Drug interactions:

Alteration of the pharmacological activity of one drug " Object" by the concomitant use of another *drug* "Precipitant" or the use of other substances as *herbal* or *dietary* substance

i,e; Drug interactions occur when patient taking two or more drugs to treat a single disorder or multiple disorders, or using drugs OTC medications or other substances as caffeine, nicotine, alcohol,…...

Classifications of drug interactions;

- **Drug-Drug Interactions**
- **Drug-Food Interactions**
- **Drug – Herbs Interactions**
- **Drug –pollutant Interactions**

The incidence of drug interactions increase;

o When the patient receives more than one drugs (polypharmacy) specially when taken at the same time or within short period of time.
o Have multiple diseases that required multiple therapies.
o Treated by more than one doctors.

Type of drugs having risk of drug- drug interactions

• Drugs with low therapeutic index
e.g: Warfarin , Digoxin, Theophylline, Lithium, ...
• Drugs affecting the vital physiology of the body
e.g: Antihypertensive drugs Antidiabetic drugs & anticoagulants
• Drugs with high capacity to bind plasma protein e.g: Warfarin , Sulfonylurea, NSAIDs.

Mechanisms of Drug-to-Drug Interactions:

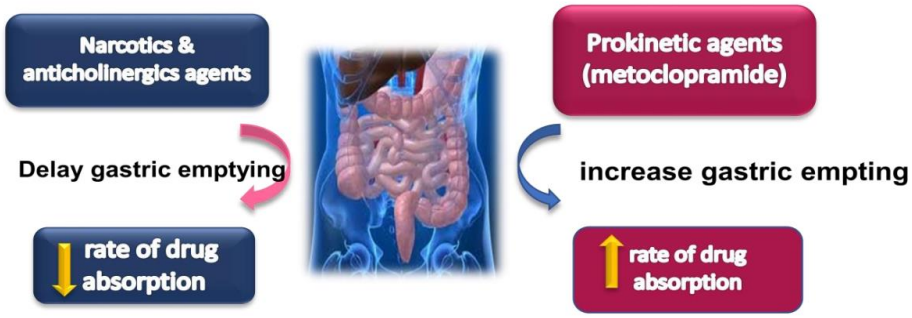
1-Pharmaceutical interactions (Incompatibility)

• It's a direct Chemical or physical interaction, occurs before administration when the drugs dissolved in solution or mixed with i.v . Infusions, where **Most interactions occur when drugs are in solution of IV.**
-e.g; a precipitate may form **(if precipitate seen in solution ,this should be discarded).**
-Interactions also occur by mixing drugs in powder, or in solution for injection
e.g; Thiopental (powder vs addition of water)

-Not all interactions of drugs leave a precipitate: **Never combine two or more drugs in the same IV container**, unless it has been proven that there is no adverse reaction *e.g:-* Ampicillin & Garamycin→ chemical acid base reaction

- Cathecholamines may (decomposed by light)

2- Pharmacokinetic Interactions
• Absorption can be altered by
1-Insoluble complex formation;
e.g. Antacids can ↓ Absorption of Fluroquinolone due to complex formation.
This minimized by administering the two drugs with a gap of 2-3 hours
2-Alteration of gut microflora:
e.g. Antibiotics reduce Gut microflora ↓ Absorption of contraceptive while ↑ absorption of digoxin
3-Alteration of gut motility:



Distribution altered by change in protein binding

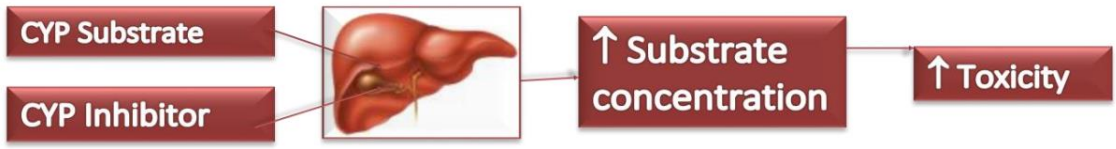
Drugs that have tendency to bind to plasma proteins or those with small vd like are contribute in D_D interaction as Sulfonylureas, NSAIDs and anti-epileptic drugs,……
are particularly liable to displacement interactions.
e.g; NSAIDs or sulfa drugs can displace warfarin → ↑ plasma level of free form of warfarin and increase the risk of bleeding.

- **Metabolism: altered by Enzyme induction or inhibition**

Some drugs decrease and others increase metabolism.

I- Drug inhibitors that decrease the rate of metabolism of other drugs (substrates) that enhance their effects and may increase the risk of their toxic effect.

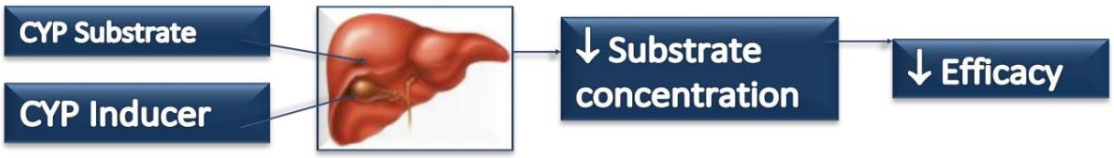
***Macrolide antibiotics, Azole antifungals, Omeprazole, Cimetidine, Ciprofloxacin, Metronidazole*.**



e.g Warfarin + enzyme inhibitor → increase risk of bleeding due to (↓ metabolism)

II- Drugs that increase rate of Metabolism (enzyme inducers) of other drugs (substrates) can reduce their effectiveness.

e.g; *Barbiturates, Phenytoin , Carbamazepine, Rifampin, Nicotine Chronic use of alcohol*.



• Contraceptive failure and loss of therapeutic effect of many other drugs have occurred due to enzyme induction.

- **Excretion altered by**

1. Competition at tubular transporters

Interaction mostly involve drugs that actively secreted by tubular transport mechanisms.

e.g; **Probencid inhibit the tubular secretion of Penicillin or cephalosporine.**

2. Change ionization by alteration of PH of urine

The Change the urinary pH alters the process **of re-absorption** of the drug leading to increase or decrease excretion.

e.g; **Alkalization of urine increases the excretion of acidic drugs as barbiturates.**

3. Pharmacodynamic interactions

In this type of drug interaction, one drug can alter the effect of other drug by affecting the interaction with the target sites **without affecting the concentration**

- This alteration result in either;

Increase in drug effect producing

- ***Additive & Summation effects***
- ***potentiation or permissive effect***
- ***Synergistic effect***

***Or oppose (decrease) of drug effect**

- *Antagonsim*

- *Additive Effects*

When drug A used with drug B each act independent on other and you have no change in their effect.

e.g; Aspirin (blood thinning)+ Acetaminophen (analgesic)= Blood thinning & analgesia.

-Summation Effects :

When both drugs have comparable pharmacological effects the net effect being the summation of both.

e.g; Acetaminophen 30%+ Diclofenac 30%= 60%.

- Potentiation or Permissive Effects

Occur when the effect of drug A is slightly increased in presence of drug B.

- e.g ; Epinephrine = 30% vasoconstriction

Epinephrine + Cortisol = 40 % vasoconstriction

-Synergistic effect

The effect results from interaction of drug A and drug B that have different mechanisms. The resultant response being much greater than that produced by each drug alone or by the summation of both drugs.

- **Aspirin + Clopidogrel**

30% + 30% = 90% or more of blood thinning

DRUG-FOOD Interactions

• The action of drugs can be modified by diet, which can alter the kinetics of drugs result in either toxicity or therapeutic failure.

- **Food decreases rate and extent of drug absorption**

– Milk and other Calcium containing foods reduce the absorption of tetracycline (bind to calcium and complex cannot be absorbed)

– Foods with high fiber foods reduce absorption of digoxin

- **Food increase rate and extent of drug absorption**

e.g; High-calorie meal doubles the absorption of antiviral drug saquinavir.

– **Impact of Food on Drug Metabolism:**

– **The Grapefruit Juice Effect;**

Grapefruit juice can inhibit the metabolism of certain drugs, thereby raising their blood levels which may be remarkable to produce unwanted effects.

– Drug-food interactions sometimes increase toxicity. The most common example is the interaction between monoamine oxidase (MAO) inhibitors (antidepressants) and foods rich in tyramine (as aged cheeses). If an MAO inhibitor is combined with these foods, blood pressure can rise to a life-threatening level.

❑ Impact of Food on Drug action:

Although most drug-food interactions concern drug *absorption* or drug *metabolism*, food may also can affect the action of drug.

e.g; foods rich in vitamin K (e.g., broccoli, cabbage) can reduce the effects of warfarin , as anticoagulant**.**

• **Timing of Drug administration and Meals**

- If absorption of drug decrease by food, and hence these drugs should be administered on an empty stomach (1 hour before a meal or 2 hours after) .
- If absorption of drug increase by food, the drug should be administered with meals.

Adverse drug reactions

undesired reaction that related to the drug, occurs at normal drug doses used in man. Adverse reactions can range in intensity from mild to life threatening which need rapid intervention and decrease in the dose or indicates caution for in future use of the same drug.

❑ Genetic factor [deficiency of enzymes e.g G6PDH..... Favism.

Classification of ADR

- The Types of reaction ; (A, B,C, D, E, and F) .
- The Duration for the appearance of reaction (Acute -60 mint. , subacute 24 hrs , delayed
- The Severity of reaction(mild, moderate &sever)

1- **Type A (Augumented) reaction**
   Predictable, dose dependent, and it's a consequence of therapeutic effect of drug but affect different Tissue. For prevention its required dose adjustment
   e.g; -Streptomycin produce Ototoxicity, nephrotoxicity
   -Captopril cause dry Cough
   -Simvastatin cause Rhabdomyolysis**.**
2- **Type B (Bizarre) Reaction**
   It is abnormal effects, dose independent and unrelated to the drug's pharmacological actions. Can be managed by discontinuation of drug.
   e.g; Hypersensitivity reactions , Hemolytic anemia ,.....
3- **Type C (Continuous) Reaction**
   The effects are usually related to the dose and duration of treatment.
   e.g; Ethambutol causes Retinopathy and NSAIDs induced Nephrotoxicity**.**
4- **Type D (Delayed) Reaction;** Carcinogenic, Teratogenic
5- **Type E (Ending of use) Reactions**
   e.g; Benzodiazepines – Rebound insomnia, agitation....
   Clonidine – Rebound hypertension.
6- **Type F (Failure of efficacy) Reactions.**