

**Adverse drug Reactions:** The drugs that produce useful, desired, therapeutic effect may also produce unwanted, undesired, harmful effect – **adverse drug reaction**. Side effect is terms referring to unavoidable secondary drug effect produced at therapeutic doses.

**Adverse drug reaction (ADR)**, as defined by the WHO, is any noxious, unintended, and undesired effect that occurs at normal drug doses – excludes undesired effect that occur when dosage is excessive “toxicity”. Adverse reactions can range in intensity from mildly annoying to life threatening.

**Toxicity:** a harmful drug reaction caused by “excessive dosing” after prolonged intake of high doses of medication or after only one large dose because of accidental poison or medication errors.

ADRs can occur with all medications – whenever a drug taken, a risk is taken. Fortunately, when drugs used properly, many ADRs can be avoided, or at least kept to a minimum

**Predisposing factors for adverse drug reactions (High-risk groups)**

- Age – adverse effects are more common in very old & the very young (Pts over 60 account for nearly 50% of all cases of adverse effects)
- Gender – increase adverse effects incidence in women
- Severe illness and multiple disease states
- Patients receiving multiple drugs than in patients taking just one

**Types of adverse effects of drugs**

<b>Types of adverse drug effects</b>		
<b>Type A</b>	Augmented pharmacological actions	Can occur in all patient Largely predictable Usually dose-related They are common and skilled management reduces their incidence, e.g. postural hypotension, hypoglycemia, hypokalemia
<b>Type B</b>	Bizarre reactions	Occur only in some people They are not part of the normal pharmacology of the drug, Not dose-related Due to unusual attributes of the patient interacting with the drug. Unpredictable for the individual The class includes unwanted effects due to inherited abnormalities (idiosyncrasy) and immunological processes
<b>Type C</b>	Chronic reactions	Due to long-term exposure, e.g. analgesic nephropathy
<b>Type D</b>	Delayed effects	Following prolonged exposure, e.g. carcinogenesis or short-term exposure at a critical time, e.g. teratogenesis.
<b>Type E</b>	Ending of use reactions	Where discontinuation of chronic therapy is too abrupt, e.g. of adrenal steroid causing rebound adrenocortical insufficiency, of opioid causing the withdrawal syndrome

## General Adverse drug reactions

- **Allergic reaction:** (also called a **hypersensitivity** reaction)

An antigen-antibody immune reaction that occurs when an individual who has been previously exposed to a drug has developed antibodies against the drug (Allergy to a drug usually begins to occur after more than one dose of the drug is given).

The type of reaction may be mild (skin rash, urticaria, headache, nausea, or vomiting) or severe (anaphylaxis).

E.g., penicillins, NSAIDs (e.g. aspirin) and sulfonamide group of compounds.

- **Gastrointestinal Effects:**

Nausea and vomiting occur with many drugs because of local irritation of the GI tract or stimulation of the vomiting center in the brain. Diarrhea occurs with drugs that cause local irritation or increase peristalsis.

More serious effects include bleeding or ulceration (most often with non-steroidal anti-inflammatory agents such as ibuprofen).

- **Drug idiosyncrasy**

Term used to describe any unpredictable, unusual or abnormal reaction to a drug resulting from a genetic predisposition. It is any reaction that is different from the one normally expected of a specific drug and dose.

Manifested by over response, under response, or an atypical response

E.g., a patient may be given a hypnotic drug to help him or her to sleep, instead of falling asleep, the patient remains wide-awake and shows signs of nervousness or excitement. Another patient may receive the same drug and dose, fall asleep, and after 8 hours be difficult to awaken.

- **Cumulative drug effect:** Accumulate of drug in the body and may be seen in patients with liver or kidney disease when the body is unable to metabolize and excrete one (normal) dose of a drug before the next dose is given.

- **Iatrogenic disease** – a disease produced by drugs:

The word iatrogenic is derived from 2 words (Greek word): iatros = physician & -genic = produce.

An iatrogenic disease is a disease that occurs as the result of medical care or treatment. Iatrogenic diseases are nearly identical to idiopathic (naturally occurring) diseases. E.g., Peptic ulcer by salicylates or corticosteroids, hepatitis by isoniazid.

- **Organ-Specific Toxicity**

- **Hepatic effects** (hepatitis, liver dysfunction or failure, biliary tract disorders)
- **Nephrotoxicity** (nephritis, renal insufficiency or failure)
- **Hematologic effects** (excessive bleeding, clot formation [thrombosis], bone marrow depression, anemias,.....).

- **A pharmacogenetic disorder:** a genetically determined abnormal response to normal doses of a drug due to abnormal metabolism of drugs.

E.g., individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency have abnormal reactions to a number of drugs include aspirin, chloramphenicol, and the sulfonamides. These patients exhibit varying degrees of hemolysis (destruction of red blood cells) if these drugs are administered.

- **Carcinogenic effect:** is the ability of a substance (medications & environmental chemical) to cause cancer results from drug-induced alterations in cellular DNA. E.g., anticancer drugs.
- **Teratogenic effect:** is the ability of a substance to cause abnormal fetal development when taken by pregnant women (a drug-induced birth defect). E.g., antiepileptic drugs and “statin” cholesterol-lowering drugs.

### **Drug Interactions: Drug – drug interactions.**

- Drug interactions have the potential to affect the outcome of therapy. Drug interaction may cause therapeutic failure or toxicity.
- Drug-drug interactions can occur whenever a patient takes two or more drugs and the action of one drug interacts or interferes with the action of another drug.
- Drug interactions may occur when two or more drugs are administered at the same time or when a short time interval exists between the administration of two different drugs
- Sometimes patient need to take two or more drugs to treat a single disorder or to treat multiple disorders.
- They may take over-the-counter drugs in addition to prescription medicines or may take caffeine, nicotine, alcohol, and other drugs that have nothing to do with illness.
- Some interactions are both intended & desired e.g. combine drugs to treat hypertension.
- In contrast, some interactions are both unintended & undesired e.g. taking an antacid with oral tetracycline causes a decrease in the effectiveness of the tetracycline

### **Drugs can interact by way of four basic mechanisms:**

- 1) **Direct chemical or physical interaction:** This interaction occur most commonly when drugs are combined in IV solutions. Frequently, but not always, the interaction produces a precipitate. If a precipitate appears when drugs are mixed together, that solution should be discarded. Because drugs can interact in solution, never combine two or more drugs in the same container unless it has been established that a direct interaction will not occur.
- 2) **Pharmacokinetic interaction:** Drug interactions can result in increased or decreased drug absorption, distribution, metabolism and renal excretion
- 3) **Pharmacodynamic interaction:** Drugs that act as antagonists at a particular receptor will diminish the effects of drugs that act as agonists at that receptor  
→prevents toxic effects or prevents therapeutic effects of the agonist

- 4) **Combined toxicity.** If drug A and drug B are both toxic to the same organ, then taking them together will cause more injury than if they were not combined.

**Consequences of drug-drug interactions (outcomes)**

- 1) **Intensification of Effects - Synergism interaction -** When a patient is taking two medications, one drug may intensify, or potentiate, the effects of the other. This type of interaction is often termed potentiative and may be beneficial or detrimental.
- 2) **Reduction of Effects – inhibitory interactions.** One drug may reduce the effects of the other, and can be beneficial or detrimental.

**Home work: Report about drug-food interactions**