ADVERSE DRUG REACTIONS

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ADVERSE DRUG EVENT (ADE)

Any untoward occurrence that may present during medical treatment,

But

Does not necessarily have a causal relationship with the treatment

- **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, antidote or prolongation of hospitalization 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.

Incidence

- **Hospital in-patients**:10-20%
- **Deaths in hospital in-patients**: 0.3-3%
- **Hospital admissions**: 0.3-5%

Worldwide – ADRs: 6th leading cause of death

US and Canada – ADRs: 4th leading cause of death

Why incidence is more ?

1) Ever-increasing number of new drugs in the market
2) Number of drugs prescribed are high
3) Medication errors
4) Lack of awareness of a system for reporting ADR'S

Common causes

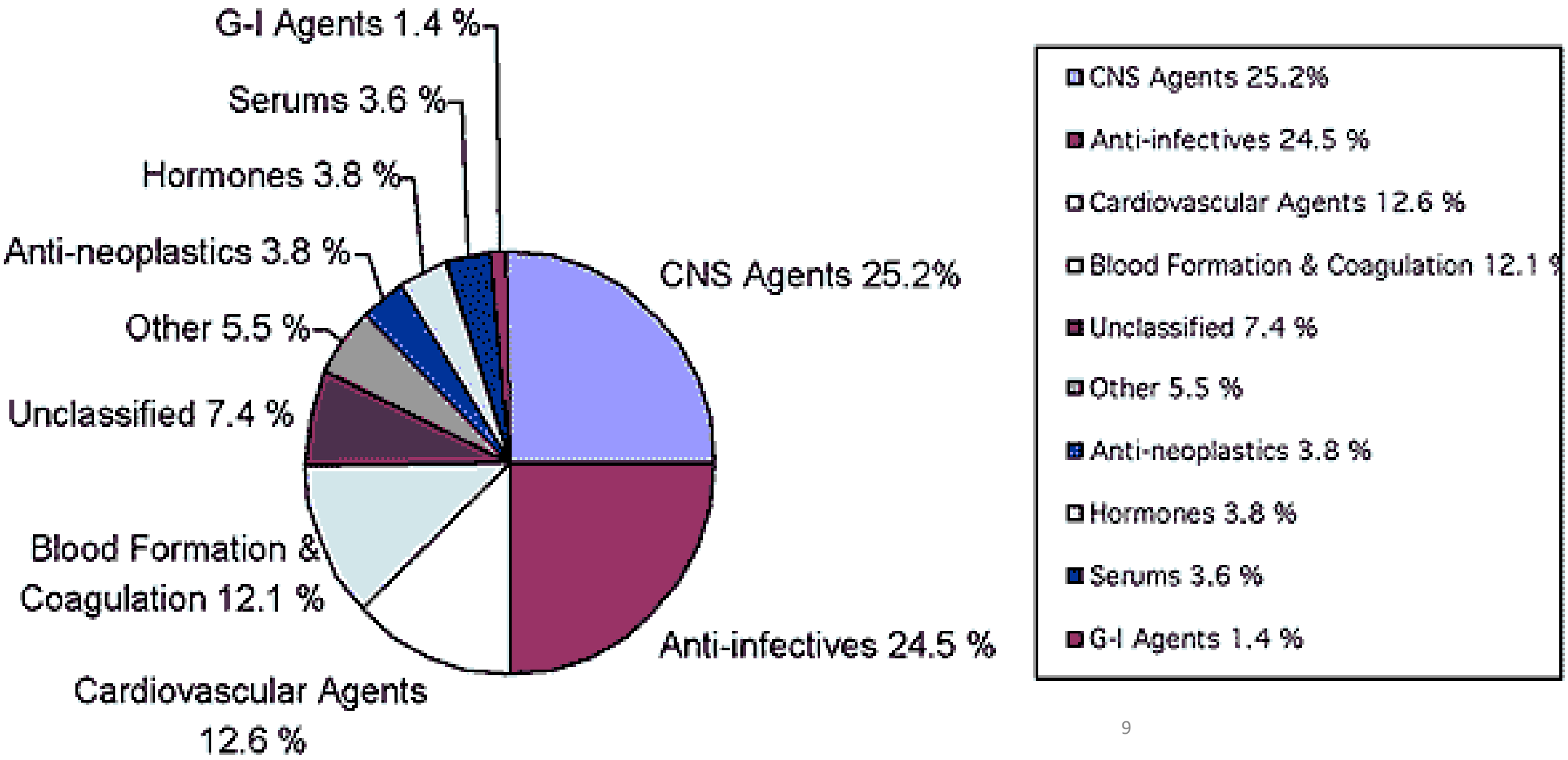
- Failing to take the correct dose at the correct times
- Overdosing
- Allergies to chemical components of the medicine
- Combining the medicine with alcohol
- Taking other drugs or preparations that interact with the medicine

Factors affecting Adverse Drug Reactions :

- Age

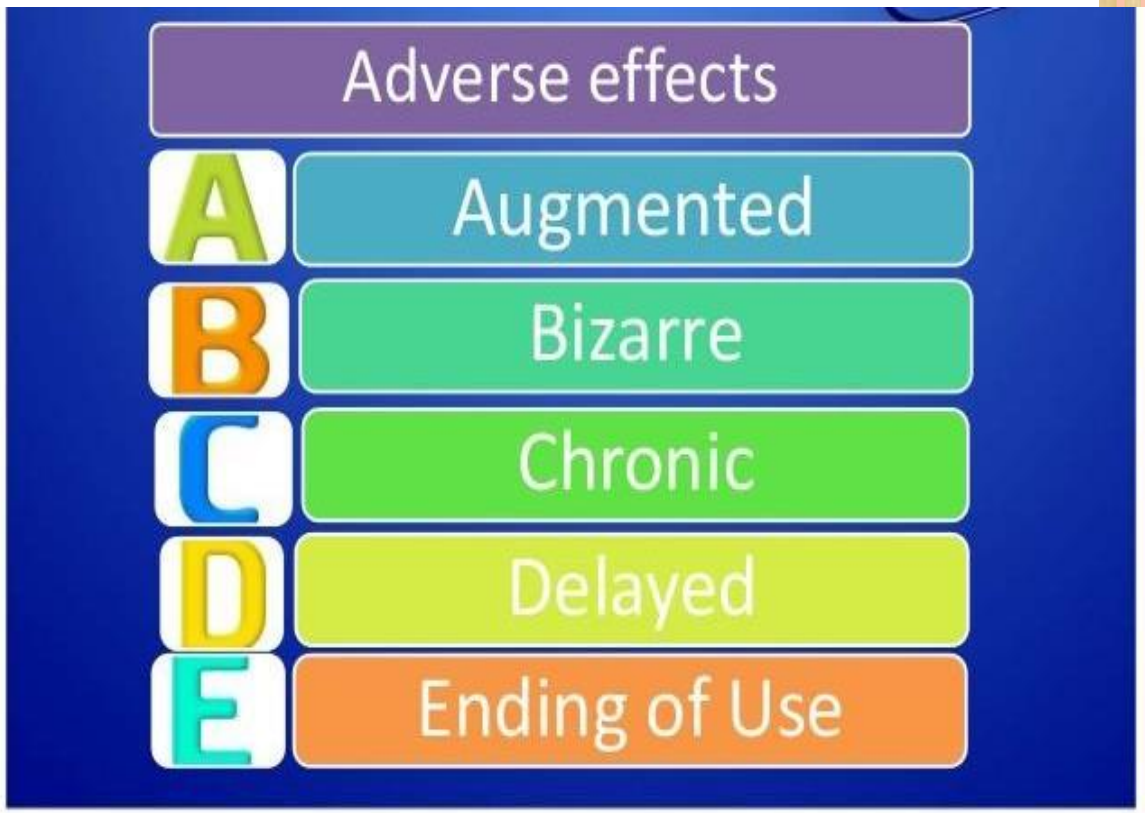
- Genetic influences
- Concurrent diseases (Renal, Liver, Cardiac)
- Previous adverse drug reactions
- Compliance with dosing regimen
- Total number of medications
- Misc. (diet, smoking, environmental exposure)

Figure 1: ADRs by Drug Class



CLASSIFICATIONS OF ADR

- A (Augmented)
- B (Bizarre)
- C (Continuous)
- D (Delayed)
- E (Ending Use)
- F (Failure of Efficacy)



Broadly

Type- A (Predictable)- Based on pharmacological properties

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

Types of ADR's in Brief:

Type	Mnemonic	Example
A	Augmented	Diarrohea due to antibiotics
B	Bizzare	Hypersensitivity due to penicillin
C	Chronic	Steroid decrease HPA axis
D	Delayed	Teratogenicity, carcinogenesis
E	End of use	Precipitation of MI by β blocker withdrawl
F	Failure	OCP failure

The hypothalamic–pituitaryl axis

Oral contraceptive pills

TYPE A- AUGMENTED

- These are based on the pharmacological properties of the drug so can be predicted.
- They are common and account for 75% of ADRs

Examples:-

- Anticoagulants (e.g., warfarin, heparin) – bleeding
- Anti-hypertensives (e.g.. α1-antagonists) – hypotension
- Anti-diabetics (e.g. insulin) - hypoglycemia

Predictable

TYPE B- BIZZARE OR UNPREDICTABLE

- Have **no direct relationship** to the dose of the drug or the pharmacological mechanism of drug action.
- Develop on the basis of:
  - Immunological reaction on a drug (**Allergy**)
  - Genetic predisposition
- More serious clinical outcomes with higher mortality and morbidity.
- Mostly require immediate withdrawal of the drug.

Un-predictable

TYPE C – CHRONIC (CONTINOUS) USE

- They are mostly associated with **cumulative-long term** exposure

Example:-

Analgesic (NSAID)– interstitial nephritis, necrosis

Predictable

TYPE D – DELAYED

- They manifest themselves with significant delay

  - **Teratogenesis -**Thalidomide
  - **Mutagenesis/Cancerogenesis**

Others:

Tardive dyskinesia – during L-DOPA Parkinson disease treatment

Predictable

TYPE E – END OF USE

- Drug withdrawal syndromes and rebound phenomenons

  - Example – sudden withdrawal of long term therapy with **β-blockers** can induce tachycardia and hypertension

Predictable

Categorized into:

- Side effects-
- Secondary effects
- Toxic effects
- Intolerance
- Idiosyncrasy
- Drug allergy
- Photosensitivity
- Drug dependence
- Drug withdrawal reactions
- Teratogenicity
- Mutagenicity and Carcinogenicity
- Drug induced diseases

Side effects

"Unwanted but often unavoidable pharmacodynamic effects of a drug at therapeutic doses"

As Extension of therapeutic effe
Atropine - dry mouth

As distinctly different effect
Promethazine – Sedation.

Side effect exploited for therapeutic use
Codeine – Diarrhoea

Secondary effects

"Indirect consequence of Primary action of a drug"

Eg:

- Tetracycline : Superinfection
- Corticosteroids : Activation of latent Tuberculosis

TOXIC EFFECTS (Poisonous effect)

- Over dose or prolonged use.
- The effects are predictable and dose related.
- The CNS, CVS, kidney, liver, lung, skin and bone marrow are most commonly involved in drug toxicity.

Intolerance

"Appearance of characteristic toxic effects of a drug at therapeutic doses"

Eg.,

- Trifluprομazine (single dose) - Muscular dystonia
- Carbamazepine (few doses)– Ataxia
- Chloroquine (single dose) - Vomiting

IDIOSYNCRASY

- It is **genetically determined abnormal reactivity** to a chemical.
- The drug interacts with some unique **feature of the individual,** not found in majority of subjects, and produces the uncharacteristic reaction.

Example :-

- Chloramphenicol produces non-dose-related serious aplastic anaemia in rare individuals.
- Barbiturates cause mental confusion in some individuals

Un-Predictable

Photosensitivity

Phototoxic	Photoallergic
• Photochemical / biological Reaction • UV - B • Hyperpigmentation & desquamation • Eg. Acute – Tetracyclines • Chronic – Nalidixic acid,	• Cell mediated immune response • UV - A • Papular & eczematous, flare & wheal • Eg., Sulphonamides, sulphonylureas,

Teratogenicity

- US FDA graded documentation of risk for causing birth defects into five categories ABCDX
- Avoid all drugs unless benefits outweighs the risks

Eg: Phenytoin

Valproate –

Aspirin

arteriosus

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 occur in all
- Occurs on re-exposure
- E.g. penicillin→1st time →stimulate antibody →Ag-Ab reaction →allergy
- Chief organ: Skin, respiratory tract, GIT, Blood & blood vessels

DRUG DEPENDENCE

- Use of drugs for personal satisfaction
- Higher priority than other basic needs, often in the face of known risks to health.

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.**
- Drugs producing physical dependence are opioids, barbiturates and other depressants including alcohol and benzodiazepines

- **Drug abuse : تعاطي المخدرات:**

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 إدمان المخدرات**

It is a pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug. Procuring the drug and using it takes precedence over other activities

- **Drug habituation (Psychological dependence)**

It denotes 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

DRUG WITHDRAWAL REACTIONS

- Sudden interruption of therapy with certain other drugs results in adverse consequences, mostly in the form of worsening of the clinical condition for which the drug was being used

- **Example:** Acute adrenal insufficiency may be precipitated by stop of corticosteroid therapy.

Mutagenicity 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.

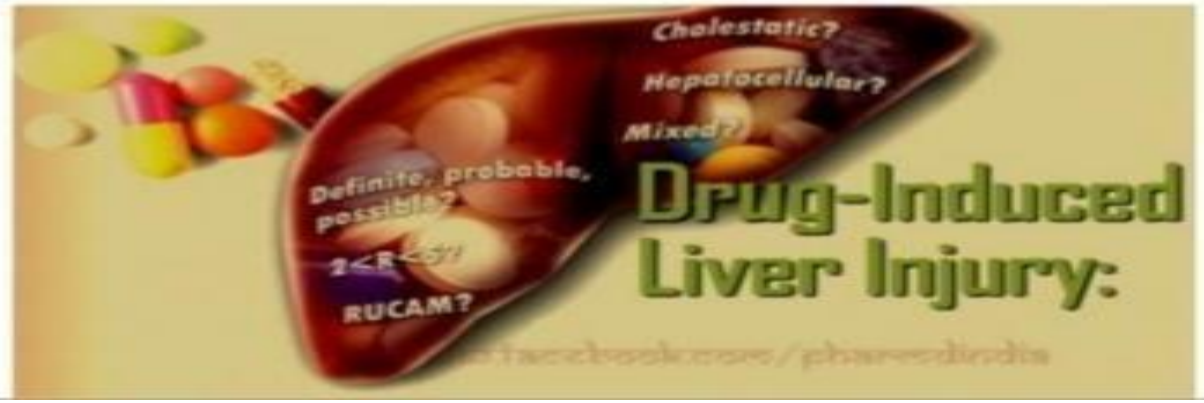
DRUG INDUCED DISEASES

- These are also called **iatrogenic (physician induced)** diseases, and are functional disturbances (disease) caused by drugs .

- Hepatitis by isoniazid and Rifampicin
- Peptic ulcer by salicylates and corticosteroids
- **Retinal damage by chloroquine**

Organ Specific ADR'S

- Hemopoietic system & bone marrow
- Liver damage/ Hepatic injury
- Renal damage



➢ Hemopoietic system & bone marrow

Sr. No.	Drugs	ADR'S
1	Quinine, Rifampicin, Sulfonamide, Thiazide	Thrombocytopenia.
2	Carbamazepine, Sulfonamide, carbimazole, clozapine	fatal neutropenia , drug allergy (type II reaction), Granulocytopenia
3	Chloramphenicol	Aplastic anemia
4	Anti cancer, cytotoxic drugs	direct bone marrow depression
5	primaquine, quinine, chloroquine, dapsone, sulfonamide(due to idiosyncracy) Methyldopa used in pregnancy	Hemolytic anemia

➢ Liver damage/ Hepatic injury –

Chloroform, Halothane, Enflurane	→	When given in repeated dose – hepatotoxicity – jaundice
Chlorpromazine, Flucloxacillin, OCP	→	Cholestatic jaundice
INH, Rifampicin, Methyldopa	→	Hepatocellular necrosis – jaundice
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 : *Glomerulonephritis.*
- Aminoglycoside (Gentamicin), Amphotericin, High dose paracetamol, Cefalothin : *Acute tubular necrosis.*
- NSAID, Lithium, Penicillamine – long term use in rheumatoid arthritis – *Acute interstitial nephritis.*
- ACEI – *Renal vascular damage.*

HOW TO RECOGNIZE AN ADR

Who can get an ADR?

Anyone who takes medicine

Differential diagnosis should include the possibility of an ADR if the patient is taking any form of medication

When To Report :

If symptoms,

- ✓ Appears soon after a new drug is started
- ✓ Appears after an increase in dose
- ✓ Disappears when the drug is stopped
- ✓ Reappears when a drug is restarted

ADR Reporting System

السلامة الدوائية أو اليقظة الدوائية
PHARMACOVIGILANCE

- هو أحد فروع العلوم الدوائية الجديدة نسبياً **والذي يهتم بدراسة كل ما يتعلق بالأثار الجانبية للأدوية والمنتجات الصيدلانية أو أي مشاكل أخرى متعلقة بإستهلاك الدواء.**
- السلامة الدوائية يعتبر العلم المسؤول عن اصدار التشريعات والتوصيات المتعلقة بسلامة الدواء تحت إشراف منظمة الصحة العالمية WHO ومنظمة الغذاء والدواء الأمريكية FDA

PHARMACOVIGILANCE

- قامت منظمة الصحة العالمية بإنشاء أول مركز دولي لمراقبة الدواء عام ١٩٧١ وبحلول عام ٢٠١٠ كان قد تم انشاء مراكز لمراقبة الدواء في أكثر من ١٣٤ دولة .
- **تم انشاء مركز التيقظ الدوائي السوري عام ٢٠١٨**
- يهدف علم السلامة الدوائية إلى الإرتقاء بالرعاية الصحية للمرضى وزيادة السلامة من استخدام الأدوية العلاجية بالإعتماد على تقارير الباحثين و مقدمي الرعاية الصحية والمرضى المعالجين

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.

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. (No new drug for new symptom).
- Ask for laboratory findings like serum creatinine etc.

Summary

- Every drug which has an effect has an adverse effect every time a drug is given risk is involved
- For rational use of drug not only its clinical indications are important but the knowledge of adverse effects as well
- Early detection of adverse effects and its proper management can be life saving in many situations
- ADR Reporting (Pharmacovigilance) plays a important role in the evolution and life history of a drug

QUESTIONS????