reaction* | *Mechanism* | *Clinical manifestations* | *Timing of reactions* | *Example* |
|---|---|---|---|---|
| Type I (IgE-mediated) | Drug-IgE complex binding to mast cells with release of histamine, inflammatory mediators | Urticaria, angioedema, bronchospasm, pruritus, vomiting, diarrhea, anaphylaxis | Minutes to hours after drug exposure | β-lactam induced anaphylaxis |
| Type II (cytotoxic) | Specific IgG or IgM antibodies directed at drug-hapten coated cells | Hemolytic anemia, neutropenia, thrombocytopenia | Variable | Penicillin induced hemolytic anemia |
| Type III (immune complex) | Tissue deposition of drug-antibody complexes with complement activation and inflammation | Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis | 1 to 3 weeks after drug exposure | Serum sickness induced by anti-thymocyte globulin |
| Type IV (delayed, cell-mediated) | MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release | Allergic contact dermatitis, maculopapular drug rash* | 2 to 7 days after cutaneous drug exposure | • Ampicillin induced skin rash<br>• Contact dermatitis after topical antihistamines |

## CROSS ALLERGY

when a drug not previously administered elicits hypersensitivity reactions because of a preexisting sensitization to a structurally related compound

- Penicillin & cephalosporins

# IDIOSYNCRASY

Unpredictable qualitatively aberrant response to a drug caused by genetically determined susceptibility

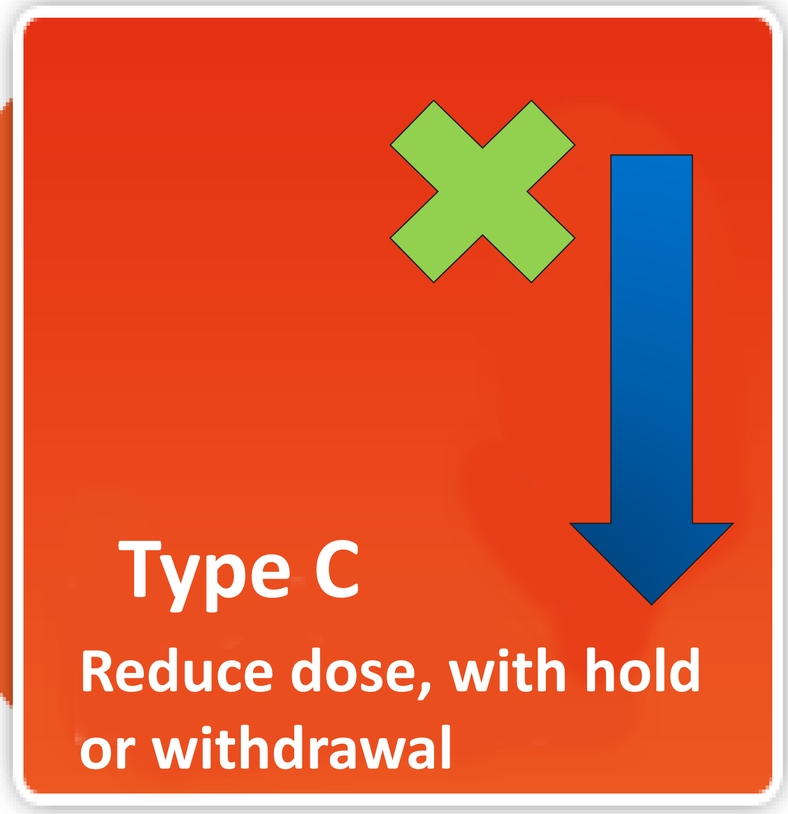
- Seen after the first dose
- Observed in a small percentage of population
- Mechanism can not be explained by the pharmacological action of the drug

- Aplastic anemia caused by chloramphenicol
- Malignant hyperthermia caused by halothane, succinylcholine & haloperidol
- Drug induced hemolysis in G6PD deficiency

# Type-C Continuous

- Due to long term continuous use of drug
- Time related
- Dose related
- Organ damage

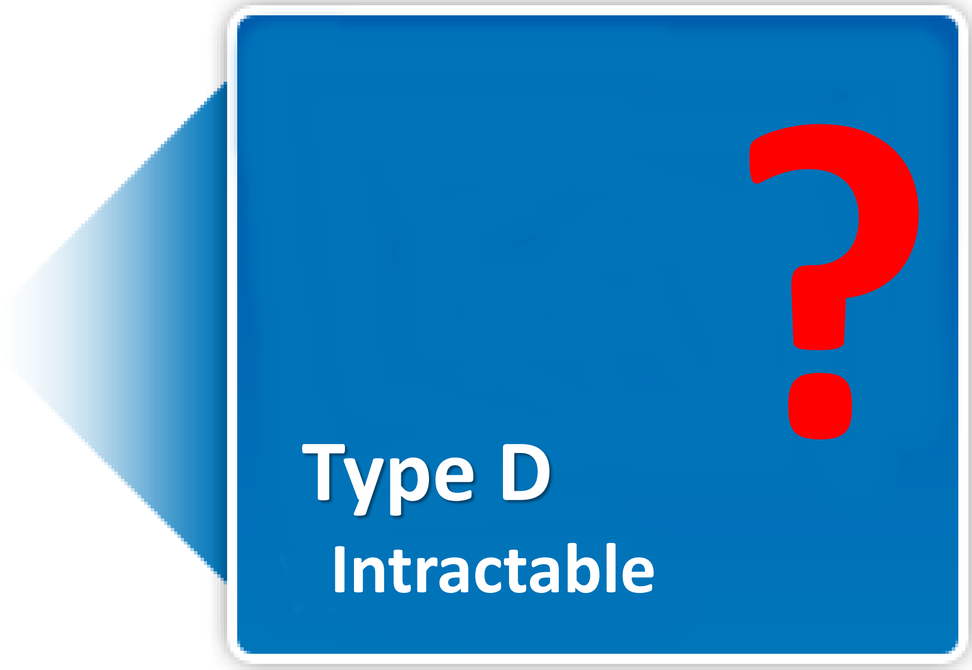
- NSAID induced nephropathy
- Osteonecrosis of jaw (bisphosphonates)



# Type-D DELAYED

- Apparent after a significant time has elapsed since initial administration of drug
- Time related

- Mutagenesis
- Carcinogenesis
- Teratogenesis




Vertical integration with Medicine and Gynecology

# Type-E END OF USE

- Occurs after abrupt discontinuation/ withdrawal of the drug
- Time related

- Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
- Rebound hypertension (clonidine)

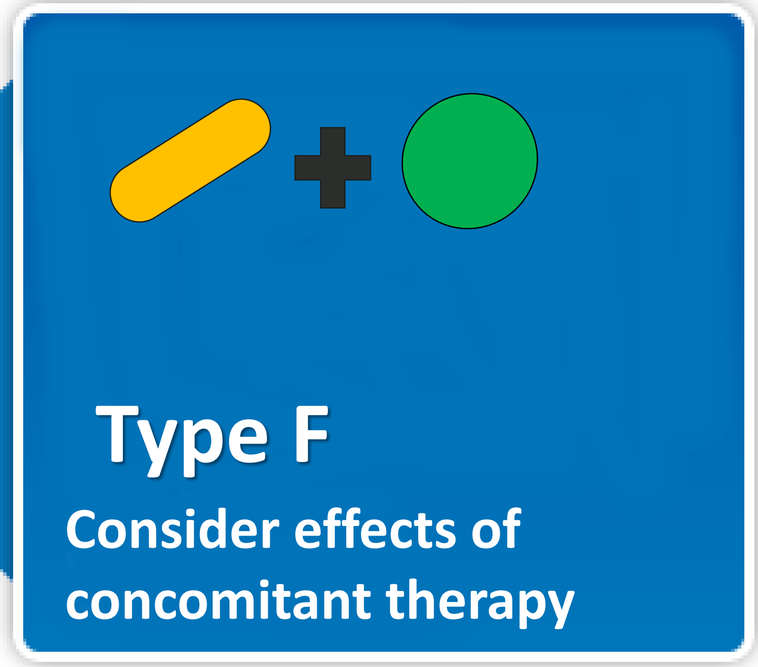
**Type E**

**Reintroduce & withdraw slowly**

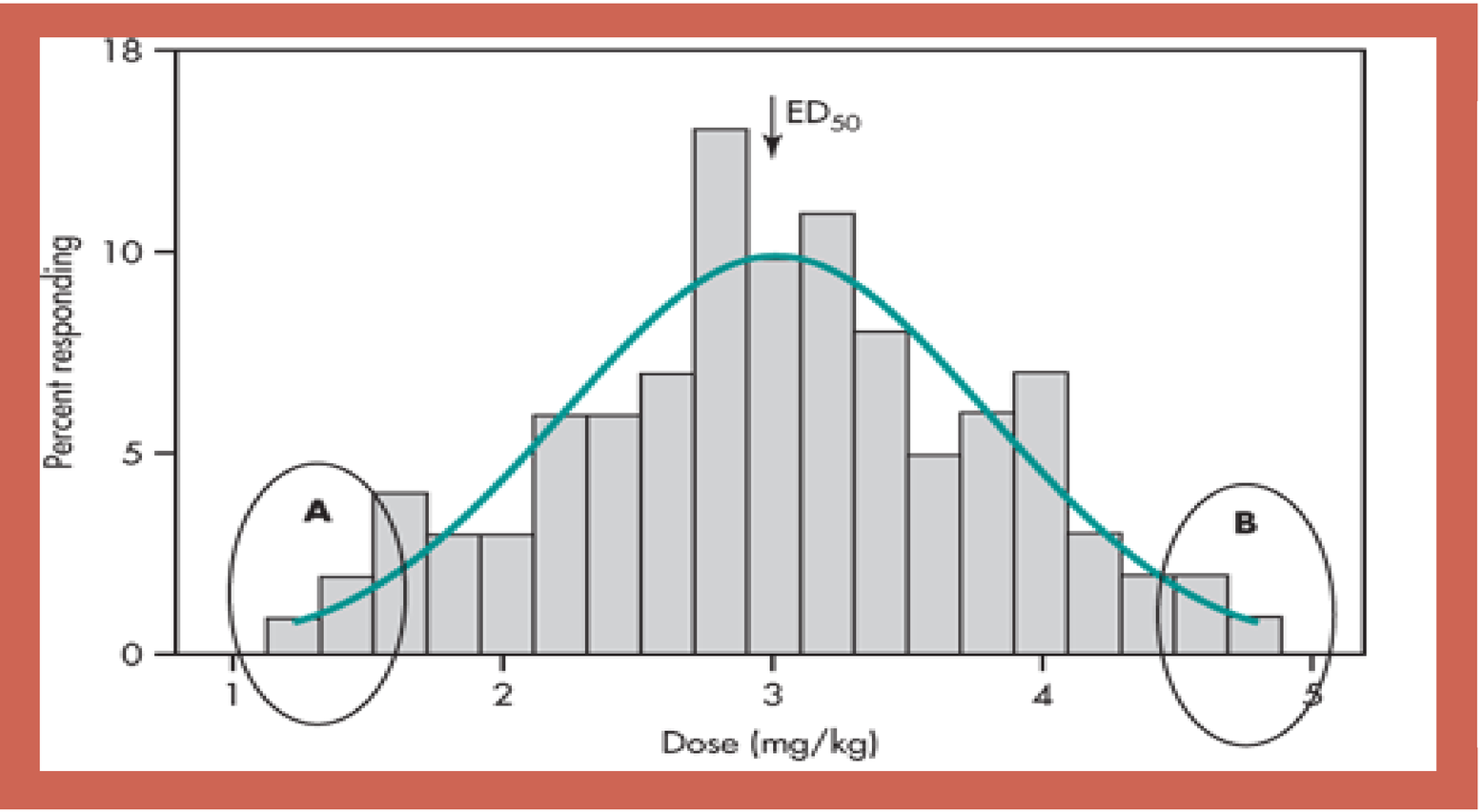
# Type-F UNEXPECTED FAILURE OF THERAPY

- Often caused by drug interactions
- Inadequate dosing (hyper responders and hypo responders)

- Inadequate dosage of an oral contraceptive when used with an enzyme inducer
- Resistance to antimicrobial agents



# Type-F UNEXPECTED FAILURE OF THERAPY




Type F

# FREQUENCY OF ADR

| Category | Frequency |
|---|---|
| Very Common | ≥1/10 |
| Common | ≥1/100 and < 1/10 |
| Un common | ≥1/1000 and < 1/100 |
| Rare | ≥1/10,000 and < 1/1000 |
| Very Rare | < 1/10,000 |

# SEVERITY OF ADR

**Classification of Adverse Drug Reactions (ADRs)**

| Severity | Description | Example |
|---|---|---|
| Mild | No antidote or treatment is required; hospitalization is not prolonged. | Antihistamines (some): Drowsiness<br>Opioids: Constipation |
| Moderate | A change in treatment (eg, modified dosage, addition of a drug), but not necessarily discontinuation of the drug, is required; hospitalization may be prolonged, or specific treatment may be required. | Hormonal contraceptives: Venous thrombosis<br>NSAIDs: Hypertension and edema |
| Severe | An ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADR. | ACE inhibitors: Angioedema<br>Phenothiazines: Abnormal heart rhythm |
| Lethal | An ADR directly or indirectly contributes to a patient's death. | Acetaminophen overdosage: Liver failure<br>Anticoagulants: Hemorrhage |

# RISK FACTORS OF ADR

## PATIENT RELATED

- Age
- Gender
- Pathophysiological states
- Genetic factors

## DRUG RELATED

- Chemical nature
- Nature of metabolite
- Dose of the drug
- Time course of administration
- Concurrent therapy

# STEPS TO REDUCE ADRs

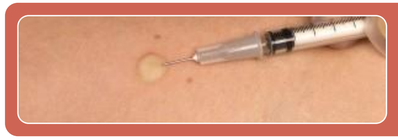
Development & marketing of safe and effective pharmaceutical drugs by Pharmaceutical companies

Tight control by drug regulatory authorities on the licensing, promotion and marketing of drugs

Tailoring the drug regimen according to individual patient **(P-drug) Rational drug therapy**

Always maintain low threshold of suspicion

Rule out history of previous adverse reactions,allergy and DDI



Administering a test dose in case of drugs prone to hypersensitivity

Monitoring drug levels to ensure compliance and prevent ADR **(Therapeutic drug monitoring)**

Report ADR

BIOETHICS

ADVERSE DRUG REACTION

# DRUG SAFETY EVALUATION

# DRUG DEVELOPMENT & EVAULATON


**IND**
**(Investigational New Drug)**

**NDA**
**(New Drug Application)**

**5-15 years**

# Pharmacovigilance

Pharmakon-------in Greek----drug
Vigilare ----------in Latin------to keep watch

Pharmacovigilance is the science & activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems

Identification of ADR

- Causal Assessment


ADR Reporting


Reported to manufacturer

Reported to FDA via DRA

**Manufacturer**

- Report to FDA (safety reports)

**FDA**

- ADR entered into database
- Safety signal identified

YES

NO

**Alerts from FDA & manufacturer**

**Regulatory changes**
Label changes
Boxed warning
Withdrawal

YES

Safety signal confirmed?

NO

No action required or continue to monitor

# RESEARCH


- Zucker, I., Prendergast, B.J. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol Sex Differ* **11**, 32 (2020). https://doi.org/10.1186/s13293-020-00308-5

# ARTIFICIAL INTELLIGENCE


- Wang, C.S., Lin, P.J., Cheng, C.L., Tai, S.H., Kao Yang, Y.H. and Chiang, J.H., 2019. Detecting potential adverse drug reactions using a deep neural network model. Journal of medical Internet research, 21(2), p.e11016.

- Syrowatka A, Song W, Amato MG, Foer D, Edrees H, Kuznetsova M, Dulgarian S, Seger DL, Simona A, Bain PA, Jackson GP. Key use cases for artificial intelligence to reduce the frequency of adverse drug events: a scoping review. The Lancet Digital Health. 2022 Feb 1;4(2):e137-48.

# JAZAKALLAH