1- Drug interactions

Drug interactions may be:

1- **Desirable:** Caffeine + Aspirin in headache

2- **Undesirable:** - Halothane + Adrenaline ➔ Arrhythmia

- MAOI + Tricyclic antidepressants ➔ Atropine like toxicity

Mechanism of drug interactions

1- Before Drug administration:

1- During Pharmaceutical formulation:

- ***Calcium lactate*** used as diluent may chelate ***Tetracycline***

2- Mixing drugs wiyh I.V infusion fluids:

- ***Ampicillin, Ascorbic acid & Barbiturates*** react with ***Dextran*** solutions
- ***Benzyl penicillin, Erythromycin, Gentamycin & Hydrocortisone*** react with ***Heparin*** solutions

3- Mixing drugs prior to administration:

- ***Thiopentone*** (Alkaline) + ***Succinylcholine*** (Acidic) ➔ Neutralization
- ***PZI*** + ***Soluble insulin*** ➔ Precipitation of soluble insulin

2- After Drug administration:

1- Pharmacokinetic interactions ➔ see before

2- Pharmacodynamic interactions ➔ see before

2- Drug Addiction

Definition:

Behavioral syndrome in which individual continues the use of the drug in a periodic or chronic way despite significant problems. There is tendency to ↑ the dose, psychic & physical dependence.

Factors affecting liability for addiction:

1- **Drug factors:**
   1- Euphoria & reinforcing properties
   2- Onset of action
   3- Tolerance
2- **Individual factors:**
   1- Genetic factors
   2- Psychic disorders
3- **Enviromental factors**

Classifications:

1- **CNS depressants:** Sedatives & Hypnotics – Alcohol – Opioids
2- **CNS stimulants:** Amphetamine – Nicotine – Cocaine
3- **Hallucinogenics:** LSD – Phencyclidine – Cannabis
4- **Volatile inhalants:** Halothane – N_2O – Nail & shoe polish

3- Vitamins

A- Water soluble vitamins

1- vit. B_1 (Thiamine):

* ***Importance:*** Act as coenzyme in CHO metabolism
* ***Deficiency:*** Beri-Beri (Dry type & Wet type)

2- vit. B_2 (Riboflavine):

* ***Importance:*** It is a constituent of Flavoprotein enzymes which act as Hydrogen carrier.
* ***Deficiency:*** Stomatitis – Glossitis – Dermatitis – Anaemia – Neuropathy

3- vit. B_6 (Pyridoxine):

* ***Importance:*** Act as coenzyme in amino acid metabolism
* ***Deficiency:*** Dermatitis – Peripheral neuritis – Anemia
* ***Uses:*** 1- Prophylactic with Isoniazide
  2- Treat vomiting of pregnancy

4- vit. B_7 (Nicotinic acid):

* ***Importance:*** It is a constituent of NAD & NADP which act as Hydrogen carrier.
* ***Deficiency:*** Pellagra (**D**ermatitis – **D**iarrhea – **D**ementia)

5- Pantothenic acid:

* ***Importance:*** It is a constituent of coenzyme a, which is essential in metabolism & fatty synthesis.
* ***Deficiency***: Neuromuscular degeneration – Adrenocortical insufficiency

6- vit. C (Ascorbic acid):

* ***Importance:***
  1- Anti-oxidant
  2- Synthesis of collagen
  3- Integrity of intercellular matrix & capillary wall
  4- Folate, CHO & Tyrosine metabolism metabolism
  5- ↑ absorption of iron by reducing ferric to ferrous
* ***Deficiency***: Scurvy
* ***Uses:***
  1- Treatment of Scurvy
  2- Treatment of met-Hb
  3- ↑ iron absorption
  4- Acidification of urine to ↑ excretion of basic drugs
  5- Anti-oxidant to protect against Cataract

B- Fat soluble vitamins

1- vit. A:

**** Importance:***

1- Anti-oxidant
2- Formation of retina
3- Growth & Development of epithelium

* ***Defenciency:*** Night blindeness – Dry skin – Urinary calculi

****Uses:***

1- Treatment of deficiency
2- Acne *(Isoretinoin)* & Psoriasis *(Etritanate)*
3- Prevention of cancer

* ***SE.:*** Hypervitaminosis A

1- Skin lesions – Hair loss
2- Pain & Tenderness of long bones
3- Headache & irritability
4- Hepatosplenomegally
5- Teratogenicity

2- vit. D: see before

3- vit. K: see before

4- vit. E:

**** Importance:*** Anti-oxidant

**** Defeciency:*** CNS degeneration – muscle atrophy – atheriosclerosis – reproductive system defect

NB.: Anti-oxidant vitamins: vit. A- C - E

4- Chelating Agents

1- **Dimercaprol (BAL):** IM for Mercury – Gold - Arsenic

2- **Dicobalt Edetate:** for Cyanide

3- **Disodium Edetate (EDETA):** IV for Ca^{++}

4- **Calcium Disodium Edetate:** IV infusion for Lead

5- **Deferoxamine:** IV infusion for Iron

6- **Deferasirox:** oral chelating agent for Iron

7- **D-penicillamine:** Orally to chelate copper in Wilson disease
Also chelate: Mercury – Lead

8- **Trientine:** for Copper

9- **Succimer:** Orally for Mercury – Arsenic - Lead

5- SOME IATROGENIC DISEASES

Drugs affecting GIT:

Drugs causing diarrhea:

1. **A**drenergic neurone depressants (eg.: guanithedine & reserpine)
2. **A**ntacid (Mg oxide & hydroxide)
3. **A**ntimicrobials (Broad spectrum)
4. **P**rokinetic drugs: Metoclopromide - Dompridone – Erythromycin - **P**arasympathomimetics (eg.: carbachol, bethanechol, neostigmine…)
5. **P**urgatives
6. **P**G analogue: Misoprostol
7. Colchicine
8. Dantrolene (skeletal muscle relaxant)
9. Oral iron (may cause black or bloody diarrhea)

Drugs causing constipation:

1. **A**tropine & atropine substitutes
2. Drugs having **A**tropine like effects
3. **A**ntacids (Aluminium hydroxide gel - Calcium carbonate)
4. Calcium channel blockers (eg.: Verapamil)
5. Opioid analgesics (eg.: morphine)

Drugs causing nausea & vomiting:

1. **Anti**gout drugs: Allopurinol
2. **Anti**parkinsonian drugs: Levodopa - Bromocriptine
3. **Anti**cancer drugs (especially cisplatin, cyclophosphamide, doxorubicin, nitrosoureas)
4. **Anti**rheumatic drugs: NSAIDs - Gold – Penicillamine - Sulfasalazine
5. Digoxin
6. Theophylline
7. Opioid analgesics
8. Oral use of: Antimicrobials - Iron - Oestrogens

Drugs causing peptic ulcer:

1. NSAIDs (except paracetamol)
2. Cortisone
3. Reserpine

Drugs affecting respiration:

Drugs causing bronchial asthma:

1. **N**SAIDs (except paracetamol)
2. **N**on-selectve β-blockers
3. **M**orphine
4. **M**uscarinic agonists as methacholine – carbachol – neostigmine

Drugs affecting CVS:

Drugs causing hypertension:

1. **C**ortisone
2. **C**ontraceptives
3. α_1-agonists as adrenaline – noradrenaline – phenylephrine

Drugs causing angina pectoris:

1. β_1-agonist: as adrenaline – isoprenaline
2. Thyroid hormone
3. Methylxanthines
4. Arteriodilators as hydralazine – minoxidil – diazoxide

Drugs causing bradycardia:

1. β-blockers
2. Parasympathomimetics
3. Noradrenaline & Phenylephrine (the cause reflex bradycardia)
4. Digitalis
5. General anesthesia
6. Some calcium channel blockers (verapamil)

Drugs causing tachycardia:

1. β_1-agonist: as adrenaline – isoprenaline – ephedrine
2. β_2-agonist: as salbutamol
3. α_1-blockers (Non selective & partially selective): as phentolamine & phenoxybenzamine
4. Ganglion blockers
5. Glucagon hormone
6. Methylxanthines
7. Arteriodilators as hydralazine – minoxidil – diazoxide

Drugs causing A-V block:

1. Digitalis
2. Verapamil
3. β-blockers
4. Methacholine

Drugs affecting eye:

Drugs causing glaucoma:

1. Parasympatholytics as Atropine
2. Ganglion blockers
3. Drugs having Atropine like effect: as: Tricyclic antidepressants & Antihistaminics
4. Vasodilators as: Nitrite , Nitrate & Histamine
5. Cortisone

Drugs affecting kidney & electrolytes:

Drugs causing nephrotoxicity

1. NSAIDs except paracetamol
2. Colchicines
3. Gold salts
4. Antimicrobial drugs (aminoglycosides – vancomycin – cephalosporins – methicillin – sulphonamides – tetracyclines – amphotericin B – acyclovir)
5. Lithium
6. Methoxyflurane

Drugs causing hyperkalemia:

1. K+ sparing diuretics
2. ACE- inhibitors
3. ARBs
4. Drugs that inhibit aldosteron synthesis (eg.: Metyrapone)
5. Succinylcholine
6. Non-selective β-blockers
7. Severe digitalis toxicity

Drugs causing hypokalemia:

1. Thiazide diuretics
2. Loop diuretics
3. CA inhibitors
4. Steroids (cortisone – aldosterone)
5. Adrenaline & other β_2 agonist

Drugs affecting CNS:

Drugs causing convulsions

1. CNS stimulants: methylxanthines – atropine – cocaine – analeptics – strychnine
2. Meperidine
3. Morphine
4. MAO inhibitors
5. Aspirin toxicity
6. Lithium
7. Antimicrobials: Penicillins (in large dose or intrathecal) - Carbapenem as imipenem – Cycloserine - Fluoroquinolones especially if combined with NSAIDs - Amphoterecin B - Oxamniquine
8. Digitalis

Drugs causing psychosis:

1. D_2-agonist as L-dopa & bromocriptine
2. Digitalis
3. Indomethacin
4. Cortisone
5. Cycloserine

Drugs causing depression:

1. Estrogen & oral contraceptives
2. Reserpine & α-methyl dopa
3. Chlorpromazine (pseudodepression)

Drugs causing extrapyramidal manifestation & parkinsonism:

1. D_2-blockers: as phenothiazine - thioxanthines – butyrophenones – metochlopromide
2. Reserpine & α-methyl dopa

Drugs causing tinnitus & vertigo:

1. Salicylates
2. Loop diuretics
3. Aminoglycosides
4. Vancomycin
5. Metronidazole
6. Minocycline
7. Indomethacin
8. Phenylbutazone

Drugs affecting hair:

Drugs causing alopecia:

1. Anticancer drugs
2. Heparin
3. Colchicines
4. Sodium valproate
5. Oxazolidinediones
6. Interferones

Drugs causing hirsutism:

1. Androgen
2. Progesterone
3. Phenytoin

Miscellaneous:

Drugs contraindicated in porphyria:

1. Barbiturates
2. Primidone
3. Chloroquine
4. Griseofulvin

Drugs causing Systemic lupus erythematosus (SLE) like syndrome:

1. Hydralazine
2. Procainamide
3. Isoniazid

Drugs causing Cushing syndrome:

Cortisone for long use

Drugs causing Gynaecomastia:

1. Digitalis
2. Spironolactone
3. Cimetidine
4. Ketoconazole
5. Reserpine & α-methyl dopa (They ↓ dopamine in CNS➔↑ Prolactin)
6. Estrogen given to males to treat cancer prostate
7. Cyproterone

Drugs causing Photosensetivity:

1. Amiodarone
2. Antimicrobialss: Tetracyclines - Quinolones – Sulphonamides – Griseofulvin
3. Piroxicam
4. Retinoids

6- CLINICAL PHARMACOKINETICS

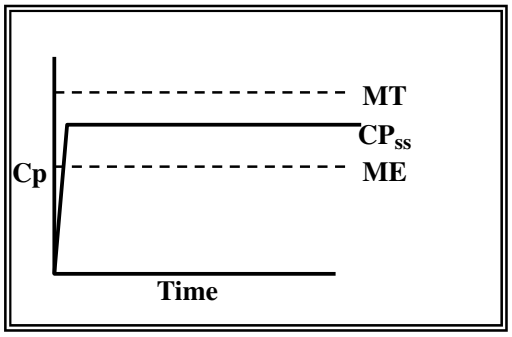
1- Loading & maintenance dose

Loading Dose: L.D.= V_d x Css (targed C_p)

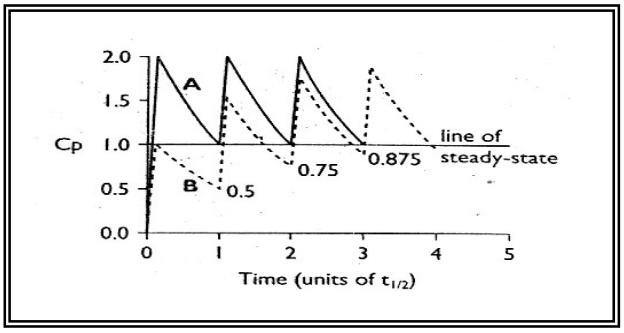
- It is the dose given at the onset of therapy to achieve rapid increase in plasma drug concentration to reach Css (steady state concentration) without toxicity.
- Used for drugs with long $t_{1/2}$ (amiodarone-digoxin) or in urgent demand.

Maintenance dose (M.D.) = C_{ss} x clearance (cl)

- It is the dose needed to keep the plasma drug concentration constant at the steady state i.e. to compensate for drug loss in between doses.
- Drugs are administered in a series of repetitive doses or continuous infusion to maintain the target plasma concentration at steady state.
- The rate of drug administration is adjusted such that the rate of input equals the rate of loss according to the equation: "M.D.=C_{ss} x CL".



Loading dose (IV injection followed by a constant infusion)
MTC = minimal toxic concentration.
MEC = minimal effective concentration.



Curve A- loading dose followed by maintenance dosing.
Curve B- maintenance dosing every half-life.

Calculation of loading dose (LD)

It follows from the above that to achieve a target C_P, the V_d of the drug must be known

I.V.$L_D = V_d$ x target C_P

e.g. to achieve a target C_P of digoxin of 1.5 µg/L, with V_d 500 L/70kg. or 0.75 mg is needed, for person 70 kg.

I.V. L_D (µg) = 500 (L) x 1.5 (µg/L) = 750 µg.

$$\textit{Oral loading dose} = \frac{\text{I.V. Loading dose}}{\text{F(fraction of drug absorbed or oral bioavailability)}}$$

With a loading dose, steady-state concentrations can be achieved quickly.

2- Elimination half life ($t_{1/2}$)

Definition: it is the time required to reduce the plasma concentration of drug to half the initial concentration.

- Rate of elimination = Cl x conc. of the drug
- Rate of elimination = K_e (elimination rate constant) x A (amount of drug in body or dose given)
- So, CL X C_p = K_e x A
- & as, C_p (conc. in plasma) = $\frac{A}{V_d}$
- So, Cl x $\frac{A}{V_d}$ = K_e x A

➔ Cl = K_e x V_d

Relationship between $t_{1/2}$, V_d and Cl :

The larger the Vd, the longer the $t_{1/2}$, i.e. it takes longer to remove drug from deep within the tissue. Similarly, the larger the Cl, the shorter the $t_{1/2}$. In other words:

$$t_{1/2} \propto \frac{Vd}{Cl}$$

- This relationship can be turned into an equation by multiplying the right side by 0.693. This strange number is the natural logarithm of 2 (i.e. In 2) and gets into the equation because the $t_{1/2}$ involves a halving, i.e. the inverse of 2.

$$t_{1/2} = \frac{0.693 \text{ x } vd}{cl_{\text{ total}}}$$

- This is one of the most important equations in clinical pharmacokinetics.
- It indicates that the t1/2 is dependent on Vd and Cl.
- Vd and Cl are the independent variables.
- if V_d of drug =1 it means that drug distribute to all parts of body

$t_{1/2} = \frac{0.693}{cl}$ here Cl = elimination rate constant (K_e)

- Decrease in renal blood flow "cardiogenic shock, heart failure, hemorrhage" leading to increase $t_{1/2}$
- Increase Vd leading to increase $t_{1/2}$
- Decrease in excretion (e.g renal failure) leading to increase $t_{1/2}$
- Decrease in metabolism (e.g hepatic insufficiency and enzyme inhibition) leading to increase $t_{1/2}$

$t_{1/2}$ is constant in drugs obeying first order kinetics.

Significance:

1- Determination of dosage intervals "frequency of drug administration" drug almost disappears after about 4-5 $t_{1/2}$.
2- It indicates the time require to attain steady state concentration (C_{ss}) or to decay from C_{ss} in a particular dosing regimen.
3- A guide to rate of accumulation during repeated dosing.
4- It is an index of drug elimination or clearance provided the V_d is 1 (one).
5- A guide to dosage schedules

Factors affecting elimination $t_{1/2}$:

1- The state of eliminating organ (ie.: liver & kidney function)

2- The delivery of the drug to the eliminating organs (eg.: plasma protein binding limits renal filtration & drugs with large V_d may escape from elimination in the tissues)

Choice of dose interval:

The dose interval is usually chosen based on :

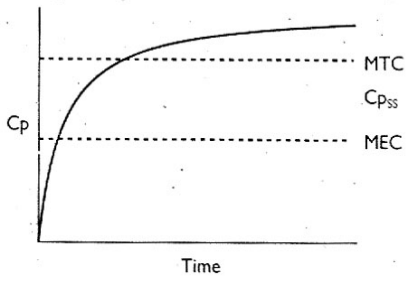
1- The $t_{1/2}$ 2- The therapeutic index of the drug. 3- Compliance

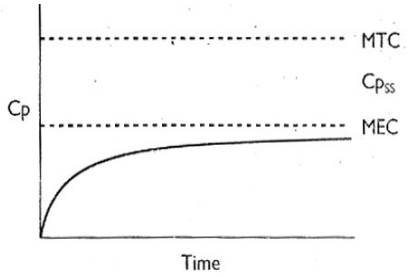
Total body Clearance (Cl) is the sum of all individual organ clearance which consists of renal clearance (Cl_r) and non-renal clearance (Cl_{nr}).

It is not possible to measure and sum these individual clearances. However, total clearance can be derived from the steady state equation

Cl_{total}= elmination rate constant (K_e) x V_d

Cp higher than desired **Cp lower than desired**





The two factors involved are excessive dosage and/or decreased Cl.

Factors causing decreased Cl are:

- normal variation.
- saturable metabolism
-genetic enzyme deficiency
-renal failure
- liver failure.
- old age.
- very young age (noenate)
-enzyme inhibition.

Dose may be too low, or Cl too high.

Factors causing increased Cl are:

-normal variation.
-poor absorption.
-high first-pass metabolism.
- Genetic hypermetabolism.
- Enzyme induction.

3- Kinetics of IV Infusion

- Rate of drug entry into the body is constant
- Elimination of drug is mostly first order
- Plasma concentration of drug rises from zero at state of infusion till reaching steady state (SS)
  (rate of drug elimination balances rate of drug administration).

Factors affecting plasma concentration of drug at steady state :

Plasma concentration of drug at steady state "Css" remain constant, and it's affected by:

$$C_{SS} = \frac{\text{Rate of infusion}}{K_e \times V_d} = \frac{\text{Rate of infusion}}{\text{Total body clearance}}$$

K_e: elimination rate Constant

V_d : volume of distribution

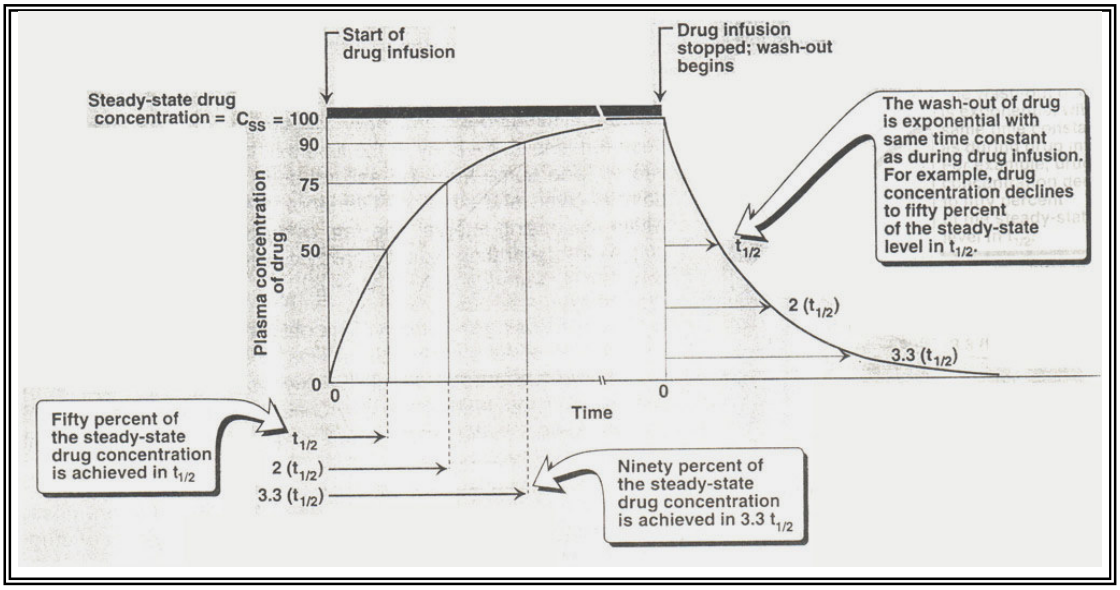
1- Rate of infusion : Css is directly proportional to rate of infusion (i.e. increase in rate of infusion leading to increase in Css but not affect rate to reach steady state.

2- Clearance : Css is inversely proportional to clearance of drug (i.e increase in Css in liver or kidney disease).

N.B: in first order kinetics, elimination rate Constant V_d and clearance are constant.

Factors affecting rate to reach steady state:

$T_{1/2}$ is the only determinant of rate to reach steady state.



Kinetics of I.V. Injection

Single I.V Injection (in two compartment model)	Multiple I.V Injection (at regular intervals)
Level of drug passes through 2 phases. 1-α phase= rapid decline in plasma drug concentration due to distribution of drug. 2-B phase = elimination of fixed fraction per unit time (1st order elimination).	Results in oscillation in plasma concentration of drug till reaching steady state concentration

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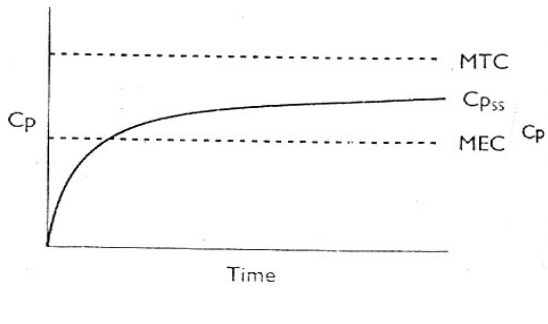
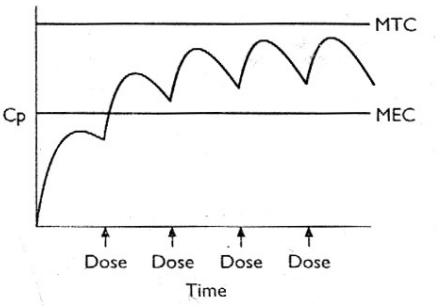
Kinetics of Oral Administration

Single oral dose	Repeated oral administration
Results in single peak in plasma concentration followed by continuous decline in drug levels.	Results in oscillation in plasma concentration that are affected by. - rate of drug absorption. - Rate of drug elimination.

Constant IV infusion **Oral Dosing**



The Cp rises to reach the desired steady state concentration (Cpss). The main determinant of the Cpss is the dose and the clearance (Cl).



The curve reflects assimilation and elimination, and intermittent administration.

4- Evaluation of New Drugs

I- Evaluation in animals

- It is conducted on experimental animals (at least two species, one of which is rodents):

a) Safety tests :

Include the following studies :

- Acute, subacute and chronic toxicity studies
- Effects on reproductive function
- Carcinogenic and mutagenic potential
- Addiction liability

b) Pharmacologic profile :

- Studying the effect of drugs on different body systems : CNS-GIT-CVS,…

II-Evaluation in humans:

- Is begun after sufficient acute & subacute animal toxicity studies have been completed:

a) Phase I
- It is done on small number of healthy volunteers.
- These trials are non-blind, i.e. both the investigator and the subject know what is being given.
- It compares human to animal responses and determines the limits of clinical dosage range.
- Pharmacokinetic measurements are often done in phase I.

b) Phase II
- It is done on small number of patients to determine safety and efficacy.
- A single blind design is often used.
- It involves comparison with an older active drug.

c) Phase III
- It is done on large number of patients.
- Double blind and cross-over techniques are frequently employed.

d) Phase IV
- It is done to monitor the efficacy and safety of the new drug under actual conditions of use in large number of patients.
- It also involves "Post-marketing Surveillance" or post-licensing studies to determine additional efficacy and toxicity after general marketing.

Placebo

- It is an inert substance given just to please the patient.

Uses of placebo:

1- In psychotherapy, sometimes a placebo does as much good (and less harm) as a potent drug with serious toxic effects.

2- In evaluation of new drugs to avoid false conclusions :
- To distinguish the pharmacodynamic effects of a drug from the psychological effects of the act of medication.
- To distinguish drug effects from fluctuations in severity of disease.

Double blind technique

- It is used to prevent the effect of bias of both doctor & patient on results.
- The patient (the first "blind" man) does not know whether he is receiving the active drug or a placebo.
- The investigator (the second "blind" man) is ignorant of whether he is prescribing a placebo or an active drug.

N.B.: In single blind studies, only the patient is ignorant.

Cross-over trial

- It is conducted to protect against errors of interpretation caused by fluctuation in severity of disease.
- It consists of alternating periods of administration of test drug, placebo and standard drug control (to which the drug is compared).
  Each patient receives the three types of medications in a random sequence.