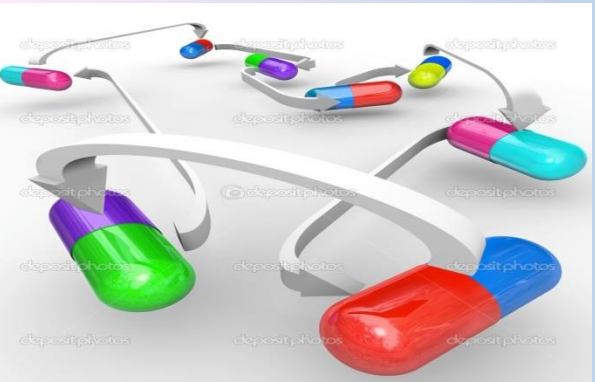
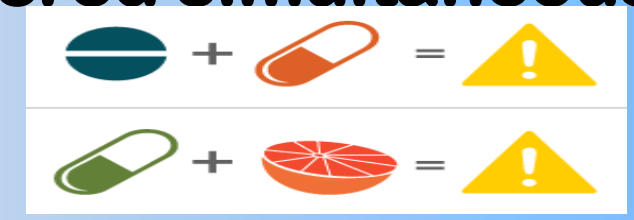
DRUG INTERACTIONS



"Drug interaction refers to modification of response to one drug by another when they are administered simultaneously or in quick succession"



Once should be vigilant about

- Drug-Drug Interactions
- Drug – Herbs Interactions (Indigenous Medicines)
- Drug-Food Interactions (Grape Fruit Juice etc.)
- Drug-Environment Interactions
- Drug-Pollutant Interactions
- Drug-and.....Interactions

"Will this prescription interact with the meds already in my drinking water?


...THE TOP PRESCRIPTION IS FOR YOUR ARTHRITIS, BUT IT MAY CAUSE A HEART ATTACK. THE SECOND PRESCRIPTION SHOULD PREVENT A HEART ATTACK, BUT IT COULD DAMAGE YOUR LIVER. THE THIRD SHOULD PREVENT LIVER TROUBLE, BUT IT MAY DESTROY YOUR SPLEEN. THE FOURTH PROTECTS THE SPLEEN BUT HAS BEEN KNOWN TO EAT AWAY THE PROSTATE. THE FIFTH.....
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- The modification in response may be **Quantitative** (In Intensity), i.e.
  - Increased or
  - Decreased
- It may be **qualitative**
  - Abnormal or a different (New) type of response is produced.
- Possibility arises whenever a patient receives **more than one drug**, and
- Chances increase with
  - More number of drugs.
  - Patient with multiple diseases
  - Patient treated by multiple doctors
  - Patients with compromised physiology
  - Patients with extreme of age (Elderly and Children)

Every Drug Interaction is Harmful ????

NO

- Several drug interactions are deliberately employed in therapeutics, e.g.
  - **ACE inhibitors + diuretics** to treat hypertension or
  - **Sulfamethoxazole + Trimethoprim** to treat bacterial infection or
  - **Furosemide + amiloride** to prevent hypokalaemia.

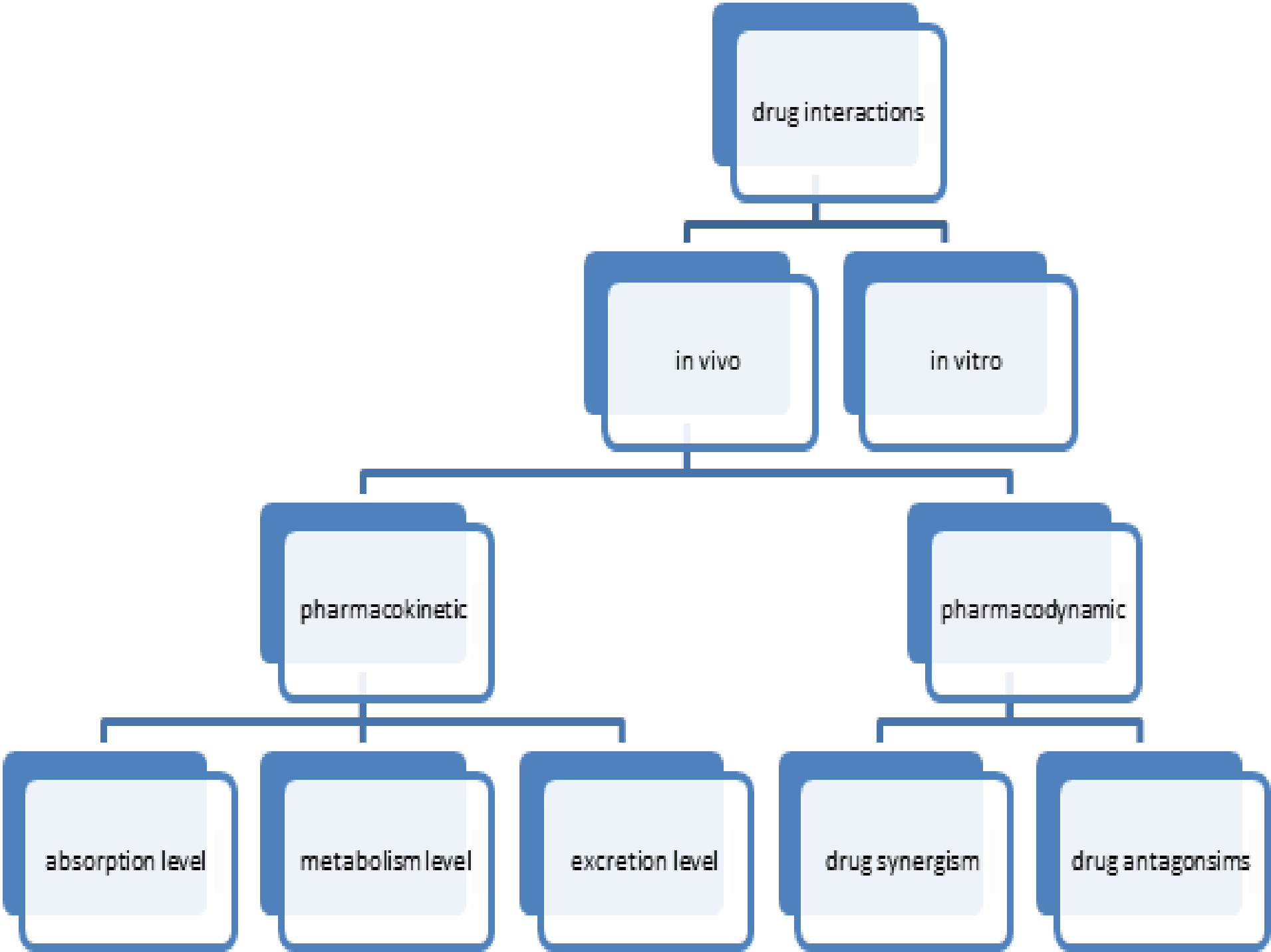
Doctor should elicit a **detailed drug history** of the patient and record all the medication that he/ she is currently on.

Drugs more likely to be involved in drug interactions

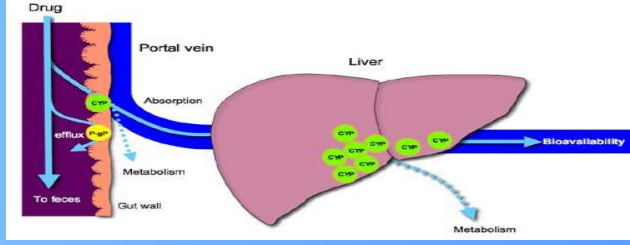
- **With Narrow therapeutic index (Low Safety Margin)**
  - Aminoglycosides
  - Digitalis
  - Lithium
- **Affecting vital physiology of the body**
  - Antihypertensive drugs
  - Anti-diabetic drugs
  - Anticoagulants
- **With high plasma protein binding capacity**
  - NSAIDs
  - Warfarin
  - Sulfonylureas
- **Metabolized by Zero Order Kinetics or Saturation Kinetics**
  - Phenytoin
  - Theophyllin

MECHANISM OF DRUG INTERACTIONS

- Drug interactions can be broadly divided into
  - **Pharmaceutical Interaction**
    - During dosage form preparation or at time of administrations.
    - Dissolving the drug in solvent,
    - Mixing drugs in powder, solution or injection forms.
  - **Pharmacokinetic (ADME)**
    - Absorption (Complex or Chelate formation, Altered stomach pH, Ionization, GIT motility, First Pass Metabolism)
    - Distribution (Protein binding)
    - Metabolism (Enzyme induction/inhibition)
    - Excretion (Altered pH, Ionization, Entero-hepatic recirculation)
  - **Pharmacodynamic (At receptor or tissue level)**


drug interactions
in vivo
in vitro
pharmacokinetic
pharmacodynamic
absorption level
metabolism level
excretion level
drug synergism
drug antagonsims

ABSORPTION



- **Insoluble and poorly absorbed complexes** in the gut
  - Example:-
    - Tetracyclines and calcium/iron salts, antacids or sucralfate
    - Phenytoin absorption is decreased by sucralfate
  - Minimized by administering the two drugs with a **gap of 2-3 hours.**
- **Alteration in Entero-hepatic recirculation**
  - Antibiotics like Tetracyclines (Broad Spectrum) markedly **reduce gut flora** that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronides and permits their **Entero-hepatic recirculation**. C**ontraceptive failure** when concurrent use of antibiotics due to lowering of the contraceptive blood levels.

DISTRIBUTION

- **Primarily due to displacement** of one drug from its binding sites on plasma proteins by another drug.
- Drugs highly bound to plasma proteins that have a relatively small volume of distribution like oral anticoagulants, sulfonylureas, certain NSAIDs and anti-epileptics are particularly liable to displacement interactions
- The drug which is in unbound form is active while portion which is in bound form woks as temporary storage.
- When the drug is displaced by the other drug or chemical the unbound form of the active drug becomes more leading to toxic level in the blood and **presenting as toxicity.**

METABOLISM

- Certain drugs **reduce or enhance the rate of metabolism** of other drugs and **affect the bioavailability**.

- Inhibition of drug metabolism may be due to competition for the same CYP450 iso-enzyme or cofactor, and attains clinical significance mostly for drugs that are metabolized by saturation kinetics.

SOME IMPORTANT INHIBITORS OF METABOLISM OF MULTIPLE DRUGS (MAO-QC)

- Macrolide antibiotics,
- Azole antifungals,
- Chloramphenicol,
- Omeprazole, SSRIs,
- HIV -protease inhibitors,
- Cimetidine,
- Quinolones (Ciprofloxacin)
- Metronidazole.

Table

CYP3A4 Inhibitors	
• Amiodarone	• Indinavir
• Amprenavir	• Itraconazole
• Aprepitant	• Ketoconazole
• Atazanavir	• Nelfinavir
• Clarithromycin	• Posaconazole
• Conivaptan	• Quinupristin-dalfopristin
• Cyclosporine	• Ritonavir
• Darunavir	• Saquinavir
• Delavirdine	• Tamoxifen
• Diltiazem	• Telithromycin
• Erythromycin	• Verapamil
• Fluconazole	• Voriconazole
• Fluvoxamine	
• Imatinib	

Risk of statin induced myopathy is increased by fibrates, niacin, erythromycin, azole anti-fungals and HIV -protease inhibitors, due to inhibition of statin metabolism.

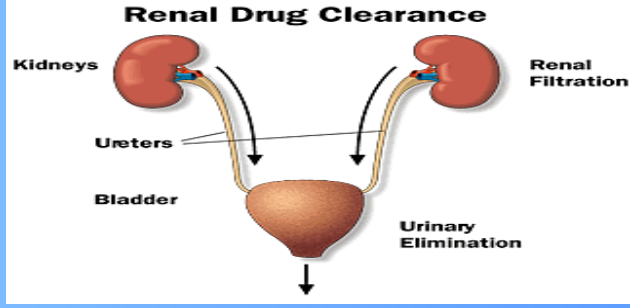
- Induction involves **gene mediated increased synthesis** of certain CYP450 isoenzymes.
- **It takes 1-2 weeks of medication** with the inducer to produce maximal effect.
- **Effects regresses gradually** over 1-3 weeks after discontinuation of the inducer

IMPORTANT MICROSOMAL ENZYME INDUCERS (RBC)

- Barbiturates,
- Phenytoin
- Carbamazepine
- Rifampin
- Cigarette smoking
- Chronic alcoholism
- Pollutants

- Instances of failure of antimicrobial therapy with metronidazole, doxycycline or chloramphenicol have occurred in patients who are on long-term medication with an inducing drug.
- Contraceptive failure and loss of therapeutic effect of many other drugs have occurred due to enzyme induction (Patient taking Rifampicin)
- Toxic dose of paracetamol is lower in chronic alcoholics and in those on enzyme inducing medication, because one of the metabolites of paracetamol is responsible for its overdose hepatotoxicity

EXCRETION



- Interaction involving excretion are important mostly in case of **drugs actively secreted by tubular transport** mechanisms. The alteration of urinary pH alters the process of reabsorption of the drug leading to increase or decrease excretion.
- Probenecid inhibits tubular secretion of penicillins and cephalosporins .
- Aspirin blocks the uricosuric action of probenecid and decreases tubular secretion of methotrexate.
- Alkalization of urine increases the excretion of barbiturates

PHARMACODYNAMIC INTERACTIONS

- These interactions derive from modification of the action of one drug at the target site by another drug, **independent of a change in its concentration**.

- This may result in an **enhanced response (synergism**), an **attenuated response (antagonism)** or an abnormal response.

Examples:-

- Excessive sedation, respiratory depression, motor incoordination due to concurrent administration of a benzodiazepine (diazepam), a sedating antihistaminic (promethazine), a neuroleptic (chlorpromazine), an opioid (morphine).

- Excessive fall in BP and fainting due to concurrent administration of α1 adrenergic blockers, vasodilators, ACE inhibitors, high ceiling diuretics and cardiac depressants.

- Excessive platelet inhibition resulting in bleeding due to simultaneous use of aspirin/ ticlopidine / clopidogrel and carbenicillin.

- Increased risk of bleeding due to concurrent use of antiplatelet drugs (aspirin, clopidogrel) with anticoagulants (warfarin).

- Abnormal responses sometimes result from **pharmacodynamic interaction** between certain drugs. (Mechanism may be explainable or unexplainable)
- e.g. Metronidazole and Cefoperazone inhibit the enzyme aldehyde dehydrogenase resulting in bizarre distressing symptoms if the patient drinks alcohol. (Disulfiram Like reaction)
- The basis of certain interactions is not explained, e.g. ampicillin has produced high incidence of skin rashes in patients treated with allopurinol.

DRUG INTERACTIONS BEFORE ADMINISTRATION

- Certain drugs react with each other and get inactivated **if their solutions are mixed before administration.**

- In practice situations, these in vitro interactions occur when injectable drugs are mixed in the same syringe or infusion bottle.

Some examples are:

- Penicillin G or ampicillin mixed with gentamicin or another aminoglycoside antibiotic.
- Thiopentone sodium when mixed with succinylcholine or morphine.
- Heparin when mixed with penicillin gentamicin/hydrocortisone.

- **Not all patients** taking interacting drugs experience adverse consequences, but it is advisable **to take due precautions to avoid mishaps in all cases** where interactions are possible.

- Two drugs have the potential to **interact does not necessarily contraindicate** their concurrent use.

- In many cases, **knowledge of the nature and mechanism of the possible interaction** may permit their concurrent use provided appropriate dose adjustments are made or other corrective measures are taken

“ It is prudent to consider the possibility of drug interaction whenever two or more drugs are prescribed to a patient, or any drug is added to what the patient is already taking”

Thanks